NEURAL BASIS OF THE NEUROLOGICAL DIAGNOSTIC POWER OF VIBROTACTILE SENSORY TESTING

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ABSTRACT

THERESA MARIE FORSHEY: Neural Basis of the Neurological Diagnostic Power of Vibrotactile Sensory Testing
(Under the direction of Dr. Mark A. Tommerdahl)

As with most other injuries and disorders, the prognosis of neurological impairment is dependent upon early and accurate detection. Likewise, after an appropriate diagnosis has been made, it is important to start the patient on an effective treatment plan. Often a clinician prescribes a medication and asks the patient to come back for a follow-up appointment. It would be highly beneficial if the clinician could instead conduct a quantitative assessment to immediately determine the effectiveness of a prescribed treatment. Our research utilizes non-invasive, non-painful tactile sensory assessments which could assist in the timely, accurate detection of neurological impairments and evaluation of the effectiveness of attempted treatments by quantifying minute changes in cortical functionality.

Unfortunately, despite the potential to use these diagnostic assessments for a broad scope of neurological impairments (e.g., alcoholism, chronic pain, concussion, and autism), the neurological base behind many of these diagnostic assessments are unclear. In other words, while the assessments found variations between these focus groups and healthy controls, there is not enough neurological context to fully explain the findings. To address the issue, the primary goal of this research was to establish a neurological basis for the results of these sensory assessments. Once understood, these quantitative

assessments could become valuable tools in future clinical applications for the diagnosis of neurological disorders.

The central goal of this study was to provide experimental evidence of a cortical mechanism that was hypothesized to be of fundamental importance in tactile perception. Based upon microelectrode recording analysis of the cortical response to various vibrotactile stimulations (cats and non-human primates), we describe two forms of cortical contrast: spatial and temporal. Those results suggest that improved cortical contrast may be important for enhancing tactile sensory perception. To test this hypothesis, we conducted a variety of tactile sensory assessments on healthy controls including frequency discrimination, amplitude discrimination, and temporal order judgment. The results of the human sensory studies are in full agreement with our basic, animal neurophysiological studies. In conclusion, human performance on those quantitative sensory tests can be used as an indicator of the functionality of the cortical mechanisms responsible for spatial and temporal contrast enhancement.

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2AFC (two-alternative forced choice)

2-D (2-dimensional)

µm (micrometers)

CCG (cross- correlograms)

CNS (central nervous system)

D2 (digit 2 – index finger)

D3 (digit 3 – middle finger)

DL (difference limen)

Hz (Hertz)

IACUC (institutional animal care and use committee)

ISI (inter-stimulus interval)

ITI (inter-stimulus interval)

MFR (mean firing rate)

msec (milliseconds)

n (number of subjects)

OIS (Optic intrinsic signal)

PC1 (principal component 1)

PC2 (principal component 2)

PCA (principal component analysis)

PSTH (peri-stimulus time histogram)

QST (Quantitative Sensory Testing)

RI (response interval)

sec (seconds)

SI (primary somatosensory cortex)

SII (secondary somatosensory cortex)

S/T (standard/test stimulus)

TOJ (temporal order judgment)

USPHS (United States Public Health Service)

VAS (visual analogue scale)

VVS (vulvar vestibulitis syndrome)

CHAPTER 1

INTRODUCTION

When it comes to illness, injuries, or disorders, it is best to detect the health issue early and start immediate treatment if possible. As with most other health complications, the prognosis of a neurological impairment relies on timely and accurate detection. A wide variety of diagnostic tests are already available to assess a broad scope of neurological impairments; however, there are instances when patients are unable or unwilling to tolerate the inconvenience, complexity, cost, or distress involved with standard testing procedures. Despite the well-known urgency for early and accurate detection, these complications could cause individuals to wait until the symptoms become overly problematic before attempting to seek a professional evaluation or treatment. Finally, after an appropriate diagnosis has been made, it is important to start the patient on an appropriate treatment plan. Clinical consultations often conclude with the clinician prescribing a medication and asking the patient to come back for a follow-up appointment. Unfortunately, it can take time for a patient to notice the effects of a new drug and the clinician needs to wait until the patient can detect these changes before requesting feedback on the effectiveness of the treatment. Although clinicians use their best judgment when prescribing a medication, not every treatment plan can work for each patient. It would be highly beneficial to a patient's prognosis if, instead of waiting for the patient to return, the clinician could instead conduct a quantitative assessment to

immediately determine the effectiveness of a prescribed treatment. Additionally, acquiring specific measures of central nervous system (CNS) functionality should reduce the potential biases (e.g. placebo effect) from subjective patient feedback and produce a more accurate evaluation of the current treatment methods.

Our current research utilizes quantitative tactile sensory assessments that could eliminate many of these typical potential clinical problems. The sensory tasks apply non-invasive, non-painful tactile stimulation to detect and quantify minute changes in cortical sensory information processing capacity. By acquiring quantitative tactile sensory diagnostics, clinicians have the potential to evaluate the broader scope of CNS functionality. The cerebral cortex is the brain's primary instrument for sensory processing, learning, memory, communication, and motor control. While the cortex is processing tactile sensory information, it is also integrating information from other regions of the CNS. Thus, with tactile sensory testing we can measure the overall functionality of the CNS in addition to determining sensory processing capability. This hypothesis supports the efficacy of these quantitative assessments in the previous literature for cases of drug use, alcoholism, chronic pain, concussion, autism, and age (Folger et al., 2008; Francisco et al., 2012; Nelson et al., 2012; Nguyen et al., 2013a, b; Tannan et al., 2008; Tommerdahl et al., 2007a, 2008; Zhang et al., 2009, 2011a, b). Clinicians can choose from a wide variety of tactile sensory assessments including reaction time, sensory detection thresholds, discrimination thresholds, adaptation measures, spatial acuity, and temporal order judgment. Despite the diverse testing procedures, the functionality of the cortex should be reflected in each of these sensory assessments. Another value of these tests is that each assessment could be impacted

differently depending on the source of the abnormality. Nevertheless, it is the potential for the results from all of these tests (within a particular focus group) to deviate from the healthy controls group that is the most beneficial for clinical diagnosis. For instance, if the information processing mechanisms which facilitate human perception are impaired, then all of the sensory tests should clearly demonstrate below normal perceptual capabilities. Additionally, these diagnostic assessments utilize rapid detecting devices that are economical and pain-free. Even in cases of chronic pain, our sensory assessments could be used to evaluate changes in cortical functionality without the need to provoke any pain in the patient (Zhang et al., 2011a). These diagnostic tests could allow the clinic to implement more cost-effective and efficient diagnosis tests while maximizing personal comfort.

However, before widely applying these tactile sensory tests clinically, we must ensure that we understand how all of these sensory tests may connect into one larger picture. In doing so, we increase the probability of applying these sensory assessments in the correct clinical applications. Regrettably, despite the potential to use these diagnostic assessments in the broad spectrum of neurological impairments, the neurological basis behind many of these tactile tests is not fully understood. Although the results of the assessments had found variations between these focus groups (compared to healthy controls), researchers lacked some of the necessary neurological context to justify their findings. To address the issue, the primary goal of this research was to establish a neurological basis to describe the results of these sensory assessments. Once understood, we believe that these quantitative assessments can be implemented in future clinical

applications and serve as valuable diagnostic tools for the diagnosis of neurological disorders.

The central goal our research was to provide experimental evidence of a cortical mechanism that was hypothesized to be of fundamental importance in tactile perception. Various means of mechanical stimulation were applied to the fingers of cats and non-human primates as the response in the primary somatosensory cortex (SI) was recorded. Based on our analysis of the spike activity in SI, we describe how two forms of cortical contrast could evolve from vibrotactile stimulation: spatial and temporal. Hypothesizing that this enhanced cortical contrast could be beneficial to tactile perception, we conducted a series of quantitative tactile sensory assessments (frequency discrimination, amplitude discrimination, and temporal order judgment) on a sample population of healthy controls. The results are highly indicative that cortical contrast is a common phenomenon that controls cortical functionality and improves tactile perception. However, our research also suggests that synchronization among spatially separate cortical regions may take precedence over enhanced cortical contrast in its ability to shape perception. Overall, we were able to conclude that human performance on the tactile quantitative sensory tests can be used as an appropriate indicator for the functionality of the cortical mechanisms responsible for spatial and temporal contrast enhancement.

CHAPTER 2

METHODS

For these studies, we measured the cortical response in monkeys and cats to vibrotactile stimulation and compared those results to records of human performance on similar tactile sensory assessments. The basic methods for these two divisions of our research (animal and human) are described in this chapter. In later chapters, specific modifications to these standard methods are individually described for each study.

2.1 Animal experimental procedures and analysis

All methods and procedures were reviewed and approved by an institutional animal care and use committee (IACUC) prior to experimentation. Our research complies with United States Public Health Service (USPHS) guidelines on animal care and welfare.

Subjects and preparation

We used adult pigtail monkeys (n=12), squirrel monkeys (n=8), and cats (n=2) as our experimental subjects. The animals were prepped for imaging and neurophysiological recordings in the following manner: (1) general anesthesia was induced using a 50/50 oxygen/nitrous oxide mixture with either 1-2% halothane or isoflurane, (2) a soft tube was inserted into the trachea for further administration of anesthetic gas, (3) polyethylene

cannulas were placed into the femoral artery for monitoring blood pressure and femoral vein for administering drugs and fluids (5% dextrose and 0.9% NaCl), (4) a 1.5 cm opening was made in the skull exposing the forelimb regions of SI, (5) a recording chamber was placed over this opening and sealed with dental acrylic, (6) dura covering the cortical region of interest was removed, (7) the recording chamber was filled with artificial cerebrospinal fluid. The surgical procedures were conducted under deep general anesthesia. To lessen the chance of drug induced cerebral edema and bacterial septicemia, methylprednisolone sodium succinate (20 mg/kg) and gentamicin sulfate (2.5 mg/kg), respectively, were injected intramuscularly. Each wound was injected with a long-lasting local anesthetic before closure with sutures and bandages. After a completed preparation, the subjects were immobilized by Norcuron and connected to positive pressure ventilation. Following these surgical preparations, the concentration of the halothane/isoflurane in the oxygen and nitrous oxide mixture was reduced to keep the subjects under a light general anesthesia during the recordings sessions. Autonomic signs (heart rate, respiratory rate, etc.) were monitored and further adjustments to the anesthetic gas mixture were made to maintain vital signs consistent with light general anesthesia. Rectal temperature was sustained at 37°C with a heating pad. Pre-experimental optical imaging assisted electrode placement.

Cutaneous stimulation

A servo-controlled vibrotactile stimulator (modified from Chubbuck, 1966) delivered precisely controlled sinusoidal vertical-displacement stimuli to the contralateral hand (monkey) or forepaw (cat). The stimulus probe (plastic cylinder 2 mm in diameter)

was positioned 500 microns past the point of skin contact and remained in contact with the skin during stimulation. Range for the stimulus could reach 1-1000 µm in amplitude and DC to 250 Hz in frequency. A computer controlled digital waveform circuit board allowed the option to choose which amplitudes and frequencies of vibratory stimuli would be administered.

Optic Intrinsic Signal Imaging (OIS)

OIS imaging of the exposed cortical surface was obtained using an oil-filled chamber capped with a near-infrared (833 nm) optical window and a 200 msec exposure time. In order to generate average absorbance images, prestimulus and poststimulus images were captured. The prestimulus images were acquired 200 msec before stimulus onset and used as references. Poststimulus images were taken approximately every second until 20 sec following stimulus onset. Average absorbance images were produced by subtracting the prestimulus image from the corresponding poststimulus image and then dividing this resulting image by the reference image. The averaged absorbance images indicate changes in infrared light absorption. These increases and decreases of absorbance reflect corresponding changes in neuronal activation (Favorov et al., 2006; Simons et al., 2005, 2007; Tommerdahl et al., 1999a, b, 2002, 2005a, b, c; Whitsel et al., 2001).

Neurophysiological recording

We obtained extracellular recordings of the unitary spike discharges in the active region of SI using tungsten microelectrodes. As determined during previous experiments, the impedance of these electrodes (3-5 Mohms when tested at 10 kHz) are appropriate for

the extracellular single-unit spike discharge activity to be recorded at high quality. The electrolytically sharpened, glass-insulated electrodes were also compatible with the amplifiers and closed-chamber recording equipment. The electrodes had been specifically designed for marking the cortex with small electrolytic lesions (using small DC currents) while still causing minimal damage to the targeted region. To record from a series of depths in a single cortical column, the electrodes penetrated SI at nearly 90^{o} angle to the pial surface. Multiple penetrations were often recorded for future cortical analysis. The recording chamber was hydraulically sealed, "closed-chamber", to minimize influence of cortical pulsations (from the cardiovascular and respiratory system) on the recordings. At a 20 KHz sampling rate, single unit and multi-unit samples (using 1-4 non-overlapping voltage windows) were recorded. Analog information (such as stimulus onset, interstimulus interval, and applied frequency) was digitized and saved with the spike data. Stimulus information for each set of recordings was reviewed and deviations in applied stimuli were removed from analysis. Von Frey-type filaments provided aid in determining the receptive field of the recorded neurons. Computations of stimulus and spike information were made with Alpha Omega and MATLAB software.

Mean firing rate (MFR) analysis

The stimulus response (firing rate in spikes/sec) was measured by counting the number of spikes in a designated time period and then dividing that count by the number of bins. We chose 40 bins per 1 second (25 msec bins) for our unit of time. With a focus on early dynamics in the stimulus response, the MFR for only the first second of stimulus response following stimulus onset was analyzed in this study. Central versus marginal neurons were determined based on their location in the microelectrode penetration and

differences in MFR among the two groups were measured. One exemplary experiment traversed and sampled the full extent of the area 3b region, and thus allowed a transitional observation of marginal, to central, and back to marginal neurons. The other exemplary experiment traversed a smaller part of area 3b and consisted of only central neurons.

Peri-stimulus time histograms (PSTH)

Similar to the MFR analysis, the stimulus response (firing rate in spikes/sec) was measured by counting the number of spikes in a designated time period and then dividing that count by the number of bins. For PSTH, we are studying the phase of the stimulus response rather than the overall activity. Here we observe at 40 msec intervals (one cycle for our 25 Hz stimulus) and examine where in the stimulus cycle spike activity occurs. We chose 1msec bins (total of 40 bins per cycle) for our unit of time. Using PSTH analysis, the stimulus response for the first four cycles following stimulus onset could be averaged together and compared to the average of the first four cycles near 1sec of 25 Hz stimulation (cycles 22-25).

Principal component analysis (PCA)

Another way to show the phase characteristics of our stimulus response was with PCA. PCA divides the data into linearly independent variables (known as principal components) and quantifies how much each variable influences the data set (Pearson, 1901). Specifically, the first two principal components (PC1 and PC2) would account for the highest degree of data variability. In this study, PCA showed the phase characteristics of the cortical response from the start of the stimulus to the 25^{th} cycle of stimulation. This means of analysis demonstrates how the phase of the cortical response can shift over time.

Both single unit and population phase dynamics were measured. The first two principal components contained over 80% of the data. A hierarchical method confirmed that the information could be accurately depicted in our 2-D PCA plot.

Cycle Raster Plot

The cycle raster plot shows the spiking activity for a given neuron in relation to the phase of the applied vibratory stimulus. Each tick mark indicates an action potential at a particular time in each cycle of vibration. These plots provide a more in depth representation of the dynamics involved in a vibrotactile stimulus response. A decreased number of tick marks from one cycle to another indicates a lower level of activity, while a change in tick mark concentration from one part of a cycle to another indicates a change in the preferred phase.

Cross-correlogram (CCG) analysis

Pairwise cross-correlograms (CCG) were used to measure synchrony among a population of SI neurons during application of flutter stimuli. The probability density was estimated using a Gaussian Kernel method (Silverman, 1986, pages 13-18) at an optimal asymptotical reference bandwidth (Silverman, 1986, pages 45-48). The reflection method (Silverman, 1986, pages 29-32) was used to find the boundary of the domain. Permuted CCGs show the firing of two neurons across various stimulus trials (versus the same trial) to demonstrate synchronization evoked by driving two neurons with the same periodic stimuli. Raw CCGs display the probabilities that the time difference between two neurons firing would take certain values within our window range (half the stimulus cycle). While not provided here, raw CCGs were generated to confirm the validity of our permuted

CGGs. Similarly to our PSTH analysis, permuted CCGs between the first four cycles following stimulus onset were averaged together and compared to the average of the first four cycles near 1sec of 25 Hz stimulation (cycles 22-25).

Degree of Entrainment

Entrainment, as measured here, refers to the position within the current stimulus cycle at which spike activity occurs. This approach to interpreting neural spike train data was first introduced by Goldberg and Brown (1969). Each spike has a particular phase angle Θ in relation to the current stimulus cycle ($0 <= \Theta < 2\pi$). The strength of entrainment for a sample population of *N* can be calculated from the phase angle and quantified by length *r* of their vector sum (Equation 2.1).

Equation 2.1

$$r = [(\sum_{i=1}^{N} \cos\Theta_i)^2 + (\sum_{i=1}^{N} \sin\Theta_i)^2]^{1/2}/N$$

The measure *r* varies between 0.0 (indicating no relationship between the timing of spike activity to the stimulus cycle) and 1.0 (indicating complete phase locking). A percentage of entrainment can be expressed by multiplying *r* by 100, where 100% entrainment implies perfect phase locking. Similar measurements of synchronization have been used in previous sensory neurophysiological literature (Goldberg and Brown, 1969; Recanzone et al., 1992; Lebedev et al., 1994, 1996; Whitsel et al., 2000).

2.2 Human experimental procedures and analysis

Subjects

102 healthy subjects were recruited for the studies. Participants ranged from 20 to 42 years of age. For initial screening, subjects completed a survey on current medications and medical history prior to the experimental tests and participants with any history of cognitive dysfunction were excluded. Subjects signed a written informed consent form after a brief description of the study was explained. The explanation included the procedures of the study, the expected duration of the experiment, and the risks of participating in the study. Subjects were otherwise naïve to the study design and issue under investigation. Subjects were reassured that their participation was entirely voluntary, and they could request to terminate the study at any time. Generally tests lasted no longer than an hour; the exact duration was dependent on subject performance on the various sensory training procedures and assessments. An Institutional Review Board reviewed and approved the experimental procedures in advance.

Sensory assessment procedure

Vibrotactile stimuli were delivered to the fingertips of each subject with a four-site mechanical stimulator (Holden et al., 2012; CM-4: Cortical Metrics Model #4, Figure 2.1). A wide variety of stimulus conditions could be delivered independently and simultaneously to each probe tip using Microsoft's .NET Framework v3.5 software. The stimulator was interfaced with a personal computer via an internal data acquisition box (DAQ) and Universal Serial Bus (USB) cable. Subjects were seated comfortably in a chair with their left arm placed on an ergonomic armrest connected to the head unit of the

stimulator. The position of the stimulus probes was rotated to optimize hand position and comfort for each subject. Typically only two stimulator probes were utilized in a given experiment. These probes made contact with the glabrous tips of the second (index, D2) and third (middle, D3) fingers of the left hand. Subjects controlled a two-button response device (wireless mouse) with their right hand. Visual cues indicating the standard/test stimulus and response intervals were provided on a computer monitor. These stimulators and experimental procedures have assessed numerous sensory information processing characteristics in a variety of subject populations (Folger et al., 2008; Francisco et al., 2008, 2012; Holden et al., 2011; Nelson et al., 2012; Rai et al., 2012; Tannan et al., 2005, 2006, 2007a, b, 2008; Tommerdahl et al., 2007a, b; Zhang et al., 2009, 2011a, b; Nguyen et al, 2013a, b).

Tracking Paradigm

The discrimination protocols utilized a modified von Békésy method (Cornsweet, 1962) to track subject perceptual performance on the attended, left hand. By means of this adaptive tracking technique, the differences between the test and standard stimuli could be adjusted based on the subject's previous response. Tracking was conducted with a bias of one for the first ten trials in order to rapidly track down toward the discriminative threshold. For instance, in the frequency discrimination assessments, a correct response led to a decrease in test frequency while the outcome of an incorrect response was an increase in test frequency. We implemented a bias of two for the remaining ten trials. In other words, for the amplitude discriminatory tests, subjects were required to provide two consecutive correct responses in order for the test amplitude to

decrease. This change in bias increases the accuracy of our threshold measurements by preventing the paradigm to track down when a subject simply guessed the correct answer (Tannan et al., 2006). Tracking paradigms were used in the frequency, amplitude, and temporal order judgment assessments.

Exemplary Tracking Paradigm for an Amplitude Discrimination test: 200 µm standard vs 400 µm test at 20 Hz

In each amplitude discrimination run, the initial test amplitude was twice the standard amplitude, while the step size of the tracking paradigm (the amplitude which the test amplitude was increased or decreased) was 10% of the standard stimulus amplitude. For instance, a 200 µm standard amplitude had an initial test amplitude at 400 µm and a 20 µm step size for tracking. Subjects could only track as low as the minimal test amplitude. To maintain a continuous difference between the test and standard stimuli, the test amplitude was always at least 5 µm above the standard amplitude. So instead of matching the 200 µm standard, for this particular amplitude discriminatory assessment the test minimum was 205 µm.

Initial test stimulus parameters needed to be well above the discrimination threshold while still being low enough for subjects to track down to their discrimination thresholds within a run of twenty trials. Previous studies have used the same tracking protocol (two-alternative forced choice: 2AFC) and determined subjects were successfully able to track down to their discrimination thresholds within twenty trials (Francisco et al., 2008; Tannan et al., 2007b).

Figure 2.1 Four site vibrotactile stimulator. Top right: During an experimental session, subjects sit comfortably in a chair with their arm resting on an arm rest that is attached to the head unit of each device.

Data Analysis and Normalization

A subject's discrimination threshold (difference limen: DL) is calculated by subtracting the standard (e.g. standard applied stimulus frequency or amplitude) from the average of the last five trials recorded in the sensory assessment. Deterioration in discrimination capacity is indicated by an increase of one's DL. The DL of the sample population was calculated as the average DL across subjects. Many of the results from the discrimination procedures were then normalized to several different baselines (Equation 2.2).

Equation 2.2

$$\text{Normalized Discrimination (\%)} = (DL_{variation}) / (DL_{baseline})$$

For example, the results of the amplitude discrimination procedure in the absence of bilateral stimulation ($DL_{baseline}$) were used as a reference to normalize the discrimination thresholds in the presence of bilateral stimulation ($DL_{variation}$). First the ratios of the DLs (Equation 2.2) were calculated for each subject. Then the average of the DL ratios across subjects was calculated. This value showed the effect of unattended hand stimulation (in comparison to the unilateral condition) on a subject by subject basis averaged across a population.

Performance across the different groups was evaluated with two-sample t-tests. Data is represented as means and standard mean errors of our sample population. Only probabilities with p-value less than 0.05 were considered statistically significant. These analytical methods, implemented for population averages and within-subject normalization, are comparable to those described in previous reports (Nguyen et al., 2013a, b; Tannan et al., 2005; Tommerdahl et al., 2007a, 2008; Zhang et al., 2011b).

CHAPTER 3

AMPLITUDE EFFECTS ON CORTICAL ACTIVITY AND PERCEPTUAL PERFORMANCE

3.1 Stronger amplitudes increase temporal contrast

Previous literature strongly suggests an enhancement of spatial contrast with greater amplitudes of vibrotactile stimulation (Simons et al., 2005). Although there is evidence that the cortical response becomes phase-locked to the frequency of vibrotactile stimulation (Ahissar and Arieli, 2001; Ferrington and Rowe 1980; Hummel and Gerloff, 2006; LaMotte and Mountcastle, 1975; Mountcastle et al., 1969, 1990; Panzeri et al., 2003; Recanzone et al., 1992; Romo et al., 2003; Whitsel et al., 2001), means of increasing the strength of this local temporal contrast are still relatively unknown. Our initial goal was to replicate the previous reports of spatial contrast (Simons et al., 2005) and determine if there is a corresponding improvement of temporal contrast (local synchronization) when the vibrotactile stimulus amplitude is increased. To test our hypothesis, we used microelectrodes to record the cortical response to varying amplitudes of vibrotactile stimulation on the hand of a pigtail monkey. The stimulus was maintained at frequency of 25 Hz.

Modifications of the standard Animal Experimental Procedure

For this section of the study, research and analysis was conducted as previously explained in the "Animal Experimental Procedures" section of the Methods Chapter. Microelectrodes recorded the response in area 3b to continuous 1 sec (minimal) durations of 25 Hz vibrotactile stimulation on the glabrous pad of the distal phalanges in 6 pigtail monkeys with a total of 47 cortical neurons. The amplitudes of stimulus vibration ranged from 10 µm to 400 µm. The analysis consisted of PSTHs, cycle raster plots, and measures for the degree of entrainment.

Results

In one exemplary experiment, 1 sec durations of 25 Hz mechanical stimulation were applied to digit 2 of an anesthetized pigtail monkey at the following amplitudes: 25 µm, 50 µm, 100 µm, 200 µm, and 400 µm. The PSTHs in Figure 3.1 demonstrate how the temporal response (in relation to 40 msec cycles of skin vibration) for one exemplary neuron experiences enhanced synchronization at stronger stimulus amplitudes. As the strength of the stimulus amplitude was increased from 25 µm to 400 µm, the initially weaker and broader response of the lower amplitude response grew sharper and narrower in the greater amplitude response. The cortical response increased in temporal contrast as the spike activity became more synchronized.

