CORTICAL DIAGNOSTICS: MEASURING BRAIN HEALTH THROUGH SOMATOSENSATION

Eric Francisco

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the School of Medicine (Biomedical Engineering)

Chapel Hill
2014

Approved by:

Mark Tommerdahl

Robert Dennis

Oleg Favorov

Richard Gracely

Jameson Holden

ABSTRACT

Eric Francisco: Cortical Diagnostics: Measuring Brain Health through Somatosensation
(Under the direction of Mark A Tommerdahl)

Overall the past several years, a number of unique quantitative tactile based sensory testing methods were designed with the intent of obtaining objective metrics that would be sensitive to alterations in cortical information processing. The design of these tasks was based on information obtained from neurophysiological studies of the nonhuman primate (NHP) cerebral sensory cortical response to a variety of modes of natural skin stimulation, and these NHP studies typically exhibit characteristics of cortical modularity, or cortical-cortical dynamics that occur between adjacent and near-adjacent assemblies of cortical neurons. The initial goal of these studies was to demonstrate cortical correlates of perception by comparing observations of stimulus evoked activity in primary somatosensory cortex of non-human primates, and a secondary goal was to demonstrate that these measures of sensory perception were altered in a predictable fashion with neurological insult. To date, observations consistent with systemic cortical alterations have been made in individuals with neurotrauma (concussion/ TBI, stroke), neurodevelopmental disorders (Autism, ADHD, Tourette's, OCD) and chronic pain (migraine, fibromyalgia, VVS, TMJD, carpal tunnel syndrome). One unifying theme of these findings is the role that cortical modularity plays in sensory information processing and that when cortical modularity is disrupted, significant quantifiable deficits in sensory information processing can be detected.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF ABBREVIATIONS

2AFC	Two-alternative forced choice
4AFC	Four-alternative forced choice
ABS	Acrylonitrile butadiene styrene
ADHD	Attention deficit and hyperactivity disorder
ADI-R	Autism diagnostic interview - revised
ADOS-G	Autism diagnostic observation schedule - generic
ANOVA	Analysis of variance
ASD	Autism spectrum disorder
CNC	Computer numeric control
CNS	Central nervous system
DAQ	Data aquistion
DL	Difference limen
EEG	Electroencephalography
FDM	Fused deposition modeling
fMRI	Functional magnetic resonance imaging
GAD	Glutamic acid decarboxylase
GABA	γ-Aminobutyric acid
MEG	Magnetoencephalography
msec	milliseconds
mTBI	Mild traumatic brain injury
NMDA	N-methyl-D-aspartate

NMDAR	N-methyl-D-aspartate receptor
NHP	Non human primate
OCD	Obsessive compulsive disorder
OIS	Optical intrinsic signal
PC	Personal computer
PCA	Principal component analysis
RF	Receptive field
RMS	Root mean squared
SI	Primary somatosensory cortex
SD	Standard deviation
SCAT-2	Sports concussion assessment tool-2
SE	Standard error
TBI	Traumatic brain injury
TD	Typically developing
TDT	Temporal discriminative threshold
TMJD	Temporomandibular joint disorder
TOJ	Temporal Order Judgment
VCA	Voice coil actuator
VVS	Vulvar vestibulitis syndrome
WASI	Wechsler Abbreviated Scale of Intelligence
WF	Weber fraction
XAFC	X-alternative forced choice

INTRODUCTION

A large number of neurological disorders (developmental, degenerative, or trauma induced) are difficult to diagnose or assess, thus limiting treatment efficacy and overall understanding. Existing solutions and products attempting to fill this gap are costly, extremely slow, often invasive, and in many cases fail to definitively (and quantitatively) diagnose or assess treatment. The somatosensory system is ideally suited for the design of a CNS diagnostic system. First, the organization of the system is such that adjacent skin regions project to adjacent cortical regions (i.e., it is somatotopic). Second, ambient environmental noise in the system can be easily controlled (i.e., it is less likely that a patient will be exposed to distracting tactile input than auditory or visual input). Third, the somatosensory system is the only sensory system that is highly integrated with the pain system, and this is often an important aspect of a patient's diagnosis. The diagnostic system our lab has developed delivers a battery of somatosensory-based tests that are conducted rapidly, much like an eye exam with verbal feedback. Neuro-adaptation, functional connectivity (e.g., cortical synchronization), and feed-forward inhibition are just a few of the cortical mechanisms that can be quantified using somatosensory testing protocols. Many of these protocols leverage tactile illusions which act as confounds on top of a basic somatosensory test, allowing each subject to serve as his or her own control. Design and validation of the perceptual metrics is accomplished via correlative studies that compare non-invasive observations of human sensory percepts with non-human primate neurophysiological studies.

The majority of sensory testing in the last few decades has been performed using less than ideal machinery and most testing designs rely heavily on a classical understanding of psychophyics. My previous colleagues have devoted much of their work to outlining general

information on how the cortex responds to tactile stimuli, through electrode/OIS studies on animals; simple somatosensory testing that correlate well with the data provided from their imaging studies; and development/improvement of the portable vibrotactile stimulator used in the majority of our experiments. The goal of this dissertation is to show how somatosensory testing can be improved through novel testing methods that are targeted at providing new diagnostic information about how the cortex functions, in the typically developing and those with neurological deficits.

The first 2 chapters of this dissertation show the foundations of current somatosensory testing. The first chapter outlines the design and improvement of the vibrotactile stimulator we use to deliver vibrations to our subjects fingertips. This device is constantly evolving into a more portable, more user friendly, and more powerful diagnostic device. The technological advancements outlined in the first chapter allowed the new novel testing paradigms, seen in chapters 3, 4, &5, to be designed and executed. The second chapter explores amplitude discrimination and its compliance to Weber's Law in the tactile modality. This paper showcases a rather simple method of measuring a subjects discriminative capacity to different intensity stimuli and how data obtained from subjects correlate with classic psychophysical principles (Weber's Law) and animal data acquired under similar testing conditions.

CHAPTER 1: CM4: A FOUR-POINT VCA BASED VIBROTACTILE STIMULATOR[1]

Overview

Current methods for applying multi-site vibratory stimuli to the skin typically involve the use of multiple, individual vibrotactile stimulators. Limitations of such an arrangement include difficulty with both positioning the stimuli as well as ensuring that stimuli are delivered in a synchronized and deliberate manner. Previously, we reported a two-site tactile stimulator that was developed in order to solve these problems (Tannan et al., 2007a). Due to both the success of that novel stimulator and the limitations that were inherent in that device, we designed and fabricated a four-site stimulator that provides a number of advantages over the previous version. First, the device can stimulate four independent skin sites and is primarily designed for stimulating the digit tips. Second, the positioning of the probe tips has been re-designed to provide better ergonomic hand placement. Third, the device is much more portable than the previously reported stimulator. Fourth, the stimulator head has a much smaller footprint on the table or surface where it resides. To demonstrate the capacity of the device for delivering tactile stimulation at four independent sites, a finger agnosia protocol, in the presence and absence of conditioning stimuli, was conducted on seventeen healthy control subjects. The study demonstrated that with increasing amplitudes of vibrotactile conditioning stimuli concurrent with the agnosia test, inaccuracies of digit identification increased, particularly at digits D3 and D4. The results are consistent with prior studies (Tommerdahl et al. 2007) that implicated synchronization of adjacent and near-adjacent cortical ensembles with conditioning stimuli in impacting TOJ performance.

---

[1] This chapter previous appeared in the Journal of Neuroscience Methods. The original citation is as follows: Holden JK, Nguyen RH, Francisco EM, Zhang Z, Dennis RG, Tommerdahl M. “A novel device for the study of somatosensory information processing.” J Neurosci Methods, 2012 Mar 15;204(2):215-20. Epub 2011 Dec 4.

Introduction

For the past several years, our research group has been working towards the development of a portable tactile stimulator that could effectively be used to study changes in sensory information processing in clinical and clinical research venues across a diverse spectrum of neurological disorders. Thus far, we have gone through several iterations in the development of this stimulator. The first prototype of the device (Tannan et al., 2005a) was used to demonstrate changes in spatial acuity with repetitive stimulation. A subsequent report described that this change did not occur with individuals with autism, strongly suggesting a lower-than-normal inhibitory response (Tommerdahl et al., 2007a). A second iteration of the device (Tannan et al., 2007a) was much more portable as well as more robust and reliable in its ability to deliver well-controlled vibrotactile stimuli to the skin. The device proved extremely useful, and a number of studies were conducted with it that demonstrated the ability to reliably and reproducibly obtain metrics of neuroadaptation (Tannan et al., 2007b), temporal order judgment (TOJ) and the impact of synchronized conditioning stimuli on TOJ (Tommerdahl et al., 2007b), the absence of the impact of those same conditioning stimuli on TOJ in individuals with autism (Tommerdahl et al., 2008), the relationship between spatial acuity and amplitude discrimination (Zhang et al., 2008), a method for the study of tactile-thermal interactions (Zhang, 2009), a reliable means for measuring amplitude discriminative capacity and a robust near-linear relationship between duration of repetitive conditioning stimuli and the impact of that conditioning on amplitude discriminative capacity (Tannan et al., 2007b), the below-normal adaptation metrics in autism (Tommerdahl et al., 2007), the impact of NMDA receptor block on adaption metrics (Folger et al., 2008), a demonstration of Weber's law (Francisco et al., 2008; Holden et al., 2011) and a robust relationship with neurophysiological data (Francisco et al., 2008), and differences in timing perception in Parkinson's Disease (Nelson et al., 2011). More recently, we have developed a newer, more portable and ergonomic model of the device, which is much more suited for a clinical or clinical research environment, and is capable of delivering vibrotactile stimuli to four fingers: the index (D2), middle (D3), ring (D4), and little (D5) fingers.

The utility of this device has been recently reported in a paper that reported phenotypic differences within a spectrum of patients with vulvodynia (Zhang et al., 2011), and in a paper that describes its utility for describing phenotypic differences within the autism spectrum via modulating vibrotactile stimuli (i.e., sinusoidal stimuli that dynamically change in amplitude), but the device itself, as well as a demonstration of its capability to deliver four-digit protocols, has not been fully described, which is the purpose of this report. In a subsequent paper, a magnet-compatible version of this device will be reported.

Methods

Hardware

The Cortical Metrics (CM-4; see Figure 1.1) stimulator was developed in our laboratories for use in series of experiments such as those described in this report. The system was designed using state-of-the-art rapid manufacturing technology to allow multiple identical systems to be built and used in different locations. Also, the use of rapid manufacturing permitted very rapid design evolution, thereby potentiating the production of special fixtures and changes to geometry as needed for special applications. The device consists of two separate parts: the main body and a detachable head unit. The flat plates of all exterior housing and other components of approximately planar geometry are direct manufactured using laser-machined 6 mm acrylic sheet, cut on a 120 Watt CO_2 laser engraving system, model number X660 (Universal Laser Systems, Scottsdale, AZ). The more complex housing and internal mechanism components are direct manufactured from ABS plus, by fusion deposition modeling (FDM) on a StrataSys Dimension bst 1200es (StrataSys, Inc., Eden Prairie, MN). The cylindrical trays forming the disks of the head unit are CNC machined from 1" thick Acetal (Delrin) plate. All housing and mechanism components and assemblies were solid modeled prior to fabrication using SolidWorks solid modeling software (SolidWorks Corporation, Concord, MA).

The internal mechanism of the head unit is comprised of identical cylindrical disks placed sideways and four abreast (130 mm in diameter, 11 mm in depth) between two plastic supports. Each disk can be independently rotated to adjust for differing finger lengths for each

test subject. A voice coil actuator (VCA) and an optical position sensor are mounted in each disk. Each VCA is attached to a plastic probe (5 mm diameter) which slightly protrudes through a hole (7 mm diameter) in the side of the cylinder. The amount of protrusion for each probe is independently adjustable as are the positions of the holes to accommodate the length of the subject's fingers. The VCAs drive the plastic stimulator probe tips according to prescribed sinusoidal waveforms. The moving components of the stimulator tips are directly manufactured from Polycarbonate (PC) by 3-D FDM as a single compliant mechanism component integrating a mounting flange, a thin-beam four-bar linkage, a magnet coil bobbin, an optical displacement sensor vane, and the extension to the mechanical stimulator tip. The compliant four-bar linkage mechanism allows the coil, optical position sensor vane, and tip to be displaced vertically along a straight line for a distance of ±1 mm. The 4-bar compliant mechanism also provides a very low hysteresis linear restoring force to center each tip vertically when no current is applied to the VCA coil. The VCA coil is 400 turns of 34 AWG magnet wire (approximately 30 Ohms total resistance), wrapped in a rectangular bobbin permanently solvent bonded into the four-bar mechanism. The entire four-bar mechanism is 5.3 mm in thickness, and is positioned such that the VCA coils sit directly between two opposed rectangular N42 rare-earth-element magnets (catalog number BCC2, K & J Magnetics, Jamison, PA) similar to those found in computer hard drives. The resulting VCA motors generate extremely linear force outputs as a function of drive current with very low hysteresis due to the "frictionless" nature of the single-piece bearing-less four-bar compliant mechanism. The position of the vibrating tips is detected by non-contacting optical displacement sensors, one for each tip, similar in configuration to ones we have previously employed in precision optical force transducers (Dennis and Kosnik, 2002). When the tips are not being driven, the optical position sensors can act as a highly sensitive contact or force sensor. By employing the optical position sensor, the tips can be driven to contact the skin, and the contact force of each tip can be adjusted independently due to the fact that the spring constant of each VCA four-bar linkage mechanism is identical.

Figure 1.1: Four Site Vibrotactile Stimulator
Each of the four probe tips is positioned by rotating the four independently positioned drums to maximize contact between finger pads and the stimulator tips. During an experimental session, subjects were seated comfortably in a chair with their arm resting on the arm rest attached to the head unit of the device. Digits D2 through D5 were then positioned for vibrotactile stimulation.

The custom electronics were designed using free CAD software from ExpressPCB (www.expresspcb.com). The printed circuit boards were manufactured using the resulting CAD files, also by ExpressPCB. The hybrid circuit includes signal amplifiers for the position sensors, an analog controller to allow either “force” or “position” control of each VCA motor and tip, a tunable analog PID controller for position control of each tip, and a bipolar push-pull high-current op-amp output stage to drive each VCA motor. This hybrid circuit is interfaced via four parallel pin connectors (2 banks of 50 pins for digital signals and 2 banks of 34 pins for analog signals) to an internal NI-USB-6259 data acquisition (DAQ) board. The DAQ board then interfaces via a USB connection to any standard PC running Microsoft Windows XP or later.

Software

A custom line-of-business application was developed for the Microsoft .Net platform using the C# programming language and Windows Presentation Foundation (WPF) framework to

control the stimulator and administer the data collection protocols. The interface was designed to be intuitive, extensible, and aesthetically pleasing. The software needed to be extensible to facilitate the development of future protocols for a device as flexible as the CM-4. The core extensibility was achieved by using a "plugin" architecture with a shell application whose function is to discover, load and execute small plugins. The shell exposes a software contract (an inheritable C# class) that is consumed and extended by each plugin. Each task described in this paper represents one such plugin. Most traditional neuropsychological protocols using the standard X-alternative forced-choice (X-AFC) tracking method (Cornsweet, 1962) can be created with only a couple dozen lines of C# code. While most plugins interact directly with the CM-4 stimulator, this is not a requirement of the plugin contract. Plugins can, for example, be designed to collect arbitrary subject information pertinent to the given study (e.g., participant demographics, relevant medical history, various surveys, etc.). The net effect is not only a significant reduction in the amount of clinical paperwork that needs to be completed by each participant, but also a marked reduction in data-entry time for clinicians. All data collected by the application are stored in an encrypted (128-bit RC4) SQLite database in a user-specified location. Each database can be shared with multiple instances of the shell application, providing a mechanism for seamless networking of CM-4 stations (Holden, et al. 2011). The software is also capable of storing, as well as creating and customizing, all relevant initialization information for each plugin, such that a given battery of protocols can be administered repeatedly and in a consistent manner, while maintaining flexibility for future projects. The batteries allow for greater reuse of each plugin, resulting in shorter development times a more efficient workflow throughout an experiment.

Protocols

In order to demonstrate exemplary use of the CM-4, a finger agnosia test, in the presence and absence of conditioning stimuli, was performed. The finger agnosia test was designed to assess the capacity of subjects to recognize and identify stimulated digits, an assessment

similar to tactile finger recognition or localization tests (Boll, 1974; Reitan and Wolfson, 1993) utilized in current neuropsychological diagnostics.

Subjects

Seventeen healthy subjects (8 males and 9 females), ranging from 22 to 57 (39.1±2.9) years of age, were recruited for the study. None of the subjects reported any neuropsychological impairment and all were naïve to both the study design and issue under investigation. The study was performed in accordance with the Declaration of Helsinki, all subjects gave their informed consent, and the experimental procedures were reviewed and approved in advance by an institutional review board.

Experimental Procedure

During an experimental session, the subjects were seated comfortably in a chair with the right arm resting on the device. Because the lengths of fingers typically vary among subjects, the positions of the probe tips were individually adjusted to ensure that they contacted the glabrous, padded tips of the fingers of each subject. These loci were chosen in order to allow the convenience of access and comfort of participants as well as for the wealth of neurophysiologic information that exists for the corresponding somatotopic regions of cortex in primates (Chen et al., 2003, 2007, 2009; Francisco et al., 2008; Friedman et al., 2008; LaMotte and Mountcastle, 1975; Mountcastle, 1969; Tommerdahl et al., 1993, 1998, 2002, 2005, 2006, 2010). As depicted in Figure 1.1, probe tip positioning was accomplished by loosening a set screw and rotating each of the drums independently to conform to the natural hand shape of each subject. After proper positioning, if the probe tips still failed to make proper contact with the digits, the tips themselves were either raised or lowered. Once adjusted, the probe tips were locked in place prior to initiation of the battery so that they would remain immobile during testing. At the start of each run, the four tips were driven towards the tips of the fingers in order to ensure good contact with the skin.

During the assessment, the device delivered constant-amplitude sinusoidal skin displacements (vibrations) via flat Delrin probes (5-10 mm in diameter) positioned to make

contact with the tips of the index (D2), middle (D3), ring (D4), and little (D5) fingers of the right hand. The independent probe tips were computer-controlled and capable of delivering a wide range of vibrotactile stimulation of varying frequencies (Hz) and amplitudes (μm). Stimulus parameters were specified by test algorithms that were based on specific protocols as well as subject responses during those protocols.

Subjects viewed a computer monitor that provided continuous visual cueing during the experimental session. Specifically, an onscreen light panel indicated to the participant when stimuli were being delivered and when subjects were to respond. Training trials were not included prior to testing, and the subjects were not given performance feedback or knowledge of the results during data acquisition. The sensory testing session was conducted by application of low frequency (25 Hz) vibration to selected fingers. Each battery of testing lasted between 15 and 20 minutes depending on the protocols being run and on subject performance. Each individual protocol typically lasted 2 to 3 minutes.

Finger Agnosia Protocol

Finger agnosia tests are typically utilized to diagnose the ability of subjects to recognize and identify stimulated digits (Boll, 1974; Reitan and Wolfson, 1993). In order to assess the ability of the subject to discriminate one digit from another, a four-alternative forced-choice (4-AFC) protocol was implemented. Figure 1.2 represents a timeline for the finger agnosia protocols evaluated. The device delivered a short pulse or tap (300 μm, 25 Hz, 40 ms) to one of the four digits in a pseudo-random order on a trial-by-trial basis, and subjects were queried as to which digit was stimulated (Figure 1.2). The simple test was used in order to determine baseline values for each subject. A more complex agnosia test was subsequently administered in which test stimuli were delivered to the skin as a tap as in the previous test (300 μm, 25 Hz, 40 ms), but in the presence of conditioning stimuli at variable amplitudes. In each case, a 25 Hz, 500 ms conditioning stimulus was delivered to all four digits at one of four amplitudes: 30, 40, 50, and 100 μm. The conditioning stimulus was delivered 500 ms prior to, and 500 ms following, the tap of the test digit (Figure 1.2). For all finger agnosia tasks, subjects indicated

which finger was perceived to have received the large amplitude tap by choosing the respective digit on an image of the dorsal side of a hand presented on a computer monitor. Test stimuli sites were pseudo-randomized on a trial-by-trial basis. The subjects were assessed on their accuracy over a total of 16 trials (4 trials for each digit as the test stimulus).

Analysis

For the finger agnosia protocols, accuracy percentages were calculated by analyzing the ratio of correct to total responses of the subjects. Percent accuracies were trial-independent and reflected accuracies across all 16 trials. The 100 μm conditioning condition was chosen for further analysis because of the significantly lower percent accuracy compared to the simple agnosia task. Percent inaccuracies were quantified for the 100 μm conditioning stimulus by calculating the frequency at which digits were incorrectly chosen. Results were calculated in this manner in order to compare percent inaccuracies with difference limens (DLs), where lower value might suggest higher accuracies and increased discriminative capabilities. The data were analyzed for significance by calculating p-values across mean inaccuracy metrics for each digit. Histograms were plotted in order to visualize the differences among each of the digits with respect to standard error of the means. Statistical t-tests were used to evaluate the difference of the performance of each subject under different conditions. A probability value of less than 0.05 was considered statistically significant.

Auditory Cue Analysis

To ensure that the stimulator did not produce any audible clues during the agnosia task, an auditory output analysis was conducted using a standard USB microphone and the open source software suite Audacity. The microphone was placed on a table 31 cm from the stimulator head unit. Four one-second recordings were created with each condition consisting of an initial 250 ms period of silence followed by a single-channel 300 μm 25 Hz sinusoidal vibration lasting 500 ms and ending with another 250 ms period of silence. Audacity provides a contrast analysis tool in compliance with the Web Content Accessibility Guidelines (WCAG 2.0),

Success Criteria 1.4.7. This tool was used to calculate the RMS amplitude in decibels (dB) during each vibration and period of silence.

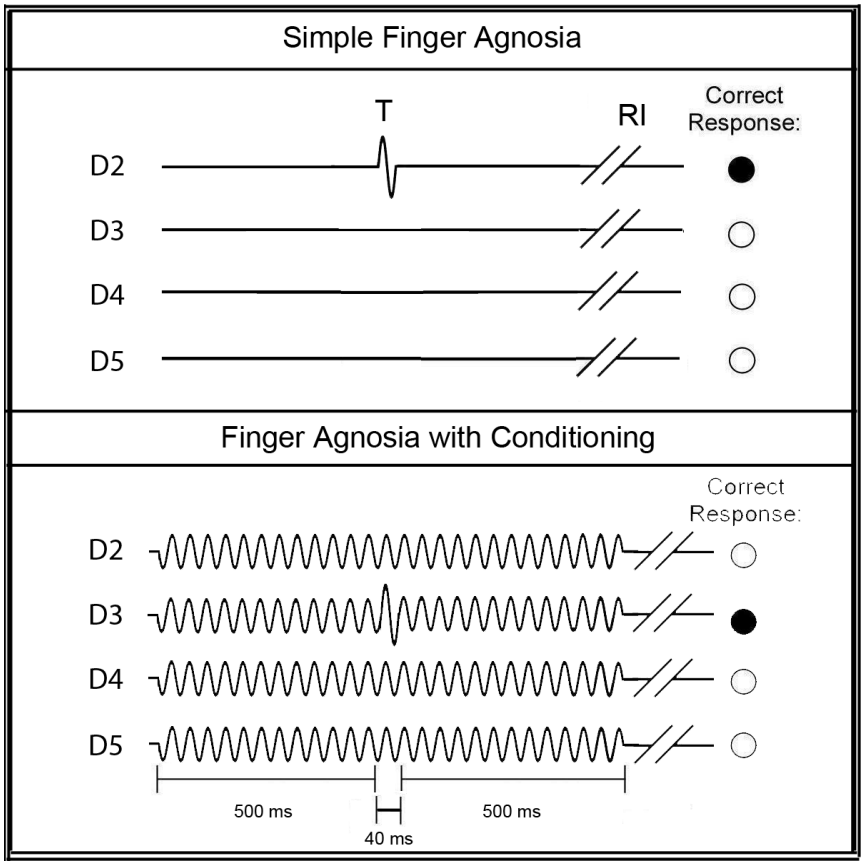

Figure 1.2: Schematics of Finger Agnosia Protocols
The simple finger agnosia assessment (top panel) consisted of a 4AFC protocol where a short test (T) pulse (300 μm, 25 Hz, 40 ms) was delivered to one of the four digits followed by a subject response interval (RI). The finger agnosia test was also conducted in the presence of conditioning stimuli of amplitudes 30, 40, 50, or 100 μm (bottom panel). The conditioning stimulus was delivered 500 ms prior to, and 500 ms following, the tap of the test digit. For all finger agnosia tasks, subjects indicated which finger was perceived to have received the large amplitude tap by choosing the respective digit on an image of the dorsal side of a hand presented on a computer monitor. Test stimuli sites were pseudo-randomized on a trial-by-trial basis.

Results

This study employed a finger agnosia protocol, in the presence and absence of conditioning stimulation, on healthy subjects in order to demonstrate the capacity of the device for delivering well-controlled vibrotactile stimuli at four independent sites. The auditory cue analysis found no indication of any auditory cues produced being produced by the stimulator during a vibration. The peak amplitude for any channel during a vibration was -42.64 dB

(silence is considered to be in the range of -30 dB for humans). The average RMS amplitude (during all vibrations) was -58.90±0.11 dB. The average RMS amplitude during the periods of silence was -58.83±0.10 dB. Comparing each condition's vibration to the immediately preceding silence yielded an average difference in RMS amplitude of 0.05±0.13 dB. The finger agnosia task was evaluated in order to quantify the ability of subjects to recognize and identify stimulated digits in the absence and in the presence of conditioning stimuli at different amplitudes. This task included seventeen healthy subjects (8 males and 9 females) ranging from 22 to 57 (39.1±2.9) years of age. As shown in Figure 1.3, the average percent accuracy in the absence of conditioning stimuli was 98.2±0.9% (n=17), and accuracy across subjects decreased with increasing amplitude of conditioning stimuli. Conditioning amplitudes of 30 and 40 μm resulted in percent accuracies of 93.7±3.0% and 94.9±4.2%, respectively, and were not statistically significant compared to subject performance in the absence of conditioning stimuli. The effect of conditioning on the finger agnosia task became statistically significant at conditioning amplitudes greater than 50 μm: 89.0±4.2% at 50 μm ($p<0.06$) and 60.0±7.6% at 100 μm ($p<0.01$). Because the conditioning stimuli at 100 μm resulted in the most significant percentage of incorrect responses compared to the simple finger agnosia protocol, the frequency of inaccurate responses for each digit was quantified (Figure 1.4). The results suggested that subjects, on average, made the largest number of inaccurate responses when the correct answer should have been D3 and D4 (percent inaccuracies of 60.0±10.0% and 55.0±14.6%, respectively). Subjects were relatively better at identifying stimulation of D2 (inaccuracy of 15.0±10.0% significantly better than that for D3, $p<0.01$) and better at identifying D5, though not statistically significantly more.

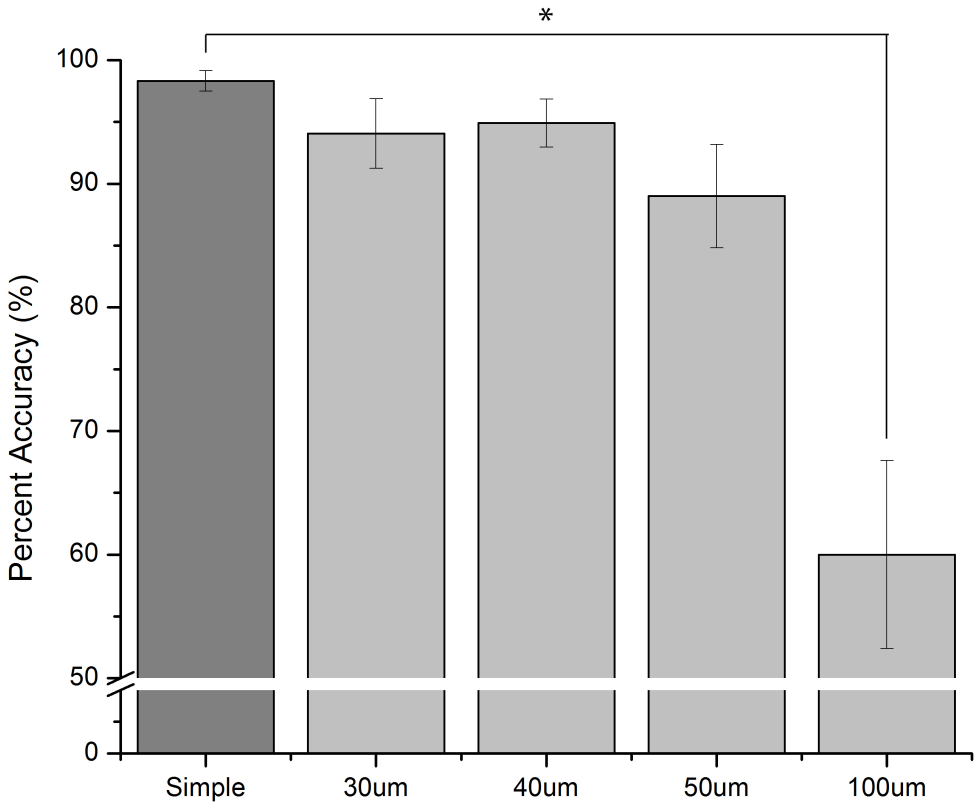

Figure 1.3: Impact of Conditioning on Finger Agnosia Task
The average percent accuracy in absence of conditioning stimuli was 98.2±0.9% (n=17). In the presence of 30, 40, 50, and 100 μm conditioning stimuli, the percent accuracies gradually decreased with increased amplitude of conditioning stimuli: 93.7±3.0% at 30 μm (n=17), 94.9±4.2% at 40 μm (n=16), 89.0±4.2% at 50 μm (n=17, $p<0.06$), and 60.0±7.6% at 100 μm(n=5, $p<0.01$).

Discussion

The delivery of sinusoidal displacements to a single skin site via mechanical transducer has been used extensively for the study of flutter vibration in both psychophysical and neurophysiological settings for a number of decades. Exemplary uses of such a device are described in Goble and Hollins, 1993; Juliano et al., 1989; LaMotte and Mountcastle, 1975; Mountcastle et a., 1969; Tannan et al., 2006; Tommerdahl et al., 1993, 1998, 2002; and Vierck and Jones, 1970. Typically, stimuli that can be delivered through mechanical transducers – vertical displacement stimulators such as the one originally described by Chubbuck (1966) – were used for studies of somatosensation and are very well equipped to deliver sinusoidal

stimuli at a frequency range (1 to 250 Hz) with amplitudes of sufficient size (between 0 and 1000 μm) to activate a broad range of mechanoreceptors. However, in order to stimulate more than one skin site — either during the course of human psychophysical testing or animal experimentation — it is necessary to position a second vertical displacement stimulator over the second skin site. Our previous device (described in Tannan et al. 2007a) was designed to address this issue by allowing dual site stimulation with automated two-dimensional probe positioning. Although the device reported by Tannan and colleagues was successfully utilized in a number of studies (Tannan et al., 2005b, 2006, 2007b, 2008; Tommerdahl et al., 2007a, 2007b, 2008), it was cumbersome and not ideal for clinical and clinical research venues.

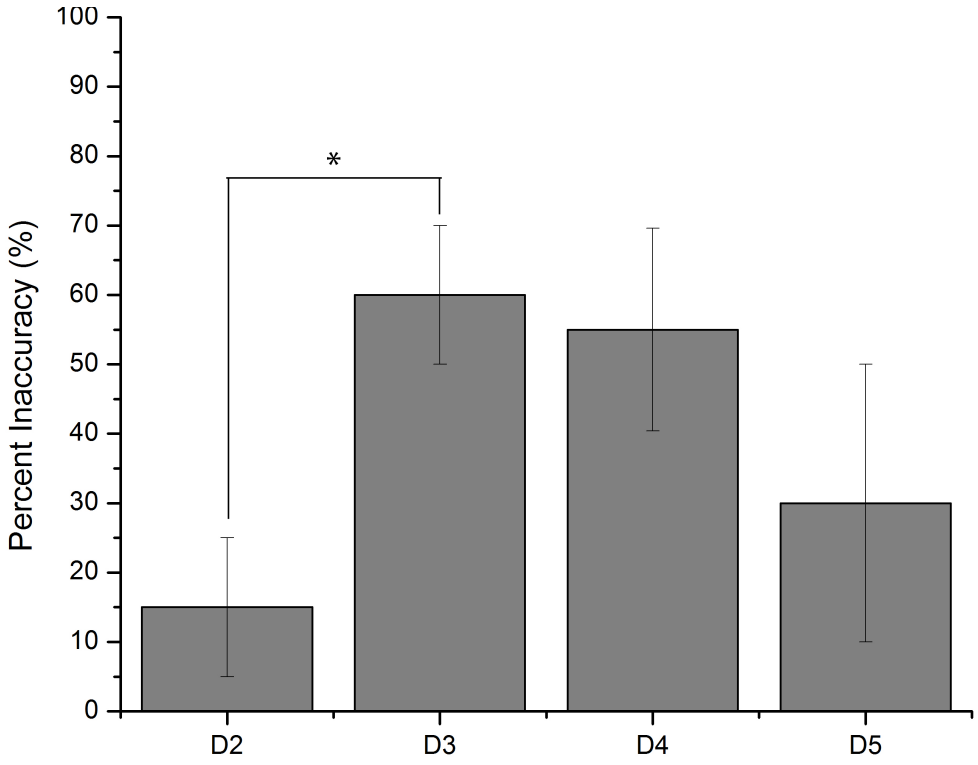

Figure 1.4: Percent Inaccuracy on Finger Agnosia with 100 μm Conditioning Stimuli
Digits D3 and D4 showed the highest percent inaccuracies of 60.0±10.0% and 55.0±14.6%, respectively. There was a statistically significant observation in accurately recognizing and identifying stimulation of D2 at 15.0±10.0% versus D3 at 30.0±20.0% ($p<0.01$) and slight discrimination difference between D2 and D4 ($p<0.08$) in the presence of the 100 μm conditioning stimuli. The other the digit combinations showed no statistical significance in discrimination capability.

The CM-4, described in this report, has the capacity to quickly and easily adjust to fit to most adult, and many juvenile, hand sizes and can deliver vibrotactile stimuli to the tips of four digits. The ability to simultaneously deliver vibrotactile stimuli to a number of digits allows for a great deal of protocol diversity.

In this report, we described a relatively simple four-site finger agnosia protocol to demonstrate the potential utility of the device. The principle finding in the results of this study is that there is an increase in inaccuracies with increases in the amplitude of concurrent conditioning stimulation delivered during the agnosia task, and the ability to perform the task accurately in the presence of that conditioning stimulation is diminished more in digits D3 and D4 than in digits D2 and D5. The decrease in accuracy with increasing amplitudes of synchronized sinusoidal stimulation is consistent with prior reports of increasing inaccuracies in temporal order judgment (TOJ) in the presence of synchronized and periodic conditioning stimuli. In a study by Tommerdahl and colleagues (Tommerdahl et al., 2007), it was demonstrated that TOJ results obtained from a number of pairs of stimulus sites — unilateral as well as bilateral — were comparable. However, in the presence of a 25 Hz conditioning sinusoidal stimulus which was delivered both before, concurrently and after the TOJ task, there was a significant increase in the TOJ measured when the two stimuli were located unilaterally on digits D2 and D3. In the presence of the same 25 Hz conditioning stimulus, the TOJ obtained when the two stimuli were delivered bilaterally was not impacted. This led to the speculation that the impact that the conditioning stimuli — which only had an impact if they were sinusoidal, periodic and synchronous — had on TOJ measures was due to the synchronization of adjacent cortical ensembles in somatosensory cortex, and that the synchronization of these cortical ensembles could have been responsible for the degradation in temporal order judgment. The conditioning stimuli in this study were also synchronized, periodic and simultaneous, and if the degradation in test performance was due to synchronization of adjacent cortical ensembles similar to what was speculated in the TOJ report, then inaccuracies due to this synchronization would be lower on the digits on the perimeter of the cortical

ensemble (i.e., D2 and D5), and the results reflect this prediction. Future studies will consider whether or not subjects with neurological disorders are not impacted by conditioning stimuli, as was found to be the case in subsequent TOJ studies (e.g., TOJ metrics of subjects with autism were not impacted significantly by conditioning stimuli; Tommerdahl et al., 2008).

The degree of inaccuracies in the different digits with increasing conditioning stimulation is also consistent with motor studies of digit interdependencies. In studying the autonomy of finger movements, intended motion in one finger often results in simultaneous movement, or enslavement, of other digits. More specifically, D3 and D4 show the most enslavement, or interdependency, of adjacent digits while D2 is characterized by the greatest independence (Häger-Ross and Schieber, 2000). In observing motor-related cortical potentials (MRCPs), the autonomous nature of D2 was shown to be significantly high while D4 showed the most dependency on other digits (Slobounov et al., 2002). In Figure 1.4, D2 demonstrates the lowest inaccuracies in the presence of conditioning stimulation while D3 and D4 exhibit the most; thus, in both the motor and sensory based studies, D2 demonstrates the most independence.