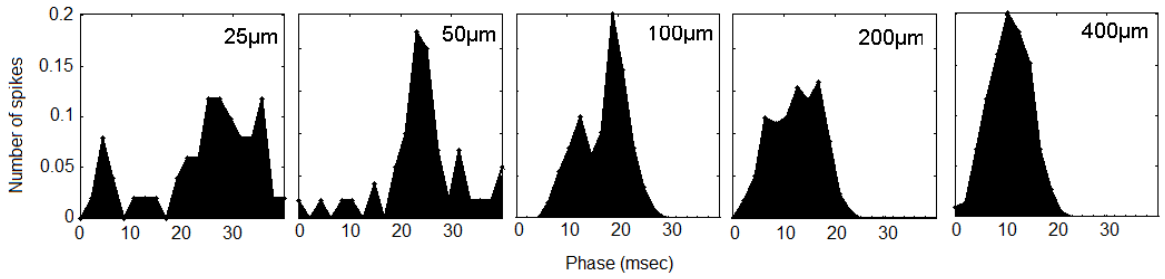

Figure 3.1 Exemplary temporal response with increasing amplitude. PSTHs of the cortical response to 5 amplitudes of 25 Hz stimulation for 1 sec. Increasing the stimulus amplitude from 25 µm to 400 µm increases the temporal contrast by eliciting a sharper response with a narrower time window.

This increase in synchronization and temporal contrast appears to be a general trend with stronger amplitudes for the cortical response. Figure 3.2 shows the spike activity in relation to cycle phase for 5 more exemplary neurons (one neuron per column) from 3 separate experiments on non-human primates to 1 sec of 25 Hz vibrotactile stimulation. For these experiments, amplitudes ranged from 10 µm to 400 µm. For each neuron, the temporal window of cortical response shrunk and the peak of activity became more prominent.

When we generated a finer detailed representation of the cortical temporal response, we again observed a stronger, narrower response in the conditions of stronger amplitude stimulation. The cycle raster plot analysis for 3 exemplary neurons from 3 separate non-human primate experiments is provided in Figures 3.3, 3.4, and 3.5. Unlike the initial PSTHs, the cycle raster plots indicate the neuronal response for each individual cycle of vibrotactile stimulation. Figure 3.3 depicts the response of an exemplary neuron to 3 sec (75 cycles) of 25 Hz mechanical stimulation at the following amplitudes: 25 µm, 50 µm, and 200 µm (left to right, respectively). The results suggest enhanced temporal contrast with greater stimulus amplitudes. The temporal window of the cortical response

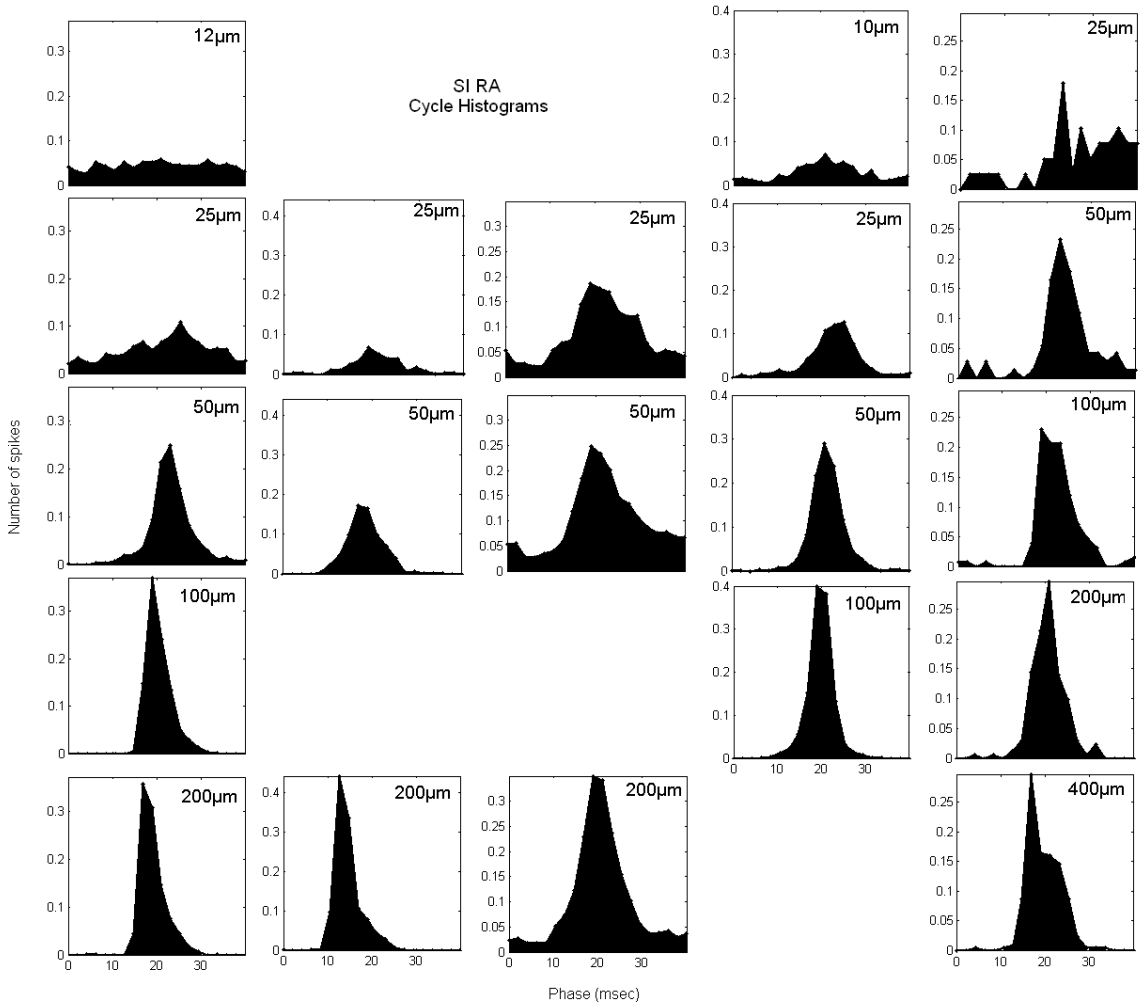

Figure 3.2 Temporal response with increasing amplitude. PSTHs of the cortical response to 7 amplitudes of 25 Hz stimulation for 1 sec. Each column of figures represents a different cortical neuron. The spike activity is on the y-axis with cortical phase in relation to the applied stimulus on the x-axis. Increasing the stimulus amplitude from 10 µm to 400 µm increases the temporal contrast by eliciting a sharper response with a narrower time window.

shrinks from approximately 30 msec in the 25 µm amplitude condition to approximately 10 msec for the 200 µm amplitude stimulation.

Figure 3.4 shows the spike activity for an exemplary neuron from a different primate experiment with 5 sec (125 cycles) of 25 Hz vibrotactile stimulation at 5 stimulus

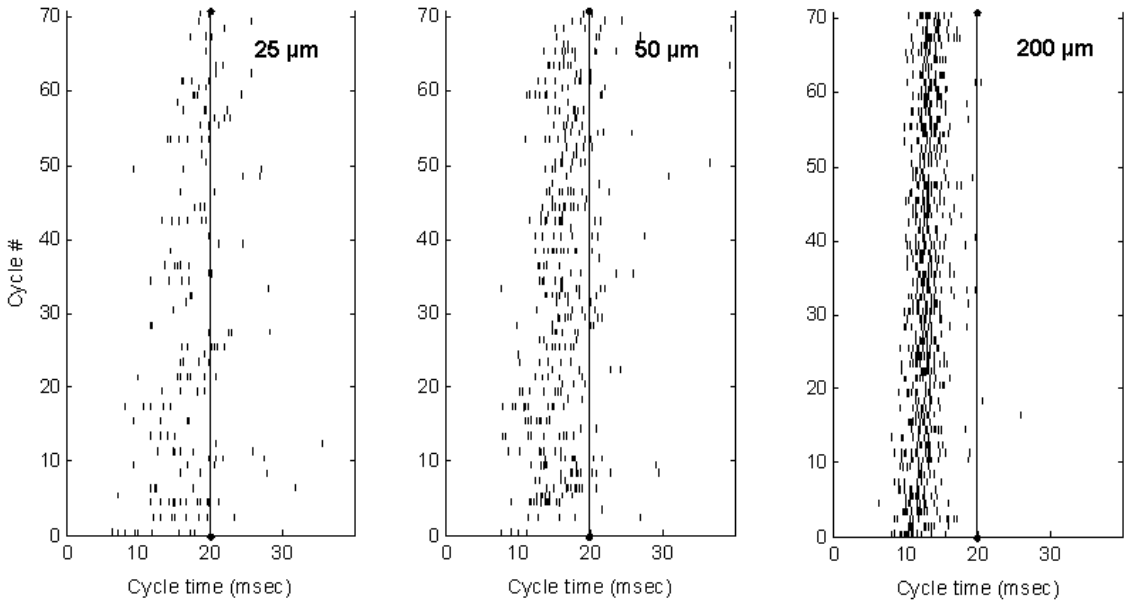

Figure 3.3 Detailed exemplary temporal response with increasing amplitudes. Cycle raster plots of the cortical response to 3 amplitudes of 25 Hz stimulation for 3 sec. Increasing the stimulus amplitude from 25 µm to 400 µm increased the temporal contrast by eliciting a sharper response with a narrower time window.

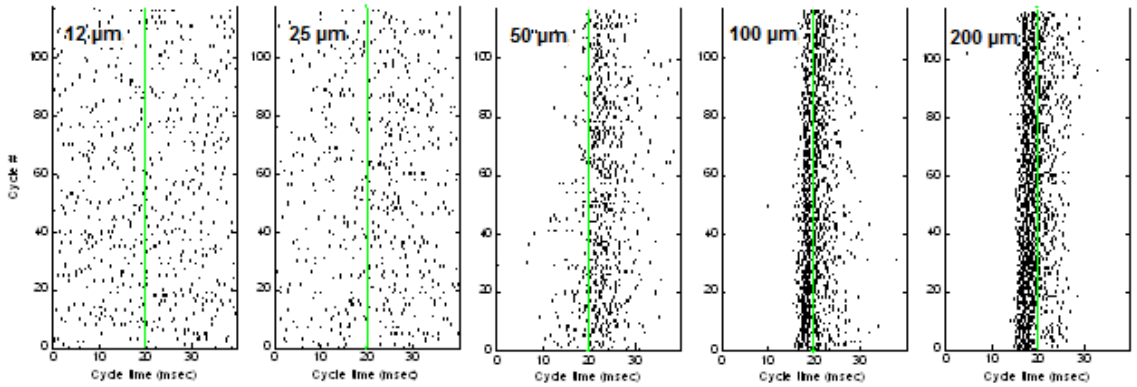

Figure 3.4 Another detailed exemplary temporal response, increasing amplitudes from 12 µm to 200 µm. Cycle raster plots of the cortical response to 5 amplitudes of 25 Hz stimulation for 5 sec. Increasing the stimulus amplitude increased the temporal contrast by eliciting a sharper response with a narrower time window.

amplitudes: 12 µm, 25 µm, 50 µm, 100 µm, and 200 µm (left to right, respectively). Again, the temporal window of response dramatically decreases with stronger stimulus amplitude. Instead of a scattered, rather randomized response as evident with 12 µm stimulation, 200 µm stimulation elicits a tight, well synchronized response that was approximately limited to 15 msec (starting at 15 msec and stopping by 30 msec) of the 40 msec cycle.

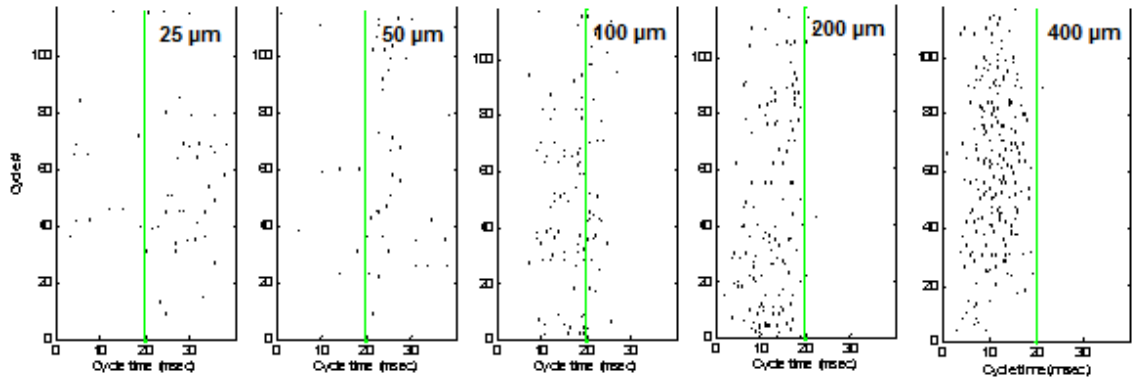

Figure 3.5 Another detailed exemplary temporal response, increasing amplitudes from 25 µm to 400 µm. Cycle raster plots of the cortical response to 5 amplitudes of 25 Hz stimulation for 5 sec. Increasing the stimulus amplitude increased the temporal contrast by eliciting a sharper response with a narrower time window.

Figure 3.5 indicates the cortical response for our last exemplary neuron from a third monkey to which 5 sec (125 cycles) of 25 Hz vibrotactile stimulation was applied. Recordings were obtained at the following stimulus amplitudes: 25 µm, 50 µm, 100 µm, 200 µm, and 400 µm (left to right, respectively). At lower stimulus amplitudes of 25 µm or 50 µm, spike activity is relatively weak and temporally scattered across the cycle. However, at higher stimulus amplitudes of 200 µm or 400 µm, the neuron mostly responded within the first half of the stimulus cycle. Furthermore, when the stimulus

amplitude was increased, there appears to be a corresponding increase in the neuronal response in addition to this enhancement of temporal contrast.

The degree of entrainment was measured for a total of 46 neurons from SI (Figure 3.6). Here, a greater percentage of entrainment is indicative of a smaller temporal window of response and suggests increased synchronization with the stimulus. Microelectrode recordings were obtained for a broad range of stimulus amplitudes from as low as 12.5 µm to high as 400 µm. In Figure 3.6, each black line represents the degree of entrainment versus stimulus amplitude relationship for 1 of the 46 neurons. The red line shows the average relationship across the entire sample population of cortical neurons. The results suggest that stronger amplitude enhances the temporal contrast of the cortical response.

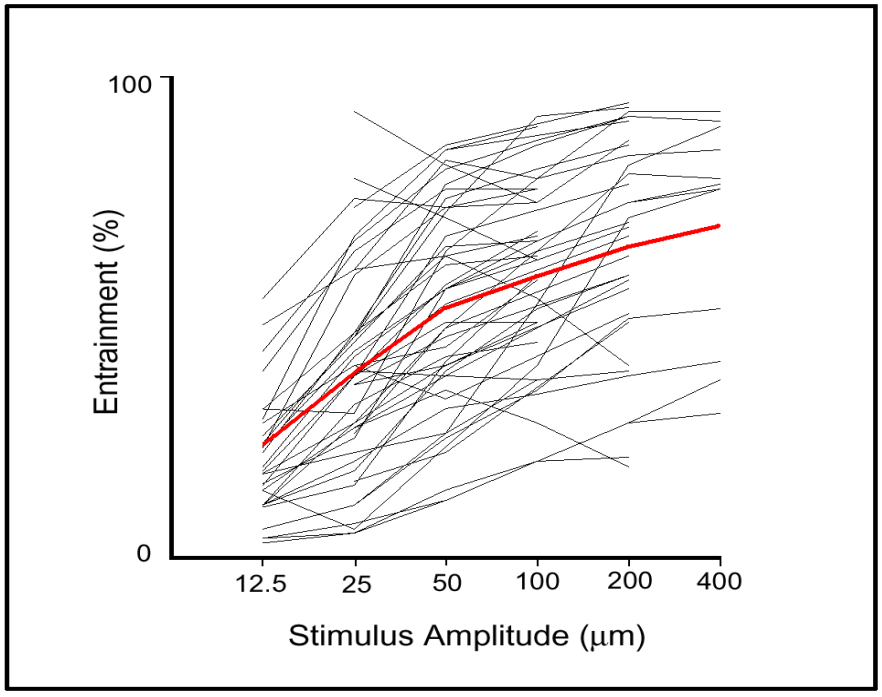

Figure 3.6 Effects of stimulus amplitude on entrainment. The average (red) degree of entrainment for stimulus amplitudes 12 µm to 400 µm for 46 cortical neurons (black). Stronger stimulus amplitudes evoked greater degrees of entrainment.

Discussion

The results of this study are highly indicative of a strong relationship between stimulus amplitude and cortical temporal contrast. Each method of analysis (PSTH, cycle raster plot, and degree of entrainment) indicated an augmented temporal contrast among neighboring cortical ensembles after an increase in amplitude of the applied periodic vibrotactile stimulus. For the entire range of amplitudes studied (15 μm – 400 μm) the evoked response in SI was well entrained with the externally applied vibrotactile stimulus; however, stronger amplitude stimuli also produced a sharper, narrower temporal window of response.

One reason for tuning the cortical response into similar patterns of spatial and temporal behavior may be to enhance the differences in cortical activity between the two responding regions in order to improve tactile perception. The same concept can be applied to daily visual situations. For a comparison, consider the two options in Figure 3.7. If someone were to ask you to choose between these two options and indicate which one is easier to read, "Option B" should be the obvious choice.

Figure 3.7 Visual contrast. Visual example of how contrast can improve perception.

The improved contrast in "Option B," helps the letters stand out more from the gray background. Now relate this visual image to the cortical response and imagine how the

cortex can turn messy vibrotactile input ("Option A" – response from weaker stimulus amplitudes) into a clearer perceptional image ("Option B" – response from stronger stimulus amplitudes). Similar to this visual scenario, we expect two prominent and narrow peaks of cortical activity ("Option B") to be less difficult for the brain to distinguish in comparison to two weaker but broader peaks in spike activity ("Option A"). In other words, this increase in synchronization (temporal contrast) should improve tactile perception since increasing cortical contrast should enhance our perceived tactile image. This enhancement of temporal cortical contrast may be especially beneficial in a tactile task such as frequency discrimination. Theoretically, frequencies should be easier to determine if the cortical response is organized into narrow, sharp channels of information.

3.2 Frequency discrimination capacity improves with stronger amplitudes

Our above study demonstrated an improved temporal contrast within the responding region of SI as the amplitude of the applied vibrotactile stimulation was increased. We hypothesize that this enhanced temporal contrast, in addition to previous observations of a corresponding spatial contrast (Simons et al., 2005), will facilitate an improved frequency discrimination capacity with stronger amplitudes of vibrotactile stimulation. To examine this question, we measured changes in frequency discrimination capacity in a population of healthy human subjects with increases in stimulus amplitude.

Modifications of the standard Human Experimental Procedure

Eighteen healthy subjects were recruited for the frequency discrimination portion of the study. Participants were college undergraduates ranging from 20 to 22 years of age. The consent and sensory assessment procedures as described in Chapter 2 Methods were followed.

Frequency discrimination assessment

The minimal frequency difference between two mechanical sinusoidal vibratory stimuli from which an individual can still successfully identify the higher frequency stimulus constitutes one's frequency discriminative capacity. For the frequency discrimination assessment, the stimulator delivered sequential vibrotactile stimuli to D2 and D3 of the left hand. This protocol requested subjects to indicate which of their two fingers received the high frequency stimulus (Figure 3.8).

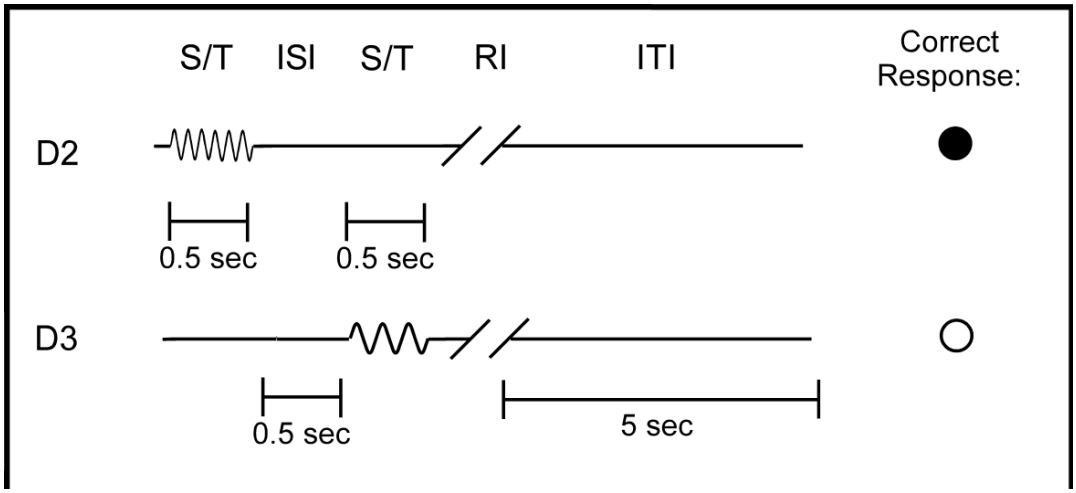

Figure 3.8 Frequency discrimination procedure. After the standard and test stimuli (S/T) were sequentially applied to D2 or D3 for 0.5 sec with a 0.5 sec inter-stimulus interval (ISI), the subject was provided with a short response interval (RI) to decide which digit received the stimulus of greater frequency. After responding, the subject waited during a 5 sec inter-stimulus interval (ITI) before the next round of stimulation.

Frequency discrimination capacity was measured with a 2AFC tracking protocol (refer to Tracking Paradigm in Methods of Chapter 2) and acquired at multiple frequency standards/tests and numerous amplitudes (Table 3.1) to measure for potential improvements in frequency discrimination at stronger stimulus amplitudes.

Table 3.1 Frequency discrimination protocol at different amplitudes

Standard Frequency	Test Frequency	Amplitudes
10 Hz	20 Hz	25 µm, 50 µm, 100 µm, 200 µm, 400 µm
30 Hz	40 Hz	25 µm, 50 µm, 100 µm, 200 µm, 400 µm

Exemplary Frequency Discrimination test: 30 Hz standard versus 40 Hz test at 200 µm

While the standard stimulus was maintained at a frequency of 30 Hz, the test stimulus started at 40 Hz and had the potential to track down by 1 Hz. The frequency of the test stimulus was always greater than that of the standard stimulus and the stimulus amplitude remained at 200 µm (for both the standard and test stimuli) for the duration of assessment. The locations of the stimuli (D2 versus D3) were randomly selected on a trial-by-trial basis.

Data analysis was consistent with our standard methods for human experimentation as indicated in Chapter 2 Methods.

Results

Preliminary results were acquired from 4 subjects (Figure 3.9). These preliminary findings indicate that there was minimal difference in the 10 Hz standard, 20 Hz test

among the various stimulus amplitudes (25 µm, 50 µm, 100 µm, 200 µm, and 400 µm). However, as evident by the lower difference limens (DL), there was a noticeable improvement in the 30 Hz standard, 40 Hz test frequency discrimination assessment as the stimulus amplitude was increased from 25 µm or 50 µm. Specifically for the higher range frequency discrimination assessment (30 Hz standard, 40 Hz test), performance at the 25 µm was significantly worse than performance at 50 µm (*p=0.034), 100 µm (*p=0.020), 200 µm (*p=0.005), and 400 µm (*p=0.039). Although the preliminary sample population was too small to draw many conclusions, the results do suggest a possible saturation of frequency discrimination performance at amplitudes above 100 µm.

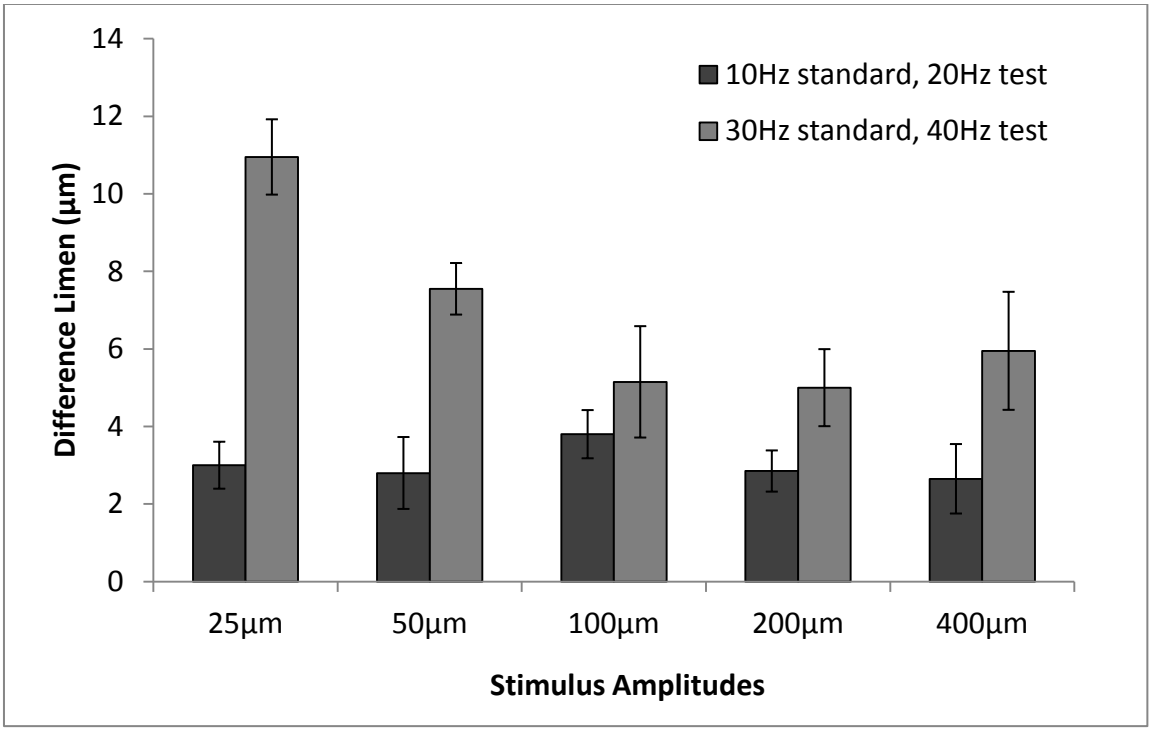

Figure 3.9 Preliminary frequency discrimination testing at various amplitudes. Insignificant differences on the 10 Hz standard, 20 Hz test among the different stimulus amplitudes. However, performance on the 30 Hz standard, 40 Hz test at 25 µm was significantly worse than performance at 50 µm (*p=0.034), 100 µm (*p=0.020), 200 µm (*p=0.005), and 400 µm (*p=0.039).