The role of neural communication between adjacent and non-adjacent cortical regions plays an important role in understanding the relationship between neurophysiological mechanisms and sensory percept. The development of new, more versatile devices and methodologies, such as presented in this report, could contribute to bridging decades of neuroscientific research with human perceptual clinical and clinical research studies. One long term goal of our research is to develop sensory based instrumentation and methodologies for the diagnosis and assessment of treatment efficacies for a broad range of neurological disorders, and building this aforementioned bridge could provide new insights into fundamental information processing mechanisms as well as generating perceptual metrics that are more sensitive to alterations in central information processing capacity.

CHAPTER 2: VIBROTACTILE AMPLITUDE DISCRIMINATION CAPACITY PARALLELS MAGNITUDE CHANGES IN SOMATOSENSORY CORTEX AND FOLLOWS WEBER'S LAW[2]

Overview

In this study, we investigated the changes in perceptual metrics of amplitude discrimination that were observed in 10 healthy human subjects with increasing intensities of stimulation. The ability to perceive differences in vibrotactile amplitude changed systematically with increasing stimulus magnitude (i.e., followed Weber's Law) in a near linear fashion ($R^2 = 0.9977$), and the linear fit determined by the amplitude discrimination task predicted the subjects' detection thresholds. Additionally, the perceptual metrics correlated well with observations from a previously reported study in which measures of SI cortical activity in nonhuman primates (squirrel monkeys) evoked by different amplitudes of vibrotactile stimulation were obtained (Simons et al. 2005). Stimuli were delivered simultaneously to two different skin sites (D2 and D3), enabling a method for the relatively rapid acquisition of the data. Stability and robustness of the measure, its rapid acquisition, and its apparent relationship with responses previously observed in SI cortex, led to the conclusion that deviations from the baseline values observed in the obtained perceptual metric could provide a useful indicator of cerebral cortical health.

Introduction

One of the fundamental questions often addressed in neuroscience is how two sensory stimuli are differentiated. Detection and integration of the differences in physical attributes of our environment is, undoubtedly, just one way in which we coordinate the processes that

---

[2] This chapter previous appeared in Experimental Brain Research. The original citation is as follows: Francisco, E., V. Tannan, Z. Zhang, J. Holden, and M. Tommerdahl. 2008. "Vibrotactile Amplitude Discrimination Capacity Parallels Magnitude Changes in Somatosensory Cortex and Follows Weber's Law." Experimental Brain Research 191 (1): 49–56.

govern how we react and respond to external stimuli. Weber initiated a discussion on how sensory stimuli are integrated into central information processing in his 1834 study of perceived intensity. In his experiments, he measured the difference limen (DL) of blindfolded subjects by giving them two weights of equal magnitudes (standard weight) to hold in each hand. He then proceeded to add slightly heavier weights (test weight) to one hand. The subject was asked to compare the weights in both hands and determine which was larger. Weber found that it was more difficult for the subject to determine that there was a difference in the weights when the standard weight was larger; in other words, the size of the DL was proportional to the stimulus strength and increased linearly as the initial stimulus strength increased (Goldstein 2007). Based on Weber's experiments, physicist Gustav Theodor Fechner developed the Weber-Fechner Law: where ΔS is the DL corresponding to the reference stimulus S, and K is a constant called Weber's Fraction. Research has shown that Weber's Fraction is usually constant for a range of stimulus intensities and can be applied to most senses, including weight, brightness, and sound frequency (Hanna et al. 1986; Gescheider et al. 1990; Stillman et al. 1993; Gescheider et al. 1996b; Gescheider et al. 1997; Scholtyssek et al. 2008).

A number of intensity related studies have been conducted in our laboratory. Most recently, we made the observation that the magnitude of the evoked optical intrinsic signal (OIS) varies in a near linear fashion in SI cortex of squirrel monkeys with the amplitude of a 25 Hz vibrotactile stimulus (Simons et al. 2005). One of the more interesting facets of that study was that while the magnitude of the centrally activated SI cortical region increased significantly with increasing amplitude, the spatial extent of the responding cortical territory did not (Simons et al. 2005). Rather, the extent of the inhibitory surround became more prominent with increasing stimulus amplitude. A similar study demonstrated that this center surround relationship was duration- as well as amplitude dependent (Simons et al. 2007). Although this does not, in concept, seem to be a surprising revelation, it could be considered antithetical to previous hypotheses proposed about the SI cortical response to different intensities of skin stimulation – specifically, that increasing vibrotactile amplitudes would lead to an increasing

spatial extent of the response in SI (Johnson 1974). Simons et al. with their subsequent stimulus duration dependent study, demonstrated and discussed how the two views are compatible (Simons et al. 2007). To summarize, brief stimuli (500 ms or less) evoke a much more spatially extensive response than longer duration stimuli, and longer duration stimuli (greater than 500 ms) more actively engage pericolumnar lateral interactions that lead to a more prominent inhibitory surround. Previous ideas about intensity perception, which were based on the increased recruitment of peripheral afferents, obviously did not incorporate the inhibitory surround and thus led to alternative ideas about the characterization of SI cortical response to increasing stimulus intensity. Nevertheless, the near linear relationship between the magnitudes of the evoked SI cortical response to supra-threshold vibrotactile stimulus amplitudes led us to posit the question as to whether or not we would observe a parallel metric perceptually. In other words, would increasing the vibrotactile amplitude of two comparison stimuli lead to a proportional increase in the DL (i.e., would Weber's Law be followed)?

Additional intensity related, but perceptually based, studies have also been conducted in our laboratory (Tannan et al. 2007b; Tannan et al. 2008; Zhang et al. 2008). The development of novel stimulus devices that can simultaneously deliver two well controlled vibrotactile stimuli (both in terms of amplitude and frequency) has made a number of studies much more pragmatic (Tannan et al. 2007b; Tommerdahl et al. 2007a; Tommerdahl et al. 2007b; Tannan et al. 2008; Tommerdahl et al. 2008a; Tommerdahl et al. 2008b). For example, simultaneous delivery of two vibrotactile stimuli to different locations allows for direct comparison between the two stimuli, and problems originating from comparison of two stimuli at the same location, such as adaptive effects by the first stimulus delivered, are automatically eliminated. The decrease in overall protocol duration (to approximately 1.5 min per standard) has made it possible to complete the multiple amplitude discrimination runs necessary for a study, such as the one described in this report, in a single 10-20 min session. In this report, the two-site amplitude discrimination protocol was executed with a number of different standard amplitudes in order to evaluate how subjects' discrimination ability changes with increasing

intensity. Additionally, this data was compared with previously reported changes in SI cortical activity obtained from squirrel monkey in order to ascertain the relationship of primary sensory cortex to perceptual capacity.

Methods

Ten subjects (22-31 years in age) were studied who were naïve both to the study design and issue under investigation. The subjects consisted of 7 males and 3 females, all right-hand dominant. The study was performed in accordance with the Declaration of Helsinki, all subjects gave their written informed consent, and procedures were reviewed and approved in advance by an institutional review board.

A two-alternative forced-choice (2AFC) tracking protocol was used to evaluate the amplitude discriminative capacity of each subject (see Figure 1.2) in a manner used in a number of previous studies that have examined dual-site simultaneous vibrotactile discriminative capacity (Tannan et al. 2005; Tannan et al. 2006; Tannan et al. 2007a; Tannan et al. 2007b; Tommerdahl et al. 2007a; Zhang et al. 2008). The subject was seated with the right arm resting comfortably on a dual-site portable vibrotactile stimulator (CM-1; for full description, see: (Tannan et al. 2007a)). Two probe tips (5 mm diameter) were positioned on the glabrous pads of digits 2 and 3 of the right hand. Digits 2 and 3 were chosen as test sites for both convenience of access (thus maximizing the test's potential in clinical applications) and because of the wealth of neurophysiological information that exists for that somatotopic region of cortex in primates. Visual cueing was provided with a computer monitor during the experimental run. Specifically, an on-screen light panel was used to indicate to the subject when the stimulus was on and when the subject was to respond. The subject was not given performance feedback or knowledge of the results during the data acquisition until all sessions were completed. At the start of each run, the two probe tips were driven towards the skin until each tip registered a force of 0.1 g, as determined by a closed-loop algorithm in the CM-1 stimulator feedback system. The tips were then further indented into the skin by 500 μm to insure good contact with the skin. An audiometer was used to ensure that no auditory cues were emitted from the

stimulator during delivery of the range of stimuli used in this study. All vibrotactile stimuli used in this study were delivered at the frequency of 25 Hz flutter.

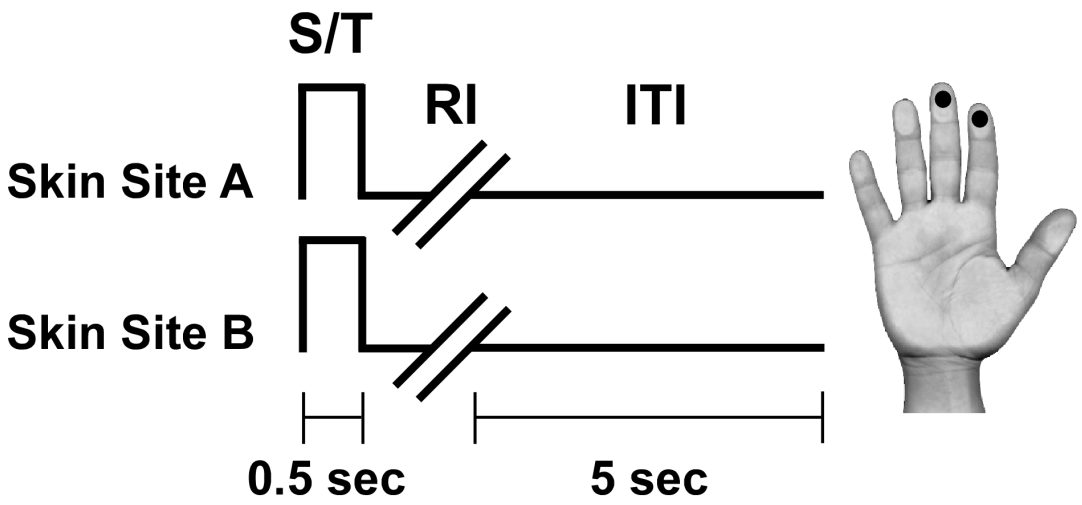

Figure 2.1: Schematic of the Protocol Used for Amplitude Discrimination
Two 25 Hz vibrotactile stimuli, the standard (S) and test (T), were delivered at the same time for 0.5 sec. A 5 sec delay (excluding subject response interval (RI)) was imposed before onset of the next trial. The subject was queried as to which stimulus felt more intense.

Amplitude discrimination was tracked for nine conditions of standard stimulus amplitude, each condition tracked in a separate experimental run: 50, 100, 200, 300, 400, 500, 600, 700 and 800 μm. During an experimental run, a vibrotactile test stimulus was delivered simultaneously with a vibrotactile standard stimulus (the standard amplitude remained constant throughout the run). The loci of the test and standard stimuli were randomly selected on a trial-by-trial basis. Stimulus duration was 0.5 sec, followed by subject response (subject was queried to select the skin site that received the most intense stimulus) and a 5 sec delay before onset of the next trial. The test stimulus amplitude was always greater than that of the standard stimulus.

Each experimental run consisted of 20 trials total. In the initial 10 trials, the amplitude of the test stimulus was modified based on the subject's response to the preceding trial — accomplished using a 1-up/1-down algorithm. This approach was selected because it enabled rapid determination ("tracking") of each subject's minimally detectable difference in the

amplitudes of two-site skin flutter stimulation (Tannan et al. 2007a). The difference between the amplitudes of the test and standard stimuli delivered on each of these initial 10 trials was adjusted on the basis of the subject's response in the preceding trial (the discrepancy in amplitude was decreased if the subject response in the preceding trial was correct; it was increased if the response was incorrect). After the initial 10 trials were completed, test stimulus amplitude was modified using a 2-up/1-down algorithm — in these trials two correct/one incorrect subject response(s) resulted in a decrement/increment, respectively, in the amplitude difference between the test and standard stimuli. The subjects' DLs were calculated by averaging the amplitude of the test stimulus in the last five trials of each run and comparing this to the standard used in each test. The step size for each condition was 5% of the standard amplitude. This value was chosen in order to maximize resolution of the method as well as to standardize the relative step size for each run. A series of training trials, each consisting of a pair of stimuli differing in amplitude by 100 μm (200 μm vs. 100 μm), were conducted prior to the first run. These amplitudes were chosen to provide only minimal challenge to the subjects performing the discrimination task during training. The subject was provided with feedback only during training trials and was allowed to continue on to the first run after answering correctly 5 times in a row. Each subject participated in a single experimental session that consisted of nine separate runs of different standard amplitude conditions (randomized in order). A single session, including actual testing time and short breaks between each run, took 30-45 min. A modified 2AFC protocol was also used to evaluate the detection threshold of each subject. For this procedure, amplitude discrimination was performed for 60 trials using a 3-up/1-down algorithm, due to the lower signal-to-noise ratio at this low-amplitude testing level. In this condition, the standard amplitude was held constant at 0 μm, thereby testing the ability of the subject to simply detect the presence of the 25 Hz stimulus.

Results

A two alternative forced-choice (2AFC) tracking protocol was used to determine subjects' capacities to discriminate between the amplitudes of two simultaneously delivered

vibrotactile stimuli and to directly compare subjects' discriminative capacities under different conditions of standard amplitude (protocol previously described in (Tannan et al. 2007b; Tannan et al. 2008; Zhang et al. 2008); also see Methods). To summarize, a tracking protocol was employed in which two stimuli were delivered simultaneously in one trial. The subject was queried as to which stimulus was more intense, and the difference between the two subsequent stimuli of the next trial was increased or decreased based on subject response. The difference limen (DL) for each subject was determined by averaging the tracking values obtained from the last five trials of each experimental run.

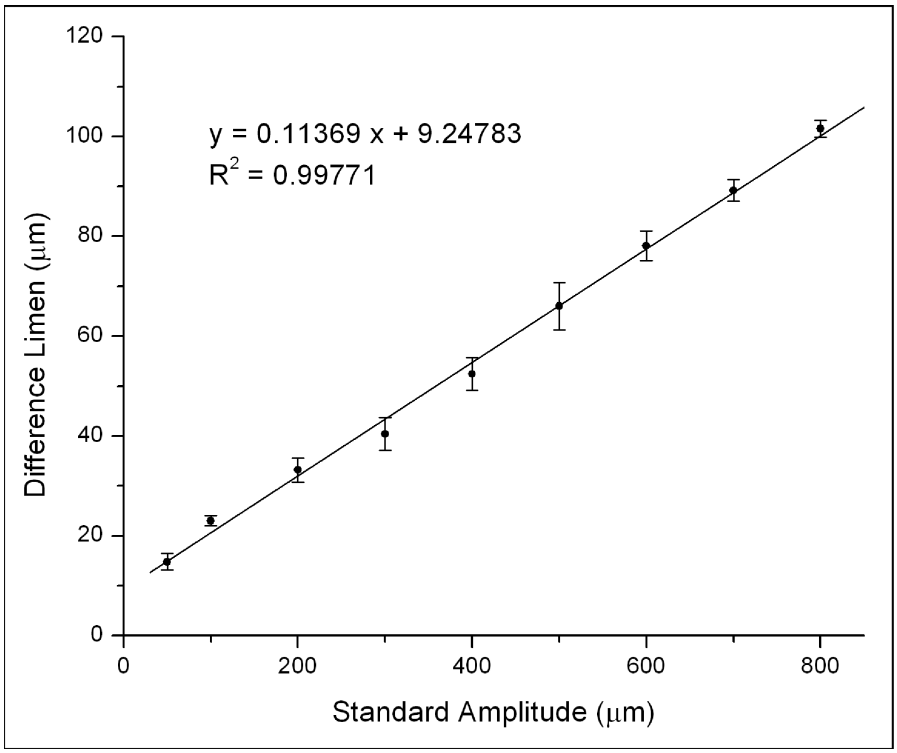

Figure 2.2: Averaged Difference Limen Values at Various Standard Amplitudes
The plotted linear regression has a correlation coefficient of 0.99771, and the y-intercept (predicted detection threshold) is approximately 9.25 μm.Two 25 Hz vibrotactile stimuli, the standard (S) and test (T), were delivered at the same time for 0.5 sec. A 5 sec delay (excluding subject response interval (RI)) was imposed before onset of the next trial. The subject was queried as to which stimulus felt more intense.

Across-subject DLs for each of the standard values are summarized in Figure 2.2. Subject performance was highly consistent, and the results demonstrated that subjects performed much better, on an absolute scale, when the standard stimulus was smaller (e.g.,

compare the DL obtained with a 50 μm standard (14.8 ± 1.26 μm) to the DL obtained with an 800 μm standard (101.6 ± 1.72 μm)). A linear least-squares fit was applied to the data, and an R^2 value of ~0.998 was obtained for the linear regression, demonstrating a remarkably strong correlation between DL and standard amplitude and thereby verifying the application of Weber's Law for this particular task. Extrapolation of the linear fit (shown in Figure 2.2) to the y-intercept yields the prediction that the detection threshold — or in other words, the ability to correctly discriminate between a vibrotactile test stimulus and a 0 μm "standard" stimulus — should be ~9.25 μm. Under the condition of 0 μm standard stimulus amplitude, a modified amplitude discrimination protocol was used (which required a much larger number of trials — see Methods) and detection thresholds were directly obtained and averaged across all subjects. Subjects were consistently able to detect stimuli at amplitudes of 9.21 ± 1.76 μm, and an independent two subject t-test verifies that there is not a statistically significant difference between the actual average detection threshold and the predicted measure derived from the linear fit to the amplitude discrimination DLs obtained with this protocol (t = 0.029, D.F. = 15, p = 0.977).

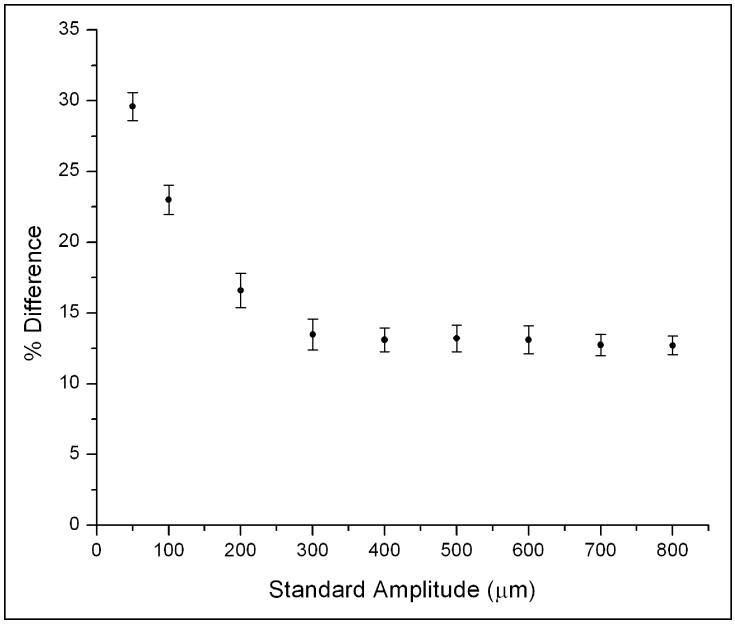

Figure 2.3: Difference Limens Plotted as Percent Difference

In order to ascertain whether or not ΔS / S was constant (i.e., whether or not the Weber-Fechner Law held true) DLs, averaged across all subjects, were re-plotted as a percent of the corresponding standard amplitude from which they were obtained (see Figure 2.3). The data suggest that DLs are proportionally higher at lower amplitudes (i.e., standard amplitude < 300 μm), then level off for higher standard amplitudes (≥ 300 μm) at a percent difference of approximately 13%. Thus, the non-linearity of this data demonstrates a deviation from the Weber-Fechner law in the region tested below 300 μm, suggesting that the Weber-Fechner Law holds true only for the amplitude discrimination tasks with the relatively higher standards.

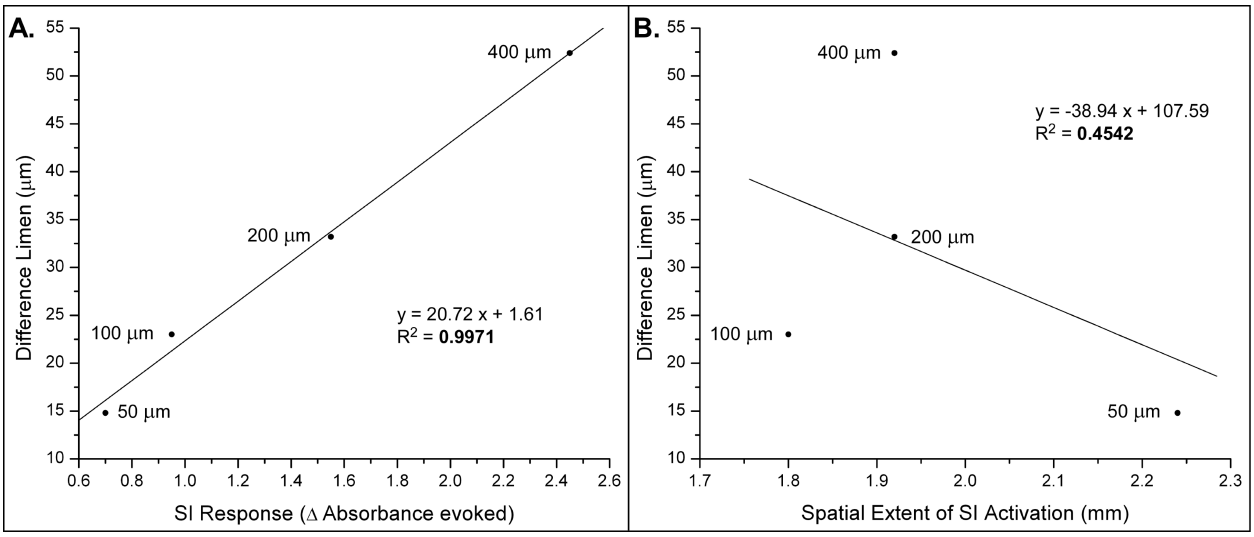

Figure 2.4: Correlating Data with Optical Imaging
Panel A. Correlation between the DLs, obtained from this study, and the maximal change in absorbance in SI, previously reported (Simons et al. 2005). As the standard amplitude increases, both DL and SI response increase in a linearly proportional manner (R2 = 0.9971).
Panel B. Correlation between the DLs and the spatial extent of SI activation. As the standard amplitude was increased, no correlation was observed (R2 = 0.4542).

In a previous study that investigated the SI response to different amplitudes of vibrotactile stimulation (at the same frequency as this study) utilizing the technique of optical intrinsic signal (OIS) imaging in nonhuman primates, we found that an increase in the amplitude of the stimulus corresponded with the increase in absorbance evoked within the region of SI cortex that receives its input from the stimulated skin field (Simons et al. 2005; Simons et al. 2007). 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). Measurement of the spatial extent of the activated SI region, on the other hand, 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, and the region of surrounding cortex underwent a prominent decrease (frequently to levels well below background) in absorbance. In order to directly compare the two principle findings of that study — the relationship of absorbance evoked by different amplitudes of stimulation and the apparent lack of correspondence of the spatial extent with amplitude of stimulation — we directly compared the DLs obtained from the results of this report with those two entities. The results from those comparisons are shown in Figure 2.4 and demonstrate that there is a very strong correlation (R2 = 0.9971) between the DLs obtained at each standard amplitude and the neural activity evoked at each amplitude. On the other hand, a much weaker (not significant) correlation was observed between the spatial extent of the cortical response and the DLs obtained at the same amplitudes (R^2 = 0.4542).

Discussion

In this study, a dual-site vibrotactile amplitude discrimination protocol was used to determine the difference limen (DL) for a number of standard amplitudes. The DLs were found to increase in a near-linear fashion with an increase in standard amplitude, thus adhering to Weber's Law for the stimulus range employed in this study (50-800 μm). Extrapolation of the linear least squares fit of the data (DL vs. standard amplitude) yielded a prediction — at the y intercept — of the detection threshold. An independent method of threshold observation demonstrated that the same group of subjects had a detection threshold very close to the one predicted (9.21 ± 1.76 μm detected vs. 9.25 μm predicted), and both values are consistent with those reported by other investigations (Gescheider et al. 1996b; Gescheider et al. 1997; Hollins and Sigurdsson 1998; Gescheider et al. 2004). Previously reported relationships of SI cortical activity (in squirrel monkey) evoked by different stimulus amplitudes were proportional to

changes observed in the perceptual metrics obtained in this study with different standard amplitudes.

One of Ken Johnson's principle contributions to the field of somatosensory neurophysiology was his emphasis on the description of linearity between subjective experience and the underlying neural activity on which it is based. In essence, he concluded that "all the available evidence points to linearity as the basic law of psychophysics" (Johnson et al. 2002). The results of this paper fully support his statement, as not only was there a linearity demonstrated in the perceptual metrics, but the perceptual metrics obtained in this study co-vary with the SI cortical response (from non-human primates) in a fashion that strongly suggests that the magnitude of the neural activity evoked in SI could be essential to the neural code of intensity discrimination. Although SI is considered primary sensory cortex, it has, nevertheless, been observed to reflect other aspects of perception exceedingly well. Chen and colleagues observed evoked SI activity between the somatotopic representations of two digit tips when the two digits were simultaneously stimulated — an apparent parallel to the perceptual illusory effects generated by the same dual site stimulus (Chen et al. 2003).
A number of other somatosensory studies suggest that the increase in stimulus intensity could be proportional to an increase in the evoked SI cortical activity. Most closely related to our SI cortical study — briefly summarized in the results section — was a study by Chen and colleagues who used the optical intrinsic signal (OIS) to demonstrate that a proportionally greater (larger magnitude) response is evoked in SI of squirrel monkeys as the amplitude (as measured by force) of a skin stimulus is increased (Chen et al. 2003). Several studies examined the global SI response using noninvasive imaging techniques in humans such as fMRI (functional Magnetic Resonance Imaging) (Arthurs et al. 2000; Backes et al. 2000; Nelson et al. 2004) and MEG (MagnetoEncephaloGraphy) (Iguchi et al. 2002; Torquati et al. 2002). In general, results from these noninvasive studies indicated that increases in stimulus intensity are accompanied by increases in the intensity of the evoked signal as well as increases in the activated volume of SI cortex. As a result, these studies predicted that amplitude might be

coded not only by the average firing rates of individual SI neurons, but also by the total aggregate of responding neurons. These population based studies seemed to confirm prior predictions of the SI neuronal population response based on reconstructions from afferent recordings (Werner and Mountcastle 1965; Johnson 1974; Connor et al. 1990; Whitsel et al. 2000; Guclu and Bolanowski 2002) and single unit cortical recordings (Mountcastle et al. 1963; Simons 1978).

Could the neural code for intensity be as simple as the above-described relationship suggests? One aspect that has not been addressed in this study is the effect that stimulus duration could potentially have on the results. A longer stimulus duration would result in both improvements perceptually, such as those that occur with adapting stimulation (Goble and Hollins 1993; Goble and Hollins 1994; Gescheider et al. 1996b; Gescheider et al. 1999; Tannan et al. 2007b) as well as changes in the SI cortical response. One of the most notable changes in SI cortical response with increasing vibrotactile stimulus duration is the increased funneling that leads to the development of a surround (Llinas and Sugimori 1980; Tommerdahl et al. 2002; Chiu et al. 2005; Simons et al. 2005). The surround appears to spatially constrain the responding cortical region (Simons et al. 2007), and within the spatially constrained area of evoked cortical activity, spatially non-homogenous patterns of response develop which are amplitude dependent (Chiu et al. 2005; Tommerdahl et al. 2005a). Such stimulus dependent patterns have been observed in other cortical studies as well (Bruno et al. 2003) that strongly suggest that minicolumnar patterns of response play a role in cortical information processing (Tommerdahl et al. 1987; McCasland and Woolsey 1988; Tommerdahl et al. 1993; Favorov and Kelly 1996; Chiu et al. 2005; Tommerdahl et al. 2005a).

There could be potential clinical implications from this study. Since the results suggest a strong correlation with SI cortical activity and the capacity for amplitude discrimination at multiple amplitudes, we would predict that a systemic cortical alteration, in which cortical activity deviates from the norm, would change a subject's capacity for amplitude discrimination. For example, the function determined by the relationship between the DL vs

standard amplitude (such as plotted in Figure 2.2) could be impacted significantly in a neurologically compromised individual, and this function could be determined relatively rapidly by deriving it from 2 or 3 DLs obtained from larger amplitude (>300 μm) standards.

Based on the data plotted in Figure 2.3, it appears that subjects are much more accurate at higher standards, most likely due to the higher signal-to-noise ratio (with "noise" determined by the baseline values of neural activity that are correlated with sub-threshold perceptual values). If this is, in fact, the case, then the data presented in Figure 2.3 would present a fairly strong argument against obtaining and interpreting threshold and/or near-threshold measures, as accuracy clearly decreases with the magnitude of the stimuli. In other words, accurate threshold detection measures necessitate much longer protocols (in the case of this study, 3 times as long) than does deriving amplitude discrimination capacity at multiple supra-threshold standards. Additionally, the multiple DLs obtained from studies such as this one can be used to determine a functional relationship; threshold detection, on the other hand, yields only one measure, and it is difficult to derive a systemic function from a single point. Although numerous studies have successfully shown differences in thresholds for different neurologically compromised subject populations (Gescheider et al. 1996a; Goble et al. 1996; Hollins et al. 1996; Kosek et al. 1996; Rocheron et al. 2002; Guclu et al. 2007; Ofek and Defrin 2007; Wiacek et al. 2007; Alary et al. 2008), relatively fewer studies have emphasized the amplitude discriminative capacities of those subject populations (Gescheider et al. 1996a; Hollins et al. 1996; Rocheron et al. 2002; Wiacek et al. 2007), most likely due to the difficulty of implementing such a study in a clinical or clinical research setting. The increased efficiency and performance that is associated with dual-site simultaneous delivery of tactile stimuli makes it much more feasible to rapidly perform amplitude discrimination studies of the type described in this report (Tannan et al. 2007a) and potentially implement in a clinical setting. Moreover, a growing number of similar studies are demonstrating significant cerebral cortical differences between a number of different subject populations (Tommerdahl et al. 2007a; Folger et al. 2008; Tannan et al. 2008; Tommerdahl et al. 2008a). Related to the issue of resolution is that an

exponential growth of brain imaging (fMRI, EEG, MEG) studies have yet to reveal significant differences that parallel those observed in studies which obtain perceptual metrics such as those in this report. Furthermore, it is highly unlikely that such brain imaging studies will be capable of detecting differences in the responses evoked by stimuli which vary in intensity by as little as 10-20%. Given the cost — both in time and in monetary expense — it may serve diagnosticians well to take a closer look at the perceptual measures that strongly reflect cortical activity and are sensitive to systemic cortical alterations.

Although some strong correlations were observed in this study, there are questions that observations of this study raise that remain to be resolved. One of the most prominent questions stems from the observation that the weaker stimuli studied (50, 100, 200 μm) had proportionally larger DLs than the stronger stimuli. At the stronger stimulus conditions, the DLs maintained a fairly constant value in proportion to the standard stimulus. While our current interpretation of this is that it could simply be a signal-to-noise issue, we cannot rule out other stimulus-dependent mechanisms. For example, the studies of Chen and colleagues (Chen et al. 2003) would suggest that stimuli delivered to adjacent digit tips, particularly when the stimuli are near equal in strength, would result in mutual inhibition of the cortical responses evoked by the two stimuli. In this scenario, the DLs observed in the weaker standard stimulus range would be more significantly impacted. Decreases in the evoked SI cortical response have been observed in a number of stimulus conditions (Tommerdahl et al. 2005b; Tommerdahl et al. 2006), and the impact of such stimuli on perceptual metrics such as those reported in this study are currently being explored.

NOVEL STIMULUS PARADIGMS

Traditional tactile sensory testing has relied heavily on delivery of single-site stimuli to the skin and querying test subjects on various qualities of those stimuli. While these methods are effective in making measures that characterize the peripheral nervous system, they lack in quantitatively assessing centrally mediated disorders of the nervous system. Additionally, the models from which the developments of such peripherally based protocols originate are based more on historical precedence of prior techniques than on a characterization of the central nervous system. This section describes the development of not only novel methods for delivering multi-site tactile stimuli, but a novel approach for sensory testing based on models derived from measures of neural population response yielded from *in-vivo* and *in-vitro* animal experimentation.

In chapter 3, the impact of a constantly changing (ramping) stimulus is explored. The testing was performed not as a "method of limits" threshold test, which has been explored exhaustively in the literature, but instead as an amplitude matching task where one stimulus maintains constant stimulus and the other is ramped to meet it. The method was extensively examined; the parameters of testing included 3 amplitudes and .9 different rates of modulation. The method was found to show drastic differences both between and within a small group of subjects diagnosed with autism (This is explored in great detail in chapter 6).

In chapter 4, a duration discrimination task is task is introduced to explore tactile temporal discrimination and its adherence to Weber's law. Previous optical imaging studies in non-human primates demonstrated that increasing the duration of a vibrotactile stimulus resulted in a consistently longer and more well defined evoked SI cortical response. Additionally, and perhaps more interestingly, increasing the amplitude of a vibrotactile stimulus not only evoked a larger magnitude optical intrinsic signal, but the return to baseline

of the evoked response was much longer duration for larger amplitude stimuli. This led to the hypothesis that the magnitude of a vibrotactile stimulus could influence the perception of its duration. Results confirm this, and also show that the opposite is true; Vibrotactile duration can influence the perception of amplitude. The data from animal studies lead us to believe that this phenomenon is mostly controlled by glia, and could also robust quantification of glia status in subjects with neuroinflammatory conditions.

In chapter 5, the effects of non-noxious thermal stimulation on tactile discriminative processing capacity were evaluated. It was determined that the subject‘s performances in the tests that involve both temporal and spatial summation of sensory information are significantly impacted by elevation of skin temperature, and these perceptual changes might reflect a shift in the balance of cortical excitation and inhibition caused by non-noxious thermal stimulation. This metric could provide a means for assessing central sensitization in patient populations that have dysfunctional mechanisms for mediating pain-touch interactions without the delivery of painful stimuli. Notably, this chapter includes a dynamic tracking of adaptation task, which uses 2 modulating stimuli to affectively measure amplitude discriminative capacity and the effects of adaptation in an extremely short and robust manner.

CHAPTER 3: RATE DEPENDENCY OF VIBROTACTILE STIMULUS MODULATION[3]

Introduction

Prolonged pre-exposure to sensory stimulation modifies discriminative capacity and alters the ability of both peripheral and CNS neurons to process sensory information. Primary sensory cortical mechanisms undergo transient, but significant alterations in response to even a brief exposure to adequate sensory stimulation. For example, both visual and somatosensory cortical pyramidal neurons undergo prominent use-dependent modifications of their receptive fields and response properties. Such modifications attain full development within a few tens of milliseconds of stimulus onset, and disappear within seconds after stimulus termination (visual cortical neurons: (Bredfeldt and Ringach, 2002; Celebrini et al., 1993; Das and Gilbert, 1995; DeAngelis et al., 1995; Dinse and Kruger, 1990; Pack and Born, 2001; Pettet and Gilbert, 1992; Ringach et al., 1997; Shevelev et al., 1998; Shevelev et al., 1992; Sugase et al., 1999); rat somatosensory cortical neurons (Khatri et al., 2004; Khatri and Simons, 2007), for review of short-term primary somatosensory cortical neuron dynamics see (Kohn, 2007; Kohn and Whitsel, 2002)).

Previously, we reported on the capacity of 20 healthy adult subjects for detecting differences in the amplitude of two simultaneously delivered 25 Hz vibrotactile stimuli in both the absence and presence of prior exposure to different conditions of adapting stimulation (Tannan et al., 2007b) with the use of a novel portable dual skin site stimulator (Tannan et al., 2007a). Results obtained from that study demonstrated that increasing durations of adapting stimulation at one of the two skin sites, in the range of 0.2 to 2.0 s, led to a systematic and progressive decrease in each subject's ability to discriminate between the two different

[3] This chapter previous appeared in Brain Research. The original citation is as follows:
Francisco, E., J. Holden, Z. Zhang, O. Favorov, and M. Tommerdahl. 2011. “Rate Dependency of Vibrotactile Stimulus Modulation.” Brain Research 1415: 76–83.

amplitudes. Delivery of adapting stimuli to both of the sites of skin stimulation prior to simultaneous delivery of the test and standard stimuli, however, led to an improvement in amplitude discrimination performance—a finding which was consistent with prior published psychophysical studies that demonstrate improvements in discriminatory capacity with much longer durations of adaptation (Goble and Hollins, 1993, 1994). The conclusion of that study was that the perceptual effects of vibrotactile adaptation could be attributed to adaptation-induced alterations of SI response.

Prior reports that proposed that vibrotactile adaptation is amplitude specific (Goble and Hollins, 1993) led us to consider that continuously changing the amplitude of a vibrotactile stimulus could modify the impact that adaptation would have on a perceptual task. We hypothesized that increasing rates of amplitude change, or stimulus modulation, would lead to a decreased impact of adaptation on the observed percept. In other words, if a stimulus presented to the skin is constantly changing, then the resulting adaptation will be effectively reduced. In this report, we describe an amplitude discrimination task in which two stimuli are presented simultaneously to the skin—one stimulus is held constant, and the other stimulus is dynamically increased from a null value up to a level that the subject perceives the two stimuli to be identical. The observations obtained indicate that the rate of the stimulus change had a significant impact on the degree to which sensory percepts were altered by adaptation. In this report, we define adaptation, or short-term cortical plasticity, as the changes that occur in sensory perception within a relatively short time frame (between 0.2 and 5 s of repetitive sensory stimulation).

Additionally, it was concluded that such measures that are sensitive to changing conditions of adaptation could prove useful for the study of subject populations that have systemic alterations of the cerebral cortex that compromise factors/mechanisms which contribute to the process of adaptation to a short duration repetitive stimulus. Subsequent reports demonstrated that subjects with autism did, in fact demonstrate a reduced impact of adaptation (Tannan et al., 2008). If the task is dependent on a subject's ability to adapt, then we

would predict that adaptation-compromised subjects would have difficulty with this task. To test this idea, we conducted a study with 12 autism individuals, previously reported to have below-normative autism metrics (Tannan et al., 2008). The results of this study lead to the speculation that there are subgroups within the autism spectrum that can be identified by differences in sensory information processing.

Results

Sensory tests were administered to measure how effectively subjects could match a constant amplitude vibrotactile stationary stimulus with a non-stationary stimulus whose amplitude was constantly increased. In order to evaluate if there was an amplitude dependency on a subject's ability to perform the matching task, three standard stimuli of 200, 300, and 400 μm were used as standard stimuli. The standard stimuli—which were 25 Hz sinusoidal stimuli whose amplitudes were held constant (i.e., they were "stationary") were delivered simultaneously with the non-stationary test stimuli whose amplitudes were increased at a constant rate. On each trial, the test stimulus was initiated at an initial value of 5 μm and incremented at multiple modulation rates (1.25, 5, 10, 15, 20, 25, 30 and 35 μm/s). The amplitude of the standard stimulus and the rate of the modulation were varied on a trial-by-trial basis in order to evaluate the rate dependency of stimulus modulation and to reduce potential training effects. The subject was instructed to indicate when the two stimuli were perceived to be the same. The end of each trial was indicated when the subject responded that the two stimuli were perceived to be identical, and the difference limen (DL) was computed to be the difference between the amplitude of the standard stimulus and the amplitude of the test stimulus at the end of the trial.

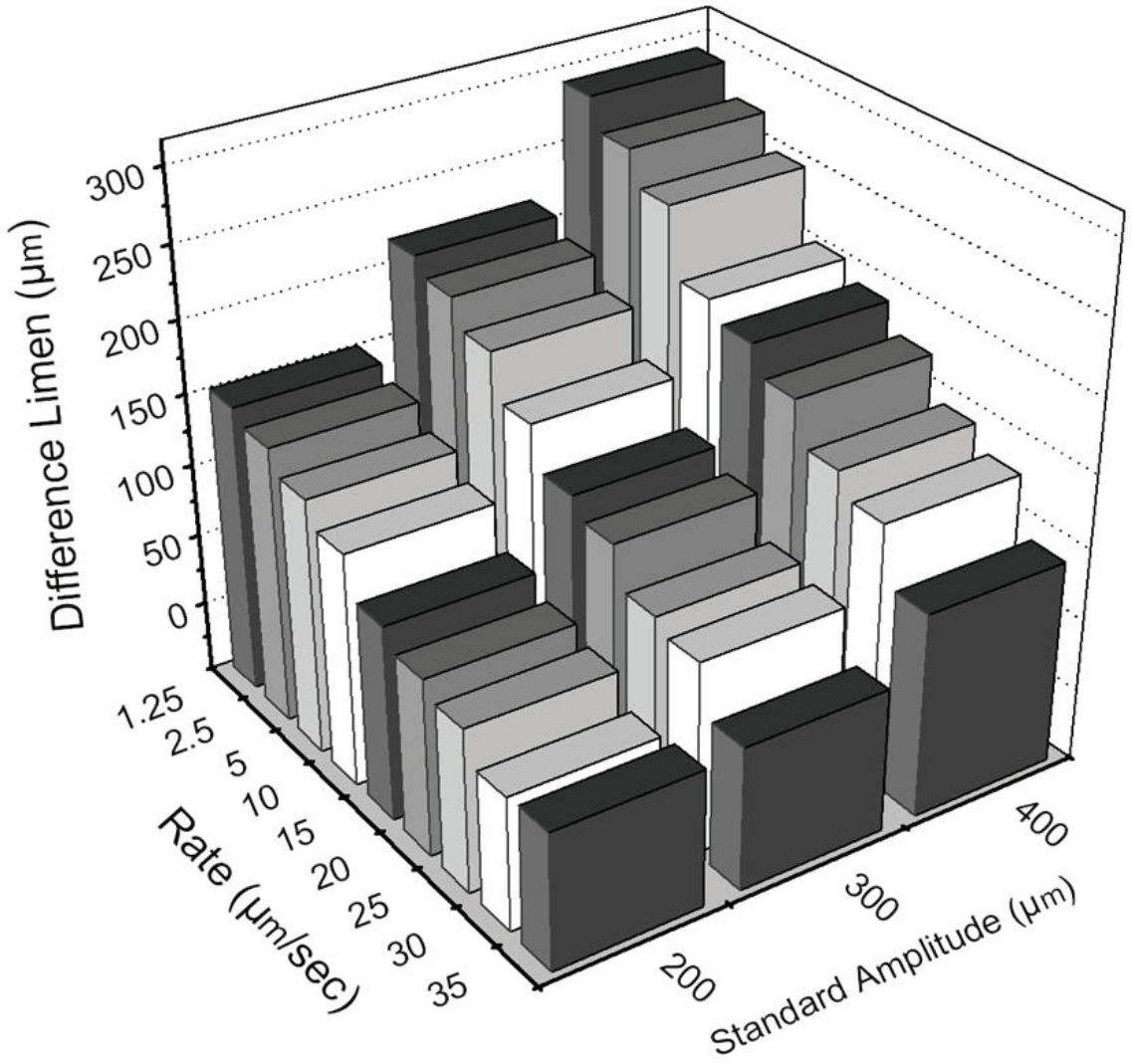

Figure 3.1: Summary of Average Difference Limens
Note the systematic increase in DL with increasing standard amplitude (as predicted by Weber's Law) and the systematic decrease in DL with increasing rate of stimulus amplitude modulation (not predicted by Weber's Law).

Fig. 3.1 summarizes the results in terms of DL obtained at different standards and modulation rates, and it demonstrates that markedly increased DL's are obtained when the rate is slowed and/or when the standard is larger. Large DLs on this task indicate the subject responded well before the two stimuli were delivered at equal amplitudes; smaller DLs indicate that the subjects perceived the stimuli to be the same when the stimuli were much closer in amplitude. Note that DLs are uniformly larger with each successively larger standard, and a systematic increase in DL can be observed with decreases in rate as well. Decreasing the

modulation rate appears to have very similar effects on the results obtained with each of the standard amplitudes. If this is the case, then examination of the relative change in DL should indicate a similar rate dependent trend for each standard amplitude.

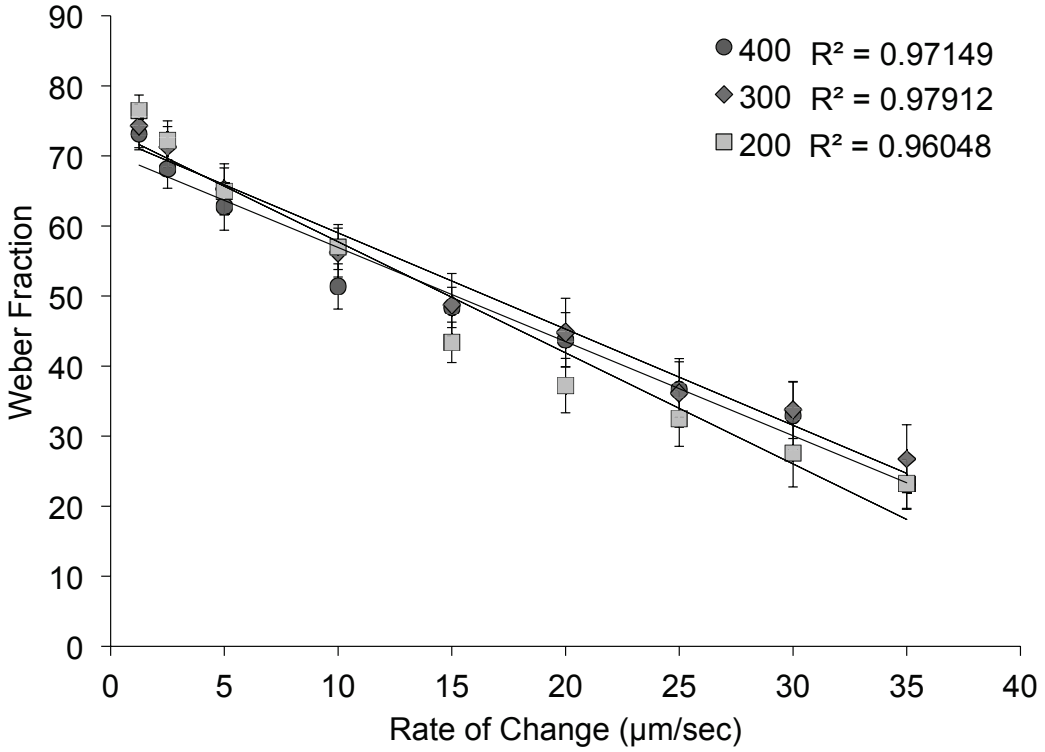

Figure 3.2: Linearity of Averaged Difference Limens
The 3 tested standards demonstrate remarkably similar weber fractions for each of the rates of amplitude modulation tested. It is clear that a change in amplitude modulation rate affects the subjects' measured Weber fractions similarly across all three tested standards.

Fig. 3.2 demonstrates such an observation. In Fig. 3.2, the Weber's Fraction (DL normalized by the amplitude of the standard stimulus) is plotted against the modulation rate, and the graph shows that regardless of the standard used the Weber's Fraction changes in the same relation to the modulation rate. The differences in the linear regression lines for the three standard stimulus amplitudes are not statistically significant (for 200 μm vs. 300 μm standards $p = 0.17$; for 200 μm vs. 400 μm standards $p = 0.13$; for 300 μm vs. 400 μm standards $p = 0.95$; statistics calculated using a t-test for significance of the difference between regression

coefficients in Batson, 1956). Similarity of the data obtained from the three standards in terms of the Weber's Fraction justifies combining the results from all 3 standard amplitudes.

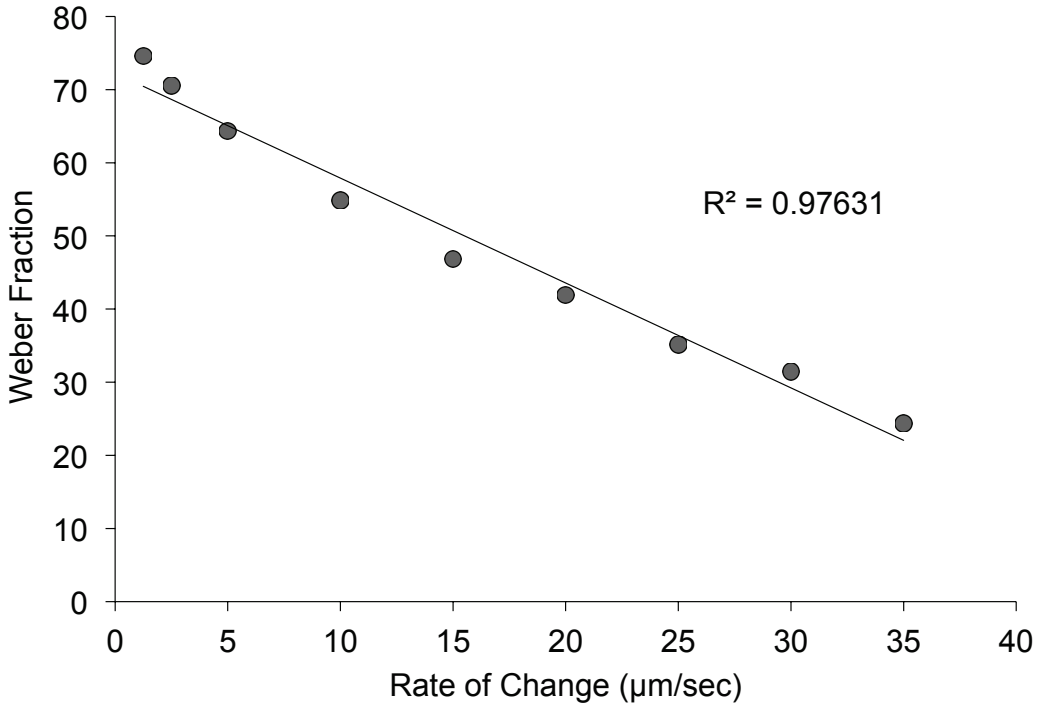

Figure 3.3: Correlation of Amplitude Modulation Rate to Weber Fraction
The results from all standards illustrated in Fig 3.2 have been averaged. Note correlation coefficient (R2= 0.9763) indicates the method to be fairly robust.

Averaging the Weber's Fractions obtained from the 3 standards results in the demonstration of a linear relationship between modulation rate and Weber's Fraction. Fig. 3.3 is a plot of the Weber's Fraction averaged across all 3 standards, and the data is linear (R^2 = 0.98). Weber's Law predicts a flat line (at 10-15% of the standard; Francisco et al., 2008) but this data shows that as the modulation rate of the stimuli is increased the measured Weber's Fraction experiences a systematic decrease.

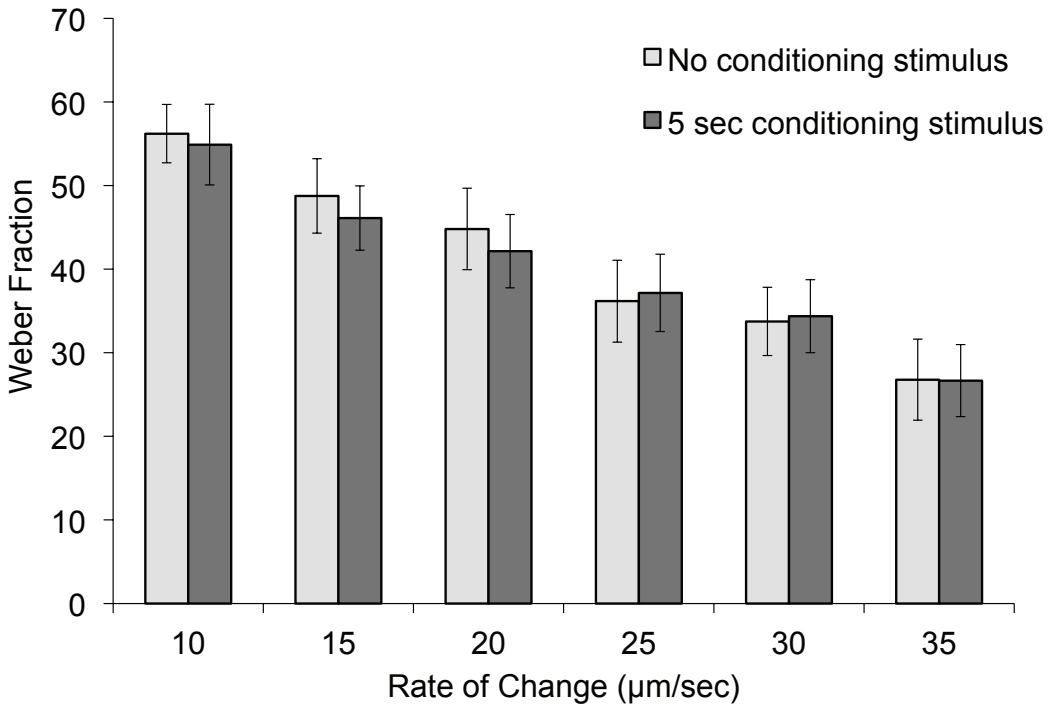

Figure 3.4: Impact of Pre-Conditioning on the Matching Task
Results from delivering a 5 second conditioning stimulus on a subset of the amplitude modulation rates demonstrates minimal impact on performance by the pre-conditioning.

At first glance, it appears that the data simply suggests that slower modulation rates impacted the results simply due to longer stimulus durations. In other words, this led to the question of whether the results were in fact rate dependent or simply duration dependent. In order to obtain additional insight into the rate vs. duration dependency of the DL, the protocol was modified by delivering 5s of conditioning stimulation at the standard test site prior to the onset of each trial. The results obtained are plotted in Fig. 3.4 as the relationship between the Weber's Fraction and the rate. Though there are some subtle differences, it is clear that the additional 5 s of conditioning stimulation at the standard stimulus site had very little impact on the results (the two distributions are fitted by the regression lines that have the probability of being the same at $p = 0.35$, calculated using Batson, 1956). Utilizing a reduced version of the above-described method (one standard, multiple rates), we conducted a pilot study on 12 subjects with autism (Fig. 3.5).

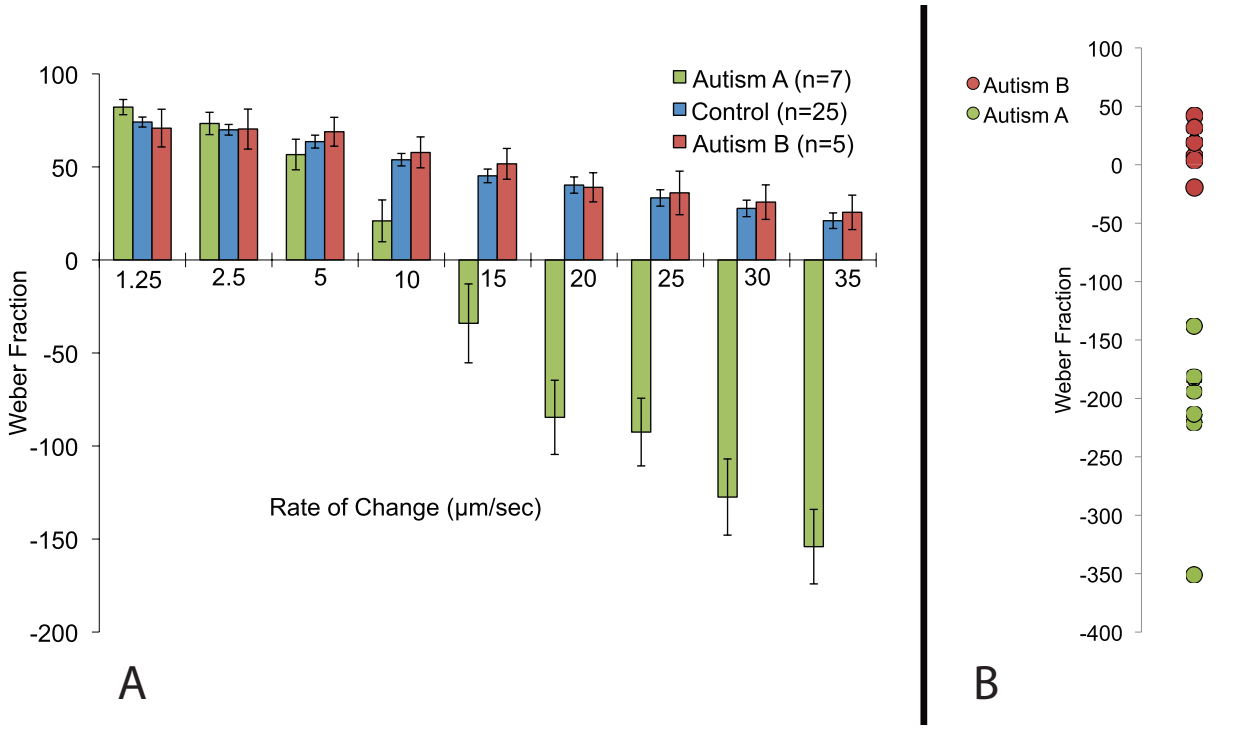

Figure 3.5: Comparison of Data Obtained from Controls vs. Individuals with Autism
Panel A. Note that at lower rates of stimulus amplitude modulation, all 3 groups behave approximately the same way. As the amplitude modulation rate is increased, a clear distinction between two groups within the autism sample emerges.
Panel B. Individual data points from autism sample at the highest modulation rate displayed in Panel A. Note the clustering of the data points.

Interestingly the results from the autism spectrum were bimodal at the higher rates of stimulus modulation. Fig. 3.5A demonstrates that while half of the subjects with autism performed very similarly to that of controls, the other half performed significantly different at the higher rates—in fact, waited to respond well beyond the point where the stimuli were actually matched. The regression line of the Autism A group differs significantly from the regression lines of the Autism B and Control groups ($p<0.001$), whereas the differences in the regression lines of the Autism B and Control groups are not statistically significant ($p = 0.90$) (Batson, 1956). Note that in Fig. 3.5B, the plot of individual data points of the autism subjects taking this test shows that there was a clear separation in performance at the 35 μm/s modulation rate. The negative DLs measured in this test indicate that the subject responded beyond the matching point of the two stimuli rather than before. Of note is that there was no difference in simple reaction time in these two groups—both of which was comparable to that

of controls (219.9 ms for Group Autism A, 220.0 ms for Group Autism B, 200 ms for age-matched controls).

Discussion

A vibrotactile amplitude matching task was performed in which a stationary, or non-changing, stimulus was compared to a non-stationary stimulus whose amplitude was increased at a fixed rate, and perceptual metrics were obtained at the different rates of stimulus modulation. In the study of 50 control subjects, DLs increased with increasing amplitude in a manner consistent with Weber's Law. Increasing the rate of stimulus modulation, on the other hand, decreased the Weber's Fraction in a manner that appears to be inconsistent with Weber's Law; in other words, increasing the modulation rate has the same effect on the DL as decreasing the standard stimulus intensity. While the increase in DLs that parallels the increase with the standard amplitude is expected (based on Weber's Law—see Francisco et al., 2008 for discussion), the decrease in DL with increasing rate is counterintuitive. At first glance, one would reason that increasing the rate of the increase in stimulus intensity would result in a more difficult matching task. However, when the process of adaptation is taken into consideration, the results can more easily be explained. First, the standard stimulus does not change, and perceptually, this means that it undergoes a significant gain reduction (i.e., is perceived to be weaker). The stimuli associated with the slower rate of growth are also adapting —the stimulus is not changing fast enough to not undergo the same gain change—and both stimuli undergo significant signal to noise ratio reductions, resulting in a larger DL. The test stimuli being delivered at a higher rate are not undergoing the same change in perceptual gain —they are probably not reduced in perceived intensity to the same degree—and a decrease in signal to noise ratio does not impact the DL as much (which is very similar to the DL that is obtained with a simple amplitude discrimination task, such as the ones described in Tannan et al., 2007a, 2007b, 2008; Zhang et al., 2009; Francisco et al., 2008).

Thus, less adaptation might actually lead to better performance at this task. At first glance, this may seem contrary to reports that demonstrated that adaptation improves a

subject's ability to discriminate between two vibrotactile stimuli differing only in amplitude (Goble and Hollins, 1994; Tannan et al., 2007b). However, while it is true that contrast enhancements are made with conditioning stimuli, it is also true that significant gain adjustments are made, and the reductions in perceived intensity that resulted from slower modulation rates clearly played a significant impact in the ability of the subjects to discriminate between the two stimuli. The effects of delivering an adapting stimulus on the perception of subsequent test stimuli—particularly the reduction in sensation—has been characterized in some detail (Craig, 1974; Delemos and Hollins, 1996; Gescheider et al., 1995; Goble and Hollins, 1993; Laskin and Spencer, 1979; Tommerdahl et al., 2005b; Verrillo and Gescheider, 1977). Many psychophysical studies have reported that the presentation of an adapting stimulus causes an increase in the detection threshold, and thus a reduction in the perceived intensity, of a subsequent stimulus (for review see Verrillo, 1985; Gescheider et al., 1995; Goble and Hollins, 1993; Verrillo and Gescheider, 1977). More specifically, Gescheider et al. showed that the threshold shift which occurred after the presentation of an adapting stimulus increased systematically with adapting stimulus duration (Gescheider et al., 1995). Thus, at first glance, it would appear that the rate dependency of the increase in DL could simply be a function of duration, which is obviously increased with slower modulation rates.

Although the principle finding of this report is that modulation rate does have a significant impact on neuroadaptation and subsequently the DL, it appeared that independent of rate, there was a duration dependency of stimulation on the DL that was consistent with prior reports. In other words, changing the stimulus modulation rate changes the exposure of the skin site to the duration of the stimulus. As the stimulus duration was increased as a consequence of slower modulation rates, DLs became larger. Based on previous studies in which we examined the duration dependency of stimuli (Simons et al., 2007; Tannan et al., 2007b), we were inclined to suspect that duration played a role in the degradation of DLs. However, the finding that a 5-second conditioning stimulus had virtually no effect on the results leads the authors to the conclusion that the DLs obtained in this study were primarily

rate and amplitude dependent. We do find this somewhat surprising, as it was our anticipation that such a conditioning stimulus at the site of the standard would have the impact of reducing the percept of the standard. We propose two possible reasons for this outcome. First, the entire duration of the shortest trial (at the rate of 35 μm/s) is approximately 5 s, with or without the conditioning stimulus. Thus, one possibility is that the reduction in gain that occurs with repetitive stimulation is effectively the same after 5 or 10s of stimulation. Although this may seem surprising when considering the significant changes in gain reduction that occur between 0.2 and 2.0 s of conditioning stimulation (Tannan et al., 2007b), it is consistent with observations that have been made in optical imaging studies of squirrel monkeys that show very little difference in the magnitude of the response after 5 vs. 10 s (Tommerdahl et al., 2002) although the contrast within and surrounding the responding cortical field is significantly enhanced (Chiu, 2006; Simons et al., 2007; Tommerdahl et al., 2002). A second, and perhaps more interesting speculation is that the combined percept of the two stimuli is impacted most significantly by the modulation rate of one of the two stimuli that are simultaneously delivered to adjacent digit tips. Since the overall percept of the simultaneously delivered stimuli is changing, then the impact of adaptation at a single stimulus site may be relatively reduced. A corollary to this second speculation is that the faster a stimulus is changing, the less adaptation —or gain reduction—that is taking place at that stimulus site. If as others have proposed vibrotactile adaptation is amplitude specific (Goble and Hollins, 1993), then continuously changing the amplitude of the stimulus would have the impact of continuously delivering a "new" or "novel" stimulus, and thus, with less adaptation at the higher rates of modulation, a smaller DL would be expected.

We hypothesized that subjects with autism—previously demonstrated to have lower than normal adaptation metrics (Tannan et al., 2008)—would perform better at this task than the control population. Our reasoning for this was quite simple: In the control condition, it appears that more adaptation (which we postulated to occur at slower rates of modulation) is detrimental to performance. Less adaptation—such as what is observed at higher rates of

modulation—results in better performance. If individuals with autism adapt poorly, then it stood to reason that they would outperform the control population on this task. The results with the autism group suggested that, for a significant subset of the group, this could be the case for one of the rates tested (10μm/s). At lower modulation rates, all subjects appeared to perform approximately the same, yet at higher modulation rates, there was a significant distinction in performance that characterized a difference between two groups of autism subjects. One working hypothesis regarding this is that adaptation is very sensitive to the duration that a stimulus is "apparently stationary". If the stimulus is modulated above a certain rate, then it becomes more difficult to adapt to, and a perceptual test which modulates stimulus amplitude at the higher rates used in this study could be a very sensitive means for assessing how well an individual adapts. The individuals with autism consisted of two groups: those whose performance was similar to that of controls, and those who performance was strikingly different. Additionally, this group of autism individuals appeared to outperform the control group at one of the modulation rates (10 μm/s). In other words, when the stimulus amplitude was modulated at this rate, this group of autism subjects was very good at matching the two stimuli. This interesting finding is being more thoroughly investigated with a larger autism cohort ($n > 50$) and will be reported in the near future.

There is considerable evidence that individuals with autism lack sufficient inhibition for normative cortical information processing (for discussion, see Tannan et al., 2008; Tommerdahl et al., 2006, 2008). Yet, why would the two groups in the autism spectrum perform differentially? One possible explanation is that it is widely recognized that a large number of factors contribute to the differential phenotypes observed in the autism spectrum, and these factors undoubtedly lead to variations in the impact that autism has on an individual's central information processing capacity. The sensory perceptual metric presented in this study could be sensitive to subtle differences in the decreased inhibition that could be attributed to the differences that exist between cortical minicolumns in autism and neurotypical populations. The inhibitory processes between minicolumns are a necessary component for the moment-to-

moment changes that normally occur in cerebral cortex with repetitive stimulation (Chiu, 2006; Favorov and Kelly, 1994a, 1994b; Kohn et al., 2000; Tommerdahl et al., 1993, 2005a), and Casanova et al. (2002) have developed a large body of evidence that demonstrates that the cerebral cortex of autism subjects is significantly modified at the minicolumnar level. Casanova also suggests that this aberrant minicolumnar structure results in the disruption of the inhibitory architecture (Casanova et al., 2003) that is required for normal function in local neural circuitry. In other words, disruption of functional connectivity at the local minicolumnar level could be responsible for or strongly correlated with the dysfunctional connectivity that leads to a degradation of the normal response to repetitive stimulation in which cortical ensembles decrease in response with increasing repetition. A subtle, but significant, change in an individual's functional connectivity at the minicolumnar level could contribute enormously to the types of differences in sensory information processing that were observed between these two groups within the autism sample. Understanding the differences in cortical information processing within the autism subject population, with methods such as the one described in this report, may prove to be effective in understanding the heterogeneity currently recognized to be prevalent in autism, and this will be more fully described in a subsequent study.

Conclusions

To our knowledge, this is the first demonstration of assessment of rate dependency of the amplitude modulation of a tactile stimulus, and several points of significance have emerged from the findings of this study. First, the methodology demonstrated that Weber's Law was adhered to when the standard amplitude was varied within the range studied. Interestingly, increasing the amplitude modulation rate gave the appearance of not following Weber's Law, as increases in the stimulus modulation rate led to decreases in the DL. However, consideration of the impact of adaptation on the stimulus percept explains this discrepancy. Second, the findings demonstrated that neuroadaptation is a relatively rapid process, and increasing the rate at which stimuli are changed alters the impact that adaptation has on perception. Third, the method appears sensitive to detecting CNS processing differences within the autism

population in that a subset of that group performs radically differently at higher stimulus modulation rates.

Experimental procedures

Fifty healthy control (typically developing; TD) subjects between the ages of 20 and 39participated in this study. They were naïve both to the study design and issue under investigation. The group consisted of32 males and 18 females; 40 who were right-hand dominant and 10 left-hand dominant. The study was performed in accordance with the Declaration of Helsinki, all subjects gave their written informed consent, and the experimental procedures were reviewed and approved in advance by an institutional review board.

Experimental sessions were conducted with the subjects seated comfortably in a chair with the right arm resting on an armrest attached to a portable four-site vibrotactile stimulator positioned on a table in front of the subject. Vibrotactile stimulation was conducted via 5mm circular probes that come in contact with subject's digit 2 (index finger) and digit 3 (middle finger). Glabrous pads of digit 2 (D2) and digit 3 (D3) were chosen as the test sites for two reasons: (1) to allow the convenience of access and comfort of the subject, and (2) because of the wealth of neurophysiological information that exists for the corresponding somatotopic regions of cortex in primates. The independent probe tips are computer con-trolled and capable of delivery of a wide range of vibrotactile stimulation of varying frequencies (measured in Hertz) and amplitudes (measured in micrometers, μm). A baseline indentation of 500 μm was used to ensure that the probe was in contact with the skin for the entire duration of the stimulation.

Participants viewed a computer monitor, which provided continuous visual cueing during the experimental session. Specifically, an on-screen light panel indicated to the subject when the stimuli were on and when the subject was to respond. Practice trials were performed before each test which allowed the subject to become familiar with the tests. The subject was not given performance feedback or knowledge of the results during data acquisition. The

sensory testing session was conducted by application of low frequency (25 Hz) vibration to the right hand's index and middle finger(s).

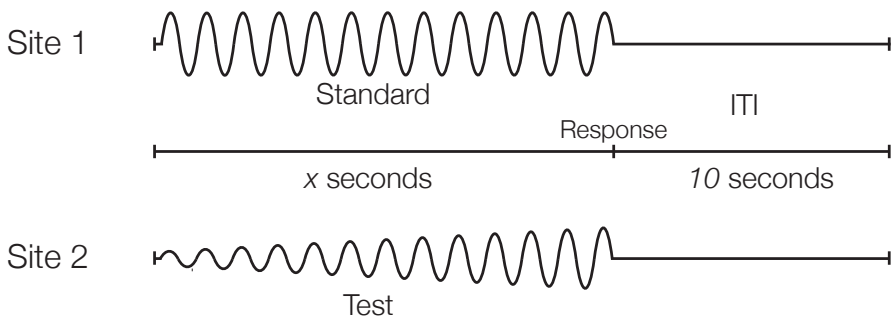

Figure 3.6: Amplitude Matching Protocol.
The "standard" stimulus (25 Hz vibrotactile stimulus at constant amplitude) was delivered randomly to either D2 or D3 on a trial-by-trial basis. On the alternate digit (D3 or D2), a 25 Hz "test" stimulus was delivered with initial amplitude of 5 microns. The amplitude of the test stimulus was increased at a constant rate, which was varied from trial to trial, until the subject responded. Stimulation was terminated when the subject responded by switch box that the two stimuli were perceived to be the same, and a 10 sec delay intervened between stimulus response and onset of the next trial.

The protocol reported in this study was designed in order to rapidly and effectively measure a subject's ability to match the intensity of two stimuli when one stimulus was held at a fixed sinusoidal amplitude, and the amplitude of a second sinusoidal stimulus was ramped (i.e., increased from an initial minimal value) to approach it. The "standard" stimulus (25 Hz vibrotactile stimulus at constant amplitude) was delivered randomly to either D2 or D3 on a trial-by-trial basis. On the adjacent digit, a 25 Hz "test" stimulus was delivered with initial amplitude of 5 μm. The amplitude of the test stimulus was increased at a constant rate (which was varied from trial to trial) until the subject responded. Subjects were instructed by on-screen directions to click a switch box using their left hand when they perceived that the two stimuli were of equal strength or intensity, i.e., when they felt the stimuli "matched" (see Fig. 3.6). Both rate and standard amplitude were varied independently and interleaved on a trial-by-trial basis using a 10-second inter-trial interval. Each subject was tested with stimulus modulation rates of 1.25, 2.5, 5, 10, 15, 20, 25, 30, and 35 μm/s at standards of 200, 300, and 400 μm. At the end of each trial, the duration of the stimuli and the amplitude difference between the test and standard (difference limen) at the moment the subject responded was recorded. Stimuli were

delivered until the subject responded, and thus, the duration of the test was variable since it was subject response dependent.

A second abbreviated “conditioning” protocol was used to measure the effect of a conditioning stimulus on the subject's ability to match the intensity of the stimulus. A 5-second conditioning stimulus was delivered to the standard stimulus site before onset of the standard or test stimulus. The protocol— as described in the previous paragraph—occurred normally after the delivery of the 5-second conditioning stimulus; the subject responded when the two stimuli felt identical and the difference limen and duration of each trial were measured and recorded. For this protocol, the duration was measured from the end of the conditioning stimulus until the subject's response. The test stimulus began immediately after the conditioning stimulus without an inter-stimulus interval. In other words, there was no break in stimulation. Rates of 10, 15, 20, 25, 30, and 35 μm/s were tested for only the 300-μm standard, and the conditioning stimulus was delivered as a 25 Hz vibrotactile stimulus at constant amplitude of 300 μm. Only rates of 10, 15, 20, 25, 30, and 35 were used because the average duration of these tests were 6–12 s and were predicted to most likely to be heavily impacted by a 5-second conditioning stimulus. The longer trials were not performed to avoid subject fatigue.