We then recruited 14 new subjects and compared their frequency discrimination capacity at 50 µm to their performance at 200 µm (Figure 3.10). The performance for both frequency discrimination assessments (10 Hz and 30 Hz standard) exhibited visibly decreased difference limens (DL). Although this slight reduction in DL does not indicate a significant improvement on the frequency discrimination task ($p=0.18$ for 10 Hz standard, $p=0.098$ for 30 Hz standard), this slight improvement is still important for our interpretations of cortical contrast. We believe with a larger sample population, the values would become significant.

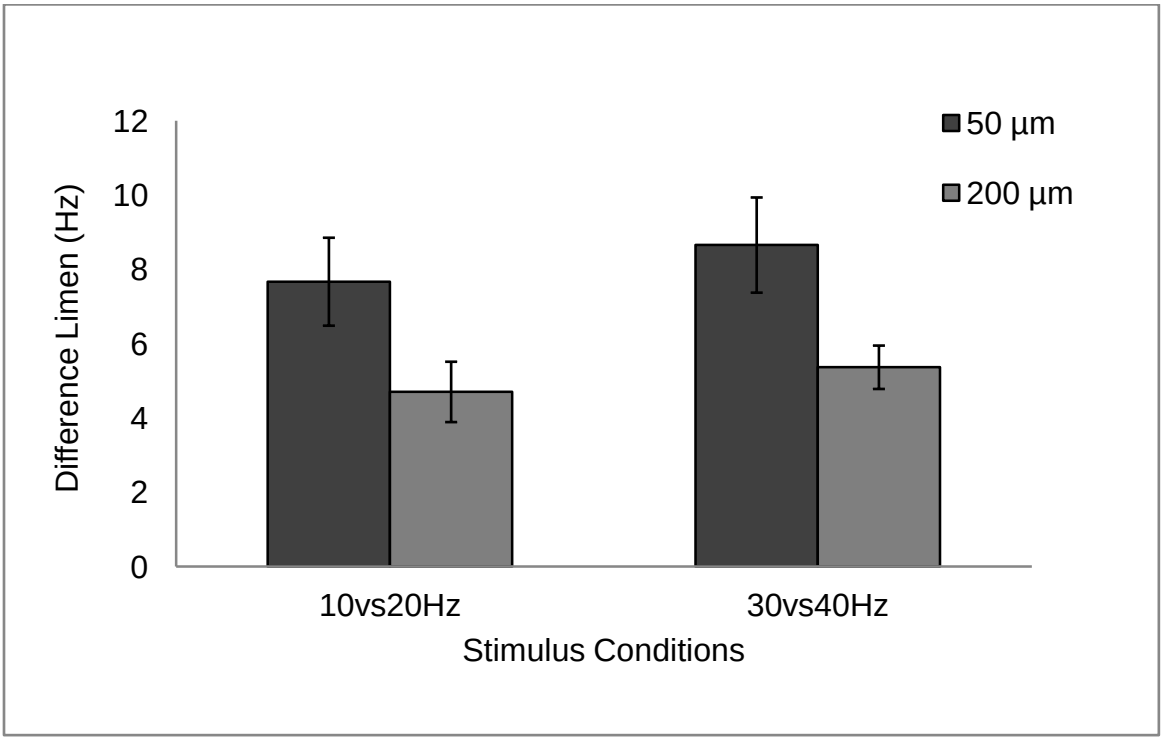

Figure 3.10 Frequency difference limens at various amplitudes. The performance for both the 10 Hz and 30 Hz (standard) frequency assessments demonstrated visibly improved performance at stronger stimulus amplitudes.

Discussion

The findings from our study in non-human primates (Section 3.1, Increased amplitude improves temporal contrast) demonstrated that increases in stimulus amplitude are associated with increases in synchronization. We hypothesized that this increase in temporal contrast should improve tactile perception by enhancing the information of higher perceptual importance. We then tested this hypothesis by comparing frequency discrimination performance at a range of stimulus amplitudes. Our results here indicate that frequency discrimination capacity does improve with greater stimulus amplitudes for frequencies discrimination tasks below and above 25 Hz.

These findings of improved frequency discrimination capacity at greater stimulus amplitudes are also consistent with previous reports of optic intrinsic signal (OIS) imaging in non-human primates, which demonstrated that an increase in stimulus amplitude (within the same range of amplitudes studied 50 μm - 400 μm) was followed by an increase of absorbance within the central responding region of SI cortex (Simons et al. 2005). However, as the absorbance within the central ~2 mm diameter cortical region increased, the surrounding ~ 1 mm of SI experienced a prominent decrease in absorbance. In other words, as the stimulus amplitude increased, the spatial contrast of the activated region of cortex became more prominent. This enhanced spatial contrast at the stronger stimulus amplitudes appears to be reflected by an increased frequency discrimination capacity at greater magnitudes of stimulation.

This increase in OIS imaging absorbance and improved performance in the frequency discrimination assessment at stronger amplitudes may be attributable to the cortex's coding of amplitude by MFR. Since both MFR and contrast increase with stronger amplitudes (Mountcastle et al., 1969; Simons et al. 2005, 2007), a greater MFR

among the centrally located and responding excitatory cortical neurons may correspond with the enhanced spatial contrast observed at the higher stimulus amplitudes. If this is true, the weak cortical dependency on utilizing MFR to encode stimulus frequency at frequencies above 25 Hz leads us to expect minimal changes to amplitude discrimination capacity at greater stimulus frequencies (Ahissar and Arieli, 2001; Ferrington and Rowe 1980; Hummel and Gerloff , 2006; LaMotte and Mountcastle, 1975; Mountcastle et al., 1969, 1990; Panzeri et al., 2003; Recanzone et al., 1992; Romo et al., 2003; Whitsel et al., 2001). Increasing the frequency of the applied vibrotactile stimulus should evoke a minimal increase in MFR within the responding region of SI, thus there is negligible enhancement of spatial contrast and theoretically only minor improvements would be observed for amplitude discrimination at higher frequencies.

3.3 Amplitude discrimination capability is variably dependent on frequency

While our previous studies demonstrated improved frequency discrimination capacity at stronger stimulus amplitudes, we believe this could result from an enhanced spatial and temporal contrast elicited by stronger MFR within the responding region of cortex. Due to the relatively independent nature of frequency on MFR above 25 Hz (Ahissar and Arieli, 2001; Ferrington and Rowe 1980; Hummel and Gerloff , 2006; LaMotte and Mountcastle, 1975; Mountcastle et al., 1969, 1990; Panzeri et al., 2003; Recanzone et al., 1992; Romo et al., 2003; Whitsel et al., 2001), we expect that increasing the frequency of the applied mechanical stimulus may not necessarily increase cortical contrast. Therefore, increasing the vibrotactile stimulus frequency from 25 Hz and above should not improve performance on an amplitude discrimination assessment.

To test our hypothesis, we measured changes in amplitude discrimination capacity due to increases in stimulus frequency among a healthy population of subjects.

Modifications of the standard Human Experimental Procedure

For the amplitude discrimination portion of the study, we recruited thirty two healthy subjects and followed the standard consent and sensory assessment procedures from Chapter 2 Methods. Participants were primarily undergraduates (range 20-22 years old) or college graduates with a mean age of 27.7 $\pm$ 6.3 years (range 21 – 42 years old).

Amplitude discrimination assessment

Methods for determining amplitude discriminative capacity were similar to that of frequency discriminative capacity. However, subjects now indicated which finger received stronger amplitude stimulus. When two mechanical sinusoidal vibratory stimuli are applied, the minimal amplitude difference at which the individual can still successfully recognize the stronger magnitude stimulus represents one's amplitude discriminative capacity. As before, the stimulator delivered simultaneous vibrotactile stimuli to D2 and D3 of the left hand, and the subject's discriminative capacity was calculated using the 2AFC tracking protocol (refer to Figure 1 and Tracking Paradigm of Chapter 2 Methods). Similar procedures for amplitude discrimination have been utilized in previous literature (Folger et al., 2008; Nguyen et al., 2013a, b; Tannan et al., 2008; Zhang et al., 2011a, b).

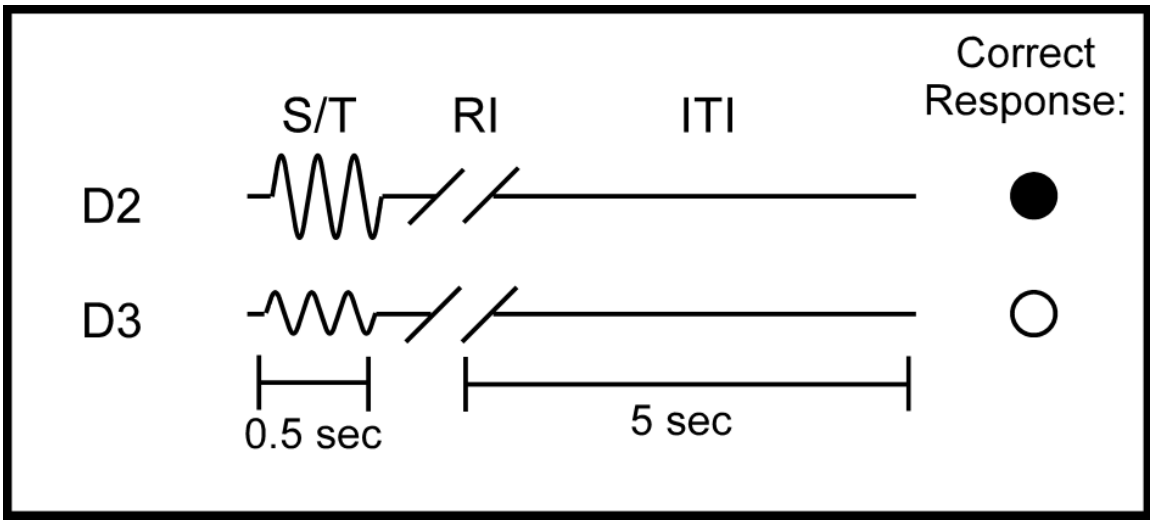

Figure 3.11 Amplitude discrimination procedure. After the standard and test stimuli (S/T) were simultaneously applied to D2 or D3 for 0.5 sec with a 0.5 sec inter-stimulus interval (ISI), the subject was provided with a short response interval (RI) to decide which digit received the stimulus of greater amplitude. After responding, the subject waited during a 5 sec inter-stimulus interval (ITI) before the next round of stimulation.

We measured amplitude discriminative capacity at multiple amplitude standards/tests and numerous frequencies (Table 3.2) to test for potential improvements in amplitude discrimination at higher frequencies. Our data analysis was consistent with the standard methods for human experimentation as previously described in Chapter 2 Methods.

Table 3.2 Amplitude discrimination protocol at different frequencies

Standard Amplitude	Test Amplitude	Frequencies
100 µm	200 µm	10 Hz, 20 Hz, 30 Hz, 40 Hz
200 µm	400 µm	10 Hz, 20 Hz, 30 Hz, 40 Hz
400 µm	800 µm	10 Hz, 20 Hz, 30 Hz, 40 Hz

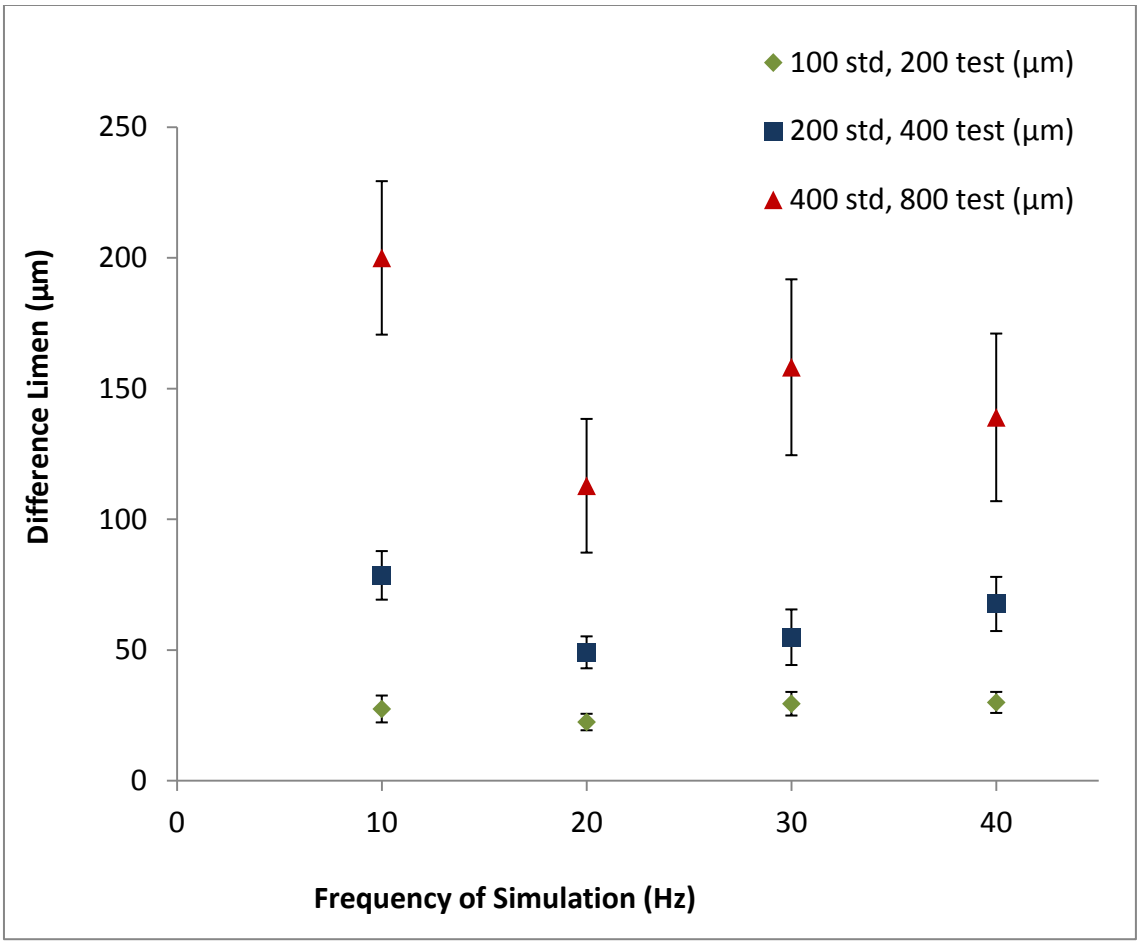

Figure 3.12 Amplitude discrimination capacity at various frequencies. A frequency increase from 10 Hz to 20 Hz slightly significantly improved amplitude discrimination capacity in the higher standard amplitude assessments (standards 200 µm, *p=0.013; 400 µm, *p=0.049). However, increasing the stimulus frequency from 30 Hz to 40 Hz did not alter amplitude discrimination capacity.

Results:

The full range of amplitude discrimination protocols were tested in 24 healthy subjects (Figure 3.12). For each of the standard amplitudes tested (100 µm, n=18; 200 µm, n=18; and 400 µm, n=6) standards) amplitude discrimination capacity was unaffected by increasing the stimulus frequency from 30 Hz to 40 Hz. Interestingly, as interpreted from a decrease in the difference limens, increasing the frequency from 10 Hz

(to 20 Hz, 30 Hz, or 40Hz) did promote slight improvements in amplitude discrimination capacity. The improvements at frequencies above 10 Hz were more noticeable and significantly greater in the higher standard amplitude assessments (200 µm, or 400 µm standard) than the 100 µm standard assessment (*p=0.013, *p=0.049 respectively for the 200 µm, 400 µm standards versus p=0.41 for the 100 µm standard).

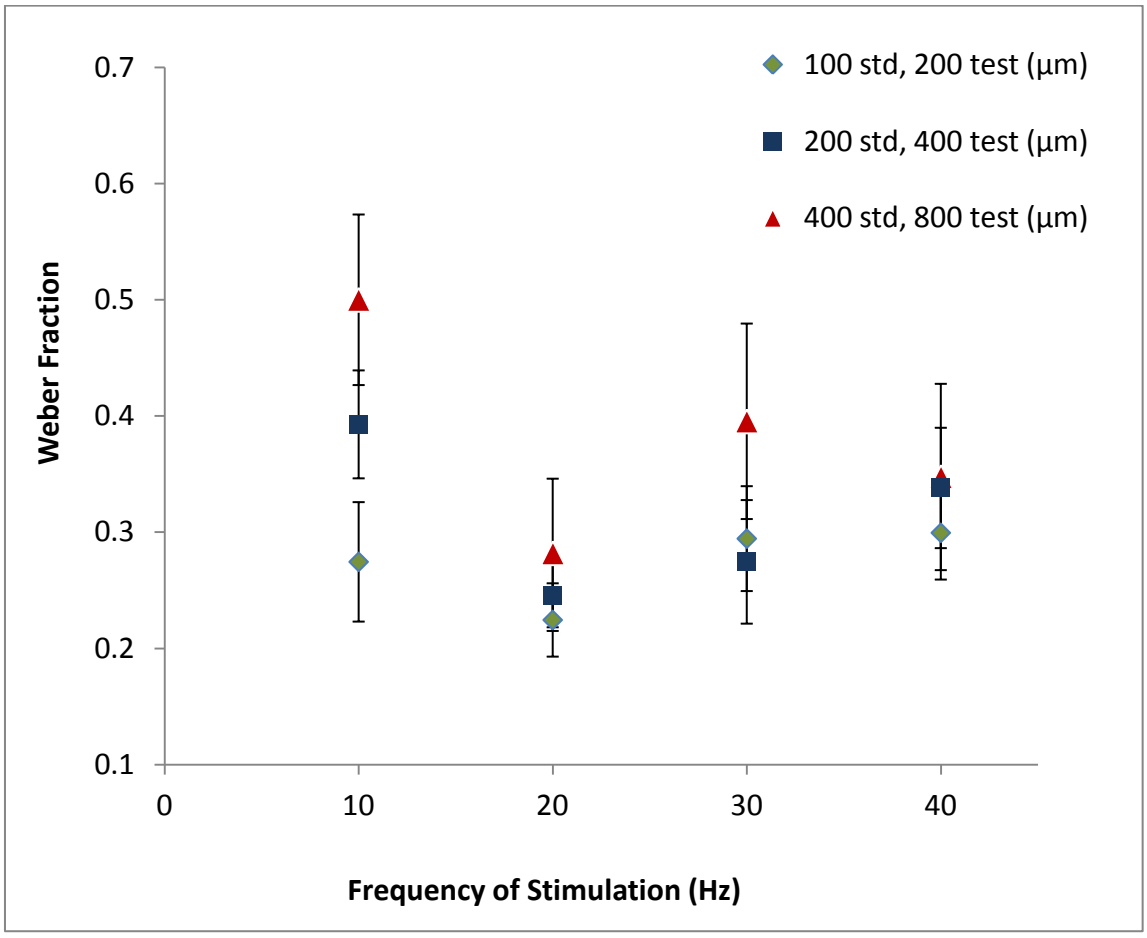

Figure 3.13 Weber fractions at various frequencies. A frequency increase from 10 Hz to 20 Hz slightly significantly improved amplitude discrimination capacity in the higher standard amplitude assessments (standards 200 µm, *p=0.013; 400 µm, *p=0.049). However, increasing the stimulus frequency from 30 Hz to 40 Hz did not alter amplitude discrimination capacity.

Weber Fractions for these amplitude discriminatory assessments (difference limens divided by standard stimulus amplitude) were then calculated for this sample population of 24 healthy subjects (Figure 3.13) to provide a different perceptive to our results. Among the 3 standard amplitudes that were tested, we observe the same trends of perceptual performance as the frequency of stimulation is increased. Amplitude. discrimination capacity remained unaffected by a stimulus frequency increase from 30 Hz to 40 Hz; however, increasing the frequency from 10 Hz improved amplitude discrimination capacity. Since the Weber Fractions are the amplitude difference limens divided by a constant (100, 200, or 400 depending on the standard amplitude), statistical significance is the same as the previous analysis. The similarities in performance among the various amplitudes suggest our findings follow Weber's Law.

14 new subjects were recruited for further analysis and their amplitude discrimination capacities at 10 Hz were compared to their performance at 40 Hz for a 200 µm standard, 400 µm test amplitude assessment (Figure 3.14). The difference limens (DL) were significantly lower in the 40 Hz condition in comparison to the 10 Hz stimulus frequency (*p=0.040, n=32) indicating significant improvement on the amplitude discrimination assessment. When analyzed on a subject by subject basis, the ratio of performance at 10 Hz over the performance at 40 Hz is 1.59 ± 0.17, which further suggests that the average subject (not just the average of our sample population) experiences a drop in when the stimulus frequency is raised.

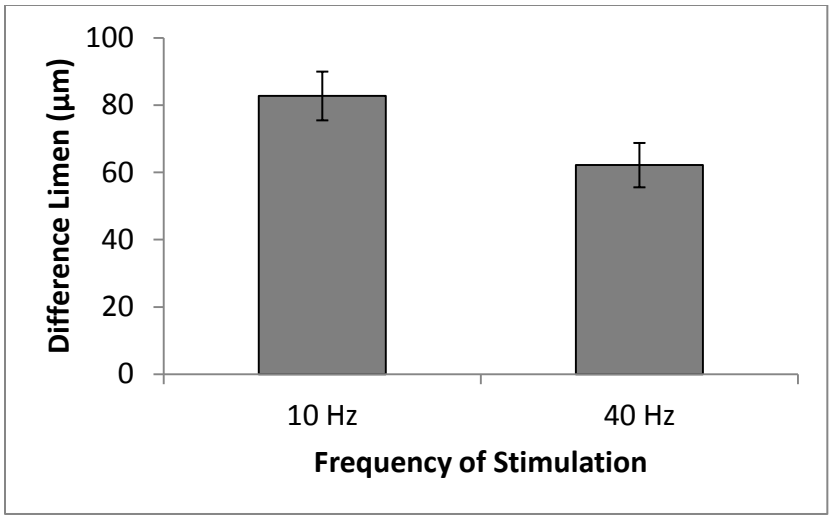

Figure 3.14 Amplitude discrimination capacity at 10 Hz versus 40 Hz. Amplitude discrimination capacity is significantly improved in the 40 Hz condition in comparison to the 10 Hz stimulus frequency (*p=0.040).

Discussion:

Our results are highly suggestive of a minimally dependent relationship of frequency on amplitude discriminatory performance for frequencies above 25 Hz. When the stimulus frequency was increased from 30 Hz to 40 Hz, amplitude discrimination capacity had not significantly improved for any of the 3 amplitude discrimination assessments that were studied (100 µm, 200 µm, and 400 µm standards). Since frequency has negligible dependency on MFR above 25 Hz, (LaMotte and Mountcastle, 1975; Mountcastle et al., 1969; Recanzone et al., 1992; Whitsel et al., 2001) changes in MFR would be minimal and MFR should fail to enhance spatial or temporal contrast to the same degree as demonstrated previously with increases in stimulus amplitude (Simons et al., 2005, previous section on 3.1 Increased amplitude improves temporal contrast). Thus, these findings support our hypothesis that contrast serves a crucial role in improving tactile perception.

Our data does suggest improved amplitude discrimination capacity when the frequency is increased from 10 Hz to 20 Hz, 30 Hz, or 40 Hz. Since frequency coding is dependent on MFR for frequencies below 25 Hz , (Ahissar and Arieli, 2001; Ferrington and Rowe 1980; Hummel and Gerloff , 2006; LaMotte and Mountcastle, 1975; Mountcastle et al., 1969, 1990; Panzeri et al., 2003; Recanzone et al., 1992; Romo et al., 2003; Whitsel et al., 2001) it is understood that an increase in frequency within the MFR dependent frequency range would elicit a corresponding increase in MFR. Therefore, when increasing the frequency from 10 Hz to the other frequencies studied, we believe spatial and temporal cortical contrast would be enhanced from this increase in MFR. As a result, this augmented contrast should lead to the enhanced amplitude discriminatory performance observed at the higher frequencies in comparison to the tactile perceptual capabilities at 10 Hz. Finally, our results are consistent with previous reports indicating that amplitude discrimination follows Weber's Law (Franciso et al., 2008; Holden et al., 2011).

From here, the next step is to determine more ways to enhance this cortical contrast and to confirm if there are corresponding improvements in tactile perceptual capabilities under these new conditions of increased spatial or temporal contrast. Our first hypothesis is that extended stimulus durations would allow more time for spatial and temporal contrast to develop.

CHAPTER 4

DURATION EFFECTS ON CORTICAL ACTIVITY
AND PERCEPTUAL PERFORMANCE

4.1 Increased spatial and temporal contrast with extended stimulus durations

Our previous findings demonstrated how an increase in stimulus amplitude could lead to improved temporal and spatial cortical contrast as well as prove an improved frequency or amplitude discrimination capacity. Published reports of OIS indicate that longer durations of vibrotactile stimulation can elicit similar improvements in spatial cortical contrast (Simons et al., 2007). Since enhanced temporal contrast corresponded with improved spatial contrast in our stimulus amplitude studies, for extended stimulus durations we would also expect an enhanced temporal contrast to correspond with the improved spatial contrast observed in previous OIS studies. To test this hypothesis, the cortical response to various durations of vibrotactile stimulation on the hand of a pigtail monkey was recorded with microelectrodes. The stimulus frequency and amplitudes remained constant during the course of each experiment.

Modifications of the standard Animal Experimental Procedure

Research and analysis was conducted as formerly explained in the "Animal Experimental Procedures" section of the Chapter 2: Methods. Microelectrodes recorded the response of area 3b neurons to continuous 1 sec minimal durations of 25 Hz, 300 μm vibrotactile stimulation on the glabrous pad of the distal phalanges for 6 pigtail monkeys

and 2 cats. A total of 77 cortical neurons were compared using MFR, PSTH, PCA, raster plot, and CCG analysis.