Using the first described protocol (without conditioning), data was collected from 12 subjects with autism spectrum disorder (ASD). Diagnoses for all 12 subjects with ASD were made using both the Autism Diagnostic Interview (ADI-R; LeCouteur et al., 2003) and the Autism Diagnostic Observation Schedule (ADOS-G; Lord et al., 1999) by a trained administrator. Autism subjects were recruited from the University of North Carolina Neurodevelopmental Disorders Research Center Subject Registry. All twelve individuals had average to above average intelligence (WASI Full Scale IQs ranged from 83 to 130) according to the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). Participants were screened for co-morbid psychiatric diagnoses, peripheral injury, and other conditions that would affect somatosensation. The subjects gave informed consent and were paid $25/h for their time. All procedures were reviewed and approved in advance by an institutional review board.

CHAPTER 4: TACTILE DISCRIMINATION OF DURATION & AMPLITUDE

Overview

There have been numerous studies on time perception. However, very few of these have involved the use of tactile stimuli to assess a subject's capacity for duration discrimination. Previous optical imaging studies in non-human primates demonstrated that increasing the duration of a vibrotactile stimulus resulted in a consistently longer and more well defined evoked SI cortical response. Additionally, and perhaps more interestingly, increasing the amplitude of a vibrotactile stimulus not only evoked a larger magnitude optical intrinsic signal, but the return to baseline of the evoked response was much longer duration for larger amplitude stimuli. This led the authors to hypothesize that the magnitude of a vibrotactile stimulus could influence the perception of its duration. In order to test this hypothesis, subjects were asked to compare two sets of vibrotactile stimuli. When vibrotactile stimuli differed only in duration, subjects typically had a difference limen (DL) of approximately 13%, and this followed Weber's Law for standards between 500 and 1500 msec, as increasing the value of the standard yielded a proportional increase in DL. However, the percept of duration was impacted by variations in amplitude of the vibrotactile stimuli. Specifically, increasing the amplitude of the standard stimulus had the effect of increasing the DL, while increasing the amplitude of the test stimulus had the effect of decreasing the DL. Since this effect paralleled what was predicted from the optical imaging findings in somatosensory cortex of non-human primates, the authors interpreted the findings to suggest that primary sensory cortex could play a significant role in timing perception in the 500 to 1500 msec range. Data from this study combined with previous neurophysiological studies, suggests that perception of duration/amplitude in this test might be controlled largely by neuron-glial interactions.

Introduction

Over the past several years, we have been designing sensory perceptual tests that were designed on the basis of neurophysiological observations — observed both from experiments that were conducted in our lab as well as published findings of others. For example, numerous studies have reported on the effects of repetitive vibrotactile stimulation on the SI evoked cortical response (Cannestra et al. 1998; J. Chiu 2006; J. S. Chiu et al. 2005; Stephen B. Simons et al. 2005; S. B. Simons et al. 2007) and from the findings reported in those studies, we predicted that sensory perceptual metrics could be impacted — by either improvement or degradation — with specific parametric changes in stimulus conditions. These perceptual findings, which proved to be robust in healthy controls (Francisco et al. 2011; Francisco et al. 2008; V. Tannan, Dennis, and Tommerdahl 2005; V. Tannan, Simons, et al. 2007; M Tommerdahl et al. 2007; Zhang, Francisco, et al. 2011), have demonstrated sensitivity to a number of neurological conditions (Folger et al. 2008; Francisco et al. 2011; Richard H. Nguyen et al. 2013; R. H. Nguyen et al. 2013; Vinay Tannan et al. 2008; M Tommerdahl et al. 2007; Zhang, Zolnoun, et al. 2011). In other words, when a subject is neurologically compromised, the mechanisms involved in these biologically based metrics partially fail, and the neurologically compromised individual demonstrates metrics that significantly deviate from normative values.

In vivo observations have revealed details about how sensory information is processed in the cortex, specifically that a relationship exists between time dependency of repetitive stimulation and the magnitude of stimulation. Using optical intrinsic signal (OIS) imaging, observations were made of the SI evoked response to changes in stimulus intensity (J. Chiu 2006; Stephen B. Simons et al. 2005) and changes in stimulus duration (J. Chiu 2006; S. B. Simons et al. 2007). In these studies, it was demonstrated that although absorbance values increased with increasing intensity, a center surround pattern was established and a relationship between the contrast of the evoked SI cortical response with increases in stimulus intensity (S. B. Simons et al. 2007; Mark Tommerdahl, Favorov, and Whitsel 2010). The time course of the OIS response for longer duration stimuli systematically increased with stimulus

duration, but perhaps more interestingly, this same time course of the OIS response also increased with increasing stimulus intensity. Figure 4.1 summarizes the OIS findings from these studies.

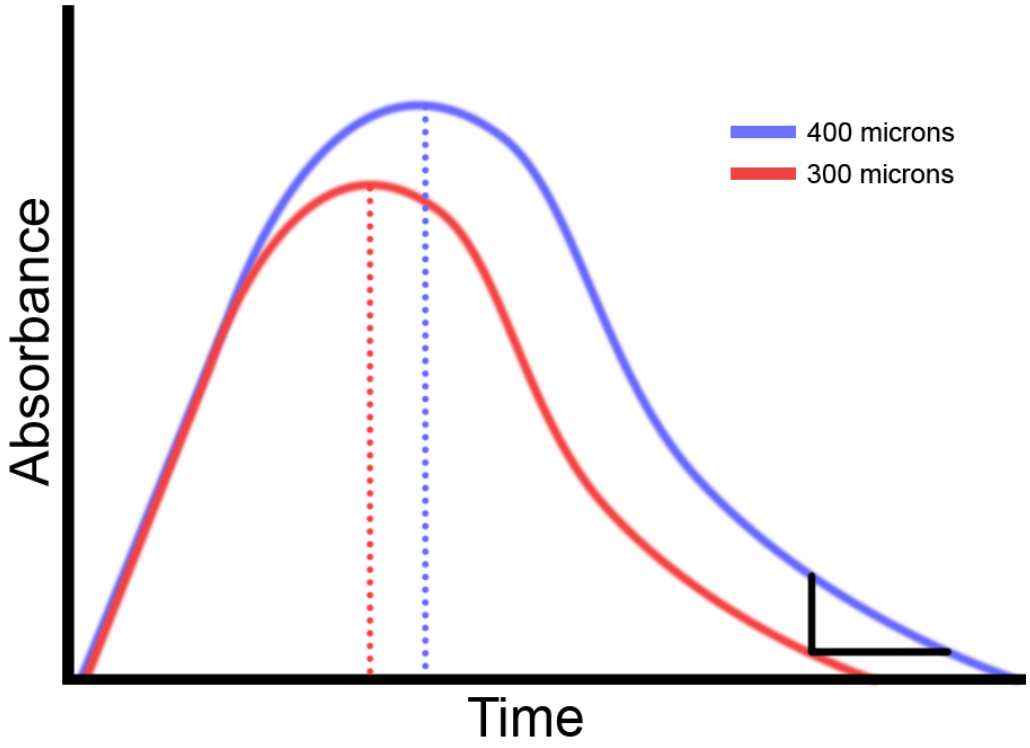

Figure 4.1: OIS Pictorialization.

Note that with an increase in stimulus intensity, there is not only an increase in the magnitude of the evoked response, but in the duration of the response. As a result of these observations, we postulated that an increase in stimulus intensity could lead to an increase in the percept of stimulus duration. To test this idea, the duration discrimination capacity of 20 healthy subjects was obtained, and the stimulus paradigm was altered to determine if stimulus intensity would have an effect on this percept. Additionally, a pilot study was conducted to determine if the same impact of stimulus intensity on duration discrimination would be present in concussed individuals.

One of the fundamental questions often addressed in neuroscience is how two sensory stimuli are differentiated. The Weber function relates the difference limen (DL) in

discrimination tasks to the intensity of the standard stimulus. This ratio, known as the Weber fraction, should remain constant across any standard if the sensory percept being tested obeys Weber's Law. Research has shown that Weber's Fraction is usually constant for a range of stimulus intensities and can be applied to most senses, including weight, brightness, smell, frequency, contrast, velocity and sound pitch (G. A. Gescheider et al. 1990; G. A. Gescheider et al. 1996; G A Gescheider et al. 1997; Hanna, Gierke, and Green 1986; Scholtyssek, Kelber, and Dehnhardt 2008; Stillman et al. 1993; Whittle 1986; Snowden and Braddick 1991; Cornsweet and Pinsker 1965; Stone and Bosley 1965; Harris 2005). Weber's Law has been thoroughly explored in tests relying on timing perception in the auditory and visual modalities, but there remains some debate about Weber's Law adherence in the temporal field. Many studies have found significantly different weber's fractions when comparing tests in the sub-second domain to tests in the macro-second domain. (0.2 & 2 sec (Lavoie and Grondin 2004), 0.2 & 1 sec (Grondin 2010), 0.5 & 3 sec (Güçlü, Sevinc, and Canbeyli 2011)) From theses results many have concluded that Weber's Law does not apply with longer duration perceptual tasks (Getty 1975; Bizo et al. 2006) or in timing perception whatsoever (Abel 2005; Allan, Kristofferson, and Wiens 1971; Allan and Kristofferson 1974; Blakely 1933; Creelman 2005; Kristofferson and Allan 1973; Rousseau and Kristofferson 1973; Stott 1933; Grondin, Ouellet, and Roussel 2001). In contrast, the majority of testing finds that duration discrimination does comply with Weber's Law within a specific range (approx. 500 ms — ~2 sec sources ((McGill and Goldberg 1968; Lapid, Ulrich, and Rammsayer 2008; T. H. Rammsayer and Lima 1991; T. H. Rammsayer 2010b; T. Rammsayer and Ulrich 2012; T. H. Rammsayer 2014; Ehrlé and Samson 2005; Halpern and Darwin 1982). The functional relationship between DL and time has been explored extensively in the auditory and visual domains, but very few studies exist on duration discrimination in the tactile domain. This study is designed to investigate tactile duration discrimination in the sub-second to plus-second (500 to 1500 msec) range.

Results

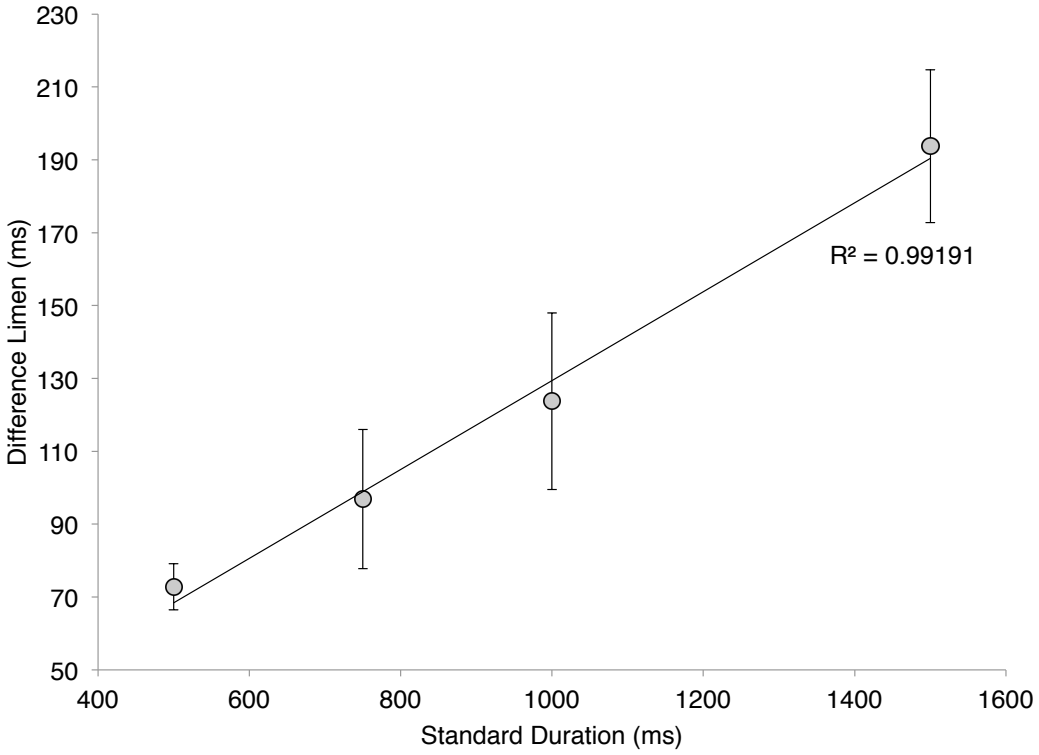

Figure 4.2: Adherence to Weber's Law
Averaged difference limen values of the twenty subjects at various standard durations (with s.e. bars). The plotted linear regression has a correlation coefficient of 0.99191.

Duration discrimination follows Weber's law.

Difference limens (DLs) obtained for duration discrimination tasks in which the standard stimulus ranged in values between 500 and 1500 msec are summarized in Figure 4.2. The results demonstrated that subjects performed significantly better on the duration discrimination task for shorter standard durations than for longer standard durations. In particular, the DLs increased from 72.8±6.3 ms, 96.9±19.1 ms, 123.8±24.2 ms, 193.8±21.0 ms for the duration discrimination tasks with increasing standard durations of 500 ms, 750 ms, 1000 ms, and 1500 ms, respectively. A linear least-squares fit was applied to the data, and an R2 value of 0.992 was obtained for the linear regression (see Figure 4.2). The high correlation coefficient demonstrated a strong relationship between DL and the duration of the standard

stimulus, thereby verifying the application of Weber's law for this particular discrimination task in the range of 500 to 1500 msec. The average measured Weber's Fraction within the tested range was 13.1% ± 0.009.

Impact of an amplitude confound on duration discrimination

The impact of amplitude on the percept of stimulus duration was assessed by introducing an amplitude confound into the duration discrimination task. Figure 4.3 illustrates that increasing the amplitude of the standard duration stimulus significantly degraded performance on the duration discrimination task. Duration discrimination difference limen values for each subject were normalized to unity for the 300 μm condition while thresholds for all other conditions were normalized to within subject performance on the task. The impact of the magnitude of the stimuli on duration was thus quantified, and was statistically significant, with respect to the 300 μm baseline condition: 1.54±0.17 at 350 μm and 2.43±0.26 at 400 μm (Pvalue < 0.005)

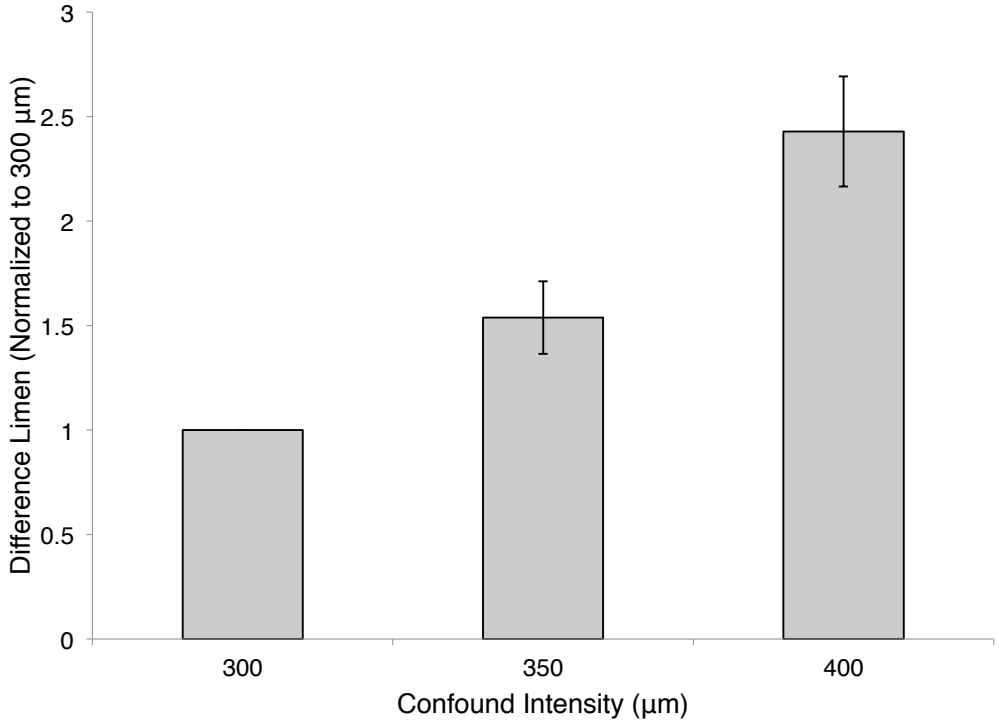

Figure 4.3: Effect of Amplitude Confound on Duration Discrimination
The measured difference limens for the duration discrimination protocol are shown normalized on a subject-by-subject basis to the 300 um condition (both test and standard are at an amplitude of 300 um).

Impact of the location of the amplitude confound

Figure 4.3 outlines the impact of changing stimulus amplitude on the standard when performing a duration discrimination task. Figure 4.4 extends on this finding by instead increasing the amplitude of the test stimulus to an amplitude of 400 μm. The findings suggest that an increase in amplitude on the test site improves the subjects' ability to perform duration discrimination, appreciably driving down their DL's. The impact is not as overwhelming (or as statistically significant) as the previous trial with the amplitude confound on the standard. The difference between the two amplitude confounds are in Figure 4.4, along side a "normal" trial with the confound completely removed (where the amplitudes of both test and standard are 300 μm).

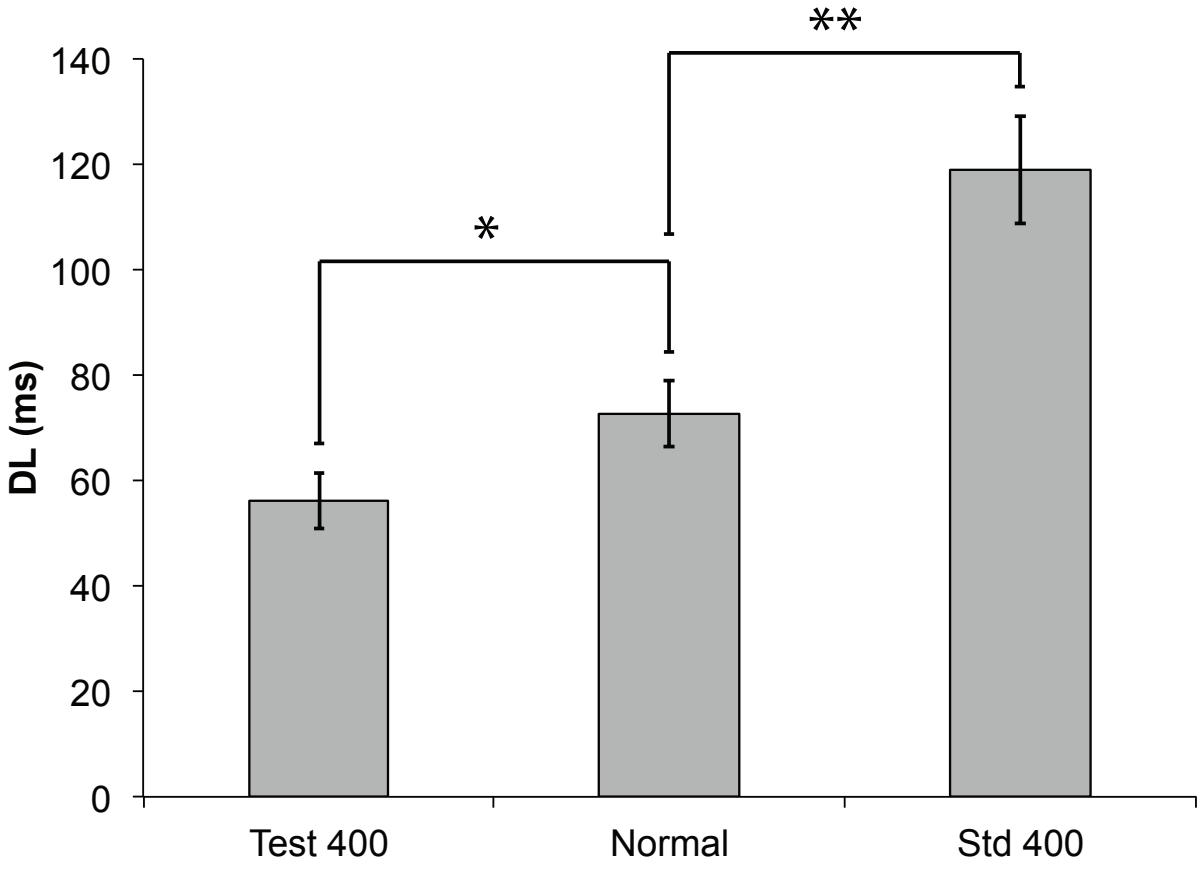

Figure 4.4: Impact of the location of the Amplitude Confound
The measured difference limens for the Duration Discrimination protocol are compared to two different amplitude confounds. In the Test 400 condition, a 400 micron stimulus was used fro the test (longer) stimulus, and for the Std 400 condition, the 400 micron stimulus was used for the standard (shorter) stimulus.

Amplitude confound impact on concussed individuals

Although healthy controls performed significantly worse on the duration discrimination task in the presence of the amplitude confound (increased standard stimulus amplitude), concussed individuals did not appear to have a significant difference in DL with the presence of the amplitude confound on the task (see Figure 4.5). Although controls demonstrated an approximate 60% increase when the amplitude confound was applied, concussed individuals had a non-significant increase in DL of approximately 3%. Thus, performance of the duration pvalue 0.0085 discrimination task in the presence of the amplitude confound appears to have improved when individuals became concussed. (the impact of the amplitude confound was diminished)

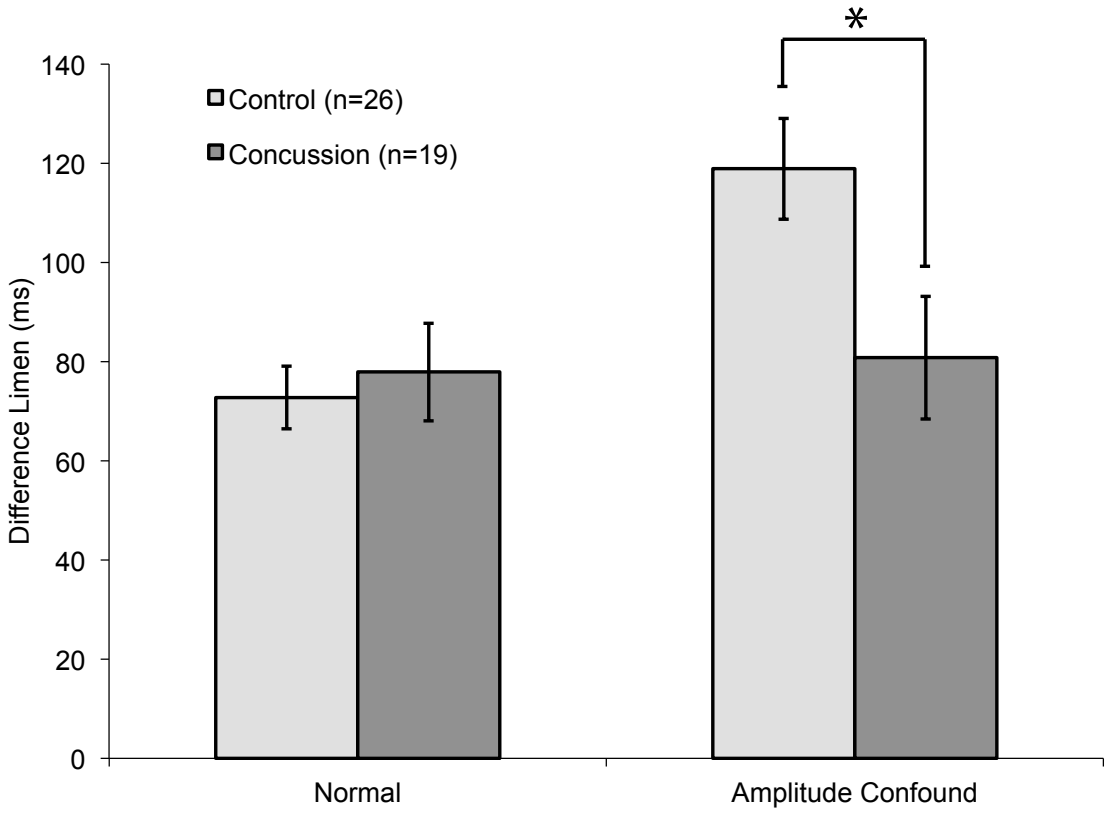

Figure 4.5: The Impact of the Amplitude Confound on Concussed]Individuals
The measured difference limens for the duration discrimination protocol of control subjects from Figure 4.3 are compared to pilot data obtained from nineteen concussed subjects. Only the 400 um Amplitude confound was used for this pilot study

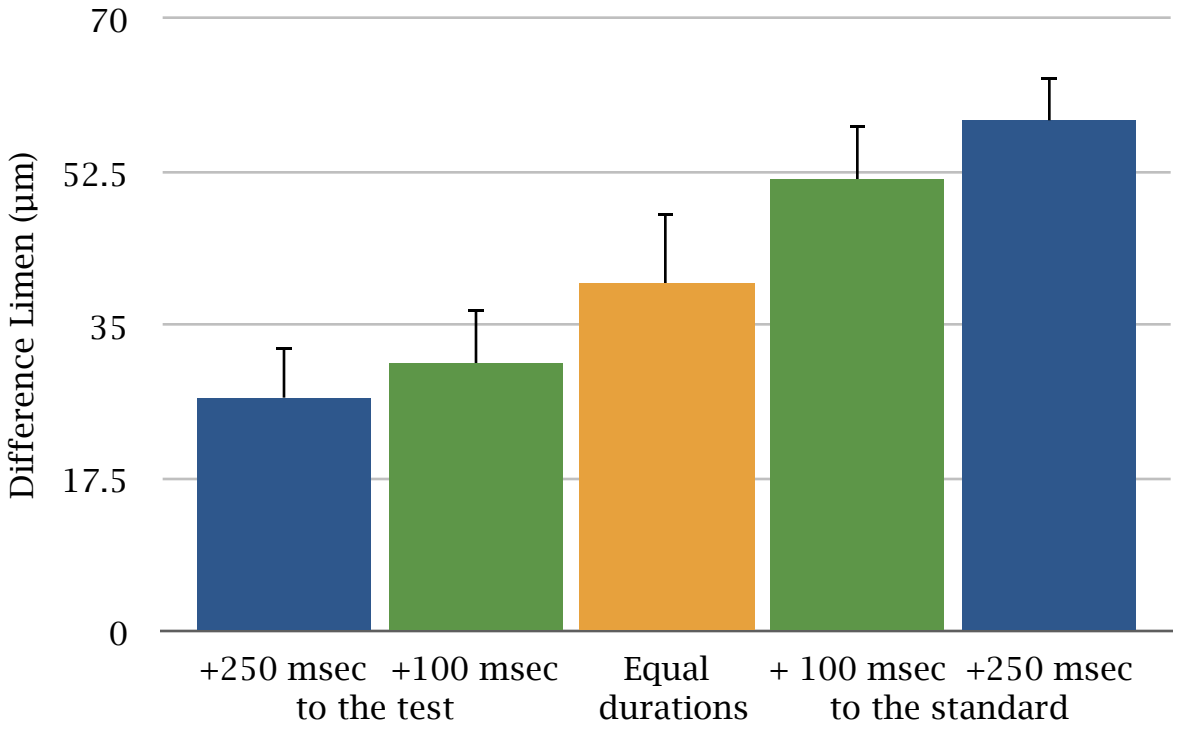

Figure 4.6: Effect of Duration Confound on Amplitude Discrimination.
The measured difference limens for the Amplitude Discrimination protocol are compared to two different duration confounds. In the test longer condition, the test was either +100 ms or +250 ms longer than the standard. The standard was 500 ms in these conditions. In the standard longer condition, the standard was either +100 ms or +250 ms longer than than the test. The duration of the test stimulus was 500 msec for these conditions.

Stimulus duration impacts amplitude discriminative capacity

A standard amplitude discrimination task, performed with sequential vibrations 500 ms in length, measured the average difference limen for these subjects to be 39.8±3.4 um for a 200 μm standard. This finding is inline with previously published amplitude discrimination values (Francisco 2008). Figure 4.6 shows that when the duration of the standard stimuli was increased from 500 ms, DLs were 51.6±9.2 μm and 58.4±5.9 μm for 600 ms and 750 ms test stimuli conditions, respectively. Alternatively, the DLs were 30.7±3.6 um and 26.7±4.9 um when the same durations were applied to the test stimuli. These results suggest that subjects perform better on the amplitude discrimination task when the higher amplitude test stimuli are longer in duration. Amplitude discriminability appears to be impacted proportionally by the length of the duration confound. The 750 ms duration confound created statistically significant

differences, compared to the confound-less condition, when applied to either the test and the standard site (P = ***). The 600 ms condition impacted the subjects amplitude discrimination in a pattern similar to that obtained from the 750 ms trial, but with slightly less significance.

Discussion

In this study, a dual-site vibrotactile duration discrimination protocol was used to determine the difference limen (DL) for a number of standard durations. The DLs were found to increase in a linear fashion with an increase in standard duration, thus adhering to Weber's Law for the stimulus range employed in this study (500-1500 ms). Previous studies have demonstrated that amplitude discrimination capacity, obtained in a similar fashion, also followed Weber's Law. In this study, the Weber Fraction (as a percentage) was 13.1 ± 0.9% for durations ranging from 500 msec to 1500 msec, and this is consistent with what was previously reported for both tactile amplitude discrimination capacity (Francisco et al. 2008) ~ 13%) and for a number of reports studying auditory and visual duration discrimination (Grondin, Ouellet, and Roussel 2001) ~ 13-14%, (Lavoie and Grondin 2004) for 2 sec (T. H. Rammsayer 2014), (T. Rammsayer and Altenmüller 2006), (Henry 1948) ~14%), These results suggest that the Weber-Fechner Law holds true not only for the amplitude discrimination task but also with the duration discrimination task with relatively high standard durations. An important finding of our results was that duration discrimination within the somatosensory system is approximately equivalent to that reported for the auditory system, and similar results have been previously published for interval discrimination (Nagarajan et al. 1998). The collection of these results suggests that discrimination of temporal information across these two sensory systems may operate through a single central timing mechanism.

A number of studies conducted using auditory stimuli have reported inconsistent Weber-Fechner fractions when measuring sub-second vs macro-second epochs (Lavoie and Grondin 2004; Grondin 2010; Güçlü, Sevinc, and Canbeyli 2011) or extremely long duration stimuli (>10 sec, Bizo 2006). The general conclusion in these papers is that this is a violation of the scalar property of time and that weber's law does not hold in the temporal field. Given the

results from this study and a number of recent studies (Lapid, Ulrich, and Rammsayer 2008; T. H. Rammsayer and Lima 1991; T. H. Rammsayer 2010b; T. Rammsayer and Ulrich 2012; T. H. Rammsayer 2014; T. H. Rammsayer 2010a), it is more likely that the sub-second standards chosen by these studies are too small to observe the properties of Weber's Law. A majority of studies (across the sensory modalities) on Weber's Law that test a large range of standards, including those on timing, show increasing Weber-Fechner fractions for extremely low standards. In most cases, the observed Weber function decreases initially as it increases from a standard of zero and attains an asymptotic value for longer standard intervals. This is a common trait of almost all Weber's Law testing. Recent studies by Lapid and Rammsayer have also outlined the subtle differences that different testing paradigms and presentation of the stimulus can cause in subjects' performance and Nagarajan has shown that training/learning can have a significant impact on subjects abilities to detect stimulus intervals. These small confounds that unsurprisingly vary from study to study could explain much of the discontinuity of Weber fractions reported in the literature.

While the adherence to Weber's law for duration discrimination with tactile stimuli in this range of 500 to 1500 msec is a new finding, we view the observations of duration discrimination obtained with the amplitude confound as being much more significant. These observations demonstrate that when the stimulus is greater in intensity, it is perceived to be longer in duration, and it appears to be in parallel with the stimulus evoked responses observed in primary somatosensory cortex. Our previous optical imaging studies with non-human primates (Stephen B. Simons et al. 2005; S. B. Simons et al. 2007) demonstrated that larger intensity stimuli have a longer time course to return to baseline. The optical imaging signal (OIS) evoked in those studies was in the near infrared range (830nm), and signals in that range correlate with extracellular K+ and cell swelling (Grinvald et al. 1991) but could also be a good indicator of glial status. Lee et al. demonstrated that when astrocyte metabolism was inhibited with fluoroacetate in a sensorimotor cortical slice preparation, the optical signal was diminished although stimulus evoked activity could still be detected neurophysiologically via

evoked potential. In other words, the neural response was still viable in the absence of the glial response, and the glial response was strongly tied to the OIS that demonstrates a longer return to baseline activity with a more intense stimulus. This separation of neural and glial activity led the authors to hypothesize that a neuroinflammatory response could involve aberrant glial response to stimulation. If the glial response is aberrant, then the amplitude confound would be predicted to have less of an impact on a task such as duration discrimination. Obviously, this logic depends on neuron-glial interactions or integration playing a significant role in sensory percept. If such integration plays a role in sensory percept, then it stands to reason that a neuroinflammatory process could have an impact on the process.

In the case for the concussed individuals that participated in this study, timing perception (or duration discrimination) was not significantly altered. However, what was altered was the impact that an amplitude or intensity confound had on their performance of a duration discrimination task. If neuroinflammation, however elusive or ubiquitous that process, plays a role in post-concussive status, then it could be a contributing factor in the alteration of the sensory percept. Thus, an increase in neuroinflammation may result in a decrease in neuron-glial integration which could subsequently diminish the sensory illusion we documented in controls, the perception of longer duration when faced with larger amplitude stimuli. Problems in timing perception have been identified in subjects with schizophrenia (Clausen 1950; Densen 1977; Connor et al. 1990; Lhamon and Goldstone 1956; Wahl and Sieg 1980; Weinstein, Goldstone, and Boardman 1958), autism (Mark Tommerdahl et al. 2008; Kwakye et al. 2011), TBI (G. Mioni, Mattalia, and Stablum 2013; Giovanna Mioni, Stablum, and Cantagallo 2013; Schmitter-Edgecombe and Rueda 2008), Parkinson's (Artieda et al. 1992; Sagar et al. 1988; Vriezen and Moscovitch 1990), and chronic pain (R. H. Nguyen et al. 2013; Zhang, Zolnoun, et al. 2011); these same conditions have also been linked to impaired glial interaction (Schizophrenia: (Bernstein, Steiner, and Bogerts 2009; Rothermundt et al. 2004) Autism: (Vargas et al. 2005; Pardo, Vargas, and Zimmerman 2005) TBI: (Giovanni et al. 2005; Mondello et al. 2012) Parkinson's: (Ec et al. 1998; Hirsch et al. 2003; Teismann et al. 2003)) Chronic Pain:

(Gosselin et al. 2010; Milligan and Watkins 2009)). The amplitude confound measure was shown in the pilot concussion study to be helpful in delineating subjects with mTBI from healthy controls, and could be used in future research to describe and measure subjects with other conditions marked by neuroinflammation.

As you can see in Figure 4.6, increased durations on the standard stimulus typically impaired performance on the amplitude discrimination task while increasing the duration of the stimuli which was higher in amplitude (the test) resulted in an increased discriminative capacity. These observations from the amplitude discrimination task demonstrate that when the stimulus is longer in duration, it is actually perceived to be stronger in intensity. However, the fact that prolonged stimulation leads to a reduction in the response of neurons to subsequent stimuli at both the peripheral and central levels of neural processing is well documented (Bensmaia et al., 2005, Chung et al., 2002 and O'Mara et al., 1988). Leung et al. (2005) demonstrated changes in the firing rate in the periphery at much longer stimulus durations and showed that extended suprathreshold vibratory stimulation applied to the skin results in a desensitization of cutaneous mechanoreceptive afferents. Based on this information, increasing the duration of the standard stimulus would have been expected to lower it's perceived amplitude, but in our testing, increasing the duration of higher amplitude stimuli resulted in lower DLs and better performance on the task. The data obtained from this study appears to be in agreement with the stimulus evoked responses observed in primary somatosensory cortex. Observations of in vivo optical imaging experiments demonstrate that the OIS is sensitive to different durations of stimulation — the signal lasts longer when the stimulus is longer (Simons 2007). This actually mimics the response observed on duration perception when the amplitude of the stimulus is increased (Simons 2005). In this particular case, the neural mechanisms responsible for adaptation may contribute very little to amplitude discrimination capability.

Changes in firing rate of peripheral afferents neither account for, nor predict, the impact of the confounds used in this study, suggesting that some other mechanism is

responsible for the illusory condition. There is increasing evidence that a correlation exists between the signals measured using OIS and changes in the volume of the extracellular fluid compartment attributable to glial swelling (Grinvald et al., 1991, 1994, 1999; Holthoff and Witte, 1996; Kohn et al., 2000). An increase in either duration or amplitude results in similar increases in absorbance measured by optical imaging, which seems to suggest that the impact of an amplitude or duration confound may be controlled by glial-neuronal interactions. If glial interactions are responsible for both the increases in OIS and thus the observed impacts of these confounds, it stands that subjects with glial disruptions, such as those with neuroinflammation, would not be impacted as severely by the confound.

Experimental Procedure

Twenty healthy subjects of different ages (18-54 years) who were naïve to the study design and issue under investigation were studied. A survey about medication and medical history was filled out by each subject before experimental tests to exclude subjects with a history of neurological impairment. The study was performed in accordance with Declaration of Helsinki, all subjects gave their written informed consent, and the experimental procedures were reviewed and approved in advance by an institutional review board.

During an experimental session, the subject was seated comfortably in a chair with his/her left arm resting on an armrest attached to the head unit of a portable four-site vibrotactile stimulator (Fig.6; CM5, Cortical Metrics, LLC; for full description of the functionally equivalent CM4, see (Holden et al. 2012)). Vibrotactile stimulation was conducted via 5 mm diameter probes that come in contact with subject's digit 2 (index finger) and digit 3 (middle finger) of the left hand. The independent probe tips were computer-controlled and capable of delivering of a wide range of vibrotactile stimulation of varying frequencies (measured in Hertz) and amplitudes (measured in micrometers, μm). Glabrous pads of digit 2 (D2) and digit 3 (D3) were chosen as the test sites for two reasons: (1) to allow the convenience of access and comfort of the subject, and (2) because of the wealth of neurophysiological information that exists for the corresponding somatotopic regions of cortex in primates. The subject's right hand was used to

indicate responses on a two-button computer mouse. During each test, the subject was instructed to indicate which finger (index/middle) perceived the longer stimulus by pressing a corresponding button on the mouse.

Visual cueing was provided with a computer monitor during the experimental runs. Specifically, an on-screen light panel indicated when the subject was to respond. An audiometer was used to make sure that no auditory cues were emitted from the stimulator during delivery of the stimuli. Practice trials were performed before each test, which allowed the subjects to become familiar with the test, and correct responses on 3 consecutive training trials were required before commencing with the data acquisition portion test. The subject was not given performance feedback or knowledge of the results during data acquisition.

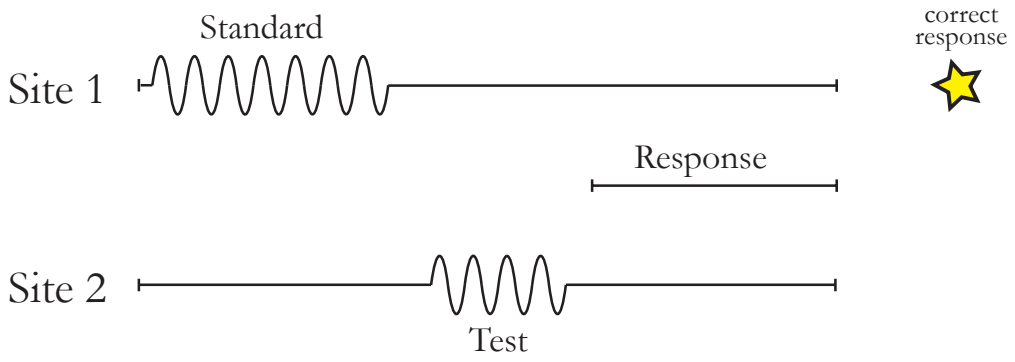

Figure 4.7: Schematics of the Duration Discrimination Protocol
During each trial of the duration discrimination task, two 25 Hz vibrotactile stimuli — the standard and test – were delivered sequentially to either D2 or D3. Subject was instructed to choose the stimulus that was perceptually longer with a response box in the response interval following the two stimuli intervals.

Duration discrimination

A two-alternative forced-choice (2AFC) tracking protocol was used to evaluate the duration discriminative capacity of each subject in a manner similar that used in a number of previous studies that have examined dual-site vibrotactile amplitude discriminative capacity (V. Tannan, Dennis, and Tommerdahl 2005; V. Tannan, Simons, et al. 2007; V. Tannan, Dennis, et al. 2007; Vinay Tannan, Whitsel, and Tommerdahl 2006; M Tommerdahl et al. 2007; Zhang et al. 2008). At the start of each run, the two probe tips were driven towards the skin until each tip registered a force of 0.1 g, as determined by a closed-loop algorithm in the CM-5 stimulator

feedback system. The tips were then further indented into the skin by 500 μm to ensure good contact with the skin. All vibrotactile stimuli used in this study were delivered at the frequency of 40 Hz flutter.

Duration discrimination was tracked for four conditions of standard stimulus duration, each condition tracked in a separate experimental run: 500, 750, 1000, and 1500. During an experimental run, a vibrotactile test stimulus was delivered sequentially either 500 ms before or after a vibrotactile standard stimulus (the standard stimulus duration remained constant throughout the run). The order (standard followed by test or test followed by standard) and loci of the stimulus was randomly selected on a trial-by-trial basis. Stimulus amplitude was 300 microns. The subject was queried to select the skin site that received the longer duration stimulus and a 5 s delay interval followed before onset of the next trial. The test stimulus duration began 250 ms longer than that of the standard stimulus and was increased or decreased by a 25 ms step size according to a 1-up/1-down algorithm for the first 10 trials. Correct responses resulted in the decreasing the duration of the stimulus while incorrect responses increased the duration of the stimulus. After the initial 10 trials, the duration was varied using a 2-up/1-down algorithm. The rationale for implementing these algorithms was to initially expedite determination of vibrotactile discriminative range and then account for response bias; this method has been extensively reported (Vinay Tannan, Whitsel, and Tommerdahl 2006; V. Tannan, Dennis, et al. 2007; V. Tannan, Simons, et al. 2007; M Tommerdahl et al. 2007; Mark Tommerdahl et al. 2007; Mark Tommerdahl et al. 2008; Francisco et al. 2008; Zhang et al. 2008; Zhang et al. 2009; Zhang, Zolnoun, et al. 2011; Zhang, Francisco, et al. 2011)

Duration discrimination with an amplitude confound

The duration discriminative capacity for each subject was tested again at the 500 msec standard using 2 different amplitude confounds (see Fig 4.4). In each of the conditions, the stimulus amplitude of the test stimulus was either 300, 350 or 400 microns, while the amplitude of the standard stimulus always remained at 300 microns. Each of the test

amplitudes (300, 350, 400) were tested completely independently using three separate 20 trial 2AFC protocols randomly interleaved in a 60 trial testing session. Thus, the duration discriminative capacity of each subject was tested with a 300, 350, and 400 micron test stimulus, while the amplitude of the standard stimulus always remained at 300 microns. The 350 and 400 micron test amplitudes were chosen to maximize the impact of the amplitude confound on the subjects discriminative capacity while reducing the perceivable amplitude difference between the two stimuli (350 vs. 300 microns is typically below a subject's amplitude discriminative capacity).

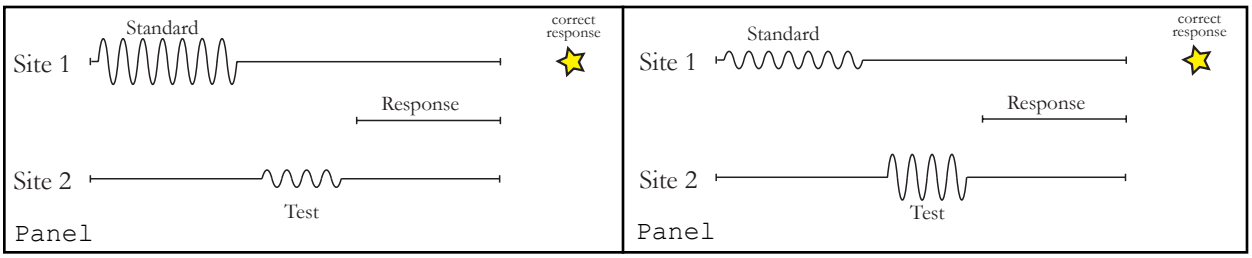

Figure 4.8: Schematics of the Amplitude Confound applied to Duration Discrimination
The logistics of this protocol are identical to the duration discrimination task explained earlier; two 25 Hz vibrotactile stimuli — the standard and test — were delivered sequentially to either D2 or D3 and the subject was instructed to choose the stimulus that was perceptually longer. The amplitudes of the test and the standard were varied to amplitudes of 300, 350, and 400 microns, while the other stimulus remained at an amplitude of 300 microns. Panel A shows the intensity confound on the standard stimulus, and Panel B shows the confound on the test.

This previously described duration discrimination task was modified to ascertain the impact of an amplitude confound on the test stimulus. A similar 60 trial test was designed with three separate 20 trial 2AFC protocols randomly interleaved but with three new conditions: one with a 400 micron amplitude confound located on the test stimulus, one with a 400 micron amplitude confound on the standard, and one with no confound located on either test or standard. All tests in this trial were simple duration discrimination tasks just like the previous test; a standard of 500 ms was used and the test stimulus started at a duration of 750 ms, tracking down with the same 25 ms step size. The subject was asked which stimulus was longer, and the subject was kept naïve to the change in amplitude.

Amplitude discrimination with a duration confound

Amplitude discriminative capacity is defined as the minimal difference in amplitudes of two mechanical sinusoidal vibratory stimuli for which an individual can successfully identify the stimulus of larger magnitude. Discrimination capacity was assessed using a 2AFC tracking protocol that has been described and implemented in a number of previous studies. For all trials of amplitude discrimination, the device delivered sequential stimuli (initial stimulus parameters: 400 mm test, 200 mm standard, 40 Hz, 20 mm step size, 500 ms ISI) to D2 and D3. As seen in the previous methods, a 60 trial test was delivered with three separate 20 trial 2AFC protocols randomly interleaved designed to test three different sets of parameters. One 20 trial set was a classic amplitude discrimination test in which both test and standard were delivered for equal durations of 500 ms, one set increased the duration of the standard to 600 ms (test remained at 500 ms), and one increased the test to 600 ms (standard remained at 500 ms). The magnitude of the test stimulus was always greater than that of the standard stimulus, but the loci of the stimuli were randomly varied on a trial-by-trial basis. Subjects were questioned as to which of the two digits received the higher magnitude stimulus, and were kept naïve to the changes in durations. The same procedure was then repeated on each subject with an increase in the duration confound from 600 ms to 750 ms.

Pilot Concussion Study

Data was collected from 19 college students who sustained a concussion (17 male, 2 female, mean age - 20.1 years, SD - 1.2 years), of which all were sports-related concussions (12 played football, 3 basketball, 3 soccer, and 1 lacrosse). All athletes were diagnosed with mTBI in the form of a concussion by a certified athletic trainer and the team physician with the help of the Sport Concussion Assessment Tool 2 (SCAT-2), had no prior history of concussion or any other diagnosed medical conditions. The subjects were tested using an abbreviated version of the “duration discrimination with an amplitude confound” procedure described above. For the concussion subjects, the standard stimulus was always held at 300 microns, and two separate 20 trial 2AFC protocols were randomly interleaved in a 40 trial sequence: one condition had an

identically intense test stimulus (300 microns) and one with the amplitude of the test stimulus raised to 400 microns. Individual scores post-concussion were compared to the previously obtained control values. All diagnostic assessments were obtained 1-2 days post-concussion. and subjects' responses during those protocols.

CHAPTER 5: THE IMPACT OF NON-NOXIOUS HEAT ON TACTILE INFORMATION PROCESSING[4]

Overview

A significant number of studies that evaluated tactile-pain interactions employed heat to evoke nociceptive responses. However, relatively few studies have examined the effects of non-noxious thermal stimulation on tactile discriminative capacity. In this study, the impact that non-noxious heat had on three features of tactile information processing capacity were evaluated: vibrotactile threshold, amplitude discriminative capacity and adaptation. It was found that warming the skin made a significant improvement on a subject's ability to detect a vibrotactile stimulus, and although the subjects' capacities for discriminating between two amplitudes of vibrotactile stimulation did not change with skin heating, the impact that adapting or conditioning stimulation normally had on amplitude discrimination capacity was significantly attenuated by the change in temperature. These results suggested that although the improvements in tactile sensitivity that were observed could have been a result of enhanced peripheral activity, the changes in measures that reflect a decrease in the sensitization to repetitive stimulation are most likely centrally mediated. The authors speculate that these centrally mediated changes could be a reflection of a change in the balance of cortical excitation and inhibition.

Introduction

Studies of human somatosensory perceptual capabilities not only have demonstrated that clear and strong interactions occur between temperature and touch, but have provided evidence suggesting that the responsible neural interaction occurs at a relatively early stage of

---

[4] This chapter previous appeared in Brain Research. The original citation is as follows:
Zhang, Zheng, Eric M. Francisco, Jameson K. Holden, Robert G. Dennis, and Mark Tommerdahl. 2009. "The Impact of Non-Noxious Heat on Tactile Information Processing." Brain Research 1302 (November): 97–105.

the somatosensory projection pathways. As examples, (1) noxious thermal stimulation applied within the same dermatome (but not at a more remote skin site) elevates the threshold for detection of cutaneous vibrotactile stimulation regardless of which mechanoreceptive channel is activated by the mechanical stimulus (Apkarian et al., 1994; Bolanowski et al., 2000, 2001), (2) experimental inflammatory pain and the pain that results from topical capsaicin application impairs tactile discriminative abilities in normal subjects (Kauppila et al., 1998), (3) patients with persistent musculoskeletal pain exhibit an elevated threshold for detection of cutaneous flutter stimulation as well as impaired ability to discriminate vibrotactile stimulus frequency (Hollins et al., 1996; Hollins and Sigurdsson, 1998), and (4) cutaneous vibration (especially at frequencies >100 Hz) significantly suppresses both clinical and experimental pain (Pertovaara, 1979; Ekblom and Hansson, 1982, 1985; Lundeberg, 1984a-e; Lundeberg et al., 1984; Pantaleo et al., 1986; Sherer et al., 1986). Additionally, neurophysiological observations from non-human primates have provided evidence for interactions between the responses evoked in SI cortex to both noxious skin heating and skin flutter stimulation (Tommerdahl et al., 1996, 1998) — interactions fully consistent with the published human psychophysical demonstrations of prominent interactions between the sensory experiences of touch and heat-evoked pain.

However, although there have been numerous studies that evaluated tactile-pain interactions that utilized heat to evoke nociceptive response, relatively fewer studies have examined the effects of non-noxious thermal stimulation on touch. Tracing back to 1846, E.H. Weber (Weber, 1846) noted that a cold coin (-4 to -7 ˚C) resting on the forehead feels heavier than a warm coin (38 to 39 ˚C), implying an effect of non-noxious temperature on the touch modality. Since then, a number of studies have reported that changes of tactile sensitivity (ex. tactile spatial acuity, punctuate pressure sensitivity, and vibrotactile sensitivity) take place with warming and cooling of the skin (Green, 1977; Green et al., 1979; Stevens et al., 1977; Bolanowski and Verrillo, 1982; Verrillo and Bolanowski, 1986; Gescheider et al., 1997). For example, Green (Green et al., 1979) examined the effect of skin temperature on the perception of roughness. The results demonstrated that warming above normal skin temperature either

enhances the perception of roughness for smooth surfaces or leaves it unchanged for rough surfaces. However, Stevens and colleagues (Steven et al., 1977) found that a small but possibly insignificant loss of sensitivity for detection of punctuate pressure appeared at skin temperatures of 40˚C and 43˚C. Other observations on the impact of elevated skin temperature on vibrotactile sensitivity also appear to be inconsistent. Weitz (Weitz, 1941) and Green (Green et al., 1977) reported that warming the skin a few degrees above normal (36 - 37 ˚C) resulted in an increase of sensitivity to high-frequency vibration (>80 Hz). However, Verrillo et al. (Verrillo and Bolanowski, 1986) reported no changes of the sensitivity on the forearm and thenar eminence as the skin temperature was increased from 30˚ to 40˚C, while Bolanowski showed only a slightly elevated threshold on detecting 25 Hz vibrotactile stimulation (Bolanowski and Verrillo, 1982).

The goal of this study was to examine the impact that non-noxious heat has on three features of tactile information processing capacity: vibrotactile threshold detection, amplitude discriminative capacity and adaptation. It was found that warming the skin made a significant improvement on threshold detection, and although the subjects' capacities for discriminating between two amplitudes of vibrotactile stimulation did not change with skin heating, the impact that adapting or conditioning stimulation normally has on amplitude discrimination was significantly attenuated by the change in temperature.

Results

In order to assess the impact that non-noxious heat has on tactile information processing capacity, comparisons of subject performance were obtained for different conditions of thermal stimulation. Protocols were employed to assess the impact of non-noxious thermal stimulation on subjects' capacities for vibrotactile detection (at room temperature, 40.5˚C, and 43˚C), amplitude discrimination (at room temperature and 43˚C), and the effect of vibrotactile adaptation on tactile discrimination capacity (at room temperature and 43˚C).

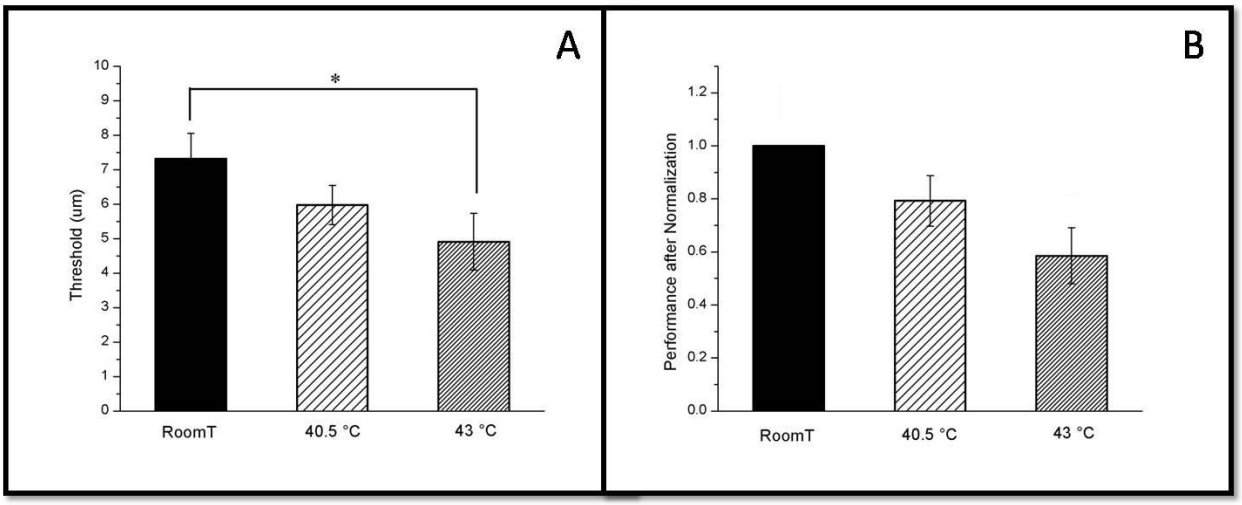

Figure 5.1: Vibrotactile Detection Thresholds under Three Temperatures
(A) The group-averaged detection threshold at 40.5 ˚C was lower than the value obtained at the room temperature condition (p = 0.18). At 43 ˚C, the detection threshold was significantly lower than that at the room temperature (p = 0.047). (B) Detection thresholds normalized on a subject-by-subject basis to the room temperature condition. The plot confirms that the subjects' performance was significantly and consistently improved over that at room temperature.

Vibrotactile thresholds decrease with increasing temperature

A Two-Alternative Forced Choice (2AFC) protocol was used to determine a subject's vibrotactile detection threshold (stimuli delivered at a frequency of 25 Hz to one of two stimulus sites and subject reports the site of stimulus detection; previously reported in Francisco et al., 2008; also see description in Methods) for each of the three temperatures. In Fig. 5.1, Panel A summarizes the group-averaged detection thresholds obtained under the three thermal conditions. Specifically, at room temperature the group-averaged vibrotactile detection threshold on finger tip was 7.28 ± 0.84um (mean±SE), which is consistent with the detection thresholds (~7um) reported by Mountcastle and colleagues (Mountcastle et al., 1972). While temperature was increased, subjects were consistently able to detect stimuli at amplitudes of 5.98 ± 0.57um (40.5˚C) and 4.83 ± 0.93um (43˚C). Note that detection thresholds decrease with increasing temperature. Thus, concurrent non-noxious thermal stimulation results in an improvement of vibrotactile sensitivity. Specifically, at 40.5˚C, the data suggest an improvement in sensitivity (or a decrease in detection threshold) when compared to the room temperature condition, although this difference was not statistically significant (p = 0.18). However, the improved sensitivity that was suggested with increased temperature in the 40.5˚C condition was

much more pronounced for the 43˚C condition, at which the detection threshold was significantly lower than that at the room temperature condition (p = 0.047). In order to determine if this trend was consistent within subjects, the data were normalized to the room temp condition, shown in Fig. 5.1 Panel B. The normalized plot confirms that subjects' detection thresholds were reduced as the thermal stimulation was increased, and strongly suggests improved detection performance with increasing temperature in the non-noxious thermal temperature range. Specifically, performance was improved over that at room temperature by ~21% at 40.5˚C, and by ~42% at 43˚C.

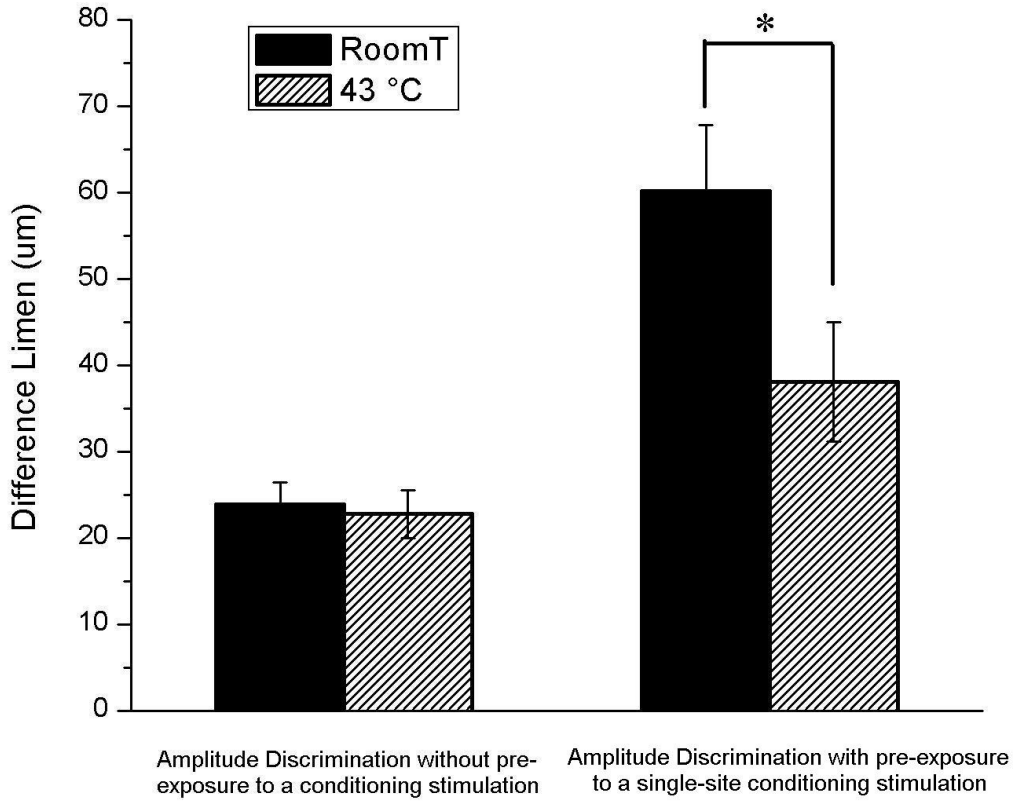

Figure 5.2: Difference Limens Obtained with Two Amplitude Discrimination Protocols
In the absence of conditioning stimuli, increasing skin temperature had little impact on a subject's vibrotactile amplitude discrimination capacity. However, when the test stimulus was preceded by conditioning stimuli (1 sec in duration), amplitude discrimination capacity was significantly impaired, as in prior studies (Tannan et al., 2007b, 2008), under both temperature conditions ($p<0.01$ at room temperature; $p = 0.032$ at 43 ˚C). However, the impairment was significantly reduced when the temperature was increased from room temperature to 43 ˚C ($p=0.043$)

Impact of temperature on a subject's amplitude discriminative capacity

A second 2AFC tracking protocol was employed to determine subjects' capacities to discriminate between the amplitudes of two simultaneously delivered vibrotactile stimuli with or without a preceding conditioning stimulus delivered to one of the stimulus sites (protocols previously reported in Tannan et al., 2005; Tannan et al., 2006; Tannan et al., 2007a; Tannan et al., 2007b; Tannan et al., 2008; Tommerdahl et al., 2007a; Zhang et al., 2008; Francisco et al., 2008; Folger et al., 2008; also see Methods). Fig. 5.2 summarizes the averaged across-subject performance for the results obtained with the two amplitude discrimination protocols (with or without single-site adaptation) at room temperature and at 43˚C. The results demonstrate that, in the absence of pre-exposure to a conditioning stimulus, subjects were able to discriminate between a 100 μm and a 123 μm stimulus (DL = 23 μm) equally well under both temperature conditions (as shown on the left hand side of Fig. 5.2). Previous reports have shown that, in normal healthy control conditions, amplitude discrimination capacity is significantly impacted with the delivery of a conditioning stimulus to one of the two stimulus sites prior to the amplitude discrimination task (Tannan et al., 2007b, Tannan et al., 2008; Folger et al., 2008). In this study, the observed subjects' performance is in a manner consistent with previous studies. Specifically, subjects' capacities for amplitude discrimination was significantly impaired with pre-exposure to a conditioning stimulus under both temperature conditions ($p < 0.01$ at room temperature; $p = 0.032$ at 43˚C). One interpretation of this impairment is that a 1 sec conditioning stimulus reduces the perceived intensity of the subsequent test stimulus to the extent that a stimulus with amplitude of approximately 160 μm (at room temperature) / 140 μm (at 43˚C) was perceived nearly the same in intensity as the 100 μm stimulus. Note that the average post-adaptation DL at room temperature increased to about 160% above the value obtained with the non-adaptation protocol, yet the averaged post-adaptation DL at 43˚C was only about 73% above the non-adaptation values. Thus, the temperature increase resulted in a significant reduction in the impairment of subjects' amplitude discrimination capacity due to adaptation ($p = 0.043$) (as shown in Fig. 5.2 on right side). In summary, as temperature was

increased, the impact of the conditioning stimulus was lessened, and subjects subsequently performed better at the post-adaptation amplitude discrimination task relative to their performance at room temperature.

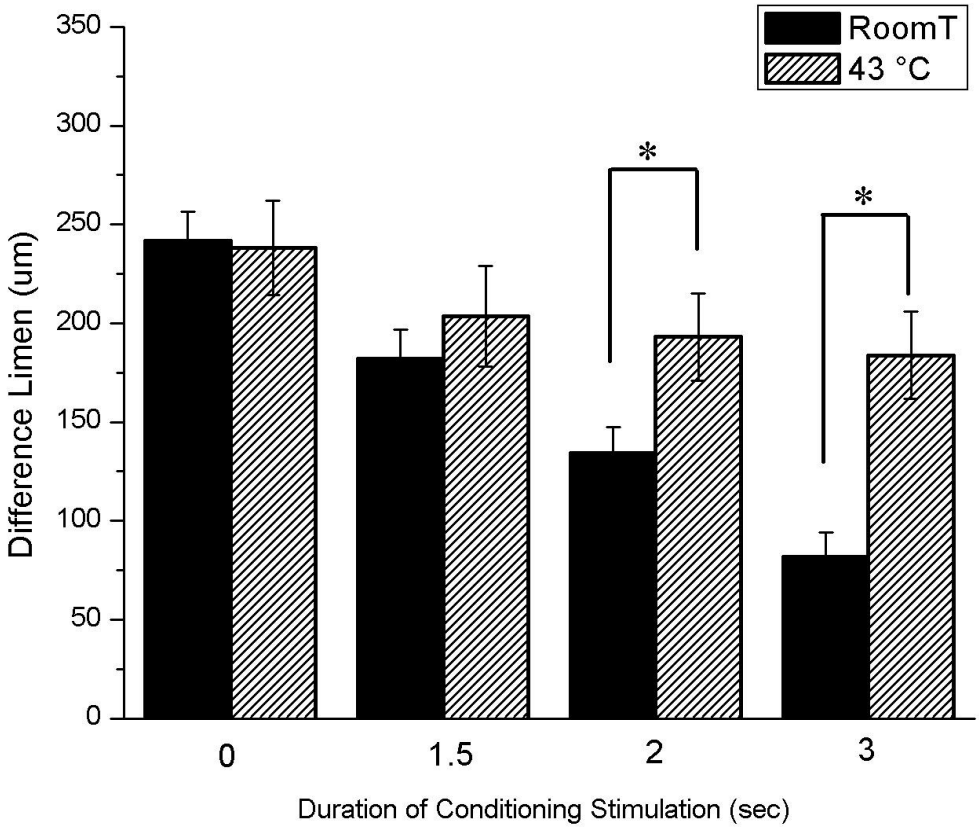

Figure 5.3: Effects of Temperature on Dual-Site Conditioning.
At room temperature, increasing the duration of the conditioning stimulation led to an improvement of performance (i.e., reduced DL). However, this improvement in amplitude discrimination capacity was significantly impacted at 43 °C. Specifically, the results obtained at room temperature were significantly different at 43 °C with 2 and 3 sec of conditioning stimulation (2 sec adaptation: $p = 0.024$; 3 sec adaptation: $p<0.01$).

Impact of temperature on dual-site conditioning

To further investigate the effects of thermal non-noxious stimulation on adaptation, a 2AFC dynamic amplitude discrimination protocol (see Methods) was employed which is able to effectively compare the degree to which a subject adapts to simultaneously delivered dual-site vibrotactile stimuli at different durations of conditioning stimulation. Four conditions of initial constant stimulus duration were employed, in separate experimental trials: 0, 1.5, 2 and 3 sec. After the initial constant stimulus period, subjects performed an amplitude discrimination task

on stimuli which diverged in amplitude at the rate of 25 μm/s (i.e., one stimulus amplitude became larger and one became smaller; see Methods for description). Fig. 5.3 summarizes the averaged across-subject performance with dual-site adaptation at the four different durations of conditioning stimulation at room temperature and 43˚C. The results show that, at room temperature, increasing the duration of the conditioning stimuli delivered to both sites of skin stimulation led to an improvement of a subject's capacity to detect the difference in amplitude between the two stimuli. For example, after pre-exposure to 1.5s, 2s or 3 s conditioning stimulus, subjects were, on average, able to attain a DL (182um, 139um, or 82 μm) that was ~75%, ~57%, or ~34%of the DL (242 μm) obtained without adaptation (under all the conditions $p < 0.01$). However, when the skin was heated to 43˚C, the improvement in amplitude discrimination previously observed with increasing conditioning stimulus durations was significantly attenuated. Specifically, after pre-exposure to 1.5s, 2s or 3s conditioning stimulus, subjects were able to attain a DL (203um, 193um, or 184um) that was ~85%, ~81%, or ~77% of the DL (238um) obtained without adaptation. Note, at the 2 s and 3 s conditioning stimulation durations, the improvement in amplitude discrimination obtained at room temperature (57% and 34%) were significantly different from the 43˚C condition (81% and 77%): 2 s adaptation: $p = 0.024$; 3 s adaptation: $p < 0.01$.

Summary and general discussion

In the present study, we investigated the effects of non-noxious heat on subjects' tactile information processing capacities. The results strongly suggest that concurrent non-noxious thermal stimulation (43˚C) enhances some aspects of vibrotactile sensitivity (e.g., detection threshold). It was also found that although the same increase in temperature had no effect on the subjects' performance on vibrotactile amplitude discriminative capacity, the non-noxious heat significantly reduced the impact that pre-exposure to vibrotactile stimuli (i.e., a conditioning stimulus) had on amplitude discriminative capacity.

In this study, the effect of temperature (within the non-noxious temperature range) on the threshold for detection of cutaneous vibrotactile stimulation was studied. The data

demonstrated a significant improvement in vibrotactile sensitivity (i.e., a decrease in detection threshold) as the temperature of the forearm rest was increased from room temperature to 43˚C. Since the 19th century, the effects of skin temperature on tactile sensitivity have been examined across a wide spectrum of temperatures, both noxious and non-noxious. Although a number of studies have demonstrated that noxious skin heating results in a robust elevation of the vibrotactile threshold (Apkarian et al., 1994; Bolanowski et al., 2000, 2001), results of the impact of non-noxious skin heating on vibrotactile sensitivity have been much less consistent (Green et al., 1979; Bolanowski and Verrillo, 1982; Verrillo and Bolanowski, 1986; Bolanowski, 1988; Gescheider et al., 1997). A number of possible factors may influence the impact of temperature on threshold detection and account for the diverse results found in previous studies. For example, many studies differed in the region of the body stimulated. In the present study, subjects' finger tips were stimulated with 25 Hz vibrotactile stimulation, and a significant decrease in threshold was found as the temperature was increased from room temperature to 43˚C. However, in a number of previous studies in which subjects' forearm and thenar eminence were utilized as stimulus sites, conflicting results were reported. For example, Bolanowski and Verrillo investigated vibrotactile threshold-frequency characteristics at different skin temperatures and found that increasing thenar eminence temperature from 25˚C to 43˚C slightly elevated subjects' vibrotactile threshold at low frequency (<100 Hz). However in another study, the same authors reported that there was no change in threshold on the forearm as the temperature was increased from 30˚C to 40˚C. Additionally, Stevens found that warming had little or no effect on touch magnitude perception on the forehead but it did result in a significant effect on the perceived intensity of the stimulus on the forearm (Stevens and Green, 1978). In addition to different stimulus sites, the inconsistent results previously observed could also be partially due to the fact that skin temperature was controlled in different manners in the aforementioned studies. For example, in a number of studies (Bolanowski and Verrillo, 1982; Verrillo and Bolanowski, 1986; Bolanowski et al., 1988) skin surface temperature of only the surround of the stimulus contactor was controlled, and thus, only the temperature of a

small skin area receiving the mechanical stimulation was controlled. In the present study, the temperature of subjects' distal forearm was elevated and as a result, a much larger skin area experienced an elevated temperature than that observed in any of the prior studies. As it is well known that spatial summation plays a significant role in temperature sense (Stevens et al., 1974; Stevens and Marks, 1971), the area of skin that is warmed could obviously play a significant role in the results.

The impact of warming on the adaptation paradigms studied in this report has not been previously reported. In fact, to the authors' knowledge, there have been no studies to date that have assessed the impact of changing temperature –either in the noxious or non-noxious range — on the impact of changes in perception that normally result from repetitive vibrotactile stimulation. There have been a number of reports on the sensitivity of adaptation on a number of aspects of somatosensory perception. Several studies reported that when the conditioning stimulus is increased in duration or amplitude, the perceived intensity evoked by subsequent test stimuli is reduced (Gescheider et al., 1979; Hollins et al., 1990; Verrillo et al., 1977). More recently, Tannan et al. demonstrated that increasing the stimulus duration at one of two stimulus sites prior to simultaneous delivery of two stimuli systematically impacted subjects' amplitude discrimination capacities (Tannan et al., 2007). The results from that study demonstrated an increase in stimulus duration is proportional to a decrease in perceived intensity, thus yielding a measure of how much a subject adapts to different durations of vibrotactile stimuli in the range of 0.2-5 seconds, and these measures are paralleled in animal studies in which observations of central and peripheral responses to repetitive mechanical stimulation were obtained. Neurophysiological studies have demonstrated that the effects of reduced intensity due to adapting stimulation are possibly attributable to a reduction in the responsivity of central neurons or in synaptic processes associated with the central neurons after prolonged or repetitive stimulation. More specifically, O'Mara and colleagues (O'Mara et al., 1988) found that extended exposure to a vibratory stimulus produced substantial reductions in the responsivity of neurons in the cuneate nucleus, but not in the peripheral

afferents. Lee and Whitsel (Lee et al., 1992) reported that repetitive brushing stimuli frequently lead individual SI neurons and neuron groups to modify their response to the repetitive afferent drive. Additionally, Lee and Whitsel (Lee et al., 1992) found that the majority (~58%) of the SI neurons sampled showed a decreased response to repetitive stimulation (3-5 Hz) of their receptive fields. In that report, it was proposed that the glutamate-mediated excitatory effects on NMDAR are to a large extent responsible for the appreciable capacities of cortical neurons to modify their physiological properties with repetitive sensory experience.