Results

Increased spatial contrast with extended stimulus durations

For the first exemplary experiment, one microelectrode penetration transversed and sampled the response to 1 sec of 300 μm, 25 Hz vibrotactile stimulation on the tip of digit 3 (D3) of a pigtail monkey. While the stimulus location was not moved during the course of this penetration, we shifted the microelectrode recording position from three marginal, to five central, and then back to three marginal locations as the penetration depth was increased (Figure 4.1a). A total of 11 SI neurons were analyzed from this single microelectrode penetration. The MFRs for this sample population of cortical neurons can be observed in Figure 4.1a. The red line indicates the level of baseline spike activity prior to vibrotactile stimulation. For all 11 cortical neurons, vibrotactile stimulation evoked an initially positive response above baseline levels of cortical activity. However, as the applied stimulation continued, the magnitude of stimulus evoked activity for each cortical neuron experienced a slow but relatively continuous decline.

Of particular interest in this study, the five central neurons elicited a greater cortical response to vibrotactile stimulation than their neighboring marginal neurons (Figure 4.1b). Although the spike activity for both central and marginal neurons underwent a prominent decline in activity over time, the cortical response for the centrally responding neurons was always stronger than their marginal counterparts. Furthermore, when we calculated the MFR ratio of marginal neurons over central

neurons, we found this ratio declines over time (Figure 4.1c). In other words, this decrease in MFR over extended stimulus durations is more drastic for the marginal neurons (Figure 4.1c).

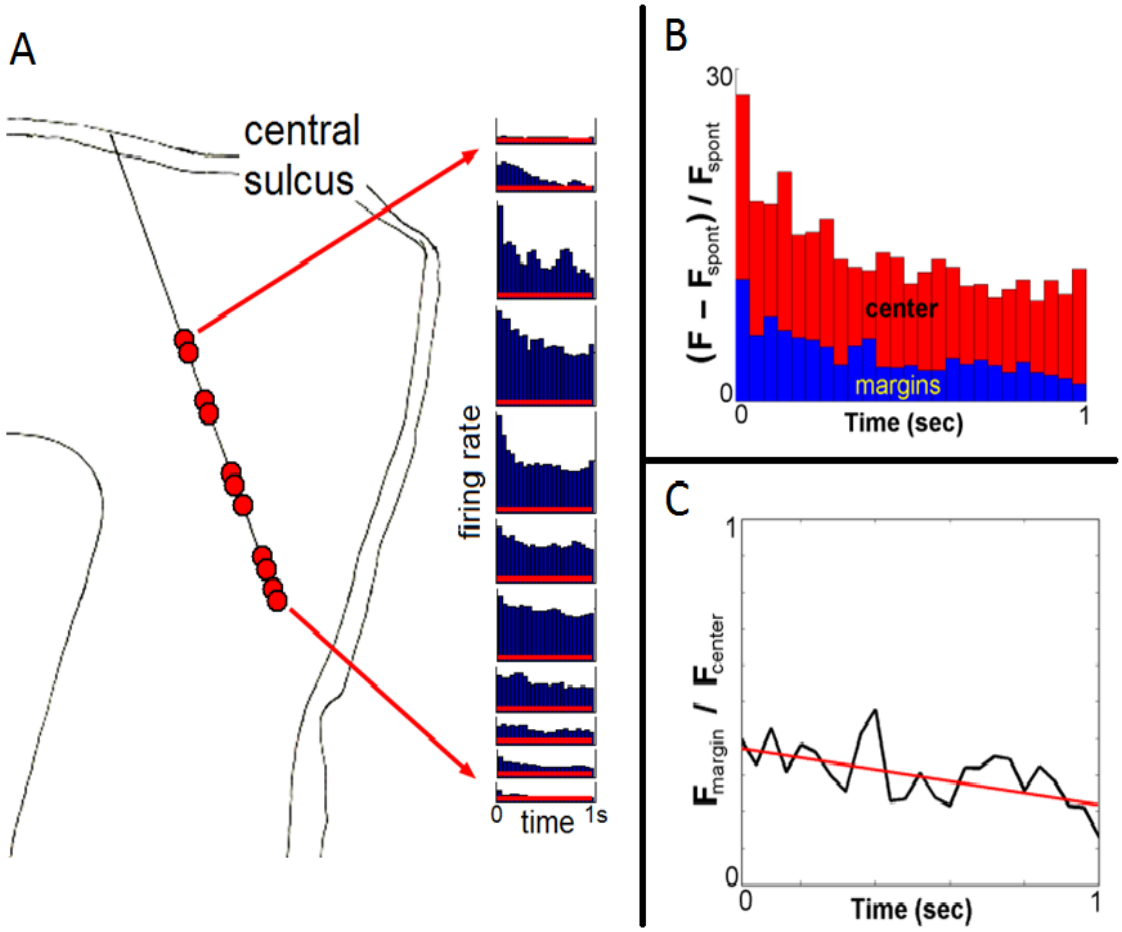

Figure 4.1 Exemplary SI penetration. The cortical response to 25 Hz vibrotactile stimulation was recorded for 6 marginal and 5 central neurons. A) The MFR for central neurons is greater than in the margins. B) Spike activity for both marginal and central neurons declined during 1 sec of stimulation. C) Spike activity declined faster among marginal neurons than cortical neurons.

Increased temporal contrast with extended stimulus durations

We then analyzed the temporal response of this 11 neuron sample population in relation to the phase of the applied 25 Hz mechanical stimulation. Figure 4.2a compares the spike activity from the start of vibrotactile stimulation (first 4 cycles or 0-160 msec) to the response around 1 sec of stimulation (cycles 22-25 or 880-1000 msec). Although the population response initially had a prominent biphasic nature, spike activity became increasingly monophasic after further stimulation. Importantly, following just 1 sec of continuous stimulation, the cortical response of this neuronal population was already noticeably coherent and well entrained to the stimulus frequency.

PCA analysis of the phase changes that evolved during this temporal enhancement indicate a clear differentiation in the cycle histogram for each neuron from early (red: first 160 msec) to late (blue: 880-1000 msec) vibrotactile stimulation (Figure 4.2b). Although the slightly scattered pattern of dots in the PCA analysis suggests the phase of each neuron is somewhat variable, the clustering of red and blue points indicates that the phase changes developing upon continuous mechanical stimulation occur together as a population. Furthermore, the tighter clustering between later phases (blue) in comparison to the early phases (red) suggests that the population response developed into phases which became increasingly similar over time.

We then computed the permuted cross-correleograms (CCG) between all 11 neurons for both early (red: first 160 msec) and late (blue: 880-1000 msec) vibrotactile stimulation. Figure 4.2c shows the average of both sets of permuted CCGs. The permuted CCGs demonstrate an increase in population entrainment as the cortical responses shift from biphasic to monophasic with extended stimulus durations.

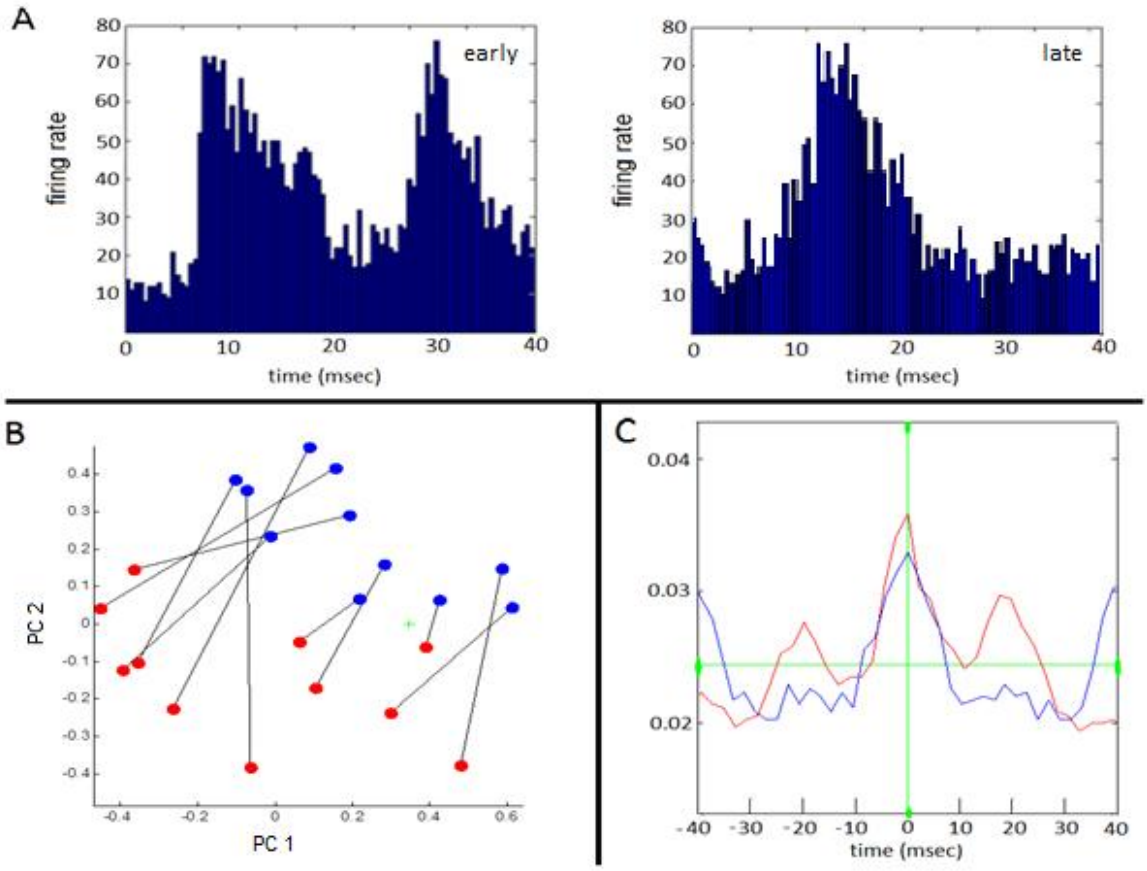

Figure 4.2 Exemplary SI population. Temporal response for a population of 11 cortical neurons in relation to the phase of 25 Hz vibrotactile stimulation. A) PSTHs comparing early (0-160 msec) to late (880-1000 msec) vibrotactile stimulation. B) PCA demonstrating how the population's phase shifts during early (red) to late (blue) vibrotactile stimulation. C) CCG indicating how the average correlation among the cortical response is stronger during late (blue) versus early (red) vibrotactile stimulation.

Raster plot analysis of an exemplary neuron, taken from this sample population of 11 neurons, provides a detailed view of how the response can gradually shift from biphasic to monophasic (Figure 4.3a). The second peak for the biphasic response residing 20-40 msec into each cycle dramatically diminishes by approximately 50 msec (12.5 cycles) of stimulation leaving a predominantly monophasic response. Figure 4.3b shows

the gradual shift in phase characteristics over time (red-initial, blue-final) as this exemplary neuron slowly develops an enhanced temporal response.

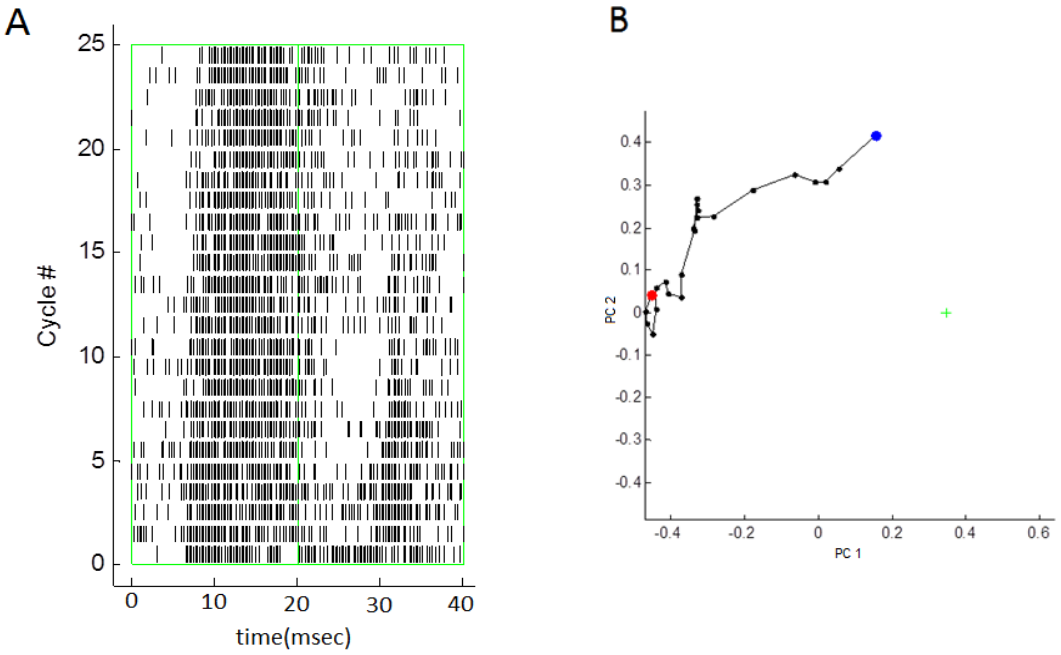

Figure 4.3 Exemplary neuron. Temporal response for an exemplary neuron in relation to the phase of 25 Hz vibrotactile stimulation. A) Cycle raster plot of the cortical activity demonstrating how a biphasic response evolves into a monophasic response. B) PCA analysis indicating how the phase of the cortical response shifts from the start of stimulation (red) during 1 sec of vibrotactile stimulation (blue - final).

A second exemplary experiment yielding 14 neurons within area 3b of SI is described in Figure 4.4. As before, we analyzed the temporal response of this sample population in relation to the phase (0-360 degrees) of the applied 25 Hz, 300 µm vibrotactile stimulation and compared the spike activity from the start of stimulation (first 4 cycles or 0-160 msec) to the response around 1 sec of stimulation (cycles 22-25 or 880-

1000 msec). Although, this initial response for particular population of neurons had already started off monophasic in nature, following extended stimulation the spike activity still evolved into a sharper, narrower monophasic response.

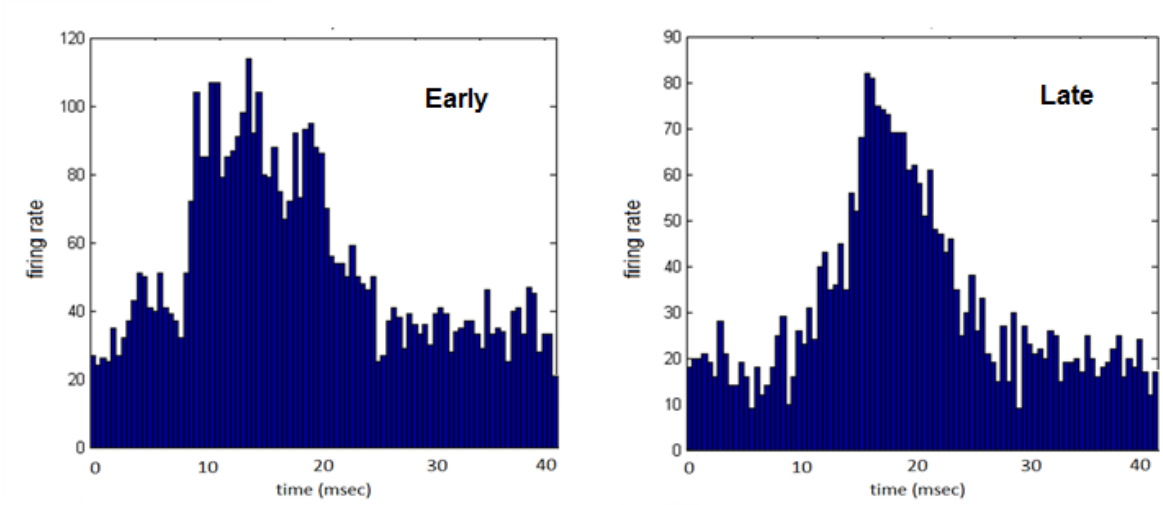

Figure 4.4 Second exemplary SI population. PSTHs comparing early (0-160 msec) to late (880-1000 msec) vibrotactile stimulation.

Discussion

Although the results from only 2 out of 8 SI penetration experiments which include 25 of 77 neurons are actually reported here, our observations were similar across each population of cortical neurons. Overall the data is highly suggestive of enhanced spatial and temporal contrast for longer durations of vibrotactile stimulation. Previous studies of OIS imaging (Simons et al., 2007) demonstrated that spatial contrast improves across the surface of area 3b over the course of 5 sec with 25 Hz mechanical stimulation. The results of our SI penetrations indicate that time also allows spatial contrast to develop perpendicular to the surface of SI. Not only had the central neurons responded more strongly to the vibrotactile stimulation, but they maintained their cortical activity longer

than their marginal counterparts. Furthermore, we found extreme degrees of temporal contrast enhancement. After only 0.5 sec of continuous 25 Hz stimulation, a population of biphasic neurons developed a prominent monophasic nature. Over a similar time course, a separate population of neurons evolved from a relatively broad monophasic response into a sharp and narrow monophasic response.

We believe this enhancement of contrast during longer continuous vibrotactile stimulation should be reflected in tactile perception. Our previous findings coupled enhanced spatial and temporal contrast from stronger stimulus amplitudes with improved frequency discrimination capability at greater stimulus amplitudes. Previously, we believed the enhanced contrast should provide a clearer perceptual picture and thus improve a person's perceptual capabilities. This evidence of improved spatial and temporal contrast with longer stimulus durations encourages us to verify corresponding improvements in tactile perception for a task such as amplitude discrimination at extended stimulus durations.

4.2 Amplitude discrimination capability unaffected by extended stimulus durations

Our preliminary experiments suggest improved frequency and amplitude discriminative capacity with enhanced spatial and temporal contrast within the responding region of SI. Past reports of OIS imaging provide supporting evidence that comparable to increasing the stimulus amplitude, extending the stimulus duration could also enhance spatial contrast (Simons et al., 2005, 2007). Although our previous human studies only explored increased cortical contrast from stronger stimulus amplitudes, we hypothesize increased contrast from longer stimulus durations should also facilitate

improved amplitude discrimination capacity. To explore this hypothesis, we compared measured changes in amplitude discrimination capacity to a change in stimulus duration.

Modifications of the standard Human Experimental Procedure

There were 55 healthy recruits for this amplitude discrimination portion of our study. Participants were college students ranging from 20-25 years of age. We followed the standard consent and sensory assessment procedures as described in Chapter 2: Methods.

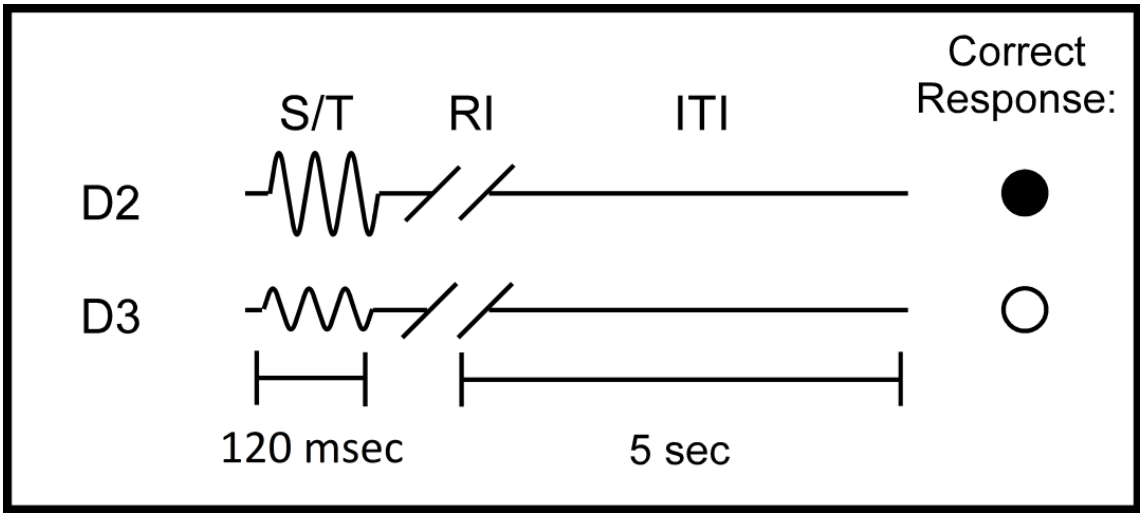

Figure 4.5 Modified amplitude discrimination procedure. Subjects indicated which finger received the greater amplitude stimulus during a brief response interval (RI). The applied stimulus was either 120 msec or 600 msec (S/T) in duration. As in the previous amplitude and frequency discrimination assessments, the inter-stimulus interval (ITI) was 5 sec in duration.

Amplitude discrimination assessment

Methods utilized to determine amplitude discriminative capacity were the same as the "Amplitude discrimination capability is variably dependent on frequency" section of Chapter 3. While the stimulator delivered simultaneous vibrotactile stimuli to D2 and D3

of the left hand, the subject's amplitude discriminative capacity was measured using a 2AFC tracking protocol (refer to Figure 4.5 and Tracking Paradigm of Chapter 2 Methods). As before, we acquired amplitude discriminative capacity at 200 µm standard and 400 µm test amplitudes; however, the duration of the stimulus was now variable between 120 msec and 600 msec (S/T) to measure potential improvements in amplitude discrimination capacity at longer stimulus durations (Table 4.1). As in the previous amplitude and frequency discrimination assessments, the inter-stimulus interval (ITI) was 5 sec in duration.

We adhered to the standard methods for human experimentation as previously explained in Chapter 2 Methods for the data analysis.

Table 4.1 Amplitude discrimination protocol at different durations

Standard Amplitude	Test Amplitude	S/T Durations
200 µm	400 µm	120 msec, 600 msec

Results

The results for the amplitude discrimination assessments (Figure 4.6) for two stimulus durations were not significantly different from one another ($p=0.27$, $n=55$). There was minimal increase in amplitude discrimination capacity at 600 msec in comparison to the performance of the same assessment at 120 msec. However, when analyzed on a subject by subject basis, the ratio of performance at 120 msec over the performance at 600 msec is 1.52 ± 0.16, suggesting that the average subject may

experience a slight drop in DL for the longer duration assessment even if the overall average of our sample population had not.

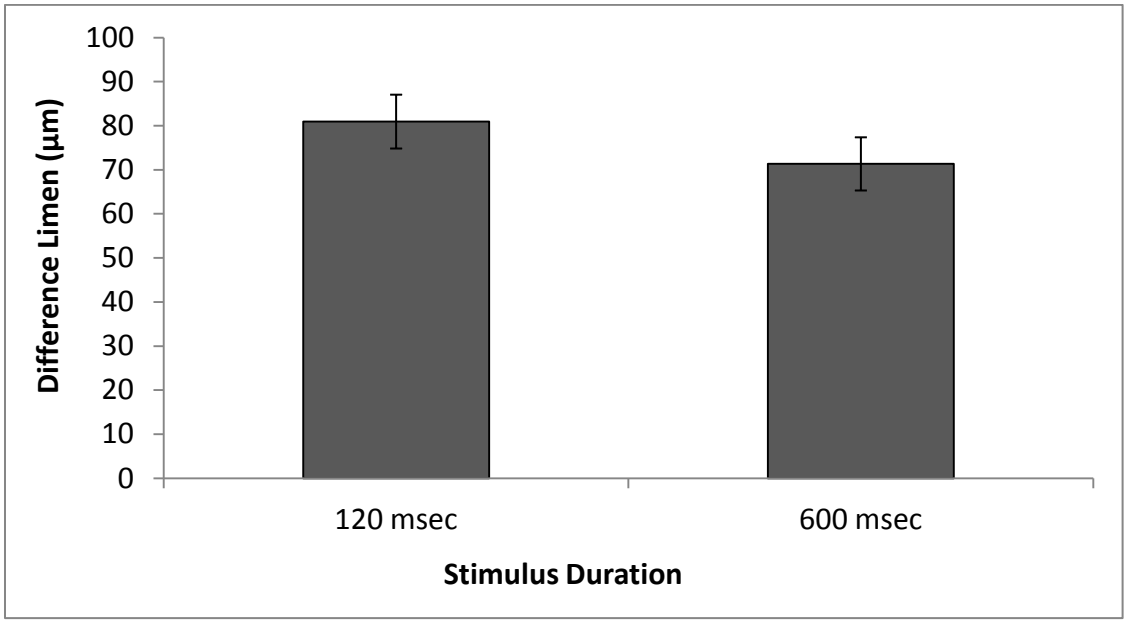

Figure 4.6 Amplitude discrimination capacity at various durations. Amplitude discrimination capacity is not significantly improved in the 600 msec condition in comparison to the 120 msec stimulus duration (p=0.27).

Discussion

The purpose of this portion of our research was to connect our previous findings of enhanced spatial and temporal contrast from longer stimulus durations to evidence of improved tactile perception capabilities under similar stimulus conditions. Our findings suggest the cortical dynamics of extended stimulus durations are more complex than our initial predictions. Amplitude discrimination capacity hardly improved during the 600 msec duration stimulus in comparison to the 120 msec stimulation. The enhancement of spatial and temporal contrast during longer vibrotactile stimulation as demonstrated in our previous research is not visibly replicated in this tactile perception task.

There are two possible reasons for these results. Perhaps improved spatial or temporal cortical contrast (as observed with the stronger stimulus amplitude conditions) does not necessarily lead to improved tactile perception. Although it is possible that the enhanced cortical contrast with the longer stimulus durations may not necessarily affect tactile perception, we believe another cortical mechanism may be instead taking precedence over the local synchronization and spatial contrast and more strongly impacting tactile perception.

Previously our results only demonstrated local synchronization among closely neighbored cortical ensembles. In other words, our results provide evidence that each digit that is stimulated has its own region of locally enhanced spatial and temporal contrast. The responding region for each separate digit may or may not be distinct from the one another. However, despite being spatially distant, we believe that increased synchronization should also occur between two digits that are simultaneously undergoing in-phase vibrotactile stimulation. If this hypothesis is correct, two digits could be working together to provide two communicating regions of locally enhanced spatial and temporal contrast. In addition to increased cortical contrast, the a processing of sensory information may further facilitate the changes we have observed in tactile perception. In other words, perhaps amplitude discrimination capacity does not improve with a longer stimulus duration because the differences between D2 and D3 can become blurred by synchronization among the two digits.