In current study, the Amplitude Discrimination with Single-site Adaptation Protocol and the Dynamic Tracking with Dual-site Adaptation Protocol measured two distinct effects of adaptation. At room temperature, during Amplitude Discrimination test, a 1 sec conditioning stimulus delivered to one of the stimulus sites reduces the perceived intensity of the subsequent test stimulus and significantly *impaired* the subjects' capacities for amplitude discrimination. However, in the Dynamic Tracking test, different durations of conditioning stimulation (1.5s, 2s, or 3s) delivered to both sites of skin stimulation led to significant *improvement* of a subject's capacity to detect the difference in amplitude between the two stimuli. In terms of the difference in the magnitude of influence of non-noxious heat on the impact of the conditioning stimulus in the two tasks, the effect of Single-site Adaptation on Amplitude Discrimination appears to be more sensitive to temperature change when compared to the effect of Dual-site Adaptation on Dynamic Tracking. The noticeable difference in the difference limen between two tasks could be explained with a couple of possibilities. 1) Two standard stimulus amplitudes (100um vs. 300um) were used. According to Weber's Law, the subjects' capability to discriminate differences in vibrotactile amplitude changes systematically with increasing stimulus magnitude. 2) Several studies have reported that the psychophysical measurement methods had a significant influence on vibrotactile thresholds (Maeda and Griffin, 1995; Morioka and Griffin, 2002). For example, Morioka and colleagues found that with intermittent stimulation the vibrotactile thresholds tended to be lower than with continuous stimulation. Therefore, during Dynamic Tracking test the continuous stimulation with

ascending amplitude might result in the higher difference limen than which recorded in the Amplitude Discrimination test with intermittent stimulation.

One of the more interesting questions that this study poses is for what reason is the impact of adaptation significantly reduced in the presence of warmth? Mechanistically, it is most likely a change in the balance of excitation and inhibition that is prevalent among cortical neurons. The changes that occur with warmth are reminiscent of the changes in tactile sensibilities that are observed in autism: subjects with autism typically have increased sensitivity to a number of stimulus modalities (Kanner, 1943; O'Riordan and Passetti, 2006), are not significantly different from controls in amplitude discriminative capacity (Tannan et al., 2008), but show a reduced response to repetitive stimulation – or less of an adaptive response (Tommerdahl et al., 2007a; Tannan et al., 2008). In the case of autism, the hyper-excitability has been speculated to be the result of inhibitory deficient circuitry, possibly linked to genetic disparity in GAD (Glutamic acid decarboxylase) which is responsible for normal conversion of glutamate to GABA (Gamma-aminobutyric acid). In the case of this study, could warmth simply be making either peripheral and/or central neurons more hypersensitive to flutter vibration? A series of studies (Green, 1977; Bolanowski and Verrillo, 1982; Verrillo and Bolanowski, 1986) demonstrated that the pacinian corpuscle (PC) channel is strongly affected by skin temperature. Since the PC channel is predominantly sensitive to high-frequency (>80 Hz) vibrotactile stimulation, its characteristic change with temperature is not inconsistent with the findings of this report, as the observations in this study were obtained with delivery of low frequency (25 Hz) vibrotactile stimuli. In similar fashion, the touch gate is activated by the presence of thermally induced pain that increases tactile thresholds (Apkarian et al. 1994), yet in the current experiment, non-noxious thermal stimulation was employed. Thus, the observation that warming the skin within the non-noxious range made an improvement on the threshold of stimulus detection could be accounted for by different mechanisms than are involved in pain-touch interactions. Within the non-noxious range of thermal stimulation, Kenton and colleagues observed that SA cutaneous mechanoreceptors were more responsive in the presence of heat

(Kenton et al., 1975, 1976). This, in effect, would explain a reduction in threshold, but would not explain a reduction in influence of conditioning or adapting stimuli, particularly in the time course that was studied (1-5 secs). Rather, the hyper-excitability produced in the presence of warmth could very well be offsetting the balance in excitation and inhibition that is normally present cortically. It should also be noted that a change in balance of excitation and inhibition via hypo-excitability, such as that observed with administration of an NMDA receptor blocker, also leads to a similar reduced adaptation effect (Folger et al. 2008). If it is the case that balance of excitation and inhibition is critical for normal adaptive responses, then one prediction that could come from this study is that subjects with less than optimal excitatory/ inhibitory balance could actually perform better at the adaptation task in the presence of heat than without. This interesting possibility is currently under investigation, and it is anticipated that metrics, such as those presented in this report, could provide a means for assessing patient populations that have dysfunctional mechanisms for mediating pain-touch interactions without the delivery of painful stimuli, if the current assumption that some of the CNS mechanisms that mediate tactile-thermal and tactile-pain interactions are shared holds true in future studies.

In summary, elevation of skin temperature can lead to decreased vibrotactile detection thresholds, a primary measure of tactile sensitivity. Metrics of derived or secondary percepts — such as amplitude discriminative capacity, show little or no effect. Tertiary measures — such as those involved in both temporal and spatial summation — are impacted significantly by elevation in temperature. Although the improvements in tactile sensitivity could be a result of enhanced peripheral activity, the changes in measures that reflect a decrease in the sensitization to repetitive stimulation are most likely centrally mediated. These centrally mediated changes reflect a change in the balance of excitation to inhibition via either an increase in excitation, a decrease in inhibition or a combination of both.

Experimental Procedures

Ten subjects participated in this study (21-28 years in age). They were naïve both to the study design and issue under investigation. The subject group consisted of 4 males and 6 females, all right-hand dominant. The study was performed in accordance with the Declaration of Helsinki, all subjects gave their written informed consent, and the experimental procedures were reviewed and approved in advance by an institutional review board.

Four separate protocols were employed to measure the effects of non-noxious thermal stimulation on vibrotactile detection, amplitude discrimination, and the impact of vibrotactile adaptation on tactile discrimination capacity. During an experimental session, the subject was seated comfortably in a chair with the right arm resting on an acrylic hand-arm rest attached to a portable dual-site vibrotactile stimulator (CM-1; for full technical description see: (Tannan et al., 2007a); for exemplary use of the device, see Tommerdahl et al., 2007, 2008; Zhang et al., 2008; Francisco et al., 2008; Tannan et al., 2007b; Folger et al., 2008). Two holes (10 mm diameter each, spaced 35 mm apart) were positioned on the hand-arm rest to allow the stimulator tips to make contact with digits 2 and 3 of the subject's right hand (right panel in Fig. 5.4). A temperature-controlled metal hand plate was fabricated to attach on the front top end of the acrylic hand-arm rest for this study. This metal hand plate was composed of 2.5 mm thick aluminum sheet (alloy 6061-T6), cut to a rectangular shape 150 x 300 mm in size. The sheet was bent to the same shape as the original hand-arm rest, and two 10 mm holes were positioned for D2 and D3 stimulation (Fig. 4). Two 15 Watt flexible heater pads with a thermocouple between them were embedded in the temperature controlled plate. A fuzzy-logic P-I-D auto-tuning temperature controller (McMaster-Carr #7981K82) was used to externally monitor and control the temperature. The auto-tuning controller automatically optimizes the P, I and D control gains to tune the system to achieve the fastest possible response with minimum temperature overshoot. The desired temperature set point was entered prior to each experimental run and held constant for the duration of the run.

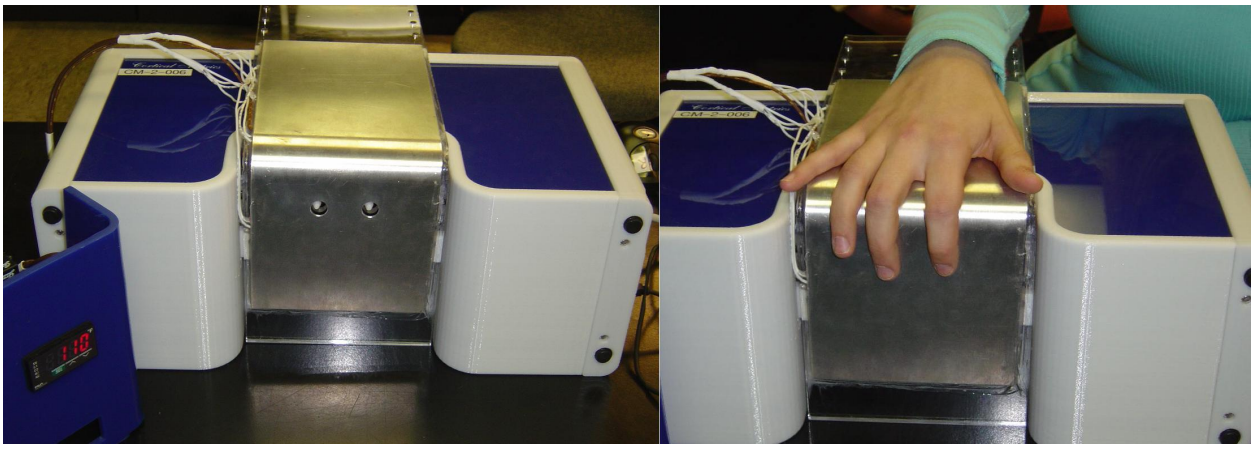

Figure 5.4: Vibrotactile Stimulator with Temperature-Controlled Plate
Two holes (10 mm diameter each spaced 35 mm apart) were positioned to allow the stimulator tips to make contact with subject's digits. During an experimental session, the subject was seated comfortably in a chair with the right arm resting on the metal hand plate. Index and middle finger were positioned for D2 and D3 stimulation.

During each test, two probe tips (5 mm diameter) were positioned on the glabrous pads of digits 2 and 3 of the right hand. D2 and D3 were chosen as the test sites for two reasons: 1) to allow the convenience of access and comfort for the subject, thus maximizing the test's potential in clinical applications, and 2) because of the wealth of neurophysiological information that exists for the corresponding somatotopic regions of cortex in primates. Visual cueing was provided with a computer monitor during the experimental runs. Specifically, an on-screen light panel indicated to the subject when the stimulus was on and when the subject was to respond. The subject was not given performance feedback or knowledge of the results during data acquisition until all sessions were completed. At the start of each run, the two probe tips were driven towards the skin until each tip registered a force of 0.1 g, as determined by a closed-loop algorithm in the CM-1 stimulator feedback system. The tips were then further indented into the skin by 500 μm to ensure good contact with the skin. All sinusoidal vertical skin displacements were delivered by the CM-1 stimulator. An audiometer was used to make certain that no auditory cues were emitted from the stimulator during delivery of the range of stimuli used in this study. Practice trials allowed the subject to familiarize with the tests, and correct responses on 5 consecutive trials were required before commencing with each test. During the experimental session, the room temperature was controlled around 25 ˚C. The subject completed all four tests (described below) first at room temperature, then after 10 minutes break, they repeated all four tests under the condition with increased hand rest

temperature: 40.5 ˚C or 43 ˚C. In each condition, the order of the four tasks was randomized across all of the subjects.

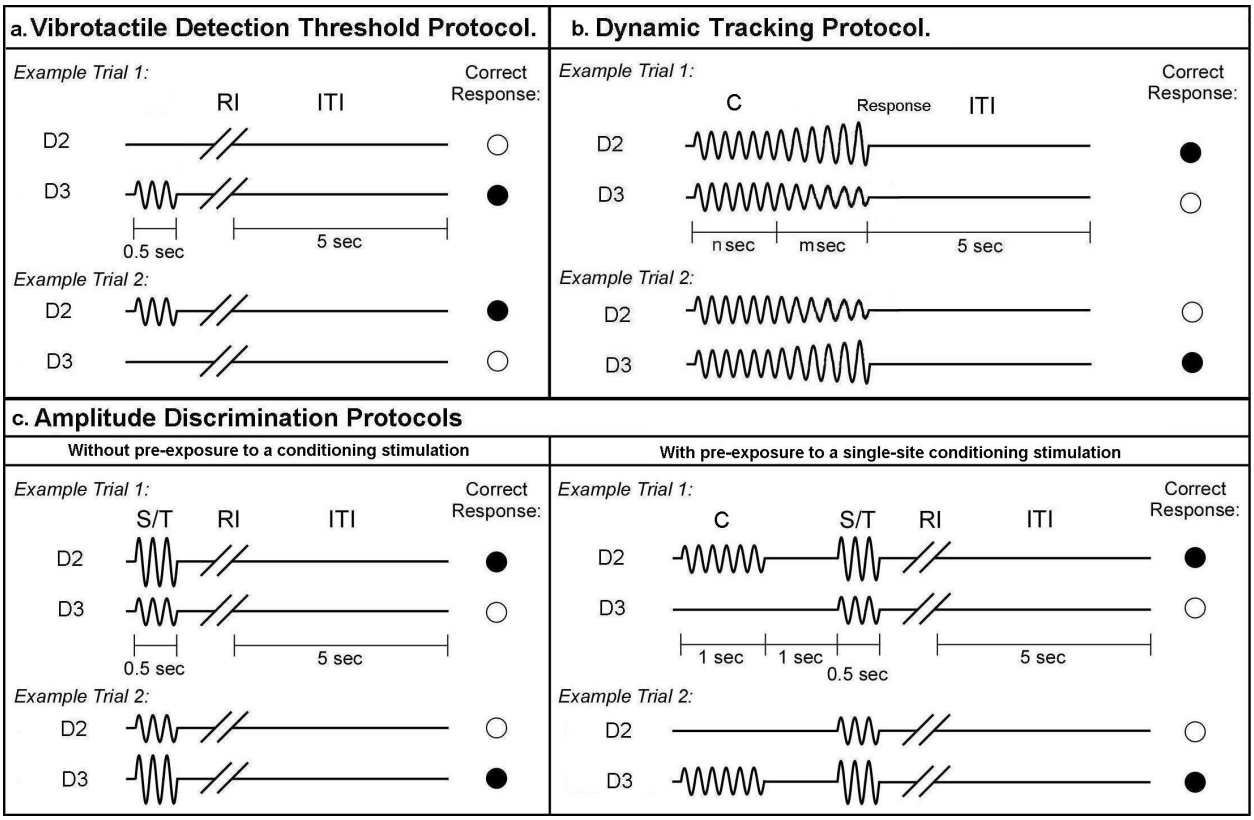

Figure 5.5: Schematics of the Protocols Used in this Study
(A) Vibrotactile detection threshold: In each trial, a 25 Hz vibrotactile test stimulus was delivered to either D2 or D3 for 0.5 sec, followed by a subject response interval (RI). A correct response resulted in a reduction in the amplitude of the stimulus in the next trial (initiated 5 sec after subject response). (B) Dynamic tracking: Two identical 25 Hz vibrotactile stimuli were delivered simultaneously for a fixed interval (0, 1.5, 2, or 3 sec). After the initial constant stimulus period, the amplitude of the two stimuli were dynamically increased/decreased, in steps of 25 μm/sec. Stimulation was terminated with subject response and a 5 sec delay intervened between stimulus response and onset of the next trial. (C) Amplitude discrimination. Left panel: Amplitude discrimination task without pre-exposure to conditioning stimulation. Two 25 Hz vibrotactile stimuli, the standard (S) and test (T), were delivered simultaneously for 0.5 sec. Subject response precedes a 5 sec delay before onset of the next trial. Right panel: Amplitude discrimination task with pre-exposure to conditioning stimulation. In this protocol, a conditioning stimulus at one of the two stimulus sites precedes the simultaneous delivery of the standard and test stimuli.

Detection Threshold

In order to measure the subject's vibrotactile detection threshold, a 20-trial Two-Alternative Forced Choice (2AFC) tracking protocol was employed (for recent description with this experimental setup, see Francisco et. al., 2008). Fig. 5.5a shows the schematic of the protocol. During each trial of the experimental run, a 25 Hz vibrotactile test stimulus was

delivered to either D2 or D3 (the stimulus location was randomly selected on a trial-by-trial basis). Stimulus duration was 0.5 sec, followed by subject response (subject was queried to select the skin site that received the stimulus) and a 5 sec delay before onset of the next trial. At the beginning of the experimental run, the test stimulus amplitude was 15 μm (all vibrotactile stimulus amplitudes reported in this study are peak-to-peak). In the initial 10 trials, the test amplitude was modified based on the subject's response in the preceding trial, accomplished using a 1-up/1-down algorithm (the amplitude was decreased if the subject's response in the preceding trial was correct; it was increased if the response was incorrect). After the initial 10 trials were completed, the test amplitude was modified using a 2-up/1-down algorithm — in the remaining 10 trials two correct/one incorrect subject response(s) resulted in a decrement/increment, respectively, in the amplitude of the stimulus. This approach was selected because it enabled rapid determination ("tracking") of each subject's minimally detectable amplitude of vibrotactile stimulation (Tannan et al., 2007a; Zhang et al., 2008; Folger et al., 2008; Francisco et al., 2008). The step size was held constant at 1 μm throughout the experimental run.

Amplitude Discrimination

Each subject's amplitude discrimination capacity was observed using a 2AFC tracking protocol that has been described and implemented in a number of previous studies (Tannan et al., 2005; Tannan et al., 2006; Tannan et al., 2007a; Tannan et al., 2007b; Tommerdahl et al., 2007a; Zhang et al., 2008; Francisco et al., 2008). During the 20-trial experimental run, a vibrotactile test stimulus (25 Hz, amplitude between 105-200 μm) was delivered to one digit pad at the same time that a standard stimulus (25 Hz, amplitude fixed at 100 μm) was applied to the other digit pad (Fig. 5.5c left panel). The loci of the test and standard stimuli were randomly selected on a trial-by-trial basis. At the beginning of the experimental run, the test amplitude was 200 μm and the standard amplitude was 100 μm. The difference between the amplitudes of the test and standard stimuli was adjusted on the basis of the subject's response in the preceding trial, such that the difference was decreased/increased after a correct/

incorrect response, respectively. The same tracking algorithm as that described for the tactile detection threshold protocol was employed, and the step size was held constant at 10 μm throughout the experimental run.

Amplitude Discrimination with Adaptation

In order to measure the gain effects that conditioning stimuli have on subsequent stimuli, the previously described amplitude discrimination protocol was modified such that delivery of the test and standard stimuli was preceded by a single conditioning stimulus to one of the two stimulus sites (Fig. 5.5c right panel). The result of such a protocol modification is that the amplitude discrimination difference limen (DL) is typically significantly elevated (Tannan et al., 2007b, 2008; Zhang et al., 2008; Folger et al., 2008). Specifically, a 25 Hz 200 μm conditioning stimulus was delivered 1 sec prior to the presentation of the test and standard stimuli. When the conditioning stimulus is delivered to the same site as the test stimulus, the effect of reducing the perceived intensity in this condition can be quantified by comparison of the DLs obtained in the adapted vs. non-adapted conditions (Tannan et al., 2007b, 2008; Zhang et al., 2008; Folger et al., 2008). The duration of the conditioning stimulus was 1 sec, which was followed by a 1 sec delay before onset of the simultaneous delivery of the test and standard stimuli. The amplitude discrimination tracking algorithm used in the previously described protocol was used to track the subject's ability to determine the most intense stimulus (i.e., the subject's DL was determined).

Dynamic Tracking of Adaptation

A novel protocol termed "dynamic tracking" was implemented to further characterize the effects of adaptation on amplitude discrimination (Fig. 5.5b). At the start of each experimental run, two vibrotactile stimuli (25 Hz; initially identical in amplitude at 300 μm) were delivered simultaneously to D2 and D3. Four conditions of initial constant stimulus duration (n sec) were employed, in separate experimental runs: 0, 1.5, 2 and 3 sec. After the initial constant stimulus period, the amplitudes of both stimuli were dynamically altered such that the amplitude of one stimulus was increased and the amplitude of the other stimulus was

decreased, in steps of 25 μm/sec. The subject was instructed to indicate the location at which the most intense stimulus was delivered as soon as the two stimuli felt distinctly different in intensity. For each experimental run, the difference limen (DL) was measured as the actual difference between the two test amplitudes at the time of subject response (m sec). D'Agostino-Pearson test ($\alpha = 0.05$) was performed to test whether the data points under each condition were sampled from a Gaussian distribution. Repeated measures analysis of variance (ANOVA) was used to evaluate the difference of the subject's performance under different conditions. Data are presented as means and standard errors (SE). A probability of less than 0.05 was considered statistically significant.

APPLICATIONS

Because of the close correlation between perception and healthy brain status, sensory assessment could be considered as an efficient approach to evaluate sensory function. However, traditional sensory testing methods mainly employ single-site stimulation which is not ideal for the study of cortical-cortical interactions. Additionally, these tests that rely on threshold testing or tests of sensitivity predominantly measure functions of the peripheral nervous system, and the small signal to noise ratio of near-threshold stimulation normally — induces large inter-subject variability. Although this intra-cortical communication involves numerous mechanisms, the tests that we developed appear specifically sensitive to the status of mechanisms currently believed by many to play major roles in the disorders of sensory cortical information processing in a number of neurological disorders — i.e., neurotransmission mediated by the inhibitory neurotransmitter gamma aminobutyric acid (GABA) and by N-methyl-d-aspartate (NMDA) receptors, and interactions/interdependencies between neurons and glial cells.

Findings on multiple subject populations have led to novel insights about the perceptual changes that occur with systemic alterations of cerebral cortical function, and provided useful information of the underlying mechanisms for the development and maintenance of different neurological diseases. A glimpse of this is seen in the preliminary data from subjects with autism in chapter 3 and the pilot concussion study in chapter 4. The next three chapters include studies completed with the sole goal of exploring sensory percept differences between populations with neurological disorders and the typically developing.

Chapter 6 is a grand overview of the autism research performed by our research group over the last decade. This chapter describes recently developed hypothesis driven methods for quantifying metrics of sensory perception based on the neurophysiological principles of

cortical modularity. Dynamically changing stimuli revealed surprising heterogeneity in the subset of patients with autism, possibly elucidating large neurological differences between those diagnosed as being on the autism spectrum. These novel sensory discrimination tests may provide (a) an effective means for biobehavioral assessment of deficits specific to autism and (b) efficient and sensitive measures of change following treatment. The methods could prove to be a useful and efficient way to detect specific neural deficits and monitor the efficacy of pharmacological and/or behavioral treatments in autism.

In chapter 7, altered central sensitization in subgroups of women with vulvodynia was studied. The results suggest that chronicity of vulvar pain leads to changes in the effect of adaptation on tactile perception, which reflect an altered central sensitization linked to dysfunction in CNS inhibitory pathways. It was proposed that vulvodynia syndromes are likely to be triggered by peripheral factors in the skin or underlying musculature, and with time and chronicity, varying degrees of central dysregulation may develop.

In chapter 8, the cortical-cortical interactions in the healthy aging population are presented. The subject‘s performance in a set of sensory-based discrimination tests demonstrated that although age-related degradations was shown during peripheral–mediated testing, effects of adaptation (cortical plasticity) was maintained in normal aging and compensates for both anatomical and physiological losses that have been shown to naturally occur with age. The major target of this study is to establish baseline data to enable the launching of a more prospective longitudinal study for the diagnostic screening of the early detection of Alzheimer‘s disease.

CHAPTER 6: THE ROLE OF CORTICAL MODULARITY IN TACTILE INFORMATION PROCESSING: AN APPROACH TO MEASURING INFORMATION PROCESSING DEFICITS IN AUTISM[5]

Background

Autism is a pervasive developmental disorder that is manifested in a number of neurological alterations. Although there is a large spectrum of behavioral excesses that includes a diverse number of traits, such as repetitive behaviors and/or sensory hyper-responsiveness, many of the neurological problems could be attributed to underlying anatomical and physiological fundamentals that demonstrate significant diversity within this spectrum and make the phenotypic description of the disorder distinctly different from that exhibited by normal physiology. Characterization of neurological features — such as cortical modularity — could lead to a better understanding of the neurophysiological fundamentals of autism. Recently, we have been developing sensory-based diagnostic protocols based on neurophysiological principles that have been elucidated in animal studies conducted both in our laboratories and those of others. One question that we have pursued in our animal studies has been the fundamental role(s) of the cortical minicolumn and macrocolumn in tactile information processing. We have developed experimental models for determining cortical correlates of perception that relate cortical activity patterns in somatosensory cortex (at high resolution in squirrel monkey studies) to measures of human perception. The minicolumnar and macrocolumnar organization of the cerebral cortex is dynamic and interactive, and the patterns of activity that are generated with stimulus-driven activity in SI cortex have been shown to be modular in nature. This determination of modularity is derived from a self-

---

[5] This chapter previous appeared in a book titled "Recent Advances in Autism Spectrum Disorders - Volume II." The original citation is as follows:
Eric Francisco, Oleg Favorov and Mark Tommerdahl (2013). The Role of Cortical Modularity in Tactile Information Processing: An Approach to Measuring Information Processing Deficits in Autism, Recent Advances in Autism Spectrum Disorders - Volume II, Prof. Michael Fitzgerald (Ed.), ISBN: 978-953-51-1022-4, InTech, DOI: 10.5772/54801

organizing process that takes place via dynamic interactions between minicolumns and columns in the cortex both during and after development. If developmental processes malfunction, then cortical organization suffers at a number of scales. Findings by Casanova and colleagues have elegantly demonstrated in post-mortem histological experiments that minicolumn organization in autism is severely compromised, as there are approximately 30% more minicolumns in the same cortical space as is normally found (Casanova, 2002). The increase in minicolumn density, and particularly the decrease in neuropil between the minicolumns (because they are now much more densely packed), led us to make a number of predictions about alterations in perceptual metrics that would occur in individuals with autism. In this paper, the neurophysiological basis of three such perceptual metrics (previously reported) is discussed.

Cortical modularity and spatial localization

In 1978, Mountcastle hypothesized that the smallest functional unit of neocortical organization, the "minicolumn", is a radial cord of cells about 30-50 μm in diameter, and that sensory stimuli activate local groupings of minicolumns (called "macrocolumns") (Mountcastle, 1978). This hypothesis subsequently received support from multiple lines of experimental evidence and led to its substantial elaboration. Structurally, minicolumns are attributable to the radially-oriented cords of neuronal cell bodies that are evident in Nissl-stained sections of the cerebral cortex and it is probable that they are related to ontogenetic columns (Rakic, 1988) and to the radially-oriented modules defined by the clustering of the apical dendrites of pyramidal neurons (Peters, 1993). Among the various elements of neocortical microarchitecture, *spiny-stellate* cells and *double-bouquet* cells (Jones, 1975, 1981; Lund, 1984) are most directly relevant to Mountcastle's concept of the minicolumn. Spiny- stellates are excitatory intrinsic cells that are especially prominent in layer 4 of primary sensory cortex. They are the major recipients of thalamocortical connections and, in turn, they distribute afferent input radially to cells in other layers. Double-bouquet cells are GABAergic cells whose somas and dendritic trees are confined to the superficial layers, and because the double-bouquet cells are more likely to inhibit cells in

adjacent minicolumns rather than in their own, they offer a mechanism by which a minicolumn can inhibit its immediate neighbors.

Some insights into the role of the minicolumn in sensory information processing have been revealed through neurophysiological experimentation. Receptive field mapping studies by Favorov and colleagues (Favorov, 1990) determined that there are abrupt shifts between receptive field centers as stimuli shift from one skin site to another. In other words, Favorov's receptive field work predicted that a perceptible but subtle shift of stimulus position would not necessarily engage a different pattern of macrocolumnar activity. Rather, the pattern of minicolumnar activity *within a macrocolumn* would be different with a shift in stimulus position up to a point. At the point at which the stimulus position crosses a boundary, the stimulus will engage a new macrocolumn and an entirely different minicolumnar pattern of response will be evoked by the stimulus. Figure 6.1 summarizes minicolumnar RF organization in the somatosensory cortex. Note that as an electrode penetration moves tangentially across a field of cortical macrocolumns (note locations of penetrations 1-30), the receptive field center (indicated on the digit tips to the right of the cortical field) moves a significant distance only after crossing a macrocolumnar border. While within the macrocolumn, the receptive field centers remain relatively closely spaced. It is also of note that the receptive field properties are constrained within the radial dimension; that is, if the electrode is moved along the radial dimension (note the penetrations denoted a-g), the receptive field center does not shift and receptive field properties will be very similar. As the description above is over-simplified, it should be noted that there is a great diversity of receptive field properties between neighboring minicolumns, and a stimulus that effectively activates one minicolumn will often be ineffective at activating that minicolumn's nearest neighbor (Favorov, 1988, 1994)

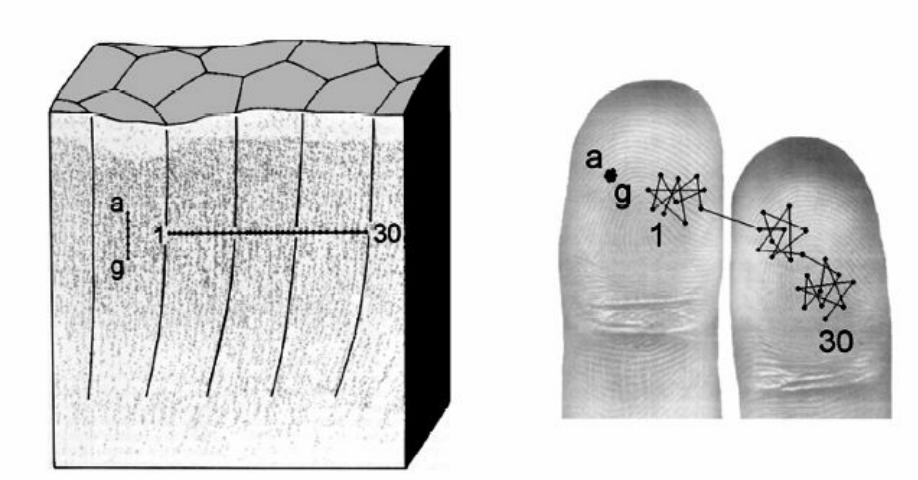

Figure 6.1: Summary of Minicolumnar RF Organization in SI Somatosensory Cortex
Left: Drawing of cross-section of Nissl-stained cortical tissue showing darkly-stained cell bodies organized in radially oriented cords, interpreted as minicolumns. Filled circles labeled a–g—sequence of neurons located within a single minicolumn; 1–30—sequence of neurons located in series of adjacent minicolumns.
Right: Sequences of RF centers (connected dots) mapped by neuron sequences a–g and 1–30. Note that RF centers for SI neurons that occupy the same minicolumn stay close together, whereas the RF centers for pairs of neurons located in neighboring minicolumns shift back and forth over large distances, and occupy totally non-overlapping skin regions when the pair of neurons occupies different SI macrocolumns.

The findings and predictions by Favorov et al were later confirmed with additional data that was obtained via optical intrinsic signal imaging (for description of technique, see (Tommerdahl, 2002)). In this study, responses evoked by vibrotactile stimuli delivered to different positions on the skin (which differed by only the width of the 2mm probe tip) showed a subtle variation within the macrocolumnar pattern within a range of stimulus positions (analyzed with the methods described in Chiu, 2005), but the global pattern did not shift until a new group of minicolumns (or macrocolumns) was stimulated. Figure 6.2 summarizes the results of one such imaging experiment in which the macrocolumnar pattern of cortical response does not significantly alter with a small shift in stimulus position until a border is crossed. Additional features of these minicolumnar patterns of activity that have been characterized are that they are stimulus magnitude- and duration-dependent (Chiu, 2005, 2006; Tommerdahl, 2005). For example, increasing the stimulus duration leads to more distinct and well-defined minicolumnar patterns of cortical activity. Additionally, the spectrum of the spatial profile of this activity evoked by the active minicolumns robustly and significantly shifts

to lower frequencies, and the spectral shifts that have been observed are consistent with the concept of increased GABA mediated lateral inhibition between minicolumns (Chiu, 2005). Perceptually, these changes in minicolumnar activity patterns with stimulus duration could parallel the increases in sensory perception that have been observed with longer stimulus durations (Tommerdahl, 2010).

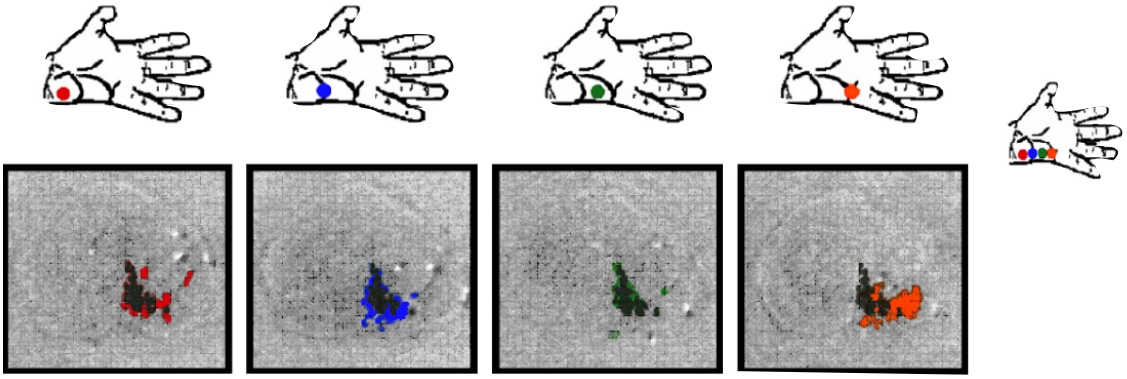

Figure 6.2: Summary of OIS Evoked Responses in SI cortex
Difference in stimulus position was equal to probe diameter (2 mm). Note the abrupt shift between the responses evoked from the stimulus placed at the first three positions vs. that of the fourth. Modified from Tommerdahl, 2002.

Casanova and colleagues have demonstrated that there is a substantial increase in minicolumn density in the parietal cortex of individuals with autism (Casanova 2002, 2003). This increase in minicolumn density results in a disproportionately large number of minicolumns becoming packed into the same cortical space and also results in a decrease in the neuropil between minicolumns. Thus, although there are now a higher density of minicolumns, there is less room for the GABA mediated lateral inhibitory connections between the minicolumns that are necessary for shaping the within-macrocolumn response that has been observed with repetitive stimulus duration (Chiu, 2005, 2006; Tommerdahl, 1987, 1993, 2005; Mccasland, 1988; Kohn, 2000). This alteration in basic cortical microarchitecture would then predict– ably contribute to an individual's sensory perception in a couple of ways. First, the increase in minicolumn density should afford an individual with autism an advantage in some sensory tasks, such as spatial localization, in which the percept would be improved. However,

below baseline GABA mediated lateral inhibition between minicolumns would mean that increasing the duration of a stimulus would not increase the resolution or distinction of the within macrocolumn pattern of minicolumnar activity to the same degree, and thus, perception would not be improved. With this hypothesis of the minicolumn's role in spatial localization in mind, we designed an experiment to evaluate the differences between the spatial localization ability of neurotypical controls and subjects with autism (Tommerdahl, 2007). In the study, a subject's ability to distinguish between two points on the skin (on the hand dorsum) was determined with two different stimulus durations – 500 msec and 5 sec (full description of the method in (Tannan, 2006; Tommerdahl, 2007)). Results from that study are summarized in Figure 6.3. Although individuals with autism outperformed controls in the shorter stimulus duration task, they did not demonstrate the nearly two-fold improvement that the controls did when the stimulus duration was extended. Thus, in the case of spatial localization, it appears that alterations in sensory percept could be accounted for by the changes that have been observed in cortical minicolumn architecture.

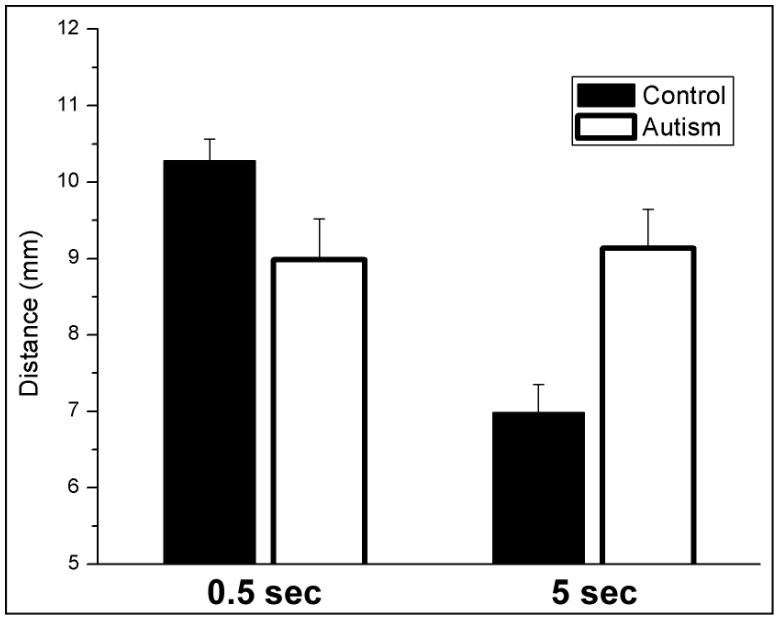

Figure 6.3: Spatial Localization of Adapting Stimulus Duration in Autism
Data displayed from the control subjects contrasts markedly from the data obtained from observations of subjects with autism. Note that subjects with autism, although they clearly outperformed the controls in the 0.5 sec adapting condition, did not improve with the 5.0 sec adapting condition.

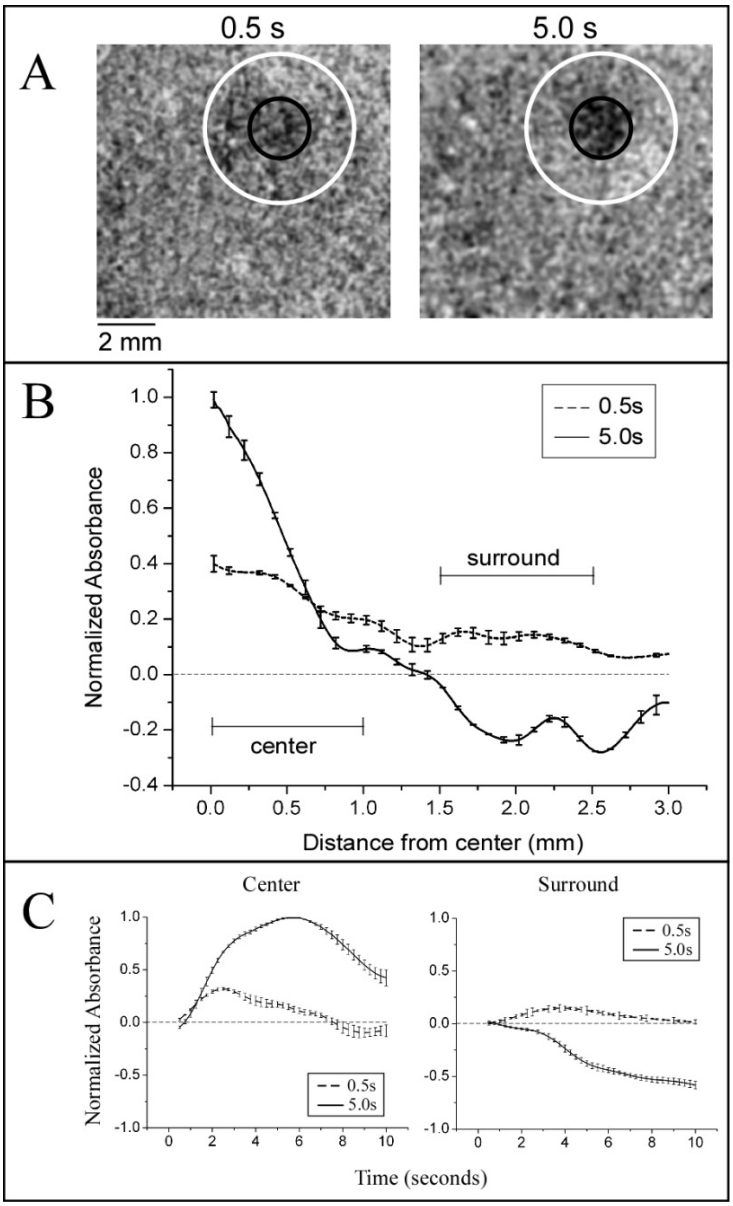

Figure 6.4: Radial Histograms of SI cortical Activity Across Subjects
Cortical activity is measured in terms of light absorbance (increased light absorbance can be correlated to increased cortical activity). Data from the center of the plot corresponds to the maximally responding SI cortical territory to the 5 sec stimulus condition. Note that at the 0.5 sec stimulus duration, there is no below-background activity.

The difference that was observed in short vs. long stimulus duration in the above-described spatial localization experiment led us to examine more directly the relationship between our previous adaptation animal studies and the role that adaptation — or conditioning stimulation — plays in sensory information processing in autism. It has been well established that conditioning stimulation — or prolonged pre-exposure to sensory stimulation —

significantly modifies discriminative capacity and alters the ability of both peripheral and CNS neurons to process sensory information. Less widely appreciated is the fact that primary sensory cortical mechanisms undergo transient and significant alterations in response to repetitive sensory stimulation. Investigation of the dynamic cortical responses evoked by repetitive stimulation has been an ongoing line of research in our laboratory. One of the focal points has been the spatiotemporal patterns of response in the somatosensory cortex evoked by skin stimulation and how these patterns influence the cortical response to subsequent stimuli. For example, the observations of a number of studies have demonstrated that the spatially distributed pattern of activity evoked in SI cortex by cutaneous flutter stimulation exhibits a prominent time-dependency (Tommerdahl, 2002; Simons, 2005; Simons, 2007). Specifically, changing the stimulus duration from 500 msec to 5 sec (such as was done in the spatial localization task described above) would result in two distinctly different patterns of response in SI cortex. Figure 6.4 compares the profiles of two SI cortical responses evoked by vibrotactile stimuli that differed only in duration (Note that the profile is a radial histogram of OIS images generated by plotting the cortical activity evoked by the stimulus as a function of the distance from the center of the region in SI that is maximally activated by the stimulus; (Simons, 2005, 2007)). With the 500 msec stimulus, the entire response profile is above-background. However, with the longer duration 5 sec stimulus, a suppressive or inhibitory region surrounds the maximally activated region. This region of inhibitory influence — which persists for several seconds — would interfere with the SI response to a stimulus applied concurrently or subsequently to skin regions in near proximity represented by neurons in that region of SI. Thus, in the case of the above-described spatial localization task, longer stimulus durations would be expected to improve performance. Since the presence of a center-surround in stimulus evoked cortical activity is commonly recognized as a function of GABA mediated pericolumnar lateral inhibition (Juilano, 1989; Kohn, 2000), and a number of researchers have described GABA deficiency as being consistent with autism (Hussman, 2001; Blatt, 2005; Casanova, 2003; Belmonte, 2004; Chao, 2010), we concluded that the lack of improvement with

increasing stimulus duration in autism subjects in the spatial localization task could be due to a deficiency in GABA mediated neurotransmission.

The improvements that are normally observed with extended stimulus durations could be attributed to stimulus-evoked inhibition that surrounds areas of excitation. Single unit studies and imaging studies using voltage-sensitive dyes likewise have shown that excitation in the responding neuronal population is accompanied by the development of a surrounding field of inhibition (Brumberg, 1996; Derdikman, 2003; Foeller, 2005; Wirth, 2004). Similarly, imaging studies that have used the OIS have shown that prolonged stimulation of a discrete skin site not only is associated with increased absorbance within the SI region representing the stimulated skin site, but also with decreases in absorbance in surrounding regions (Simons, 2005; Moore, 1999; Tommerdahl, 1996, 1999). Regions of decreased absorbance (increased reflectance) such as that described in Figure 6.4 are widely believed to be indicative of decreases in neuronal spike discharge activity (Grinvald, 1985, 1991; Whitsel, 2003), possibly resulting from stimulus-evoked inhibition at these locations. Thus, there is a great deal of evidence that the suppressed or below-background activity observed suggests that stimulus-evoked inhibition is responsible for the improvements in performance that are normally observed with repetitive stimulation. However, it appears that in the case of autism, there is sufficient evidence to speculate that the normal center-surround relationship in cortical patterns of activity does not fully develop.

Cortical modularity and adaptation

In addition to changes in spatial contrast, as described above, repetitive stimulation also results in temporally defined changes of cortical activity, the most prominent of which is a reduction in cortical response with extended stimulus duration. At the single cell level, both visual and somatosensory cortical pyramidal neurons undergo prominent use-dependent modifications of their receptive fields and response properties with repetitive stimulation. These modifications can attain full development within a few tens of milliseconds of stimulus onset, and can disappear within seconds after the stimulus ends (visual cortical neurons:

(Bredfeldt and Ringach, 2002; Celebrini et al., 1993; Das and Gilbert, 1995; DeAngelis et al., 1995; Dinse and Kruger, 1990; Pack and Born, 2001; Pettet and Gilbert, 1992; Ringach et al., 1997; Shevelev et al., 1998; Shevelev et al., 1992; Sugase et al., 1999; Kohn, 2007) alternatively — for review of short term cortical neuron dynamics in visual cortex, see (Kohn, 2007; Smith, 2008); for review of short-term primary somatosensory cortical neuron dynamics see (Kohn & Whitsel 2002; Tommerdahl, 2010).

Optical imaging studies have also characterized the short-term dynamics of the population-level response of squirrel monkey contralateral primary somatosensory (SI) cortex using different amplitudes and durations of vibrotactile stimulation (Tommerdahl et al, 1996, 2002; Chiu et al., 2005; Simons et al., 2005, 2007). The results of these optical intrinsic signal (OIS) imaging studies demonstrated a strong correlation between the amplitude of 25 Hz vibrotactile (flutter) skin stimulation and the response magnitude evoked in SI. In addition to the systematic changes in the spatial pattern of response in SI that correlated with increases in the amplitude and the duration of the stimulus, increasing the stimulus duration led to differences not only in the peak magnitude of the evoked cortical response, but also in the relative rates of rise and decay of the magnitude of the evoked intrinsic signal. These differences in the rates of rise and decay could impact the refractory period following a stimulus during which the magnitude of the response to a subsequent stimulus is diminished (Cannestra et al, 1998).

In order to assess the impact that adaptation has on perception, experiments were designed to directly measure the change in amplitude discrimination capacity that occurs with prior stimulus exposure (or prior conditioning stimuli). The studies demonstrated that a subject's ability to discriminate between two simultaneously delivered vibrotactile stimuli — differing only in amplitude and location — was very robust and repeatable across a large number of (healthy) subjects but was very sensitive to varying conditions of pre-exposure to sensory stimuli (Tannan, 2007). Changing the duration of the conditioning stimulus delivered to one of the two sites before the amplitude discrimination task significantly altered a subject's

ability to determine the actual difference between the two stimuli. One significant finding of that study was that specific durations of conditioning stimuli altered the subject's amplitude discriminative capacity in a predictive and quantifiable fashion (see Figure 6.5). The test and standard stimuli were preceded by an adapting stimulus at the site of the test stimulus (ranging from 0.2 to 2 sec in duration). Note that single site adapting stimulation leads to a progressive and systematic decrease in performance with increasing adaptor duration (Tannan, 2007).

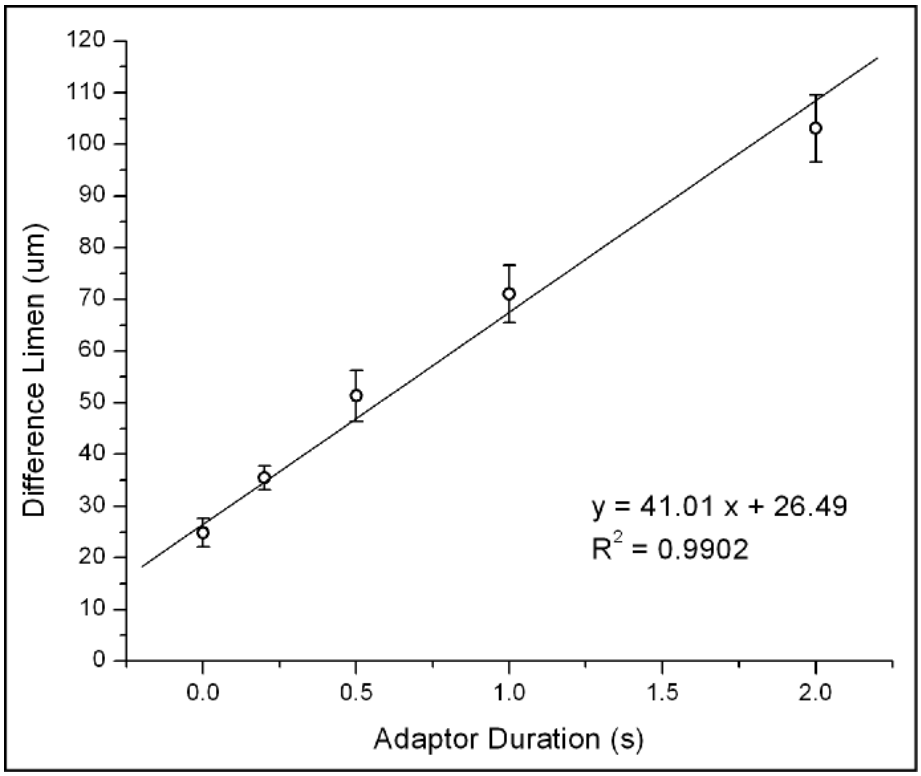

Figure 6.5: Comparison of Amplitude Difference Thresholds to Adaptation
The test and standard stimuli were preceded by an adapting stimulus at the site of the test stimulus (ranging from 0.2 to 2 sec in duration). Note that single site adapting stimulation leads to a progressive and systematic decrease in performance with increasing adaptor duration .

This finding indicated that the method could be viewed as a reliable indicator of the influence of adapting stimuli on cortical response, as changes in peripheral response are not mediated at these short stimulus durations (for discussion, see (Tannan, 2007)).

Conditioning stimuli did not have as pronounced an impact on the amplitude discriminative capability of subjects with autism as it did with the control group (Rinehart, 2006). In Figure 6.6, results obtained using identical methods from subjects with autism and

controls are compared. Note that adaptation (i.e., a 1 sec conditioning stimulus at one stimulus site prior to the amplitude discrimination task) resulted in the control subjects performing significantly worse than they did in the absence of adaptation. However, in the case of the autism subjects, the impact of prior history of stimulation was not as significant, and the amplitude discrimination metric was not impacted to the same degree as it was in the controls. Thus, the ineffectiveness of a conditioning stimulus in this study repeated the findings of the spatial localization studies, in that adapting stimuli had little or diminished effect — positive or negative — on the sensory discriminative performance of individuals with autism.

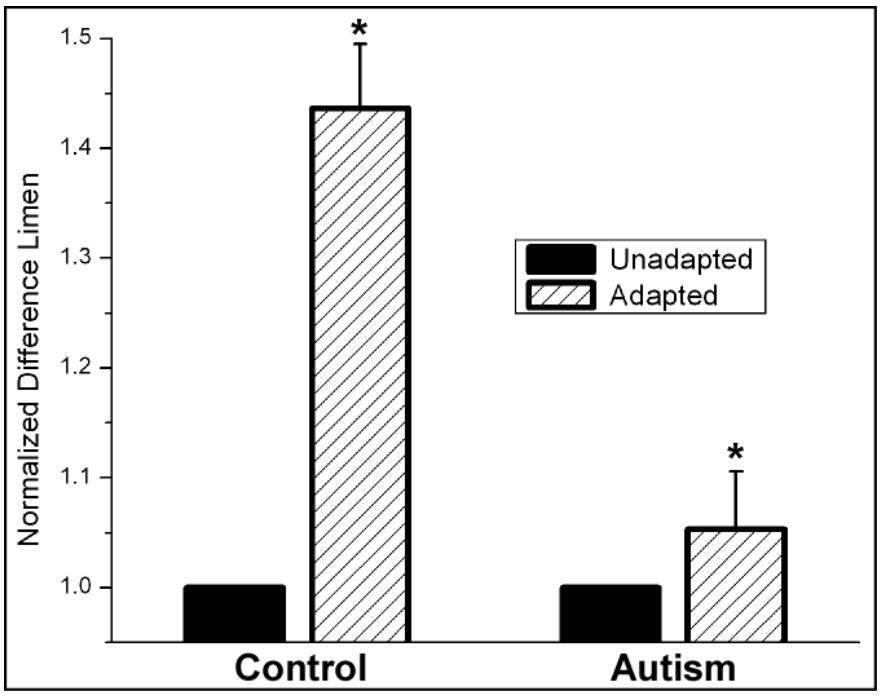

Figure 6.6: Comparison of Difference Limens Normalized to the Unadapted Condition
Note that for both the control and the autism group, 1 sec adaptation resulted in an elevated difference limen (* ANOVA; $p < 0.01$). The control group showed a greater impairment with adaptation (~45%) than the autism group (~5%).

Note that for both the control and the autism group, 1 sec adaptation resulted in an elevated difference limen (* ANOVA; $p < 0.01$). The control group showed a greater impairment with adaptation (~45%) than the autism group (~5%) (Tannan, 2008).

Cortical modularity and synchronization

There are a number of autism studies that have described Parkinsonian-like motor characteristics and/or postural control problems, which could be attributed to deficits of the basal ganglia portion of the frontostriatal system (Rinehart, 2006; Takarae, 2007). These deficits in sensorimotor control could be derived, in part, from the role that the frontostriatal system plays in an individual's timing perception as well as the coordination that is required between cortical regions during sensorimotor tasks. Timing perception, which can be measured with some relatively simple temporal discriminative measures (such as TOJ: temporal order judgment and TDT: temporal discriminative threshold) — is most often accounted for by the frontostriatal system largely as a result of these measures being sensitive to lesions to the supplementary motor area (SMA), posterior parietal cortex, and basal ganglia (Lacruz, 1991; Pastor, 2004). Also because of the fact that above-average TOJ thresholds occur in subjects with known damage to these same cortical areas (dyslexia (Laasonen et al., 2000), dystonia (Sanger et al., 2001; Tinazzi et al., 2002; Tinazzi et al., 1999), and Parkinson's disease (Artieda et al., 1992)). Most recently, it was found that individuals with autism also have below-average timing perception capacity (Tommerdahl et al, 2008). This timing deficit could be accounted for by differences in a number of structures, particularly in the frontostriatal system, that have been implicated in autism (e.g., basal ganglia (Haist et al., 2005; Herbert et al., 2003; Hollander et al., 2005; Langen et al., 2007; Rojas et al., 2006; Sears et al., 1999; Voelbel et al., 2006) ; caudate nucleus (Langen et al., 2007); thalamus (Hardan et al., 2006; Hardan et al., 2008), and impaired white matter connectivity in the frontal lobe (Lee et al., 2007)).

In addition to the role that the frontostriatal system may have in the perceptual timing deficits of autism, the role of synchronization (or lack of synchronization) in autism has gained a certain degree of prominent attention. Uhlhaas and Singer (Uhlhaas & Singer, 2006) recently reviewed the experimental evidence that suggests that functional connectivity is reduced in autism, primarily based on fMRI studies (Castelli,2002; Just, 2007; Koshino, 2005;Villalobos, 2005; Kana, 2006; Cherkassky, 2006) that examine the coordinated activity between different

areas of the cerebral cortex. A few studies, using MEG and EEG, have found gamma oscillations, which are considered to be important in the process of coordinating cortical activity, to be below normal in subjects with autism (Brown, 2005; Wilson, 2007). From the perspective of cortical modularity at both the minicolumnar and macrocolumnar scales, synchronization at the local cortical level should also be impacted. Casanova and colleagues have suggested that the aberrant minicolumnar structure that they have found in autism could result in the disruption of the inhibitory architecture (Casanova et al., 2003) that is required for normal function in local neural circuitry. Disruption of functional connectivity at the local minicolumnar level could be responsible for, or strongly correlated with, the dysfunctional connectivity that has been observed across large-scale cortical areas.

There is a rapidly growing appreciation in neurobiological research of the important contributions to sensorimotor function of coordinated across-neuron patterns of spike discharge activity within the neocortical areas activated by sensory stimuli (for comprehensive review see Whittington, 2000). In particular, stimulus-induced, time-dependent (dynamic) across-neuron synchronization of action potential discharge and the associated oscillatory modulation of spike firing are common and prominent properties of neocortical networks devoted to the processing of sensory information. The tendency of sensory neocortical networks to generate synchronized oscillations in response to stimulation has raised the possibility that synchronization may play a prominent role in some aspects of sensory perception. We examined whether or not synchronization could impact the topography of temporal perception (Tommerdahl, 2007). The goal of the study was to elucidate the impact of stimulus-driven synchronization on adjacent cortical ensembles and the spatio-temporal integration of information that results from those ensembles being temporally linked or bound by a common synchronizing input. More specifically, we demonstrated that temporal order judgment (TOJ – a measure obtained from determining the minimal inter-stimulus interval necessary for a subject to detect the temporal order of two sequentially delivered peripheral stimuli) and temporal discrimination threshold (TDT) in neurotypical subjects were significantly

impacted when two synchronized (but low amplitude) vibrotactile stimuli were delivered concurrently to the dual test stimulus sites. The conclusion of that study was that the stimulus-driven linkage between topographically adjacent sites resulted in an increase in TOJ threshold and TDT (or worse performance), most likely because these cortically adjacent or near-adjacent regions were being driven with a simultaneous and identical sinusoidal pair of tactile stimuli which contributed to a loss in spatio-temporal contrast (Tommerdahl, 2007).

A subsequent question that was then addressed was whether or not individuals with autism experience a decrease in timing perception (as measured by TOJ and TDT) if the same concurrent synchronizing stimuli were delivered during the TOJ/TDT tests. If neurologically compromised individuals — such as those with autism — have distinct systemic cortical deficits, and these deficits extend to local neuronal circuitry connectivity, then the abnormal functional connectivity between adjacent and/or near adjacent cortical ensembles would hypothetically decrease the effect that stimulus-driven synchronization has on the TOJ or TDT task (i.e., performance on the task would not degrade). Comparisons of the control vs. autism results (previously reported in Tommerdahl, 2007, 2008) are shown in Figure 6.7. Note that with concurrent stimulation, individuals with autism do not suffer the same decrease in sensory discriminative performance that controls do. In other words, the functional linkage in controls that becomes rapidly established, due to local synchronization effects, appears to perceptually bind the two stimulus sites (in this case, digits two and three) to an extent that it becomes more difficult to identify the temporal order between the two sites. Thus, as in the case of adaptive responses, it appears that there is a loss of an ability to integrate both spatial and temporal information in autism.

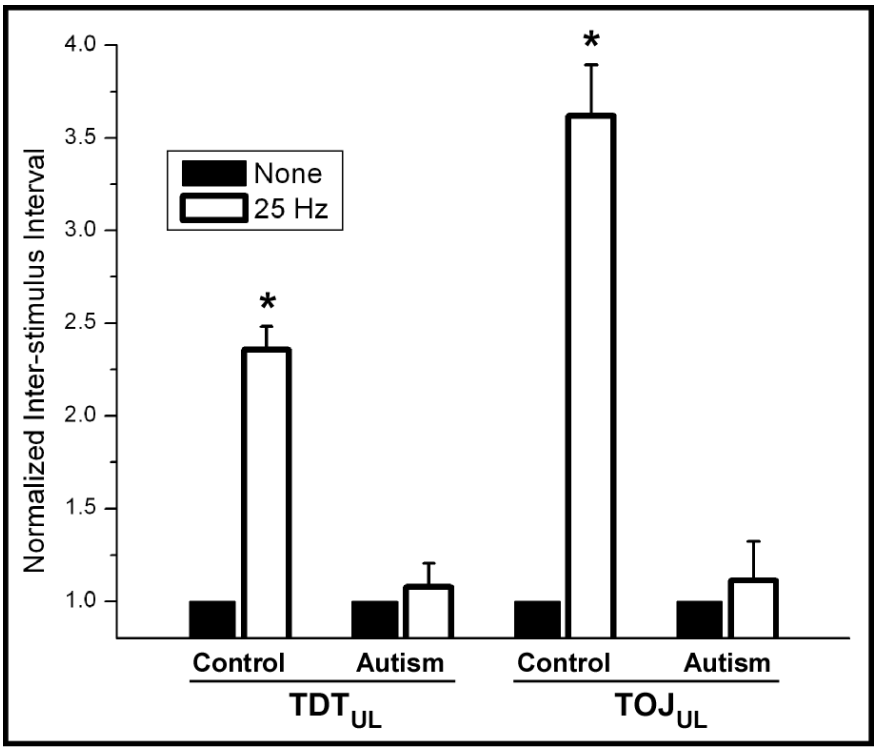

Figure 6.7: TDT and TOJ Performance Metrics with/without 25 Hz Conditioning
The 25 Hz conditioning stimulus significantly impaired TDT by ~240% ($p < 0.01$) and TOJ by ~360% ($p < 0.01$) for the control group, whereas the autism group showed no significant change for either measure.

What could account for the reduction in TOJ performance in Typically Developing (TD) controls? Functional connectivity between neighboring cortical regions normally leads to a reduction in TOJ performance in healthy controls with the introduction of the synchronized conditioning stimuli, and this is predicted by recordings from *in vivo* animal studies. Consider the results displayed in Figure 6.8. Extracellular recordings were obtained from SI cortical regions corresponding to D2 and D3 in the squirrel monkey. When a vibrotactile pulse was delivered to D2, a significant above background response was evoked at D2 (top left quadrant) but not at the D3 representation (top right quadrant). However, when sub-threshold synchronized sinusoidal stimuli were delivered to both digits prior to the pulse (bottom half of Figure 6.8), the pulse at D2 evokes a response at both the D2 and D3 representations (note absence of evoked activity before zero msec during sub-threshold stimulation).

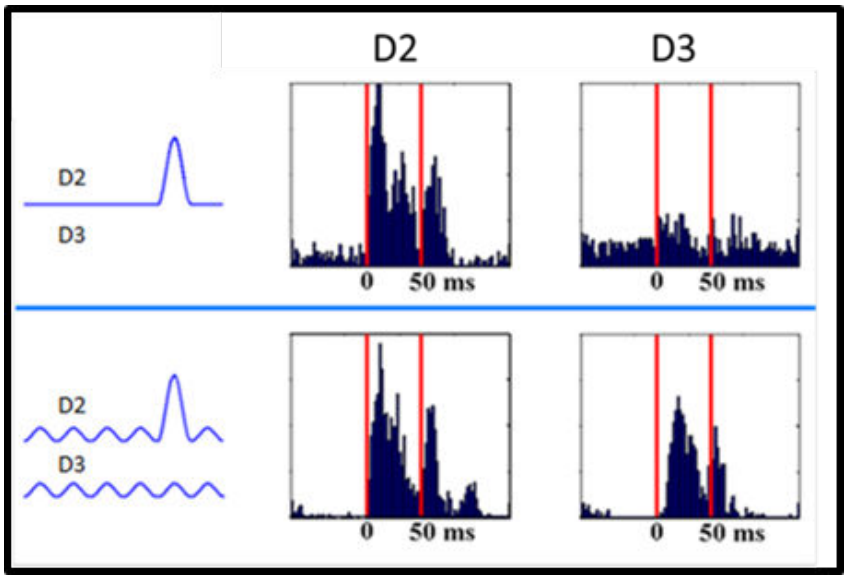

Figure 6.8: Extracellular Recordings Obtained from SI in the Squirrel Monkey
When a vibrotactile pulse was delivered, a significant above background response was evoked at D2 but not at the D3 representation. When sub-threshold synchronized sinusoidal stimuli were delivered to both digits prior to the pulse, the pulse at D2 evokes a response at both the D2 and D3 representations.

From this type of data, we hypothesized that this response was the result of functional connectivity between adjacent and/or near adjacent cortical ensembles. In other words, the conditioning stimuli delivered prior to the TOJ task engaged the cortical ensembles in the D2 and D3 cortical representations to be in concert, and delivery of a simple stimulus to one digit (D2) resulted in a near simultaneous response at the representation of another digit (D3). Thus, it would be predicted that delivery of synchronized conditioning stimuli would impact the topography of temporal perception (Tommerdahl, 2007). However, individuals with autism do not suffer the same decrease in sensory discriminative performance that neurotypical controls do. In other words, the functional linkage that becomes rapidly established in TD individuals to local synchronization effects. appears to perceptually bind the two stimulus sites does not occur in autism (Tommerdahl, 2008). Thus, an extrapolation of this is that, utilizing measures impacted by stimulus driven synchronization, there is significant hypo-connectivity in autism at the level of local cortical ensembles.

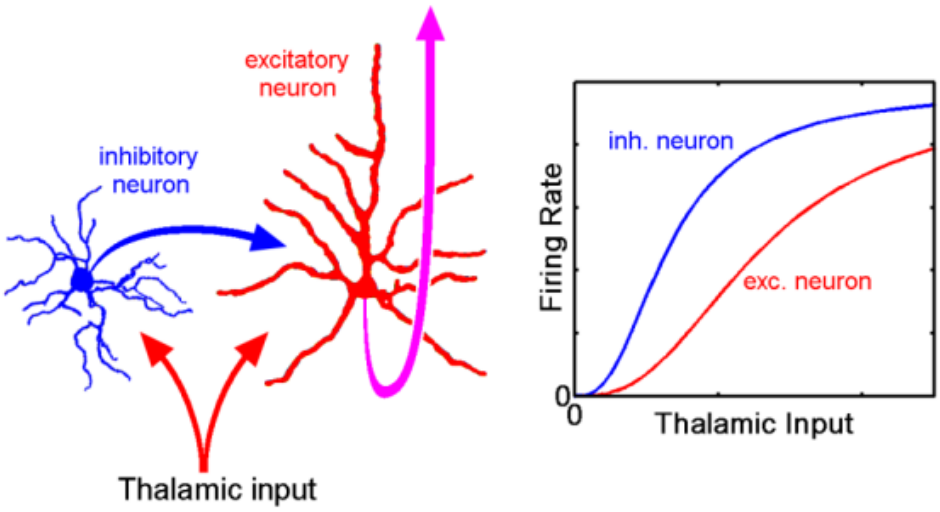

Figure 6.9: Visual Representation of Feed Forward Inhibition

Interim Summary

In the previous 3 sections, we described sensory-based diagnostic protocols that were based on neurophysiological principles that have been elucidated in animal studies. In the following sections, we describe additional protocols based on hypotheses that have not yet been tested in *in vivo* animal models, and it is anticipated that these protocols will add further insight into differences in fundamental mechanisms of information processing between TD and Autism Spectrum Disorder (ASD) individuals.

The role of sub-threshold stimulus-evoked inhibition

A major well-documented feature of cortical functional organization is the presence of prominent feed-forward inhibition in the input layer 4 (see Figure 6.9). Local layer 4 inhibitory cells receive direct thalamocortical input and in turn suppress responses of neighboring layer 4 excitatory cells to their thalamocortical drive, thereby sharpening their RF properties (Douglas, 1995; Miller, 2001; Bruno, 2002; Alonso, 2005; Sun, 2006; Cruikshank, 2007). These inhibitory cells are more responsive to weak (near-threshold) afferent drive than are the excitatory layer 4 cells and thus they *raise* the threshold at which excitatory layer 4 cells begin to respond to

peripheral stimuli. Sensory testing of stimulus detection threshold is particularly well-suited for probing feed-forward inhibition, considering that stimuli just below the detection threshold will be too weak to vigorously engage other layer 4 mechanisms besides thalamocortical excitation and feed-forward inhibition (such as lateral excitation, recurrent or feedback inhibition, or activity-driven adaptation).

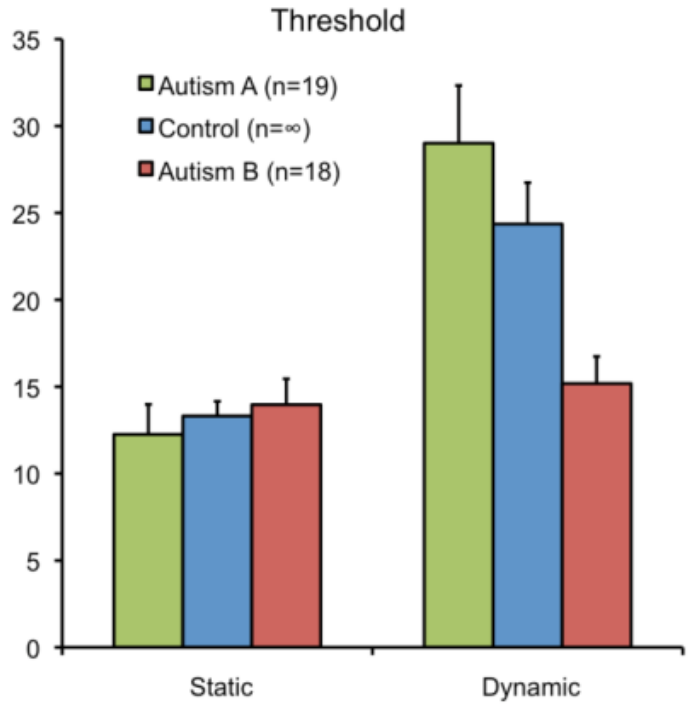

Figure 6.10: Static Thresholds vs. Dynamic Thresholds using a Ramping Stimulus.

Tactile thresholds were collected in two distinct manners. The "static thresholds were measured using a 20-trial Two Alternative Forced Choice (2AFC) Tracking protocol. During each trial a 25 Hz vibrotactile test stimulus (lasts 500 ms) was delivered to either D2 or D3; the stimulus location was randomly selected on a trial-by-trial basis. Following each vibrotactile stimulus, the subject was prompted to select the skin site (D2 vs. D3) that perceived the stimulation. After a 5sec delay — based on subject response — the stimulation was repeated until the completion of the 20 trials. The stimulus amplitude was started at 15μm and was modified based on the subject's response in the preceding trial. During the "dynamic" threshold detection, a 25 Hz vibrotactile stimulus was delivered to either D2 or D3 (the

stimulus location was randomly selected on a trial-by-trial basis). The amplitude of the stimulus was initiated from zero and increased in steps of 2 μm/s. The subject was instructed to indicate the skin site that received the stimulus as soon as the vibration was detected. Multiple trials were conducted with a random delay between trials and the results from those trials were averaged for each subject. For a complete experimental explanation, see (Zhang, 2011a, 2011b; Francisco, 2008)

In our comparative study of typically developing vs. autism individuals, we found that subjects with autism exhibit significantly greater diversity in their detection thresholds on fingertips than control subjects, with two groups emerging (designated as Group A and Group B). Based on cluster analysis of several measures, the data that we have obtained thus far strongly suggests two distinct clusters within the spectrum. Group B autism individuals have dynamic thresholds lower than controls (thus suggesting reduced feed-forward inhibition) and group A autism individuals have dynamic thresholds higher than controls (thus suggesting enhanced feed-forward inhibition). Inhibitory neurogliaform cells in layer 4 use both $GABA_A$ and $GABA_B$ receptor-mediated inhibitory synaptic transmission (Tamas, 2003); in other inhibitory cell classes, $GABA_B$ receptors are located in the presynaptic membrane and used for autocontrol). $GABA_B$-mediated inhibition develops and lasts much longer than $GABA_A$-mediated inhibition. We believe we detect the $GABA_B$ component of feed-forward inhibition in our new “dynamic:” variant of the basic (“static”) detection threshold test, in which we deliver vibrotactile stimuli of gradually increasing amplitude (starting at zero and growing at a rate of 2 μm/s) until the subject detects the vibration. Interestingly, this time-extended mode of stimulus delivery prominently elevates the detection threshold (compare “static” and “dynamic” plots in Figure 6.10), presumably by fully activating slow $GABA_B$ inhibition in addition to fast $GABA_A$ inhibition. Again we find that autism subjects exhibit greater diversity on this test than controls: group A autism individuals have static thresholds below controls, but dynamic thresholds above controls (suggesting reduced $GABA_A$ inhibition, but elevated $GABA_B$

inhibition), while group B autism have the opposite relations. Thus, if alteration of GABAa vs. GABAb inhibition influences the impact of sub-threshold mediated activation, then the two aforementioned autism populations should, if treated pharmacologically, respond differently to a GABAb agonist, such as baclofen. If this is the case, then a simple measure such as that described above could predict whether or not this particular treatment would be effective.

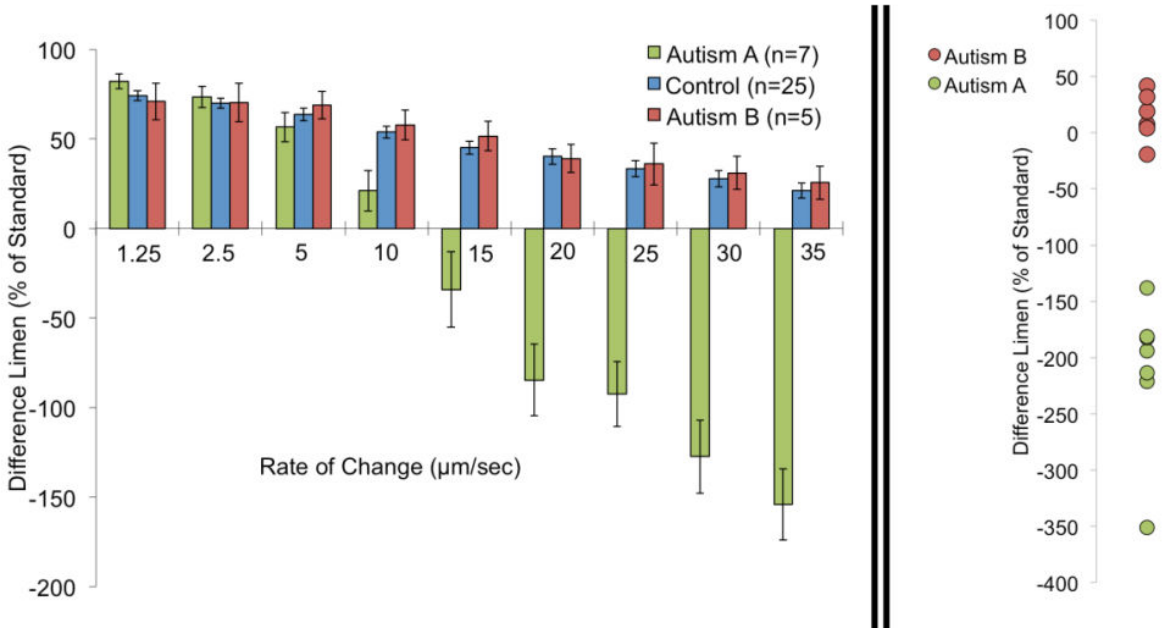

Figure 6.11: Difference Limens for Various Rates of Amplitude Modulation
Left Panel: Comparison of data obtained from typically developing controls vs. individuals with autism. Note that at lower rates of stimulus amplitude modulation, all 3 groups behave approximately the same way. As the amplitude modulation rate is increased, the responses of one of the autism groups diverge distinctly from the responses of the other subjects. Note that the negative Weber fraction indicates that the subject responded beyond the matching point of the two stimuli rather than before.
Right Panel: Comparison of individual data points from the highest modulation rate displayed in Panel A. Note the clustering of the data points within each of the groups of subjects.