CHAPTER 5

SPATIALLY DISTINCT CORTICAL REGIONS COMMUNICATE DURING TACTILE PERCEPTION

5.1 Synchronization across spatially distinct cortical regions

Previously our studies only addressed how vibrotactile stimulation can increase local synchronization within local cortical regions. However, for normal daily function, the human brain must simultaneously process and integrate information from multiple sensory projections. With this in mind, we hypothesize that vibrotactile stimulation may be able to facilitate synchronization across spatially distinct cortical regions. To test the hypothesis, we will apply simultaneous vibrotactile stimulation to two digits of a squirrel monkey and record the cortical response in hopes of monitoring possible synchronization among distant cortical regions.

Modifications of the standard Animal Experimental Procedure

For this section of the study, research and analysis was conducted as previously explained in the "Animal Experimental Procedures" section of the Methods Chapter. Microelectrodes recorded the response in area 3b to vibrotactile stimulation on the glabrous pad of the distal phalanges for 8 squirrel monkeys for a total of 80 cortical neurons. Modes of stimulation included simple pulse, simple 25 Hz vibration, and complex stimulation (25 Hz vibration with a pulse). An exemplary stimulation protocol

can be observed in Figure 5.1. Analysis consisted of peri-stimulus time histograms (PSTH).

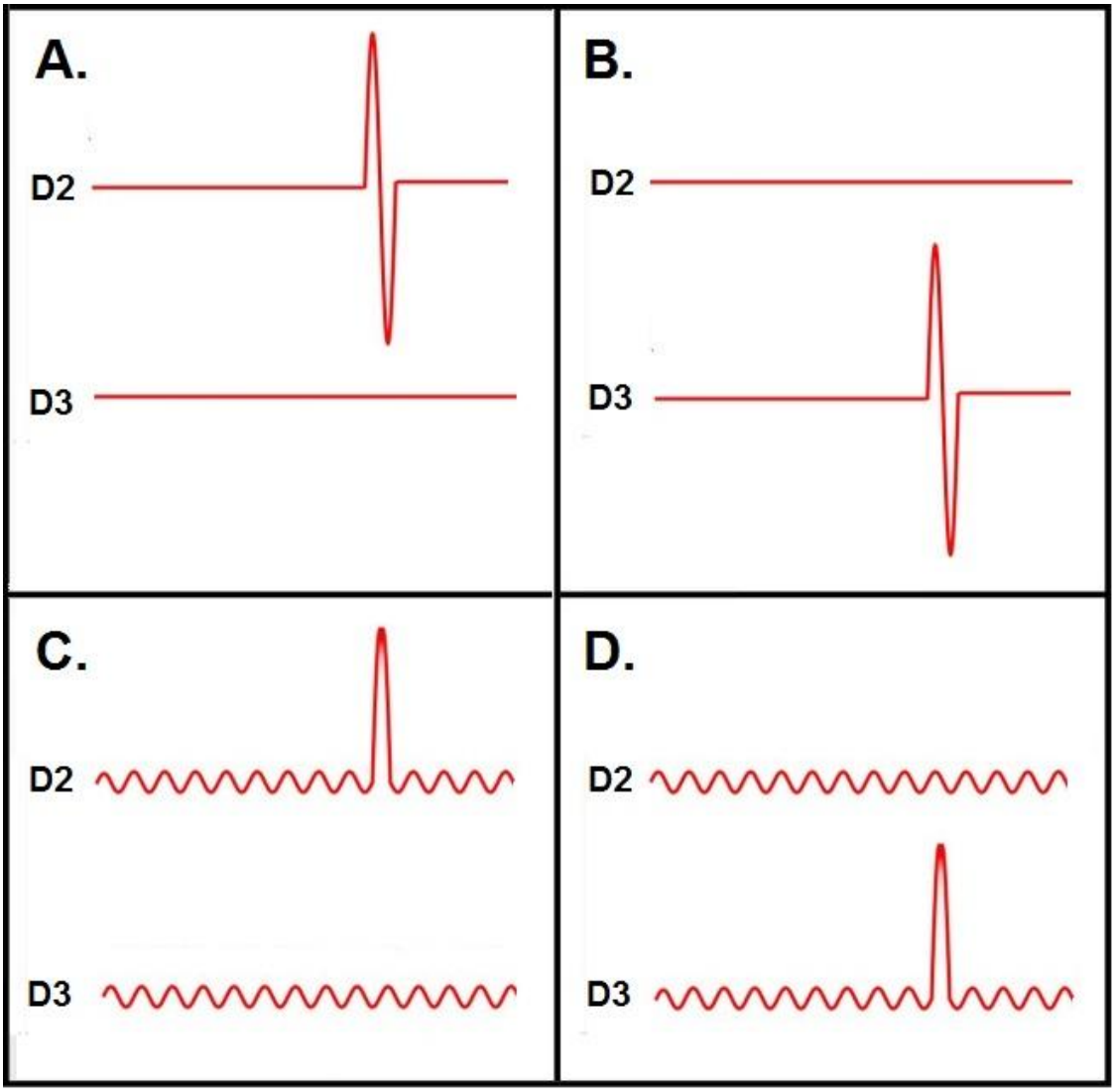

Figure 5.1 Exemplary stimulation protocol. Various modes of stimulation were tested in this study. A) A simple mechanical pulse is delivered to D2 when no stimulation is delivered to D3. B) A simple mechanical pulse is delivered to D3 when no stimulation is delivered to D2. C) Simple vibration at 25 Hz with a delayed mechanical pulse is delivered to D2 when simple vibration is delivered to D3. D) Simple vibration at 25 Hz with a delayed mechanical pulse is delivered to D3 when simple vibration is delivered to D2.

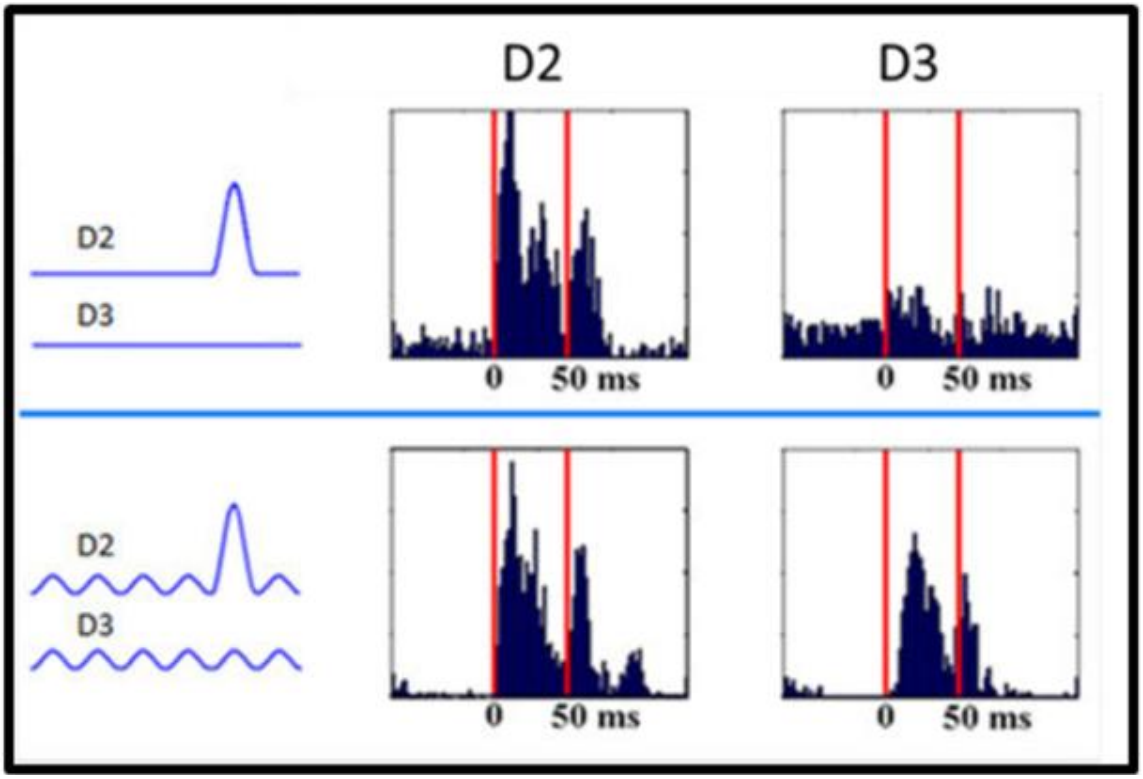

Figure 5.2 Exemplary experiment. The cortical response to D2 and D3 vibrotactile stimulation. Delivering a mechanical pulse to D2 evoked a prominent response in the cortical region of D2 both with and without preconditioning synchronized vibrotactile stimulation (left quadrant). Vibrotactile stimulation also appears to have inhibitory effects on the baseline levels of cortical activity (top versus bottom half).

Results:

The extracellular spike response for the SI cortical regions corresponding to digit 2 (D2 – index finger) and digit 3 (D3 – middle finger) from vibrotactile stimulation on the hand of a squirrel monkey are provided in Figure 5.2. The start of the simple mechanical pulse is indicated with the red line at 0 msec. While delivering a simple mechanical pulse to D2 evoked a prominent response in the cortical region representing D2 (top left quadrant), only minimal changes were observed in the region representing D3 (top right quadrant). Alternatively, when synchronized sinusoidal vibrations were simultaneously applied to both digits prior to pulse delivery (bottom of Figure 5.2), a

pulse on D2 now evokes a response in the corresponding cortical regions of both D2 and D3. Furthermore, when comparing baseline levels of activity prior to pulse stimulation (the cortical response prior to 0 msec), vibrotactile conditioning (bottom of Figure 5.2) appears to inhibit the cortical response that can otherwise be observed without prior stimulation (top of Figure 5.2).

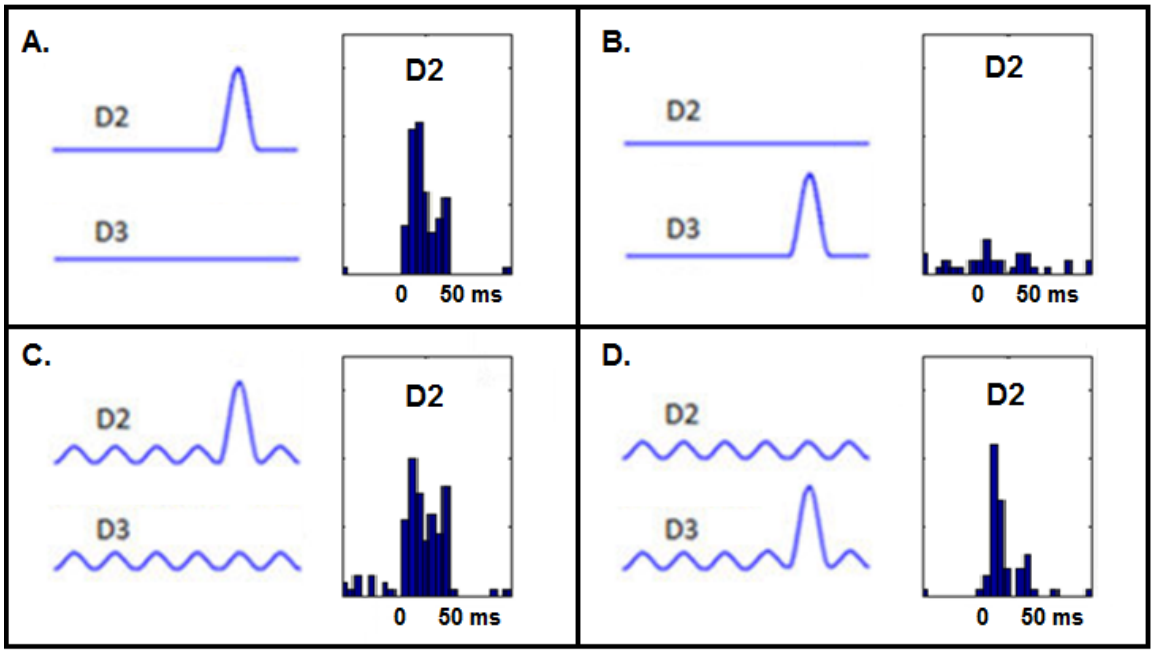

Figure 5.3 Second exemplary experiment. The cortical response to D2 and D3 vibrotactile stimulation. Delivering a mechanical pulse to D2 evoked a prominent response in the cortical region of D2 both with and without preconditioning synchronized vibrotactile stimulation (left quadrant). Vibrotactile stimulation also appears to have inhibitory effects on the baseline levels of cortical activity (top versus bottom half).

The extracellular spike response for the SI cortical regions corresponding to D2 from mechanical stimulation on the hand (D2 and D3) of a different squirrel monkey can be demonstrated in Figure 5.3. As before, delivering a simple mechanical pulse to D2 evoked a prominent response in the corresponding cortical region of D2 (Figure 5.3a);

however, no such changes were observed in D2 cortical activity when the same simple mechanical pulse was applied to D3 (Figure 5.3b). Alternatively, when synchronized sinusoidal mechanical stimulation was simultaneously applied to both D2 and D3 prior to pulse delivery (Figure 5.3 c-d), the pulse on D3 now evokes a response in the corresponding cortical region of D2 (Figure 5.3d). Perhaps due to initially weak baseline levels of activity prior to pulse stimulation, potential inhibition due to vibrotactile conditioning is not as obvious as in the previous exemplary experiment.

Discussion

Although our previous studies only demonstrated how local synchronization could occur within local cortical ensembles, the results of this study demonstrate how a preconditioning vibrotactile stimulus can promote two otherwise separate cortical projections (D2 and D3) to respond together. While vibrotactile stimulation can locally enhance spatial and temporal contrast, it also appears to improve overall cortical networkability. Perhaps this improved processing of sensory information between "separate" cortical regions from vibrotactile stimulation makes it difficult to perceive the two digits separately. As a result, this could explain the minimal improvement in amplitude discrimination capacity that was demonstrated with longer stimulus durations.

Even though enhanced cortical contrast and overall networkability may have allowed us to observe improvement in both the amplitude and frequency discrimination assessments, it is possible that these conditions are not ideal for all of our tactile tests. In other words, while the same degrees of cortical communication may be helpful in a task like amplitude discrimination, it could potentially reduce performance on a temporal order judgment task. In fact, we believe this synchronization across cortical regions could

significantly lower temporal order judgment capacity. Judging from these cortical observations, if we were to recruit human subjects and deliver preconditioning vibrotactile stimulation to D2 and D3 prior to a simple mechanical pulse on just D2, we would expect subjects to elicit a strong cortical response in the corresponding region of D2 and also a weak response in the region representing D3. As their cortical projections respond together, the digits may become rather indistinguishable from each other. In other words, the subjects could feel as though both digits are being simultaneously stimulated. Following similar preconditioning vibrotactile stimulation of D2 and D3, if we were to deliver a mechanical pulse first to D2 followed by a pulse on D3, we would expect the respective cortical regions to each respond to both pulses. Thus, it should be more difficult for the subjects to distinguish which mechanical pulse occurred first since it may feel as though both digits were stimulated twice. Our next task was to then test our hypothesis of decreased temporal order judgment (TOJ) from preconditioning vibrotactile stimulation.

5.2 TOJ capacity diminishes with preconditioning vibrotactile stimulation

Although increased local synchronization has demonstrated improved amplitude and frequency discriminative capacity, we hypothesize that increased distant synchronization would instead diminish temporal order judgment (TOJ) capability. When two spatially distinct cortical regions are synchronized, activity in one cortical projection from vibrotactile stimulation should elicit a response on the other cortical projection even when the other cortical region is not mechanically stimulated. We hypothesize that this diminished ability to separately evoke a response in the two cortical regions will decrease

performance in the TOJ assessment. We measured the temporal order judgment capabilities in a healthy sample population in the presence of preconditioning vibrotactile stimulation. A range of amplitudes were used for the conditioning stimulation in order to elicit a range of contrast enhancement within the responding region of SI.

M*odifications of the standard Human Experimental Procedure*

We recruited eighteen healthy subjects to participate in the temporal order judgment (TOJ) portion of our study. Although the mean age was 25.5 $\pm$ 2.9 years, the participant age ranged from 21 to 31 years. Standard consent and sensory assessment procedures were followed as previously explained in Chapter 2: Methods.

Temporal order judgment assessment

Methods for determining temporal order judgment capacity were similar to that of the previous assessments. When two mechanical pulses are sequentially applied, the minimal duration between pulses with which the individual can still successfully recognize the order of stimulation represents the person's temporal order judgment (TOJ) discriminative capacity. As before, the subject's discriminative capacity was calculated using the 2AFC tracking protocol (Tracking Paradigm of Chapter 2 Methods). The stimulator delivered simultaneous 25 Hz conditioning vibrotactile stimuli to D2 and D3 of the left hand including two sequential mechanical pulses (Figure 5.4). To measure the potential reduction of TOJ capacity to increased stimulus amplitudes, a number of conditioning amplitudes were tested: 0 µm, 10 µm, 20 µm, 40 µm, 60 µm, 80 µm, and

100 µm. Similar procedures for TOJ have been utilized in previous literature (Tommerdahl et al., 2007b, 2008).

The standard methods for human experimentation as previously described in Chapter 2 Methods for data analysis were utilized for this portion of the study.

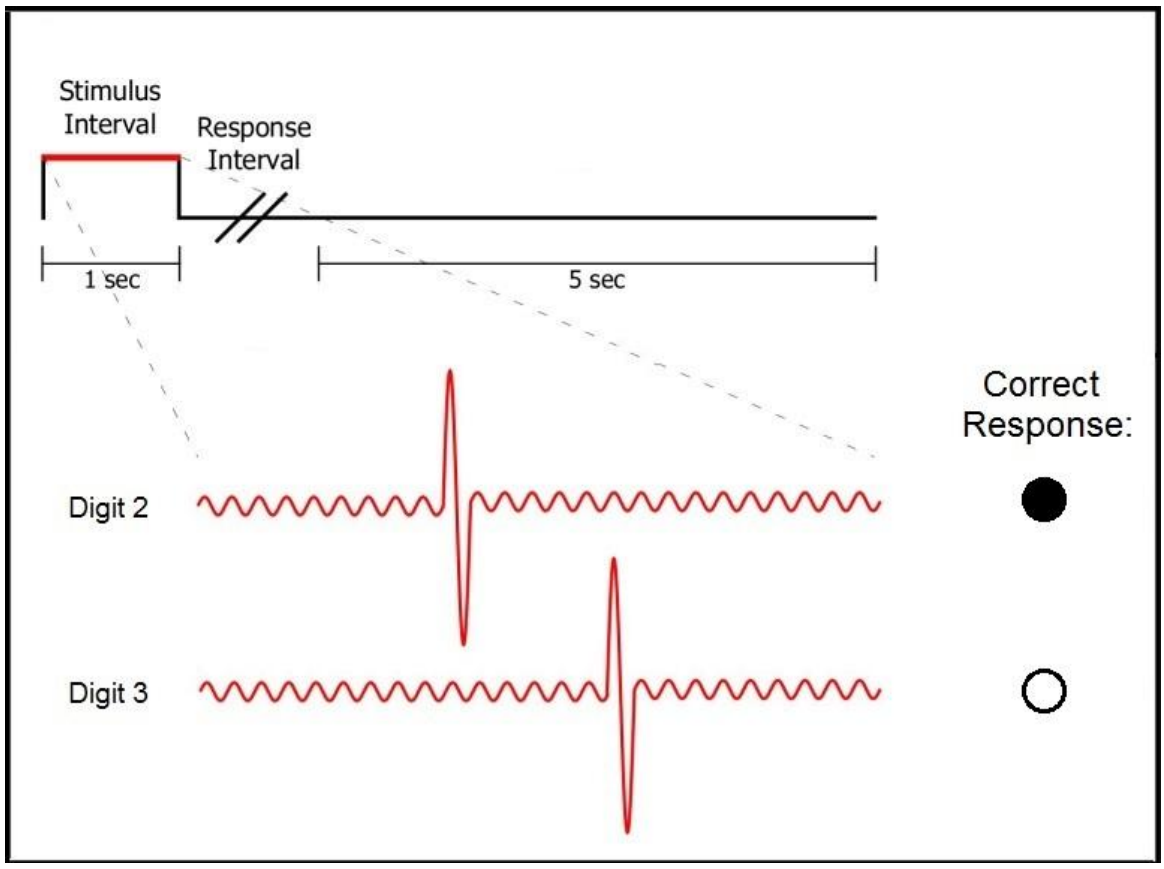

Figure 5.4 Temporal order judgment procedure. The subjects were given a brief response interval to indicate which finger received the first mechanical pulse. As in the previous assessments, the inter-stimulus interval was 5 sec in duration.

Results

As the conditioning stimulus was increased from 0 µm to 100 µm, there was a prominent increase in the minimal interstimulus interval necessary for successful temporal order judgment (TOJ) (Figures 5.5 and 5.6). Based on the slope of the fitted tread line (red line Figure 5.5), an amplitude increase by 1 µm corresponded with a 0.61 msec increase in TOJ interstimulus interval (R^2 = 0.96). Using the zero amplitude conditioning stimulus as a reference point, only a slight increase of interstimulus interval was evident for the 10 µm (p=0.23) condition. However, increasing the stimulus amplitude to 20 µm or higher produced a significant increase of interstimulus interval (*p= 0.013, 0.0022, 0.014, <0.001, <0.001 respectively.)

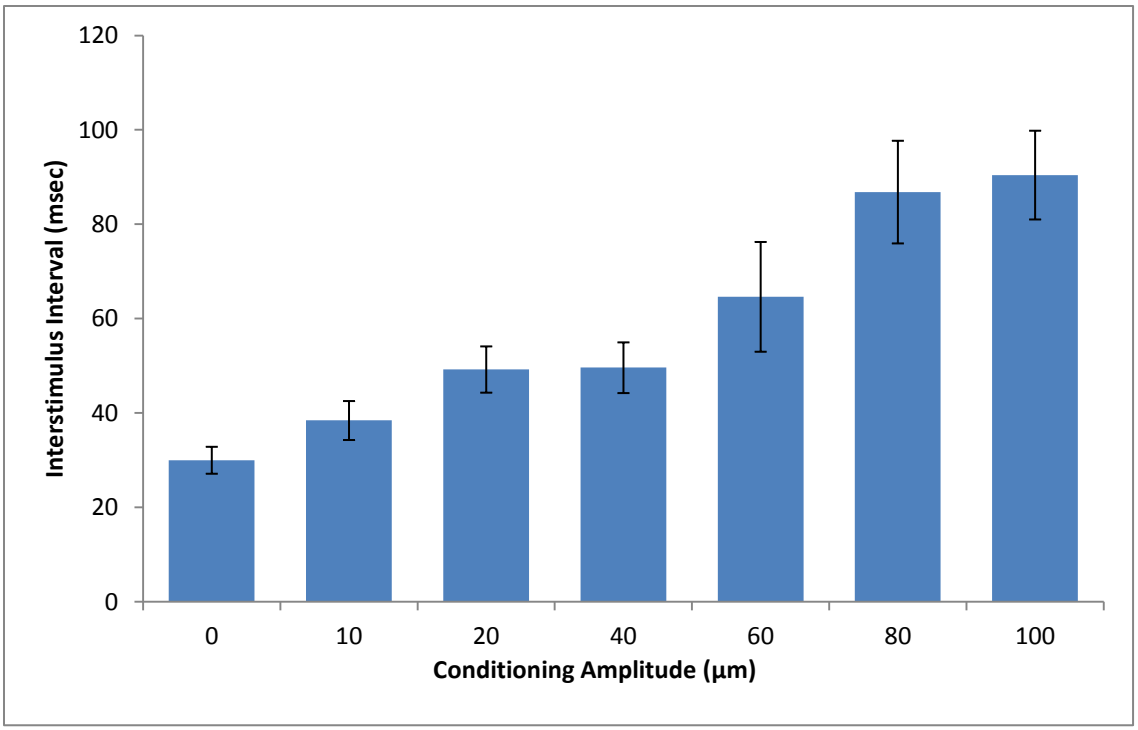

Figure 5.5 Temporal order judgment capacity at various conditioning amplitudes. Reduction of TOJ capacity from the average baseline difference limen with increasing amplitudes of conditioning vibrotactile stimulation.

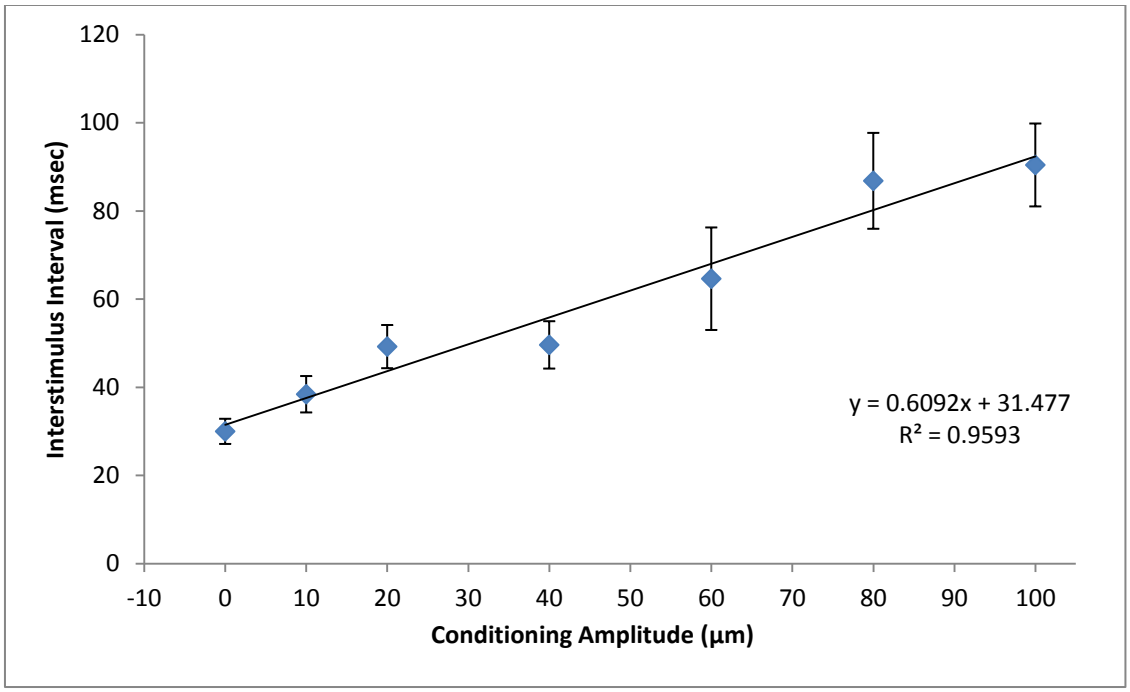

Figure 5.6 Linear fit temporal order judgment capacity. A linear fit of the reduction of TOJ capacity from the average baseline difference limen with increasing amplitudes of conditioning vibrotactile stimulation.

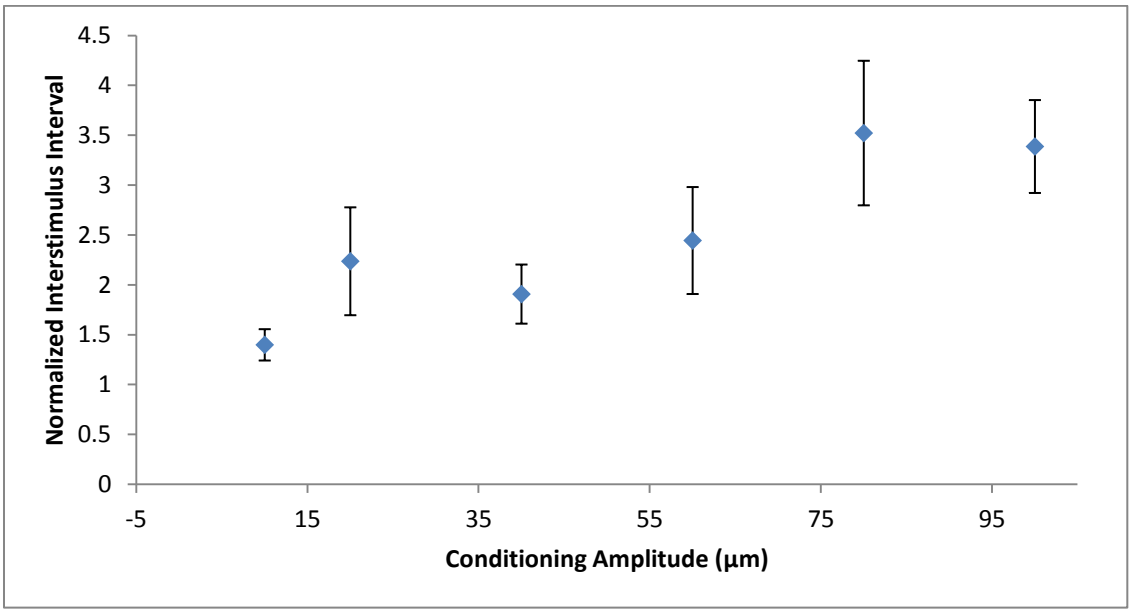

Figure 5.7 Normalized temporal order judgment capacity. An average subject by subject reduction in TOJ capacity when compared to the baseline (no conditioning stimulation) assessment.

When normalized on a subject by subject basis to the zero amplitude conditioning stimulus condition (unity in Figure 5.7), we again observe an increased interstimulus interval with stronger conditioning amplitudes. In comparison to unity, the full range of conditioning amplitudes tested (10 μm, 20 μm, 40 μm, 60 μm, 80 μm and 100 μm) have a significantly greater interstimulus interval (*p=0.022, 0.035, 0.0071, 0.015, 0.0029, <0.001 respectively). This suggests our results are true for both the average of our population as well as on the level of each individual.

Discussion

Despite the presence of two digits providing enhanced cortical contrast and local synchronization with a greater amplitude stimulus, increased networkability between the two separate cortical ensembles from vibrotactile conditioning appears to lower TOJ capacity. Furthermore, the results indicate that stronger stimulus amplitudes lead to greater reductions in TOJ capability. This suggests that higher stimulus amplitudes produce an even stronger cortical networkability making longer interstimulus intervals necessary in the TOJ assessment.

5.3 Bilateral stimulation suggests communication across cortical hemispheres

Our study suggests synchronization and spatial contrast can enhance tactile perception by increasing networkability among spatially distinct cortical areas. There is also evidence that similar interactions may occur across cortical hemispheres. Previous neurophysiological experiments have demonstrated a decrease in primary somatosensory (SI) cortical activity when evoked by a contralateral stimulus with analogous ipsilateral

stimulation (Tommerdahl et al., 2005a, 2006; Reed et al., 2011). Hypothesizing from our preceding reports of enhanced cortical contrast improving tactile perception, we would expect this reduction of cortical response to lead to diminished tactile capabilities. In corresponding perceptual literature, reports support our hypothesis and have indicated that tactile sensory perception is degraded with stimuli to the body site contralateral to the test. For instance, detection thresholds are increased when an interference stimulus is located at a homologous across hemisphere skin site (Levin and Benton, 1973), localization of tactile stimuli on the digits is influenced by stimulus delivery on the opposite hand (Braun et al., 2005), spatial acuity on one hand decreases when stimuli are delivered to the opposite hand (Tannan et al., 2005), and delivering stimuli on the opposite hand also interferes with frequency discrimination (Harris et al., 2001). There also exists a striking correlation among previous literature where, under similar stimulus conditions, SI cortical activity evoked by bilateral stimulation is ~30% less than the activity evoked by the contralateral condition (Tommerdahl et al., 2005a, b; 2006) and the percept of spatial acuity is respectively decreased by approximately the same amount in the bilateral versus contralateral stimulus condition (Tannan et al., 2005). Based on the previously-mentioned reports in which interference stimuli degraded some aspect of sensory perceptual performance across the body mid-line, we sought to test the hypothesis that amplitude discriminative capacity of an attended hand would degrade when simultaneously delivering stimuli to the unattended hand.

To test this idea, we delivered two different conditions of nonspecific stimulation to the unattended hand. In the first case, we matched the frequency of stimulation for the amplitude discriminative task (25 Hz) and in the alternate condition, 200 Hz vibration

was delivered to the unattended hand. The higher frequency condition of 200 Hz differentially activates the SI cortex (Tommerdahl et al, 1999a, b, 2005a; Whitsel et al, 2001) where amplitude discrimination is proposed to take place (Simons et al, 2005; Francisco et al 2008). However, this is not a clear indication that the 200 Hz condition would have a dissimilar impact task performance when compared to the 25 Hz condition. If performance modifications are comparable, and if both the 200 Hz and 25 Hz stimuli on the unattended hand does have an impact on performance, then the difference in performance could be attributed to the same mechanism where cross-hemisphere connectivity degrades cortical contrast.

Additionally, while one aim of this study was to determine if performance would be degraded under certain stimulus conditions, there is still a possibility for performance improving with changes in bilateral stimulus conditions. Our previous studies focused on improvements to amplitude and frequency discriminative capacity with improved spatial and cortical contrast. Furthermore, literature demonstrates how spatial acuity improves with the addition of high frequency stimuli (Tannan et al., 2005) and non-noxious thermal stimulation improves detection thresholds and amplitude discriminative capacity (Zhang et al., 2009). Thus, there appears to be specific interactions across hemispheres at the digit level (Fabri et al., 2005; Van der Knaap and Van der Ham, 2011) and, for this reason, two of the stimulus conditions delivered in the study were designed to address the question of whether or not the specificity of the pattern of stimulation to digits on an unattended hand would have an influence on the percept of stimulus patterns applied to the attended hand. For example, if the stimuli at digit 2 (D2) on both hands are greater than the stimuli at digit 3 (D3) on both hands, would this specificity improve or degrade

performance on the task? We believe specificity may overcome the typical perceptual changes observed with modifying cortical contrast.

Modifications of the standard Human Experimental Procedure

Thirty-eight healthy subjects were recruited for the bilateral portion of the research. Participants ranged from 20 to 66 years of age (mean=32.4, standard deviation=14.1). Although the participant age is rather diverse, it should not affect the results of our current study. Previous reports indicate that although reaction speed and sensory thresholds may change with age, discriminative capacity and adaptation metrics remain unchanged (Zhang et al., 2011b). The consent, sensory assessment procedures, and analysis as described in Chapter 2 Methods were followed.

Figure 5.8 Bilateral modifications to stimulator placement. So that the bilateral conditions could stimulate both hands simultaneously, the device cabling was modified so to use two stimulators. Left: CM-4 Stimulator. Right: Overhead view of left and right hands positioned on two head units for the bilateral protocols.

Bilateral sensory assessment

While the unilateral condition involved applying vibrotactile stimuli to just the fingertips of the subject's left hand, the bilateral condition consisted of stimulating both

the left and right hands simultaneously. For these experiments, the device cabling was modified so that two stimulators could be used instead the usual one (Figure 5.8). Subjects verbally indicated their response and the test administrator transmitted this response to the computer with a wireless mouse.

Bilateral amplitude discrimination

The usual amplitude discrimination procedure (As indicated in Chapter 3. Section 3.3) was used to determine the amplitude discriminative capacity of the unilateral condition (amplitude discrimination in the absence of stimulation to the unattended, right hand) (Figure 5.9). These assessments were conducted at a 200 µm standard versus 400 µm test held constant at 25 Hz on the subject's left hand. In the bilateral condition, the same amplitude discriminatory test was conducted in the presence of vibrotactile conditioning stimuli on the unattended, right hand (Figure 5.9). In other words, stimulus parameters for amplitude discrimination in the bilateral condition were the same as in the unilateral condition for the attended, left hand. The stimuli applied to digits D2 and D3 of the left hand (attended hand, AH) consisted of a test stimulus (ranging 400 µm to 205 µm) that was applied to one finger and a standard stimulus that was applied to the other (fixed at 200 µm). The amplitude of the test stimulus was always greater than that of the standard stimulus, but the loci of the stimuli (D2 versus D3) were randomly selected between the paired digits on a trial-by-trial basis. Both the standard and test stimuli for the attended hand were kept at a frequency of 25 Hz.

For the right hand (unattended hand, UH), two static and two congruency conditions were tested. For the static conditions, stimuli delivered to the unattended hand

were either 25 Hz or 200 Hz (Figure 5.9; unattended hand). 200 μm was chosen for the standard amplitude of the 25 Hz condition so the unattended hand would have the same stimulus amplitude as the standard stimulus of the attended hand. An amplitude of 50 μm was used in the high frequency condition (200 Hz) to prevent the stimulus from seeming overly intense for the subject. The parameters of the stimuli on D2 and D3 of the right hand (UH) were equal and held constant in frequency and amplitude. For instance, when a 25 Hz, 200 μm stimulus was applied to D2 of the right hand (UH), the same stimulus was applied to D3 of the same hand. Similar was true for the 200 Hz, 50 μm condition.

For the congruency test conditions, stimulus amplitudes on the paired digits on the right hand (UH) were not equal (Figure 5.9; unattended hand). Similar to the stimulus parameters for the digits of the left hand (AH), one digit of the right hand pair received a stimulus of higher amplitude than the other digit (either 400 or 200 μm; both at 25 Hz). The amplitudes were chosen for the unattended hand to match the maximum test stimulus amplitude (400 μm) and the standard stimulus amplitude (200 μm) of the attended hand. A frequency of 25 Hz was used for the unattended hand to equal the frequency of the test and standard stimuli of the attended hand. For a congruent condition, the stimuli of greater amplitude occurred on the same digit on both hands (i.e. when the amplitude of $D2_{AH}$>$D3_{AH}$ on the left hand (AH), then $D2_{UH}$>$D3_{UH}$ on the right hand (UH)). For an incongruent condition, the stimuli of greater amplitude occurred on different digits on both hands (i.e. when the amplitude of $D2_{AH}$>$D3_{AH}$ on the left hand (AH), then $D3_{UH}$>$D2_{UH}$ on the right hand (UH)).

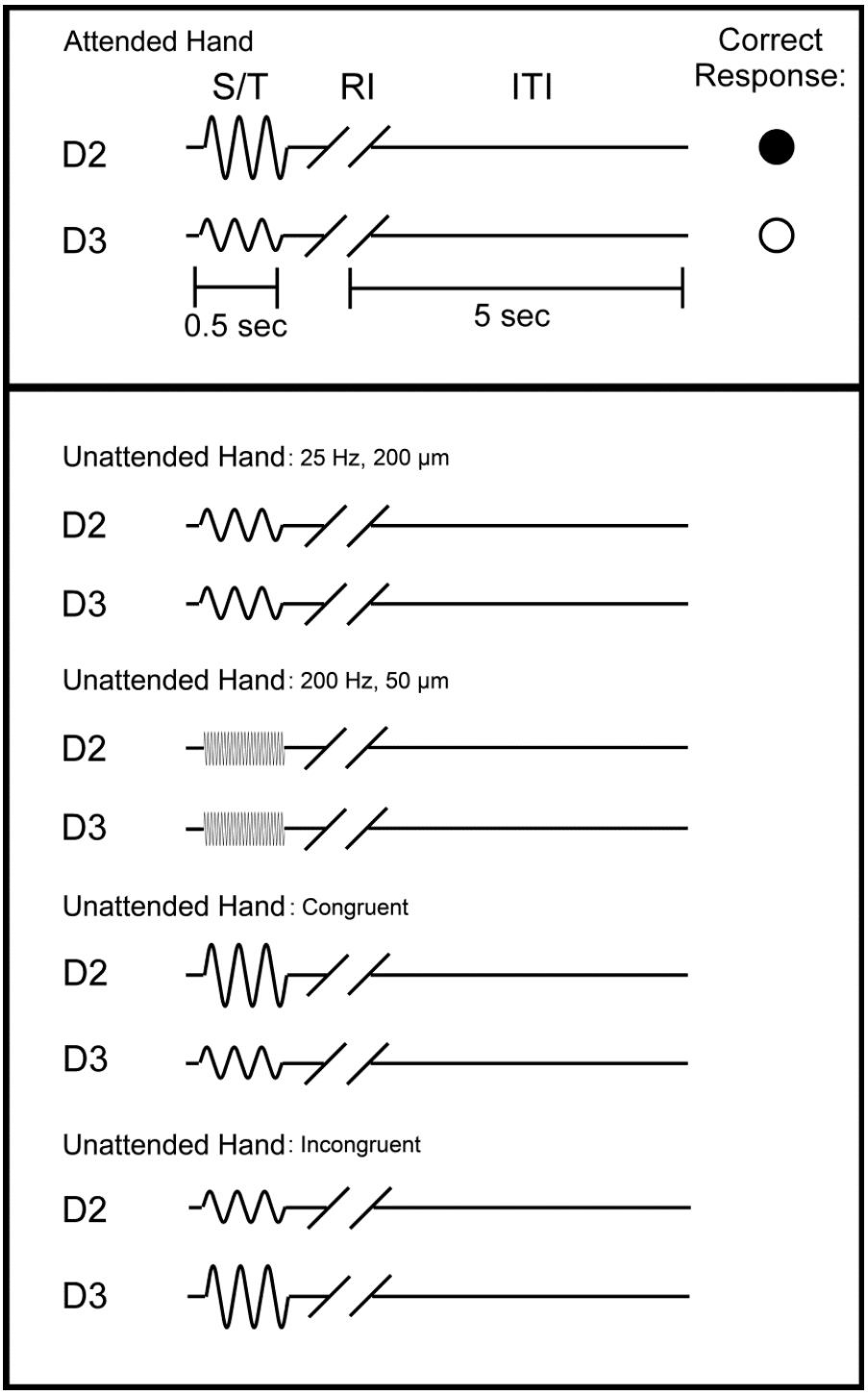

Figure 5.9 Bilateral amplitude discrimination procedure. The attended hand received stimulations in accordance with the simple amplitude discrimination protocol. The unattended hand received simultaneous stimulations under one of four different conditions varying by frequency or by congruency. For all protocols, the subject responded (response interval - RI) to a 0.5 second delivery of the standard/test (S/T) stimuli with an inter-test interval (ITI) of 5 seconds.

Results

Impact of delivering equal amplitude stimuli to the unattended hand on amplitude discriminative capacity

Equal amplitude conditioning stimuli delivered to the unattended hand results in a relative degradation in amplitude discriminative capacity on the attended hand.

Averaging the observations obtained across all subjects, the DLs obtained using the simple amplitude discrimination task (no stimulation of unattended hand) were slightly higher although not significantly different than the DLs measured in the presence of equal amplitude 25 Hz stimulation on the unattended hand (Figure 5.10; p=0.43, n=38). Furthermore, 200 Hz stimulation on the unattended hand also faintly reduced amplitude discriminative capacity (p=0.23, n=38). The raw average DLs comparing the two different frequency conditions displayed no statistic difference (p=0.76) from each other. However, group average analysis fails to account for potential differences in DLs on a subject by subject basis – an important aspect of performance is how much of an impact stimulation has on the attended hand.

In order to determine whether the observed effects of the two types of unattended hand conditioning were consistent across subjects, the individual data points were compared to those obtained with the simple amplitude discrimination task. Data was evaluated on a subject-by-subject basis by determining the percentage change in amplitude discriminative capacities from the unilateral to bilateral stimulus condition. Such calculations allow for the difference in performance between the conditions of unilateral and bilateral stimulation to be emphasized: how well a subject performs on the unilateral task is irrelevant and the measure of interest is the alteration that the secondary condition introduces (in this case, stimulation of the unattended hand at 25 Hz or 200

Hz). The percentage change amplitude DLs show that the effect of the same applied frequencies (25 Hz) on both the attended and unattended hands, at an amplitude equal to the standard stimulus on the unattended hand (200 μm) resulted in a weak 52.3±18.7% decrease in performance as compared to the unilateral amplitude discriminative task. Additionally, applying a higher frequency stimulus at 200 Hz showed a slight increase in DL of 32.2±14.7% in the bilateral condition. Although neither the 25 Hz nor 200 Hz condition had a significant hindrance on performance, a faint impact on performance is still evident.

Effect of delivering unequal amplitudes of 25 Hz stimuli to the unattended hand on amplitude discriminative capacity: conditions of congruent vs. incongruent stimulation

Conditioning stimuli delivered to the unattended hand that are incongruent with those delivered to the attended hand degrade amplitude discriminative capacity while congruent conditioning has no impact.

Averaging the observations obtained across all subjects demonstrated that there were no statistically significant differences between DLs from the simple amplitude discrimination task (no stimulation of unattended hand) and those measured in the presence of congruent patterns of stimulation to the digits of the unattended hand (Figure 5.10; $p=0.17$, $n=38$). However, performance in the incongruent assessment had demonstrated a significant reduction of discrimination capacity ($^*p<0.001$, $n=38$). The data also demonstrates a significant difference between the congruent and incongruent conditions ($^*p<0.001$).

Similar to the above described analysis, the data were again evaluated on a subject-by-subject basis by calculating the percentage change in amplitude discriminative

capacities under the different conditions of unattended hand stimulation to the simple condition of stimulation to only the attended hand. The percentage change in DLs for

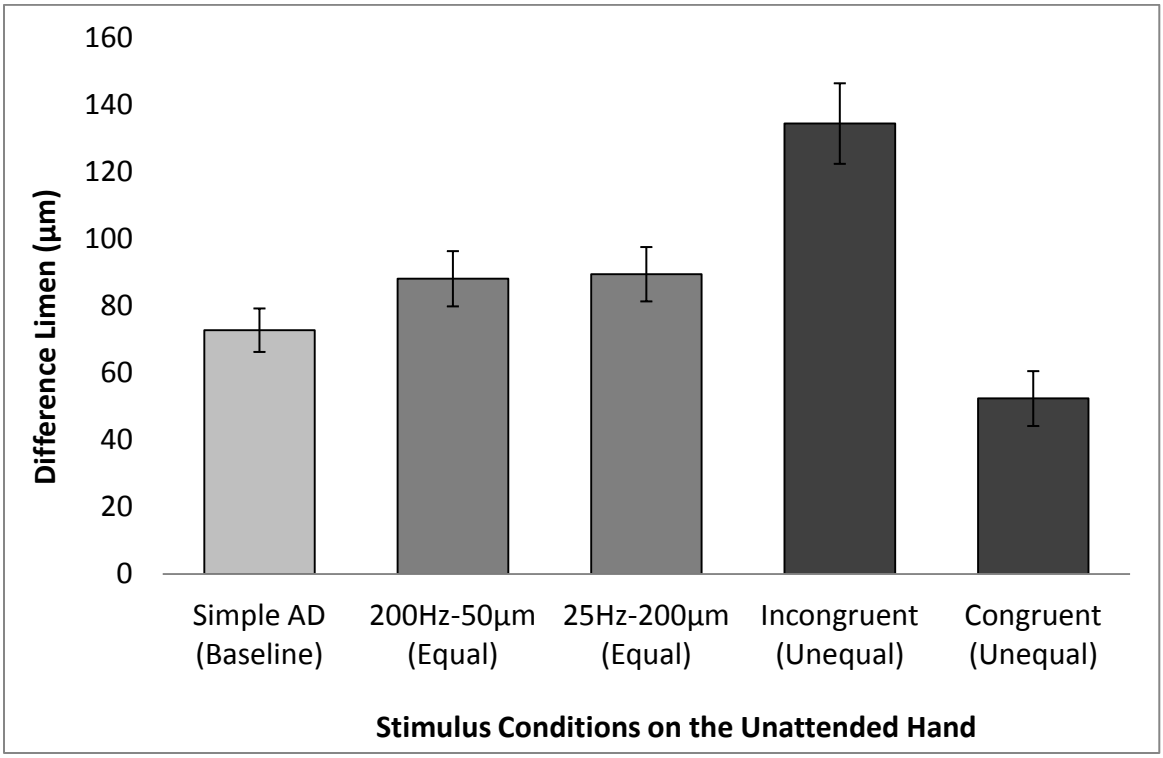

Figure 5.10 Amplitude discrimination capacity with unattended hand stimulation. Data obtained from simple amplitude discrimination task (no unattended hand stimulation) is compared to amplitude discrimination capacity obtained under different conditions of unattended hand stimulation. The equal amplitude 25 Hz, equal amplitude 200 Hz, and incongruent conditions yielded a reduced performance in comparison to the simple condition ($p= 0.43$, $p=0.23$, and $*p<0.001$ respectively). Data obtained from the congruent conditions was not different the baseline simple amplitude discrimination condition ($p=0.17$).

amplitude discrimination show that incongruent stimulation on the unattended hand has a more pronounced effect on amplitude discrimination than the conditions of equal amplitude (25 and 200 Hz). While application of congruent stimuli at the same frequency to both hands resulted in a 0.8±17.6% difference in discriminative capacity compared to

the simple condition, incongruent stimulation significantly worsened amplitude discrimination performance by 160.2±28.7%.

Discussion

Evaluation of the average population performance indicated three conditions as causing a decrease in the ability to perform the amplitude discrimination task, with one condition of statistical significance. Delivering equal amplitude stimuli of 25 Hz or 200 Hz to the unattended hand elicited a decrease in amplitude discriminative capacity. While incongruent application of stimuli to the unattended hand significantly hindered amplitude discriminative capacity, administration of congruent stimuli to the unattended hand occasionally improved performance. By conducting the percentage change of amplitude discriminative capacity in the unattended hand conditions to the DLs measured with stimulation on only attended hand, our analysis on a subject by subject basis again indicated that three of the conditions delivered to the unattended (right) hand resulted in decreases in the ability of the subject to perform the amplitude discrimination task. Our results support our hypothesis that enhanced cortical contrast is crucial for improved tactile perception. We hypothesized that weaker central excitatory activity among a population of responding neurons would elicit a diminished contrast with the inhibited cortical surround and lead to degraded perceptual performance. Alternatively, increasing excitatory cortical activity would have improved amplitude discriminatory ability by enhancing contrast within the cortical response.

Previous literature on cortical activity evoked by contralateral peripheral stimulation of the digits demonstrates that the response in SI and SII has an excitatory nature which maintains its magnitude for the full duration of 25 Hz stimulation

(Tommerdahl et al., 1999a, b). Similarly, a 200 Hz contralateral stimulus continuously elicits an excitatory activity in a population of responding SII neurons (Tommerdahl et al., 1999b). However, while a 200 Hz contralateral stimulus initially evokes an excitatory response in SI, cortical activity rapidly decreases following the first 3 seconds of stimulation (Tommerdahl et al., 1999a, b). This study utilized stimulus durations of 0.5 seconds, which is well within the excitatory phase of the SI response to a 200 Hz stimulus. Despite different means of SI activation through 25 Hz versus 200 Hz vibrotactile stimulation, the effects observed with the addition of an ipsilateral stimulus suggest similar cortical mechanisms. SI activity evoked by conditions of contralateral, ipsilateral and bilateral stimulation in the cat show that the magnitude of response in SI evoked by 25 Hz contralateral stimulation is reduced in the presence of an ipsilateral stimulus (Tommerdahl et al., 2005a, b), and similar results have been found in the non-human primate (Tommerdahl et al., 2006). To our knowledge, optical research has yet to be published displaying the effects of introducing a 200 Hz ipsilateral stimulus to 25 Hz contralateral stimulation. Nevertheless, we assume results from the 200 Hz bilateral condition would be comparable to 25 Hz as long as stimulus durations do not exceed 3 seconds. Particularly with 25 Hz stimulation, one explanation for reductions in performance under the bilateral condition could be a decrease in contrast between the activities evoked by adjacent and/or near adjacent cortical ensembles in SI and SII that reflect stimulus evoked input from adjacent skin sites.

The most straightforward part of the results to explain is that the ability of a subject to discriminate between stimulus amplitudes on the attended hand slightly decreases when two equal stimuli are delivered to D2 and D3 of the unattended hand. For

the bilateral condition, the presence of an ipsilateral stimulus produced a reduction in contrast due to the overall decrease in activity (Tommerdahl et al., 2005a; 2006). Furthermore, a very similar model to that as was used in this study was proposed for a report of tactile spatial acuity (Tannan et al., 2005) in which spatial acuity was made worse by delivering a stimulus on the unattended hand. It is relatively easy for one to visualize that decreasing the overall activity in SI would decrease overall contrast between the two sites of SI activation and most likely play a prominent role in the determination of which of the two vibrotactile stimuli are stronger. After all, our previous work demonstrated how improved amplitude and frequency discrimination capacity corresponds with enhanced spatial and temporal contrast.

However, in terms of this study, the most significant point of the equal amplitude conditions is that their effects on amplitude discriminative capacity are relatively equal. This reduces the possibility that the impact of the 25 Hz and 200 Hz equal amplitude conditioning stimuli could simply be "distracting"; otherwise, the results from these two conditions would be rather different. In general, subjects indicated that the 200 Hz at 50 μm stimulus felt more intense than the 25 Hz at 200 μm. If the equal amplitude conditions were simply distracting the subjects from the amplitude discriminatory task, we expected the perceivably more intense stimulus would have led to a greater reduction in DL. However, since both 25 Hz and 200 Hz conditions had equally diminishing effects on amplitude discrimination capacity, the stimuli on the unattended hand were not assumed to be distractions.

There is a weak impact on amplitude discriminative capacity when both hands are receiving the same pattern of unequal amplitude stimulation, but there is a significant impact when the patterns of stimulation delivered to the two hands are incongruent.

As with these equal amplitude conditions, we expected a similar reduction of contrast between the excitatory surround and laterally inhibited cortical response due to an overall decrease in central excitatory activity in the unequal amplitude conditions. As a consequence of applying unequal amplitudes, we anticipated inhibition in both digits from ipsilateral stimuli with slightly greater inhibition from the larger stimulus. The congruent application of stimuli on the unattended hand would thus drive down the stronger amplitude digit response more than the weaker digit response on the attended hand (Figure 5.11). This mechanism would lead to an overall reduced perceived difference between the two amplitudes and result in diminished amplitude discriminative capacity in the congruent condition. Inversely, the incongruent condition would enhance performance on the discriminatory task. However, when the same two fingers from opposite hands are receiving the stronger stimuli (congruent condition), subjects did not perform worse than they do in the unilateral condition as they do when other conditions of stimulation are delivered to the unattended hand. In fact, the DLs of the population in the congruent condition was often lower than amplitude discrimination thresholds of the unilateral condition. Thus, in the congruent application, a mechanism other than inhibition must be present to allow perceptual performance to remain intact. Furthermore, the possibility of the ispilateral stimuli simply serving as a distraction during our sensory assessments is doubtful. Since a distracter stimulus would take away subject ability to focus on the sensory test, we would have expected a reduction amplitude discriminative capacity with an ipsilateral distraction. The congruent condition instead displayed improved discriminative thresholds.

When an incongruent stimulus was delivered to the unattended hand, again we hypothesized that there would be a slight reduction in contrast enhancement of the stimulus evoked response, simply because there is a decrease in the overall magnitude of the response in SI contralateral to the test site. . However, the unequal levels of inhibition would have enhanced amplitude discriminative capacity by driving down the weaker amplitude stimulus more than the stronger amplitude and therefore accentuating the perceived amplitude differences (Figure 5.11). Instead, the results of this study indicate a mechanism other than inhibition must occur when incongruent stimulus amplitudes are applied to the unattended hand. When the two fingers from opposite hands received conflicting sensory information about which digit was receiving the stronger stimulus, subjects performed significantly worse on the same discriminatory task. Both congruent and incongruent assessments suggest a mechanism other than inhibition is contributing to tactile performance.

Perhaps the unequal amplitude assessments exhibit a degree of digit specificity. This idea seems logical – grabbing objects with both hands undoubtedly benefits from fingers working together and making determinations of sensory percept in a unified manner. When information to the same two fingers on opposite hands is presented to appear very different, information is not integrated in the same manner as when information presented to the same two fingers is congruent. With incongruent stimuli, the digits with one hand are no longer working together with the other hand. Instead the hands are trying to process contradictory information which could lead to the perceptual difficulty demonstrated in the results. A parallel situation can be demonstrated in a visual context. The Stroop Effect is a common phenomenon in visual perception (Stroop, 1935).

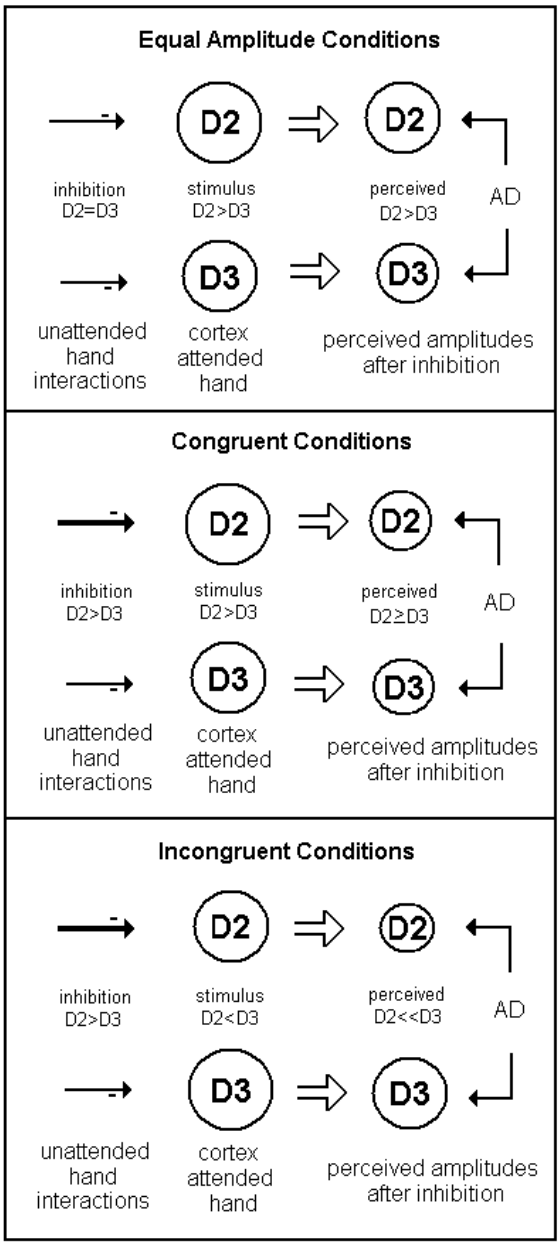

Figure 5.11 Inhibition models of cross-hemisphere activity. The level of inhibition SI neurons of the unattended hand exhibit on the cortex of the attended hand is dependent on stimulus amplitude. In this figure, a larger diameter circle indicates that the stimulus is greater in perceived amplitude. A larger arrow indicates stronger inhibition. (Top) Equal amplitude conditions of either 25 Hz or 200 Hz on the unattended hand uniformly inhibit digits 2 and 3 of the attended hand maintaining in perception that D2 is greater than D3. (Middle, Bottom) Alternatively, unequal amplitude conditions experience excitation and the effects are no longer equivalent. Perceived amplitude differences are reduced in the congruent condition and enhanced in the incongruent condition. Amplitude discriminatory assessments (AD) were used to examine the effects of inhibition on perceptual interactions between D2 and D3 of the attended hand.

First subjects are asked to name the color of a word where the color of the text matches the name of the color (i.e. RED). If subjects are asked to perform the same task when the color of the text no longer matches the name of the color (i.e. RED), then reaction times are often reduced and the probability of indicating an incorrect color is increased. A similar phenomenon known as feature binding has been proposed in perception by Gray and Singer (1989), where the oscillatory nature of the cortical response is believed to temporally coordinate spatially separate cortical regions based on the context of stimulation. Thus, a form of specificity could enhance contrast in congruent stimulation and diminish contract with incongruent stimulation.

An alternative explanation would be ipsilateral excitation. Opposite to increased ipsilateral inhibition, enhanced central cortical excitation would provide sharper contrast with the laterally inhibited cortical neurons of each responding region. This mechanism of enhanced cortical excitation would also lead to an increased perceived difference between the two amplitudes on the attended hand by driving up the response from the stronger amplitude digit more than activity from the weaker amplitude and thus support the results displaying an improved amplitude discriminative capacity in the congruent condition. The results showing greater discriminative thresholds in the incongruent condition could similarly be supported by increased SI excitation. Despite a slightly improved digit specific contrast from the overall increased excitation, incongruent ipsilateral stimuli would reduce the perceived amplitude differences through cortical excitation and diminish amplitude discriminatory capacity. Perhaps ipsilateral stimuli can variably elicit inhibition or excitation. The current nature of the network may be a context dependent feature. This dependency relies on the particular parameters of each stimulus

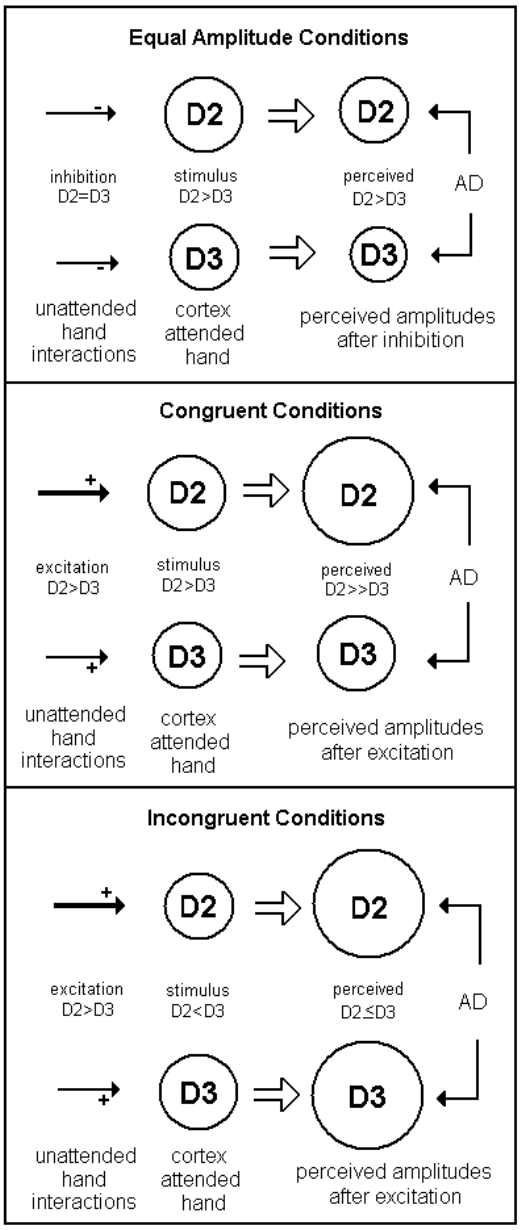

Figure 5.12 Models of cross-hemisphere activity. The nature of the network is context dependent. The level of inhibition or excitation that SI neurons of the unattended hand exhibit on the cortex of the attended hand is dependent on stimulus amplitude. In this figure, a larger diameter circle indicates that the stimulus is greater in perceived amplitude. A larger arrow indicates stronger inhibition. (Top) Equal amplitude conditions of either 25 Hz or 200 Hz on the unattended hand uniformly inhibit digits 2 and 3 of the attended hand maintaining in perception that D2 is greater than D3. (Middle, Bottom) Alternatively, unequal amplitude conditions experience excitation and the effects are no longer equivalent. Perceived amplitude differences are enhanced in the congruent condition and reduced in the incongruent condition. Amplitude discriminatory assessments (AD) were used to examine the effects of inhibition or excitation on perceptual interactions between D2 and D3 of the attended hand.

where the network may switch from eliciting inhibitory versus excitatory responses. For instance, presenting variable ipsilateral conditions to a contralateral stimulus produces inhibition in the equal amplitude assessments yet excitation when amplitudes are unequal (Figure 5.12).

Although inhibitory and excitatory cortical circuits work together to form balanced networks of activity (refer to Zhang and Sun, 2011c for a recent review), changes in the individual circuits could cause shifts in network balance (Heiss et al., 2008; Hull et al., 2009; Klingner et al., 2011). This leads us to believe that it could possible for the nature of the cortical network to shift from inhibitory to excitatory based simply on context of the tactile input. While there are some indications that ipsilateral input elicits an excitatory cortical response (Zhu et al., 2007; Nihashi et al., 2005), there are also implications of ipsilateral input instead evoking an inhibitory response (Hlushchuk and Hari, 2006; Lipton et al., 2006). Although contralateral stimulation was found to be reduced in the presence of an ipsilateral stimulus (Tommerdahl et al., 2005a; 2006), previous bilateral studies are limited in number. The possibility of an ipsilateral stimulus producing an excitatory response still exist and can later be tested directly via *in vivo* animal studies, similar to those that have been conducted previously investigating the bilateral interactions in SI cortex (Tommerdahl et al, 2006).

CHAPTER 6

DISCUSSION

6.1 Cortical Metrics in comparison to other Quantitative Sensory Testing

An important turning point in clinical testing was reached nearly four decades ago when the first clinical paper on quantitative sensory testing (QST) was published (Fruhstorfer, 1976; Zaslansky and Yarnitsky, 1998). Fruhstorfer and colleagues were pioneers in developing a relatively swift and simple means for measuring warm, cold, and thermal pain thresholds. QST provided a straightforward and repeatable procedure to measure thermosensibility in a non-invasive, non-painful manner. Previously, psychophysical methods for measuring thermosensbility had been too intricate or time consuming to be reasonably applied in the clinical setting (Murray and Hagan, 1973; Murray and Safferstone, 1970; Kenshalo, 1970). Since then, QST techniques have evolved to measure other percepts of sensation such as vibration (Arezzo and Schaumburg, 1980; Arezzo et al., 1983; Bleeker, 1986; Lipton et al., 1987) and touch (Dellon et al., 1992, 1997). Why is it important to quantify a person's sensory capabilities? By providing researchers and clinicians with the ability to quantify sensory perception, QST can similarly be utilized as a tool for measuring and detecting sensory deficiencies. While conducting QST evaluates the sensory functionality of the CNS, impairments of sensory perception should also be reflected in abnormalities of cortical functionality. The ability to apply QST to a variety of modalities further increases the

possibilities for measuring cortical defects. Specifically, QST can rapidly quantify how a medication, CNS injury, or neurological disorder may reduce neurological functionality while only providing a minimal amount of discomfort to the test subject. (For recent reviews on the benefits of QST refer to the following: Chong and Cros, 2004; Gruener and Dyck, 1994; Moloney et al., 2012; Shy et al., 2003; Yarnitsky and Pud, 2004; Zaslansky and Yarnitsky, 1998.)

Generally, QST quantifies the capabilities of these separate modalities through (a) sensory detection thresholds, (b) pain tolerance levels, or (c) sensation estimates. Many people are already familiar with a form of sensation estimates. Often times when a patient is in pain, the practitioner will ask the patient to rate that pain on a scale of 1-10 where 10 is the most unpleasant feeling possible. A similar method of QST can be used to measure the magnitude of sensation from suprathreshold stimuli. In fact, the main clinical application of sensation estimation is with pain (Price, 1988). In clinical practice, a visual analogue scale (VAS) is typically used to measure the degree of chronic pain a subject has been experiencing (Price et al., 1983). First the patient adjusts the intensity of an experimentally induced painful heat stimulus to correspond with the lowest, average, and highest intensities of recent painful experiences. This initial training allows the patient to develop a mental scale of perceived sensation magnitude from “no sensation” to “the most intense sensation imaginable”. Following this, the subjects make assessments for the intensity of a variety of applied heat stimuli and then assign an estimation of sensation (from no sensation to the greatest sensation) to each condition. This quantification of sensation is particularly useful in that it provides a means for researchers and clinicians to determine if a patient is hypersensitive and has a higher

magnitude estimation of pain. For instance, a recent study compared women with vulvar vestibulitis syndrome (VVS) to healthy women controls and found that women with VVS are more susceptible to higher magnitude estimations of pain (Granot and Lavee, 2005). Although sensation estimates are most often used to assess pain, QST can utilize non-painful stimulus conditions.

Sensory thresholds and tolerance levels are typically measured in one of two ways: limit or level. For the method of limits, the subject is exposed to a stimulus of changing intensity. The subject either indicates the onset of sensation from a stimulus of increasing intensity or the loss of sensation from a stimulus of decreasing intensity. Although these dynamic tests require the participant to have a quick reaction time, by averaging the sensory threshold (or tolerance levels) from increasing stimulation to that of decreasing stimulation the error from reaction time is potentially reduced. On the other hand, the method of levels removes potential error from subject reaction time. Instead, these assessments have a designated time interval for the subject to respond. Following a short stimulus interval, the subject responds with a simple "yes" or "no" to indicate if the previous stimulus condition evoked a sensation (Cornsweet, 1962; Sekuler et al., 1973). If the subject responded correctly, the stimulus intensity for the next trial is lowered. As with the method of limits, the initial stimulus could begin either above or below the subject's threshold or tolerance level; however, for the method of levels, each stimulus interval is of a fixed intensity and duration in a given trial. Alternatively, the assessment can provide one interval with the stimulus and another interval without the stimulus. Here the subjects would be required to choose which interval contained the stimulus (Dyck et al., 1978). If the subject correctly chose the interval with the stimulus, the intensity of the

next stimulus would be reduced. The subject should only choose incorrectly if the stimulus was not actually perceived. Thus, if the subject incorrectly chose the interval without the stimulus, the intensity of the next stimulus could be increased. Unfortunately, the subject still has a 50% chance to correctly guess the stimulus containing interval when no sensation was ever actually perceived. Therefore, subjects fluctuate for numerous trials around their actual threshold value and the final threshold value is calculated by averaging the last several trials of the assessment. Naturally, this method of levels is much more time consuming than the method of limits.

Cortical Metrics is our research group's modification to the previous standards of QST. Cortical Metrics assessments are by nature a form of vibrotactile and touch QST. As with QST, techniques are non-invasive and non-painful and use tactile stimulation to rapidly detect and quantify minute changes in cortical information processing capacity (Holden et al., 2012). Furthermore, the stimulators are reusable, portable, and simple to use, making Cortical Metric technology cost-effective as well as efficient. While the assessments themselves are simple to administer, the sensory measurements calculated from the Cortical Metric testing maintain a high resolution for quantifying cortical function. The primary differences between Cortical Metrics and QST are with the individual assessments. As a reminder, QST typically measures sensory detection thresholds, pain tolerance thresholds, or sensation estimates. Although Cortical Metrics does measure an individual's ability to detect the presence of a stimulus (detection threshold); however, our sensory assessments takes QST to a whole new level with new techniques that have been developed to measure a person's ability to quickly respond (reaction time), undergo adaptation, determine stimulus placement (spatial localization),

distinguish stimulus differences (amplitude or frequency discrimination thresholds), and determine temporal order of stimuli (temporal order judgment) (Folger et al., 2008; Francisco et al., 2008; Holden et al., 2012; Nguyen et al., 2013a, b; Tannan et al. 2005, 2006, 2007a, b, 2008; Tommerdahl et al., 2007a, b, 2008; Zhang et al., 2008, 2009; 2011a, b).

Previous literature has used these particular metrics to measure changes in CNS functionality. For instance, studies demonstrate that while people have higher detection thresholds and slower reaction times with increasing age, their discrimination thresholds and ability to experience adaptation remains unaffected (Zhang 2011a). Extensive studies on autism have revealed that subjects with autism, when compared to healthy controls, exhibit reduced adaptation effects most likely due to their below average levels of GABAergic inhibitory neurotransmission (Francisco et al., 2012; Tannan et al., 2008; Tommerdahl et al., 2007a, 2008). Other differences in CNS processing such as those which arise from injury (chronic pain, concussion) and substance use (alcohol, NMDA antagonist, dopamine) have been measured by applying cortical metrics (Folger et al., 2008; Nelson et al., 2012; Nguyen et al., 2013a, b; Zhang et al., 2009, 2011a, b).

As with standard QST, a two-alternative forced choice (2AFC) paradigm is used to track subject performance for each of the Cortical Metric sensory assessments. One test in particular, amplitude discrimination, measures the minimal amplitude difference between two mechanical sinusoidal vibratory stimuli from which an individual can successfully identify the stimulus that is stronger in magnitude. With the 2AFC adaptive tracking method, the difference between the amplitudes of the test and standard stimuli are adjusted on the basis of the previous response. Correct responses resulted in

decreasing the test amplitude while incorrect responses resulted in increasing the test amplitude on subsequent trials. Similar to typical QST, during the first ten trials tracking is conducted with a bias of one (one correct answer tracks decreases amplitude, one incorrect answer decreases amplitude) in order to rapidly track down to a discriminative threshold. However, for our Cortical Metric assessments the remaining ten trials implement a bias of two where subjects are required to provide two consecutive correct responses for the test amplitude to decrease. This change in bias increases the accuracy of the results of the run by decreasing the probability of guessing (Tannan et al., 2006). Each run typically consists of twenty trials in which subjects are able to track down to the smallest test amplitude that they can consistently differentiate from the standard amplitude: the amplitude discrimination threshold (difference limen; DL) (Francisco et al., 2008; Tannan et al., 2007b).

Besides providing these slight variations to the standard QST to enhance the typical tracking procedures, Cortical Metrics has provided improved ways for data analysis. The current reviews for QST are most critical of the objectivity involved with the assessments (Chong and Cros, 2004; Gruener and Dyck, 1994; Moloney et al., 2012; Shy et al., 2003; Yarnitsky and Pud, 2004; Zaslansky and Yarnitsky, 1998). Environmental factors such as lighting, ambient temperature, noise, and other potential distractions could potentially skew the test results. Methodological factors such as test instructions, test protocols, test protocol order, and stimulus conditions could also influence assessment measures. The subjects may also be uncooperative, lack the necessary attention, or become fatigued if testing sessions are lengthy. However, so long as each subject performs the full series of necessary assessments during one short

experimental period, our ability to normalize the data on a subject by subject basis decreases the likelihood of these often unavoidable factors impacting the sensory test results (Nguyen et al., 2013a, b; Tannan et al., 2005; Tommerdahl et al., 2007a, 2008; Zhang et al., 2011b).

The initial analysis for the Cortical Metric sensory assessments is similar to general QST protocol for calculating sensory thresholds and pain tolerance levels. First the discriminative thresholds (DLs) from the sensory test were calculated for each subject by averaging the amplitudes of the last five trials recorded in the tasks. In an exemplary amplitude discrimination test, the standard amplitude is subtracted from the mean of the last five trials to give the subjects DL. For example, Cortical Metric testing takes the analysis one step further than standard QST calculations by comparing the performance to various sensory tasks on a subject by subject basis. Consider the bilateral study where an equivalent amplitude discrimination assessment had been conducted on the same subjects with additional unattended stimulation on the subjects' opposing hand. The results of the amplitude discrimination procedure in the absence of additional stimulation (DL_{single}) could then be used as a baseline to normalize the discrimination thresholds in the presence of additional stimulation (DL_{double}) (Equation 6.1).

Equation 6.1

$$\text{Normalized Amplitude Discrimination (\%)} = (DL_{double}) / (DL_{single})$$

The ratios of the DLs could then be calculated for each subject and the average of these DL ratios across subjects would show the effect of unattended hand stimulation (in comparison to the baseline single hand condition) on a subject by subject basis. So long

as the sensory assessment methods remain unchanged, the possibly unavoidable differences in environmental factors between test subjects may be partially canceled out by determining these DL ratios on a subject by subject basis.

As with most QST, Cortical Metric testing is simple, rapid, non-invasive, and non-painful. However, Cortical Metrics is a form of vibration and touch QST that goes beyond the typical assessments of sensory thresholds by providing new tests for quantifying tactile perception. The methods and analysis for the Cortical Metric sensory assessments have also been improved from the standard QST procedures in order to further enhance the quality of the quantified sensory measures. In addition to these mentioned improvements from the previous characteristics of typical QST, the Cortical Metric assessments maintain the cost-effective and efficient nature that is definitive of QST since the stimulators are reusable, portable, and simple to use. As a result, Cortical Metrics has the potential to be utilized as a valuable tool for diagnosing neurological disorders in a clinical environment.

6.2 Representation of vibration in the primary somatosensory cortex in relation to perception

Studies from previous literature have already conducted widespread research on how neurons within each stage of the somatosensory pathway, from peripheral afferents to primary somatosensory cortical neurons, respond to and encode various properties of vibrotactile stimuli such as skin location, amplitude, and frequency (Mountcastle et al., 1993; for a review: Mountcastle, 2005). The location of the stimulus on the skin is reflected in the location of the stimulus-evoked activity in the somatotopic map of SI (refer to Killackey, 1995; and Parpia, 2011 for reviews). Most areas of the body localize

their response to external stimuli at a specific region in the primary somatosensory cortex. For instance, applying stimulation to the fingertips of a primate is known to activate area 3b of SI (Chen et al., 2005; Nelson et al., 1980; Sur et al., 1982; Tuunanen et al., 2003; Whitsel et al., 2001; Zhang et al., 2007). Stimulus amplitude, however, is not represented in the same manner as stimulus location. Instead, stimulus amplitude is reflected through the mean firing rate (MFR) of the responding SI neurons (Mountcastle et al., 1969). In other words, stimulus location determines where activity is evoked in the cortex while stimulus amplitude regulates the strength of this activity. Similarly to stimulus amplitude, stimulus frequency is partially represented in the MFR of neurons responding in SI (Romo et al., 1998; Luna et al., 2005; Salinas et al., 2000). The MFR of the cortical response grows linearly with an increase in stimulus frequency until reaching a maximum at approximately 25 Hz. At stimulus frequencies above 25 Hz, the MFR becomes frequency-invariant (Whitsel et al., 2001). Instead of being dependent on MFR at these higher frequencies, stimulus frequency is primarily reflected by the phase-locking of responding cortical neurons to the frequency of the stimulus (Ahissar and Arieli, 2001; Ferrington and Rowe 1980; Hummel and Gerloff , 2006; LaMotte and Mountcastle, 1975; Mountcastle et al., 1969, 1990; Panzeri et al., 2003; Recanzone et al., 1992; Romo et al., 2003; Whitsel et al., 2001). Over time, the neuronal response approaches a similar frequency as that of the applied stimulus. In other words, the periodicity of SI neuron firing becomes a direct representation of the periodicity of the stimulus (Eytan and Marom, 2006; Khatri et al., 2009).

Unfortunately, previous literature has not been able to explore these coding mechanisms in the depth we hope to acquire. The perceived intensity of a vibrotactile

stimulus was found to generally increase with stimulus amplitude or frequency (Hollins and Roy, 1996). Thus, attempting to analyze each mechanism separately with human studies was rather difficult. Since intensity is a factor of frequency and amplitude, it is relatively simple for a subject to confuse frequency difference with intensity difference (Dunlap, 1911). In hopes of eliminating intensity cues during the frequency discrimination assessment, researchers developed procedures of intensity matching (Gerdjikov et al., 2010; Gescheider and Joelson, 1983; Gesheider et al., 1994; Goble and Hollins, 1994; Goff, 1967; LaMotte and Mountcastle, 1975; Mountcastle et al., 1990). Prior to performing frequency discrimination, these researchers requested that subjects match various stimuli to a standard based on their subjective intensities.

Following research efforts to remove intensity cues, studies later indicated that a subject's perceived vibrotactile frequency has an inconsistent dependency on stimulus frequency and amplitude across subjects (Morley and Rowe 1990, Roy and Hollins, 1998). This led us to believe that intensity matching prior to a frequency discriminatory assessment may not be necessary. What if we instead requested subjects to indicate which stimulus had the higher frequency in a tactile sensory assessment that only varied in frequency? Now imagine we maintain equal stimulus amplitudes (50 μm) for one frequency discriminatory task and then conduct the same frequency discrimination assessment at a different stimulus amplitude (200 μm). Our findings indicate that this measure of frequency discrimination capacity (for frequencies below and above 25 Hz improves with greater stimulus amplitudes. Interestingly, comparing a similar measure of amplitude discrimination (based on amplitude difference) at frequencies of 10 Hz, 20Hz, 30Hz, and 40 Hz resulted in a significant difference in amplitude discrimination capacity

below 25 Hz but minimal difference above 25 Hz. These results suggest that our tactile sensory assessments provide valuable evidence supporting previous literature without attempting to match our stimulation in intensity.

However, what mechanisms can elicit such improvements in frequency discrimination at higher amplitudes? In a previous study that investigated the SI response to different amplitudes of vibrotactile stimulation (at the same 25 Hz frequency as this study) utilizing the technique of optical intrinsic signal (OIS) imaging in non-human primates, Simons et al. (2005) reported that an increase in the amplitude of the stimulus corresponded with the increase in absorbance evoked within the responding region of SI cortex. The relationship between the maximal change in absorbance and stimulus amplitude was characterized by a near-linear function within the range of amplitudes studied (50-400 μm). On the other hand, measurement of the spatial extent of the activated SI region showed that higher amplitudes of stimulation did not produce a more extensive region of SI activation. Instead, as the amplitude was increased, average peak absorbance within an ~2 mm diameter SI region increased with the amplitude of stimulation while the region of surrounding cortex underwent a prominent decrease in absorbance (often to levels well below background). In other words, an increase in contrast of neural activity in SI occurs with increasing stimulus amplitude.

This enhancement of cortical contrast at higher stimulus amplitudes may be the mechanism behind improved frequency discrimination at higher amplitudes. Furthermore, since both MFR and contrast increase with stronger amplitudes (Mountcastle et al., 1969; Simons et al. 2005, 2007), a greater MFR among centrally locating responding excitatory cortical neurons may correspond with the enhanced

frequency discrimination capacity demonstrated at the higher amplitudes. In other words, a prominent dependency of amplitude coding on MFR could be why amplitude can have such a strong influence on tactile perception. On the other hand, increasing stimulus frequency from 25 Hz and above did not improve tactile perception since an increase in central MFR may be weak or nonexistent. Although frequency is partially represented by MFR, at least up to 25 Hz, frequency is primarily coded by periodicity (Ahissar and Arieli, 2001; Ferrington and Rowe 1980; Hummel and Gerloff , 2006; LaMotte and Mountcastle, 1975; Mountcastle et al., 1969, 1990; Panzeri et al., 2003; Recanzone et al., 1992; Romo et al., 2003; Whitsel et al., 2001). Thus, since MFR is not as crucial for frequency coding (especially above 25 Hz), it is not necessary to elicit an intense MFR increase from slight increases in stimulus frequency. However, this reduced dependency on MFR also suggests that cortical contrast also remains rather unaffected by a frequency difference. In other words, increasing stimulus frequency does not increase contrast within the responding region of cortex and intensity perception is not improved. Our human perceptual studies and neurological evidence are in full support of these theories.

Our human studies are unique from previous work in multiple ways; primarily, we chose not to do intensity matching. We realized that rating a subject's performance on frequency discrimination at different equal amplitude conditions and similarly evaluating amplitude discrimination capacity at various equal frequencies are valuable assessments that should no longer be overlooked. Now we have a general understanding of how a vibrotactile stimulus is directly represented in SI, and we have suggested that increasing MFR enhances the contrast between neighboring cortical ensembles. Are there other possible mechanisms in which the cortex can further refine and clarify this contrast and

enhance perceptual performance? Is it possible for cortical interactions to instead reduce perceptual performance by a reduction in cortical contrast?

Previous literature on cortical activity evoked by contralateral stimulation demonstrates that the response in SI has an excitatory nature can maintain strong in magnitude for the full duration of 25 Hz stimulation (Tommerdahl et al., 1999a, b). SI activity evoked by conditions of contralateral, ipsilateral and bilateral stimulation show that the magnitude of response in SI evoked by 25 Hz contralateral stimulation is reduced in the presence of an ipsilateral stimulus (Tommerdahl et al., 2005a, b, 2006). Such reductions in SI cortical activity with bilateral versus contralateral stimulation could lead to a reduction of cortical contrast and account for the reductions in tactile sensory perception that occurs. Between two studies with similar 25 Hz stimulus conditions, SI cortical activity evoked by bilateral stimulation was approximately 30% below the activity evoked in the contralateral condition (Tommerdahl et al., 2005a, b; 2006) and spatial acuity displayed an approximately equal reduction between bilateral and contralateral conditions (Tannan et al., 2005). Our results similarly show reductions of perceptual performance in an amplitude discriminatory assessment where 25 Hz is applied to the ipsilateral hand while amplitude discrimination is tested on the contralateral hand. Decreasing the overall activity in SI appears to decrease the overall contrast between centrally excitatory and laterally inhibitory responding regions of SI activation and lead to a diminished amplitude discrimination capacity. Potentially due to the same mechanism of contrast, spatial acuity (Tannan et al., 2005a), threshold detection (Levin and Benton, 1973), stimulus localization (Braun et al., 2005), and frequency

discrimination (Harris et al., 2001) have also been reported to be reduced with the introduction of a stimulus on the opposite side of the body.

Inhibitory and excitatory cortical circuits work together to form balanced networks of activity (for a recent review: Zhang and Sun, 2011). In fact, numerous neurological disorders arise from abnormalities in cortical networkability (Horwitz and Horovitz, 2012; for a review Rowe, 2010). However, changes in the individual circuits can cause lesser shifts in network balance (Heiss et al., 2008; Hull et al., 2009; Klingner et al., 2011). Would it be possible for the nature of the cortical network to shift from inhibitory to excitatory based on context of the tactile input? There is already potential evidence of this in the ipsilateral condition. Although there are some indications ipsilateral input eliciting an excitatory cortical response in previous literature (Zhu et al., 2007; Nihashi et al., 2005), there are also implications of ipsilateral input evoking an inhibitory response (Hlushchuk and Hari, 2006; Lipton et al., 2006). While the effect of contralateral stimulation was found to be reduced in the presence of an ipsilateral stimulus (Tommerdahl et al., 2005a; 2006), the past bilateral studies are limited in number and the possibility of an ipsilateral stimulus producing an excitatory response is still a possibility. These ideas can later be tested directly via *in vivo* animal studies, similar to those we have conducted previously that investigate bilateral interactions in SI cortex (Tommerdahl et al, 2006). Interestingly, our results from the bilateral human sensory testing suggest inhibition occurs when equal amplitude ipsilateral stimuli are applied to the unattended hand during contralateral sensory assessments while excitation occurs when the ipsilateral stimuli are unequal in amplitude.

To summarize, flutter representation in SI is refined when contrast is increased among neighboring neurons within the responding region of cortex. Previous OIS imaging demonstrated that an increase in absorbance was evoked within the responding region of SI cortex for stronger stimulus amplitudes (Simons et al. 2005, 2007), and we hypothesized that this leads to enhanced cortical contrast and improved tactile perception. However, another way to explain this sharpening and enhancement of centrally located excitatory neurons is with local synchronization. Essentially this enhancement of contrast could compliment local synchronization. Our findings indicate an increase in contrast between central and marginal responding cortical neurons over the duration of a continuous vibrotactile stimulus, increased synchronization between centrally located excitatory neurons with longer duration stimuli, as well as an increased amplitude discrimination capacity at longer stimulus durations. Thus, our work supports the hypothesis that tactile perception is enhanced when the contrast among a population of neighboring neurons and synchronization among the centrally located excitatory neurons is increased. Further complementing our hypothesis of greater amplitudes enhancing cortical contrast, our results demonstrate that stronger stimulus amplitudes enhance synchronization among neighboring cortical ensembles. One possibility is that the enhancement of local synchronization is actually a form of enhanced cortical contrast. Perhaps our previously discussed sharpening and enhancement of cortical activity from increased spatial contrast also corresponds with an increased temporal contrast. In other words, what we know as local synchronization, a temporal sharpening and enhancement of the responding region of cortex, could actually be a mechanism of temporal contrast.

6.3 Role of synchronization in information processing

The mechanisms with which the cortex processes information are diverse, partly because of the abundant sources of sensory information the central nervous system (CNS) receives. The CNS, composed of the brain and spinal cord, coordinates activity for all parts of the human body. The CNS integrates and processes the information it receives and then translates that knowledge into action. Due to the extensive role the CNS plays in our everyday life, disorders of the CNS by disease, medication, or trauma can affect an individual in many different ways. Neurological impairments may affect an individual's mental abilities of understanding, retaining, or communicating information or an individual's physical abilities like motor skills. Two common examples of neurological impairment are autism and cerebral palsy. While autism is characterized by impaired communication and social interaction skills, cerebral palsy affects motor control. Although the symptoms are different, both are acquired from damage to the CNS.

The brain coordinates activity among a large number of neurons, both within and across various specialized brain regions. Since sensory information from visual, audio, and somatosensory cortices is constantly integrated as we attempt to comprehend and interact with our surroundings, this integration and processing of multiple sensory inputs into networks of cortical activity is necessary for normal daily functionality. Now we ask what mechanisms facilitate the proper integration and processing for these networks of cortical information. One mechanism in particular has been widely accepted as crucial for successful the integration of cortical information: synchronization (refer to Uhlhaas and Singer, 2006; Uhlhaas et al., 2009 for reviews). Synchronization occurs when neurons in the cortex become engaged in coordinated activity.

Just as numerous neurological disorders arise from abnormalities in cortical networkability (Horwitz and Horovitz, 2012; refer to Rowe, 2010 for a review), a similar variety of neurological impairments are also observed with abnormal neuronal synchronization (refer to Lestienne, 1999; Uhlhaas and Singer 2006; Uhlhaas et al., 2009 for reviews). This ability of neurons to form both local and distant cortical networks is influenced by many of the same factors which effect synchronized neuronal oscillations (Isaacson, 2011, Kremkow et al., 2010a, b; Okun and Lampl, 2008). Naturally, similar neurological disorders should occur if the mechanisms are closely related. One theory believes synchronization could serve as a potential mechanism for generating functionally coherent ensembles from broad distributions of neural activity (Review Singer 1999). Although only a few studies have attempted to directly measure local synchronization, previous literature does indicate that synchrony can develop among neighboring populations of cortical neurons (Hummel and Gerloff , 2006; Whitsel et al., 2001; Zygierewicz et al., 1998). Evidence also suggests synchronous oscillations do have the ability to temporally bind spatially distributed intracortical information (Buzsáki and Draguhn, 2004; Engel and Singer, 2001; Engel et al., 2012; Hummel and Gerloff , 2006; Senkowski et al., 2008; Tallon-Baudry and Bertrand, 1999). The latest research indicates that this temporal binding may even occur across separate cortical areas (Hagiwara et al., 2010). To summarize, synchronization is necessary due to its ability to integrate information among and across both local and distributed cortical networks. This information had prompted us to re-evaluate previous literature and to attempt to observe how synchronization develops in SI.

Initially we needed to determine which type of synchronization we wanted to analyze. There are two separate categories of stimulus-related oscillatory activity that can develop into synchronization: evoked or induced oscillations (Tallon-Baudry and Bertrand, 1999). Evoked synchronization occurs when the cortical response is phase-locked to the onset of the external stimulus. Induced synchronization develops when an external stimulus engages a cognitive process which has its own self-regulated pace of oscillations. While both evoked and induced oscillations are important for proper CNS functionality, there is a specific advantage to analyzing evoked synchronization (Uhlhaas and Singer, 2006). Analysis of induced oscillations is more complex since the frequencies of oscillation are not phase-locked to the external stimulus. A small change in one stimulus parameter could make changes to every characteristic of the induced oscillation: frequency, magnitude, shape, or phase. Instead, vibrotactile stimulation can be used to evoke oscillations and keep analysis rather simple. Slightly altering one stimulus parameter could change the phase, magnitude or shape of the oscillation; however, the frequency of oscillation would correspond with the external stimulus. For these reasons, our study uses evoked oscillations to study the dynamics of synchronization.

Although evoked neuronal synchronization can be produced by several other means, there are innate benefits of using vibrotactile stimulation as a driving force for these oscillations. A vibrotactile stimulus is complex in that it has both spatial and time characteristics; however, the evoked temporal patterns in the cortical response allow calculations to remain relatively straightforward (Talbot et al., 1968). This simplicity allows us to observe the effects of manipulating several individual parameters like stimulus amplitude, frequency, or duration and still be able to interpret our findings with

a rather uncomplicated analysis. Additionally, the natural ability of external vibrotactile stimuli to quickly evoke a phase-locking response allows us to directly observe the entire evolution of synchronization. Cortical neurons near and far begin to oscillate together shortly after onset of a vibrotactile stimulus and this synchronization slowly degenerates upon stimulus offset.

To reiterate, by evoking neuronal oscillations through vibrotactile stimulation, synchronization can develop both locally among a neighboring population of responding cortical neurons (Hummel and Gerloff , 2006; Whitsel et al., 2001; Zygierewicz et al., 1998) and globally across broadly distributions cortical networks (Engel and Singer, 2001; Engel et al., 2012; Senkowski et al., 2008; Tallon-Baudry and Bertrand, 1999; Buzsáki and Draguhn, 2004) compelling the integration and processing of cortical information. Interestingly, synchronization may also serve another purpose. While simultaneously integrating and processing, synchronization appears to enhance and clarify this cortical information.

Our results indicate that synchronization, evoked by vibrotactile stimulation, allows a neighboring population of cortical neurons to sharpen and increase their peaks of activity. In other words, as the phase difference between responding neurons decreases and the spike activity of a neighboring population of cortical neurons begins to fire more closely together, the contrast of the cortical response becomes more prominent as well. Hence, synchronization may be one mechanism for enhancing temporal contrast. Combining previous optical intrinsic signal (OIS) imaging research of spatial contrast to human perceptual studies suggests that tactile perception is enhanced with greater spatial contrast. As the amplitude of the applied stimulus increases, the contrast between

centrally responding excitatory and laterally inhibitory neurons increases (Simons et al. 2005, 2007). Our current research indicates that an improvement in subject frequency discrimination capacity also corresponds with a stimulus amplitude increase. Hence, increasing spatial contrast can enhance tactile perception. Similarly to enhancing spatial contrast, local synchronization may improve tactile perception by increasing temporal contrast.

Furthermore, the results of our animal research also support the hypothesis that synchronization can occur among spatially distinct cortical regions. Interestingly, cortical measures of temporal order judgment were reduced with stronger amplitudes of preconditioning stimulation implicating that increased synchronization beyond the individual locally responding cortical regions can make it more difficult to distinguish differences between the two stimuli. Perhaps also due to a rather spatially distinct form of synchronization developing between the initially separate responding regions, performance on the amplitude discrimination assessments at extended stimulus durations did not improve despite enhance spatial contrast and local synchronization (temporal contrast). Furthermore, the results of the bilateral studies are highly indicative that communication across cortical hemispheres can either improve or reduce tactile capabilities depending on the context of stimulation (equal amplitude, unequal amplitude) on the unattended hand. Overall, synchronization's primary role in the central nervous system may be its ability to generate and integrate both local and global networks with coordinated cortical activity as well as to enhance and clarify the information that is being processed.

6.4 Overall conclusions

The results of this research in combination with reports from related literature provide suggestive evidence that contrast is a crucial mechanism for processing cortical information and improving human tactile perception. Optic intrinsic signal (OIS) imaging studies (Simons et al., 2005, 2007) demonstrate an enhancement of spatial contrast with increased amplitudes and extended durations of a sinusoidal vibrotactile stimulus. Under similar conditions, our electrophysiological research in cats and non-human primates also indicate an increase in temporal contrast with stronger amplitudes and longer stimulus durations. Furthermore, extended stimulus durations were found to enhance spatial contrast for a neighboring population of SI neurons over time. Our human perceptual studies suggest that this increase in contrast (spatial or temporal) generally clarifies tactile perception and leads to improved tactile sensory capabilities when attempting to compare the amplitude or frequency differences between two stimulus conditions. Additionally, this research has determined the opposite situation in which lowering cortical contrast with inhibitory effects from equal amplitude ipsilateral stimulation has reduced amplitude discrimination capacity.

Our findings also indicate that synchronization can be made on either local scale (between neighboring cortical ensembles) or on a more global scale (across cortical hemispheres). Specifically, the data representing synchronization on a global scale provides an explanation for instances when synchronization is not beneficial to particular tactile perceptual tasks. As indicated in the amplitude discrimination assessment at extended stimulus durations or temporal order judgment assessment with conditioning vibrotactile stimulation, despite enhanced cortical contrast, by causing two cortical areas

to respond similarly, synchronization among spatially separate cortical regions can diminish tactile capabilities.

Most importantly, this research bridges the gap between neurophysiology and tactile perception. While previous studies have utilized the same tactile sensory tests and determined variability in tactile processing capabilities among a series of neurological disorders (Folger et al., 2008; Francisco et al., 2012; Nelson et al., 2012; Nguyen et al., 2013a, b; Tannan et al., 2008; Tommerdahl et al., 2007a, b, 2008; Zhang et al., 2009, 2011a, b), with this research clinicians now have a neurological basis to describe the cortical differences among these diverse focus groups.

6.5 Future research

Although our current electrophysiological findings have been promising, the results are not strong enough to be certain that cortical contrast is indeed a primary mechanism for enhancing cortical information. OIS imaging has alluded to enhanced spatial contrast over time, but imaging techniques with a higher spatial resolution or greater depth would better demonstrate the evolution of spatial contrast with extended stimulus durations. Additionally, even though longer stimulus durations and stronger amplitudes have been linked with increased contrast and enhanced tactile sensory performance, a direct link between greater cortical contrast and improved perceptual performance has not been established. In response to our findings, we would like to propose two aims for future research: 1) to observe the simultaneous development of spatial and temporal contrast during the course of vibrotactile stimulation, and 2) to directly observe this enhanced contrast improving human perception. Our primary areas

of interest involve further electrophysiological research, 2-photon imaging, and optogenetics in awake and trained non-human primates.

Our first interest for future work involves electrophysiology in awake and trained non-human primates. The previous microelectrode recordings were done in anesthetized cats and primates. The results had great implications for cortical contrast; however, cortical contrast was never monitored while an animal was actually performing a tactile assessment. An improved means for analyzing cortical contrast would be to train non-human primates to perform a series of the same tactile assessments that had been used in the corresponding human studies. For instance, our human studies indicated improved amplitude discrimination capacity with longer stimulus durations, with the reasoning being that increased temporal contrast (synchronization) at the longer stimulus durations elicited improved tactile perceptual performance. Imagine if a monkey were trained to perform the amplitude discrimination assessment at two durations of stimulation. We could quantify improvement in tactile sensory assessment and compare it to any corresponding increases in spatial and temporal contrast which may have taken place during the course of this sensory task. Unfortunately these methods would be time consuming and challenging since it could be difficult to train a non-human primate in performing tactile assessments; however, the training is possible and it could lead to direct evidence supporting how cortical contrast can enhance tactile perception.

Another method we would like to utilize involves two-photon microscopy (Denk et al., 1990). Unlike OIS imaging which captures an image of the exposed cortex, two-photon microscopy allows very high resolution up to depths of 600 μm. (For a review on optical brain imaging refer to Hillman, 2007). In other words, this method of imaging

would allow us to observe the evolution of spatial contrast with high-resolution across a series of depths. This procedure would be much improved over electrophysiology. Microelectrode placement itself is rather crude and, although minimal, the microelectrodes do cause damage as they pass through SI and multiple penetrations at a broad range of depths into SI must be recorded for a thorough observation of even minute cortical regions. There have been numerous previous reports where two-photon microscopy has been successfully used to study the behavior of neuronal networks (refer to Garaschuk et al., 2006 for a review). As with the electrophysiological studies, a stronger understanding of cortical contrast would result from imaging in an awake monkey that has been well trained in performing the tactile assessments. However, despite this difficulty, the ability to measure enhancement of spatial and temporal contrast at multiple depths while simultaneously quantifying increases in tactile perception would greatly improve our knowledge of the role of contrast in cortical perception.

Optogenetics is known for its high spatial and millisecond scale temporal resolutions (for a recent review, refer to Fenno et al., 2012 or Mei and Zhang, 2012). In comparison to OIS imaging, optogenetics has a much higher spatial and temporal resolution and should therefore provide a sharper understanding of cortical contrast. Furthermore, if we can target specific neurons and use light pulses to control cortical activity, we could attempt to induce cortical contrast and should be able to repeatedly observe the dynamics of this contrast enhancement over a wide population of cortical neurons as well as confirm if the increased cortical contrast does improve tactile perceptual performance (for a review on behavioral optogenetics: Bernstein and Boyden,

2012 or Kravitz and Kreitzer, 2011). As explained previously, this could be done with electrophysiology. Although it is possible to observe the activity of a responding population of neighboring cortical neurons by electrophysiological means, as stated before, the task is not a simple one. Ideally as with the electrophysiological analysis, awake and trained non-human primates would perform a variety of tactile sensory assessments as their changes in cortical contrast are monitored. While conditioning vibrotactile stimulation would be necessary to observe the effects of a preconditioned cortical contrast on tactile performance for electrophysiology or two-photon imaging, with optogenetics this cortical contrast can be controlled more precisely and perhaps produced more strongly with light. Perhaps the most important reason for using optogenetics is the potential of inducing tactile sensory impairment by a controlled reduction of cortical contrast. This should be observed more simply in optogenetics while it would be potentially very difficult with electrophysiology. In doing so, we could find supporting evidence that enhanced cortical contrast is not simply an epiphenomenon that just happens to frequently occur with improved tactile perception, but instead facilitates the clarification of sensory information in the somatosensory cortex. Similar experiments have already been conducted utilizing optogenetics as a tool for understanding the interaction among oscillations among cortical networks of activity (Piña-Crespo et al., 2012; Sohal et al., 2009). In 2012, Tiesinga published a review on current motifs in health and disease which greatly promoted optogenetics and its "promise of circuit interrogation" (Tiesinga, 2012). Unfortunately, the current literature is limited and attempts to use optogenetics to observe cortical contrast on a spatial and temporal scale has not yet been conducted. Although there has been recent success in studying non-

human primates (Chen et al., 2012; Han, 2012), much of the optogenetics research thus far has been conducted on rodents. Few non-human primate experiments have modulated local cortical activity (Diester et al., 2011; Han et al., 2009) and even fewer have observed the behavioral implications (Gerits et al., 2012; Cavanaugh et al., 2012). It appears that no optogenetics research has yet been conducted in the somatosensory cortex of non-human primates. Thus, one challenge to utilizing optogenetics is that optogenetics is still on the horizon. We may have to overcome unforeseen difficulties and learn as we go.

To reiterate, we believe the results of this research can serve as preliminary data for three areas of interest in future research. Our goal is to use electrophysiology, 2-photon imaging, and optogenetics of trained non-human primates, for the purpose of answering these two primary questions: 1) produce supporting evidence for the simultaneous development of spatial and temporal contrast over time, and 2) produce supporting evidence that this contrast developing over time does improve tactile sensory performance. Our procedures for assessing human tactile sensory perception have revealed differences in cortical processing that arise from injury (chronic pain, concussion), substance use (alcohol, NMDA antagonist, dopamine), and neurological disorders (autism) (Folger et al., 2008; Francisco et al., 2012; Nelson et al., 2012; Nguyen et al., 2013a, b; Tannan et al., 2008; Tommerdahl et al., 2007a, b, 2008; Zhang et al., 2009, 2011a, b). Perhaps all of these differences are due to modifications in the ability of the cortex to augment contrast. If we can further support that cortical contrast is a crucial mechanism for human sensory perception, we will obtain a much better understanding of the implications for when contrast in cortical information processing becomes impaired.

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