Temporal integration: Rate dependent modulation of vibrotactile stimuli

The difference that we observed with static vs. dynamic thresholds encouraged us to explore the impact that changing the rate of amplitude modulation would have on sensory percept performance at supra-threshold levels. In the dynamic threshold task, an amplitude modulation rate of 2 μm/s was used to deliver a *sub-threshold* stimulus. Delivering higher rates of amplitude modulation at above threshold values yields very different results. In the data

presented below, a subject's ability to match two stimuli was assessed at nine different rates of amplitude modulation (one stimulus was held at steady state values, the other was increased until it was perceived as a match; (Francisco, 2008)). At the lowest rates, subjects performed comparably to the dynamic threshold task (Autism group A performed worse than controls and Autism B, though not significantly). With an increasing rate of modulation, from 1.25 to 10 μm/s, the Autism A group demonstrated a decreasing Difference Limen (DL). As the rate increased above 15 μm/second, this group began performing significantly worse in that the test stimuli was increased well beyond the value of the standard stimulus (resulting in the "negative" DL). It appears that this group was unable to temporally integrate information from the stimuli, and future in vivo studies will examine the role that different neurotransmitter systems play in such temporal integration.

Generating an individual CNS profile from multiple measures

A battery of protocols yields multiple parameters that can be used to build a CNS profile of a subject. Since each of the tests are influenced by some mechanisms more than others (e.g., adaptation will influence the evoked cortical response during conditioning prior to a TOJ task, but synchronization of cortical ensembles appears to have the predominant outcome on that task), combining the results from multiple tasks — with each task characterized as an independent vector of performance for some aspect of CNS information processing — would predictably yield a unique individual CNS profile. To fully appreciate the differences between subject populations, we utilized a modern mathematical approach for multi-variable analysis. Quantitative performance of each subject on the battery of *N* sensory tests was treated as localizing a subject in an *N*-dimensional "cortical metrics" space (i.e., an abstract space in which each coordinate axis corresponds to one of the battery's sensory tests). Principal Component Analysis (PCA) was then used to graphically display the test-performance data collected in the different subject populations. Figure 6.12, for example, was generated using PCA on 8 metrics, and it clearly separates individuals with autism (orange) from TD controls (blue) with a 99% confidence level that the two populations are different (using a t-squared Hotelling test). Our

long term goal with this work is to develop metrics that have the requisite sensitivity to reflect the impact that treatments or interventions have. It is anticipated that successful treatments would result in a shift of the autism values towards the more tightly clustered control values.

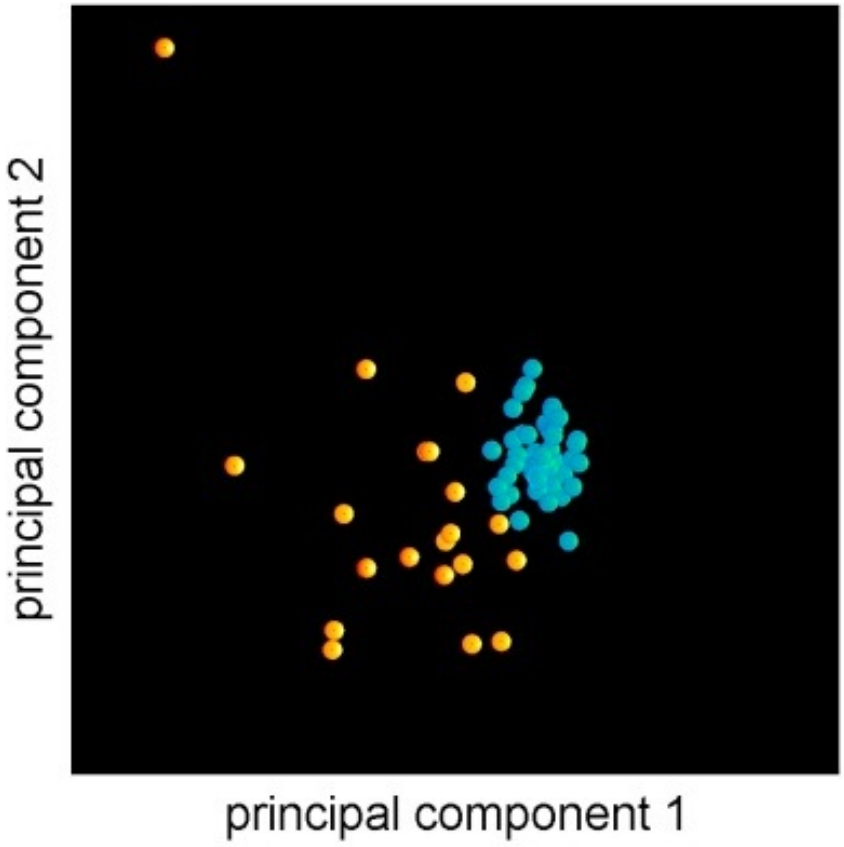

Figure 6.12: Principal Component Analysis
PCA Analysis was used to examine the performance of two populations on 8 different metrics. The analysis clearly separates individuals with autism (orange) from TD controls (blue). (99% confidence using a t-squared Ho– telling test)

Conclusions

Adults with autism exhibit inhibitory deficits that are often manifested in behavioral modifications such as repetitive behaviors and/or sensory hyper-responsiveness. If such behaviors are the result of a generalized deficiency in inhibitory neurotransmission, then it stands to reason that deficits involving localized cortical-cortical interactions — such as in sensory discrimination tasks — could be detected and quantified. This chapter describes recently developed hypothesis driven methods for quantifying metrics of sensory perception

based on the neurophysiological principles of cortical modularity. These novel sensory discrimination tests may provide (a) an effective means for biobehavioral assessment of deficits specific to autism and (b) efficient and sensitive measures of change following treatment. The methods could prove to be a useful and efficient way to detect specific neural deficits and monitor the efficacy of pharmacological and/or behavioral treatments in autism.

CHAPTER 7: ALTERED CENTRAL SENSITIZATION IN WOMEN WITH VULVODYNIA[6]

Overview

Altered central sensitization has been linked to dysfunction in CNS inhibitory pathways (e.g., GABAergic), and metrics of sensory adaptation, a centrally mediated process that is sensitive to this dysfunction, could potentially be used to identify women at risk of treatment failure using conventional approaches. Twelve women with vulvodynia and twenty age-matched controls participated in this study, which was conducted by sensory testing of the right hand's index and middle fingers. The following sensory precepts were assessed: 1) vibrotactile detection threshold; 2) amplitude discrimination capacity (defined as the ability to detect differences in intensity of simultaneously delivered stimuli to two fingers); and 3) a metric of adaptation (determined by the impact that applying conditioning stimuli have on amplitude discriminative capacity). Participants did not differ on key demographic variables, vibrotactile detection threshold, and amplitude discrimination capacity. However, we found significant differences from controls in adaptation metrics in one subgroup of vulvodynia patients. Compared to healthy controls and women with a shorter history of pain (n=5; duration (yr) = 3.4 ± 1.3), those with a longer history (n=7; duration (yr) = 9.3 ±1.4)) were found to be less likely to have adaptation metrics similar to control values. Chronic pain is thought to lead to altered central sensitization, and adaptation is a centrally mediated process that is sensitive to this condition. This report suggests that similar alterations exist in a subgroup of vulvodynia patients.

---

[6] This chapter previous appeared in the Clinical Journal of Pain. The original citation is as follows: Zhang Z, Zolnoun DA, Francisco EM, Holden JK, Dennis RG, Tommerdahl M (2011) Altered Central Sensitization in Subgroups of Women With Vulvodynia. Clin J Pain. 2011 May 17

Introduction

Vulvodynia is a heterogeneous family of idiopathic pain disorders affecting upward of 16% of reproductive age women in the US (Danby and Margesson 2010). It is characterized by both provoked and unprovoked pain in and surrounding vulvar skin, mucosa and underlying musculature. Clinically, vulvodynia is classified into subgroups based on anatomical location (vulvar mucosa vs. hairy/non-hairy epithelium) and temporal characteristics as provoked vs. unprovoked. While a given patient may experience both provoked and unprovoked pain, the most common complaint is that of provoked pain on contact, precipitated by tampon use or intercourse. Unlike unprovoked pain — where the clinical examination is non-specific — the majority of women with provoked pain have localized tenderness in vulvar mucosa (a.k.a. vestibule) (Harlow, Wise, and Stewart 2001). Additionally, women with provoked vulvodynia tend to be younger, and in most instances unaware of their condition until coital debut or the first attempt at using a tampon.

While both peripheral and central abnormalities have been implicated in vulvodynia, the extent to which peripheral vs. central factors contribute to the pain state in an individual patient remains unknown. A substantial portion of women with vulvodynia show hypersensitivity at extra-genital sites (e.g., arms and feet); this non-specific hypersensitivity has conventionally been attributed to changes in 'central sensitization' caused by the chronic pain state. To date, clinical signs and symptoms associated with central dysregulation in subgroups of women with vulvodynia remains unknown. Thus, understanding of the mechanistic (central vs. peripheral) implication of clinical signs and symptoms in vulvodynia is a necessary first step towards individualized, symptom based treatment approach.

Current literature (Danby and Margesson 2010; Giesecke et al. 2004; Gunter 2007) suggests that symptoms of vulvodynia are likely to be triggered by peripheral factors in the skin and/or underlying musculature. With time (and chronicity), varying degrees of central dysregulation may develop. In this setting, patients may experience superimposed unprovoked (spontaneous) pain in otherwise unaffected tissue. Thus, investigating clinical correlates of

central involvement in vulvodynia (e.g., how sensory information processing is altered) may provide us with a unique opportunity to investigate the mechanisms of clinically similar disorders (e.g. localized pain at the vulvar vestibule vs. generalized vulvar pain). Once the fundamental mechanisms of the centrally vs. peripherally mediated vulvar pain is understood, this knowledge will enable the development of robust research and clinical tools that could improve diagnosis and lead to informed therapeutic options.

In this study, we investigated sensory information processing in subgroups of patients with vulvodynia and healthy controls. The quantitative sensory testing methodology utilized in this study has been demonstrated to be sensitive to systemic cortical alteration (Folger et al. 2008; Tannan et al. 2008; Tommerdahl, Tannan, Cascio, et al. 2007), and in pilot studies, has been shown to return to normative values with treatment (Tommerdahl; personal communication, 2010). In this study, we hypothesized that women who had experienced a longer time course with pain and/or had unprovoked symptoms are more likely to have measures consistent with altered central sensitization when compared to healthy control subjects or those subjects who had experienced a shorter duration of provoked pain.

Materials and Methods

In this study, a convenience sample of twelve women with vulvodynia and twenty healthy controls without gynecological pain were recruited from the University of North Carolina, Pelvic Pain Clinic and the surrounding community, respectively. The groups did not differ in basic demographic characteristics. All the participants were naïve both to the study design and issue under investigation. The study was performed in accordance with the Declaration of Helsinki, all subjects gave their written informed consent, and the experimental procedures were reviewed and approved in advance by an institutional review board.

Experimental sessions were conducted with the subjects seated comfortably in a chair with the right arm resting on an arm rest attached to the head unit of a portable four-site vibrotactile stimulator (Fig. 7.1; CM4; Cortical Metrics, LLC). Vibrotactile stimulation was conducted via 5 mm probes that come in contact with subject's digit 2 (index finger) and digit 3

(middle finger). Glabrous pads of digit 2 (D2) and digit 3 (D3) were chosen as the test sites for two reasons: (1) to allow the convenience of access and comfort of the subject, and (2) because of the wealth of neurophysiological information that exists for the corresponding somatotopic regions of cortex in primates. The independent probe tips are computer controlled and capable of delivery of a wide range of vibrotactile stimulation of varying frequencies (measured in Hertz) and amplitudes (measured in micrometers, μm). Stimulus parameters are specified by test algorithms that are based on specific protocols and subjects' responses during those protocols.

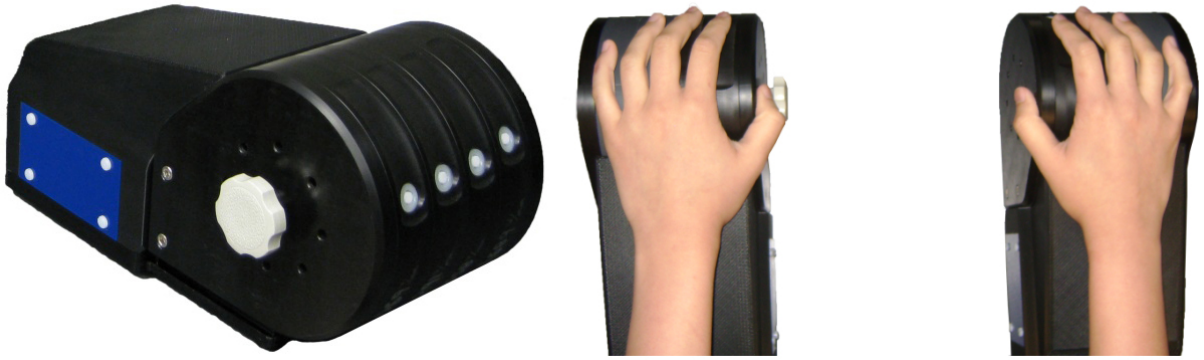

Figure 7.1: Images of the Multi-Site Vibrotactile Stimulator.
Stimulators are positioned by rotating each of the 4 independently positioned drums to maximize contact between fingers and the stimulator tips. During an experimental session, the subject was seated comfortably in a chair with the right arm resting on the arm rest attached to the head unit of the stimulator. Index and middle finger were positioned for D2 and D3 stimulation.

Participants viewed a computer monitor which provided continuous visual cueing during the experimental session. Specifically, an on-screen light panel indicated to the subject when the stimulus was on and when the subject was to respond. Practice trials were performed before each test which allowed the subject to become familiar with the tests, and correct responses on 5 consecutive training trials were required before commencing with each test. The subject was not given performance feedback or knowledge of the results during data acquisition.

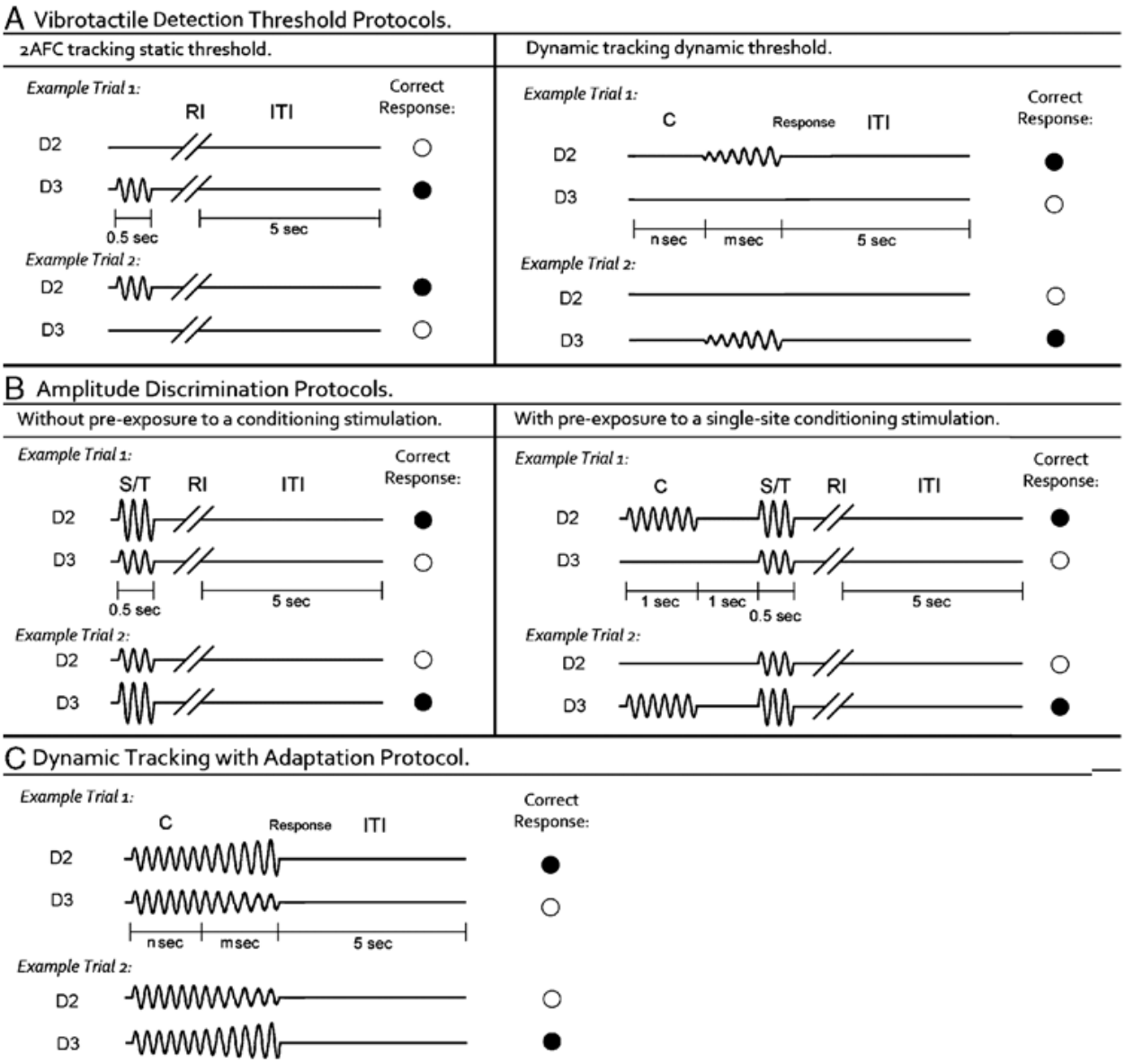

Figure 7.2: Schematics of the Protocols Used in this Study.
Panel A: Vibrotactile detection threshold protocols. Left panel: 2 Alternative Forced Choice (2AFC) tracking protocol: In each trial, a 25 Hz vibrotactile test stimulus was delivered to either D2 or D3 for 0.5 second, followed by a patient response interval (RI). Participant was prompted to select the skin site that perceived the stimulus. A 5-second inter-trial interval (ITI) intervened between stimulus response and onset of the next trial. Right panel: Dynamic tracking protocol: A delay period (variable n = 0, 1.5, 2, or 3 s) without any stimulation was applied. After the initial delay, a 25 Hz vibrotactile stimulus was delivered to either D2 or D3. The amplitude of the stimulus was initiated from zero and increased in steps of 2 mm/s. The stimulation was terminated with participant response to the perceived stimulus (variable m = subject response time).
Panel B: Amplitude discrimination protocols. Left panel: Amplitude discrimination at baseline: Two 25 Hz vibrotactile stimuli, the standard (S) and test (T), were delivered simultaneously for 0.5 seconds. Participant was asked to choose the stimulus that was perceptually larger. Right panel: Amplitude discrimination task with preexposure to conditioning stimulation. A 25 Hz conditioning stimulus (C) was delivered 1 second before the presentation of the test and standard stimuli.
Panel C: Dynamic tracking with adaptation protocol: Two identical 25 Hz vibrotactile stimuli (conditioning stimuli) were delivered simultaneously for a fixed interval (variable n = 0, 1.5, 2, or 3 s). After the initial constant stimulus period, the amplitude of the 2 stimuli were dynamically increased/decreased, in steps of 25 mm/s. Stimulation was terminated with patient response to the location at which the most intense stimulus was delivered (variable m = subject response time)

The sensory testing session was conducted by application of low frequency (25 Hz) vibration to right hand's index and middle finger(s). The protocols-from start to finish lasted approximately 30 minutes and consisted of the following 5 modules: (1) static detection threshold; (2) dynamic detection threshold; (3) amplitude discrimination between two concurrent and stationary stimuli; (4) the impact of single-site adaptation on amplitude discrimination capacity; and (5) dynamic amplitude discrimination. Exemplary use, technical description and neurobiological basis of individual modules have previously been described in detail (Folger et al. 2008; Francisco et al. 2008; Tannan et al. 2008; Tannan, Simons, et al. 2007; Tommerdahl, Tannan, Cascio, et al. 2007; Zhang et al. 2009). An overview of the procedures and the previously published normative findings is provided below.

Static detection threshold

Each participant's vibrotactile detection threshold was measured using a 20-trial Two Alternative Forced Choice (2AFC) tracking protocol (for recent description with this experiment setup, see previous studies (Francisco et al. 2008; Tannan, Dennis, and Tommerdahl 2005; Tannan, Dennis, and Tommerdahl 2005; Tannan, Whitsel, and Tommerdahl 2006; Zhang et al. 2009). The left panel of Fig. 7.2a shows the schematic of the protocol. During each trial a 25 Hz vibrotactile test stimulus was delivered to either D2 or D3; the stimulus location was randomly selected on a trial-by-trial basis in order to minimize subject's inattention and distraction. Following each vibrotactile stimulus, the subject was prompted to select the skin site (index (D2) vs. middle (D3) finger) that was perceptually larger. After a 5 sec delay — based on subject response — the stimulation was repeated until the completion of the 20 trials. The stimulus amplitude was started at 15 μm and was modified based on the subject's response in the preceding trial. A 1-up/1-down algorithm was used for the purposes of amplitude modification in the first 10 trials. For example, the stimulus amplitude was decreased by 1 μm if the subject's response in the preceding trial was correct. However, it was increased by the same amount if the response was incorrect. After the initial 10 trials, the amplitude was varied using a 2-up/1-down algorithm (two correct/one incorrect subject response(s) resulted in a

decrement/increment, respectively, in the amplitude of the stimulus). The rationale for using 1up/1down algorithm in the first 10 trials was to expedite determination of subject's vibrotactile discriminative range without affecting the results, and this approach has been previously reported (Tannan, Dennis, et al. 2007; Tannan et al. 2008; Zhang et al. 2009; Zhang et al. 2008; Folger et al. 2008; Francisco et al. 2008; Tannan, Simons, et al. 2007).

Dynamic detection threshold

At the beginning of each trial (as shown in Fig. 7.2a, right panel), a delay period which includes no stimulation was applied. Four conditions of delay (n sec) were employed, in separate trials: 0, 1.5, 2, and 3 sec. After the initial delay, a 25 Hz vibrotactile stimulus was delivered to either D2 or D3 (the stimulus location was randomly selected on a trial-by-trial basis). The amplitude of the stimulus was initiated from zero and increased in steps of 2 μm/sec. The subject was instructed to indicate the skin site that received the stimulus as soon as the vibration was detected. The subject's detection threshold was calculated as the average of the stimulus amplitude at the time of subject response (msec).

Amplitude discrimination at baseline

Each subject's amplitude discrimination capacity was assessed using a 2AFC tracking protocol that has been described and implemented in a number of previous studies (Tannan, Dennis, et al. 2007; Tannan et al. 2008; Zhang et al. 2009; Zhang et al. 2008; Folger et al. 2008; Francisco et al. 2008; Tannan, Simons, et al. 2007). As shown in Fig. 7.2b left panel, during the 20-trial experimental run, a vibrotactile test stimulus (25 Hz, amplitude between 105 and 200 μm) was delivered to one digit pad at the same time that a standard stimulus (25 Hz, amplitude fixed at 100 μm) was applied to the other digit pad. The loci of the test and standard stimuli were randomly selected on a trial-by-trial basis. At the beginning of the experimental run, the test amplitude was 200 μm and the standard amplitude was 100 μm. The difference between the amplitudes of the test and standard stimuli was adjusted on the basis of the subject's response in the preceding trial, such that the difference was decreased/increased after a correct/incorrect response, respectively. The same tracking algorithm as that described for the

tactile detection threshold protocol (2AFC tracking protocol) was employed to track the subject's ability to determine the most intense stimulus between the test and standard stimuli (i.e., the subject's difference limen (DL) was determined). The step size was held constant at 10 µm throughout the experimental run.

Amplitude discrimination with single-site adaptation

In order to measure the effects that conditioning stimuli have on subsequent test stimuli, the previously described amplitude discrimination protocol was modified. As shown in Fig. 7.2b right panel, a 25 Hz 200 µm conditioning stimulus was delivered 1 sec prior to the presentation of the test and standard stimuli. When the conditioning stimulus is delivered to the same site as the test stimulus, the gain effect of adaptation (reducing the perceived intensity) can be quantified by comparison of the amplitude discrimination DL obtained in the adapted vs. non-adapted conditions (Tannan et al. 2007, 2008; Zhang et al. 2009). The amplitude discrimination tracking algorithm used in the previously described protocol was employed.

Dynamic amplitude discrimination

To further characterize the effects of adaptation on amplitude discrimination, a dynamic tracking protocol was implemented (for recent description with this experimental setup, see previous study (Zhang et al. 2009). At the start of each run (shown in Fig. 7.2c), two vibrotactile stimuli (25 Hz; initially identical in amplitude at 300 µm) were delivered simultaneously to D2 and D3. Four conditions of initial constant stimulus duration (n sec) were employed in separate experimental trials: 0, 1.5, 2, and 3 sec. After the initial constant or stationary stimulus period, the amplitudes of both stimuli were dynamically altered such that the amplitude of one stimulus was increased and the amplitude of the other stimulus was decreased at the rate of 25 µm/sec. The subject was instructed to indicate the location at which the most intense stimulus was delivered as soon as the two stimuli felt distinctly different in intensity. For each trial, the DL was recorded as the actual difference between the two test

amplitudes at the time of subject response (m sec). Averaged DLs were obtained for the four different durations of conditioning stimuli that preceded each trial.

Analysis

Repeated-measures analysis of variance (ANOVA) was used to evaluate the difference of the subject's performance under different conditions. Data are presented as means and standard errors (SE). A probability of less than 0.05 was considered statistically significant.

Results

The present study compared women with vulvodynia and matched healthy controls in a series of sensory perceptual measures that assessed: (1) vibrotactile detection threshold on the fingertip; (2) amplitude discrimination capacity; and (3) the impact of conditioning stimuli on amplitude discrimination capacity. The results show that patients with vulvodynia deviated very little from that of healthy controls in most of the sensory measures obtained in the absence of conditioning stimuli — such as threshold detection and amplitude discriminative capacity, although the patients with vulvodynia demonstrated a tendency to have lower tactile thresholds on the fingertips than controls. Most importantly, the measures of the effects of conditioning stimuli on amplitude discrimination revealed that the patients' data clustered into two distinct sub-groups (which will be referred to as Group A and Group B). Group B data was very similar to that obtained from healthy control subjects, and Group A demonstrated a significantly reduced impact of adaptation on the sensory percept. While the average ages and demographics of the two sub-groups were not significantly different, there was a significant difference in the duration that the two sub-groups of patients had pain: Group A (n=7) subjects had suffered from vulvodynia for a long duration (average duration: 9.3 ± 1.4 years; average age: 35.7 ± 3.2 years); and Group B (n=5) subjects had suffered from vulvodynia for a relatively shorter duration (average duration: 3.4 ±1.3 years; average age: 34.6 ± 4.3 years).

Detection Thresholds

Figure 7.3 summarizes the group-averaged detection thresholds. As shown in the left panel of Fig. 7.3, the group-averaged static thresholds observed were 12.37±1.34 μm for

controls, 9.77±2.23 μm for patients in Group A, and 10.32±1.85 μm for patients in Group B. The data suggest an elevated sensitivity for patients with vulvodynia compared to controls, although this difference was not statistically significant (Group A vs. controls: p=0.35; Group B vs. controls: p=0.51). This finding is consistent with data reported by Pukall (Pukall et al. 2002) which showed that women suffering from vulvodynia had a lower tactile threshold than controls at sites distant to the genitalia area.

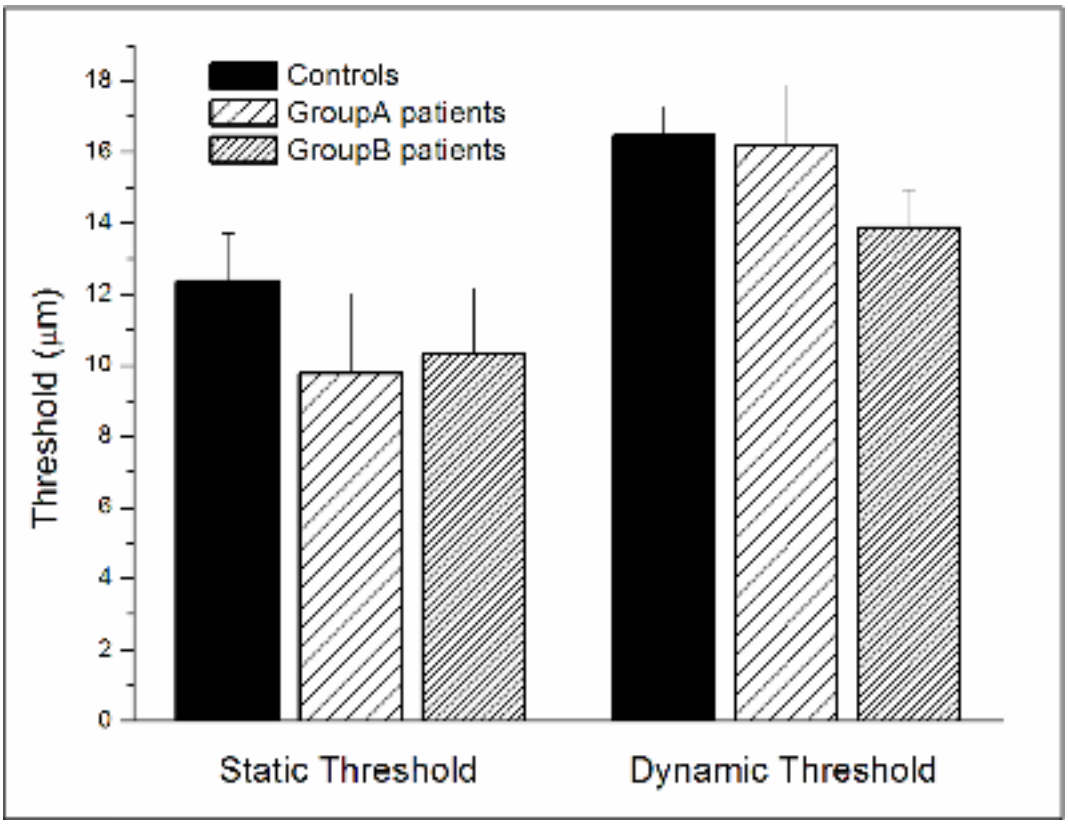

Figure 7.3: Summary of Group-Averaged Vibrotactile Detection Thresholds
No significant difference was observed on the static thresholds between any patients group and controls. The group-averaged dynamic thresholds of patients with vulvodynia did not significantly differ from that of controls, while data from patients in Group B show a trend for lower dynamic threshold than controls.

Since several studies have reported that psychophysical measurement methods had a significant influence on vibrotactile thresholds (Maeda and Griffin 1995; Morioka and Griffin 2002), in current study, the subject's vibrotactile threshold was also measured by a dynamic tracking protocol. The group-averaged dynamic thresholds are shown in the right panel of Fig. 7.3. There was no significant difference between the controls and two vulvodynia patients

groups, although data from patients in Group B showed a lower (though not statistically significant) dynamic threshold than controls.

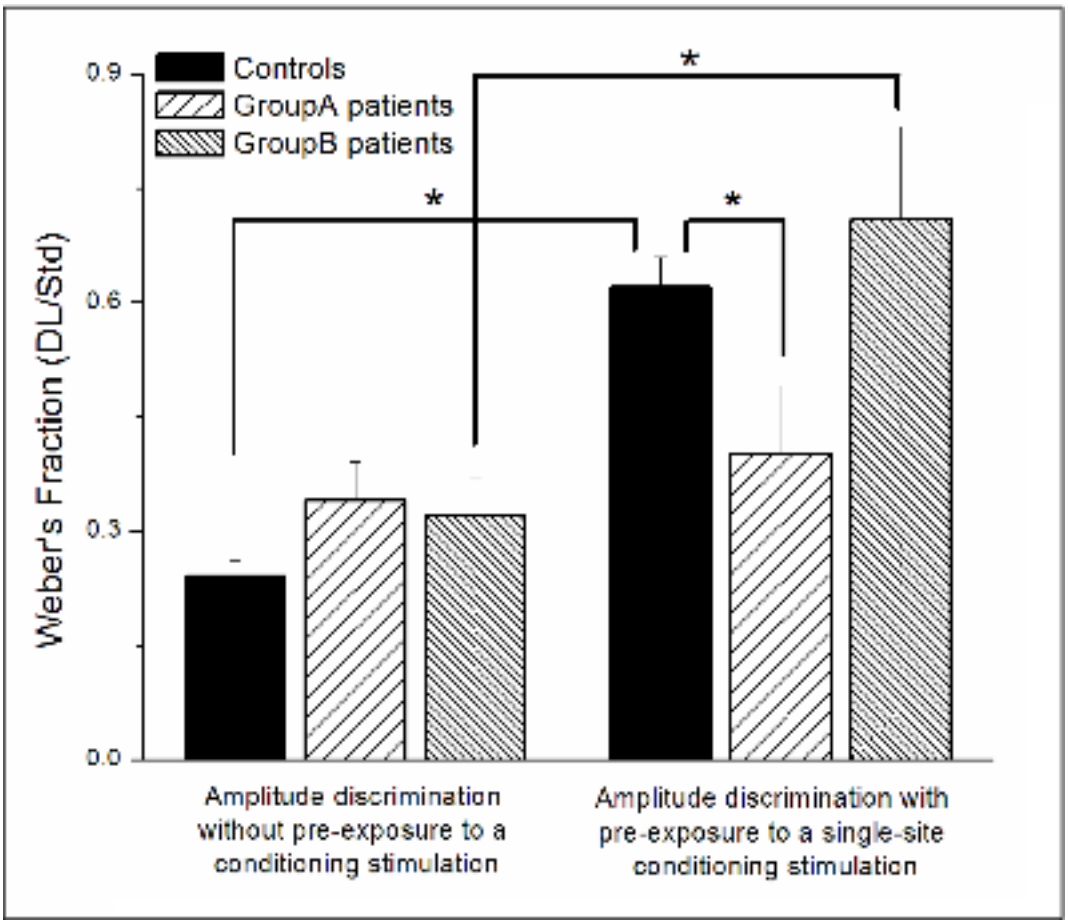

Figure 7.4: Comparison of Weber's Fraction with/without Conditioning
In the absence of conditioning stimulus, no significant difference was observed between the performance of controls and sub-groups of vulvodynia patients. Pre-exposure to a single-site conditioning stimulation causes a significant degradation of performance in the controls and the patients in Group B. However, patients in Group A performed equally well under both adapted and un-adapted conditions.

While amplitude discrimination capacity was not significantly different between the controls and patients with vulvodynia, the impact of conditioning stimuli on performance during this task revealed that the vulvodynia subjects were clustered into two distinct sub-groups. Figure 7.4 summarizes the group-averaged performance during amplitude discrimination tests for the controls and two sub-groups of patients with vulvodynia. Weber's fractions (WF) were determined by normalizing each subject's DL to the amplitude of standard

stimulus (100 μm). As shown in the left panel of Fig. 7.4, during which amplitude discrimination was measured in the absence of conditioning stimulus, there was no significant difference in performance between the controls and groups of vulvodynia patients. Specifically, control subjects were able to discriminate the difference between the test and standard stimuli that is 24.4% of the standard amplitude (WF = 0.244), and the patients in Group A and Group B were able to discriminate respectively 33.5% (WF = 0.335) and 31.6% (WF = 0.316) of the standard amplitude. However, pre-exposure to a single-site conditioning stimulus dramatically changed the subjects' performance (shown in Fig. 7.4, right panel). While the WF of controls and patients in Group B is significantly elevated in the adapted condition compared to the un-adapted condition, patients in Group A performed equally well under both adapted and un-adapted conditions. Previous reports have demonstrated that single-site adaptation impairs control subject's amplitude discrimination capacity (Tannan, Dennis, et al. 2007; Tannan et al. 2008; Zhang et al. 2009; Zhang et al. 2008; Folger et al. 2008; Francisco et al. 2008; Tannan, Simons, et al. 2007). One interpretation of the impairment observed in current study is that a 1 sec conditioning stimulus reduces the perceived intensity of the subsequent test stimulus to the extent that a test stimulus with amplitude of approximately 162% (controls)/171% (Group B) of the standard amplitude was perceived nearly the same in intensity as the standard stimulus. Comparing to the significant degradation of performance of the controls ($p < 0.01$) and the patients in Group B ($p = 0.017$) due to adaptation, no change was observed in the patients in Group A ($p = 0.52$). Moreover, under the adapted condition the group-averaged performance is significantly different between controls and patients in Group A ($p = 0.036$). Therefore, conditioning stimulation significantly impaired the performance of the controls and the patients in Group B, but has no effects on the patients in Group A.

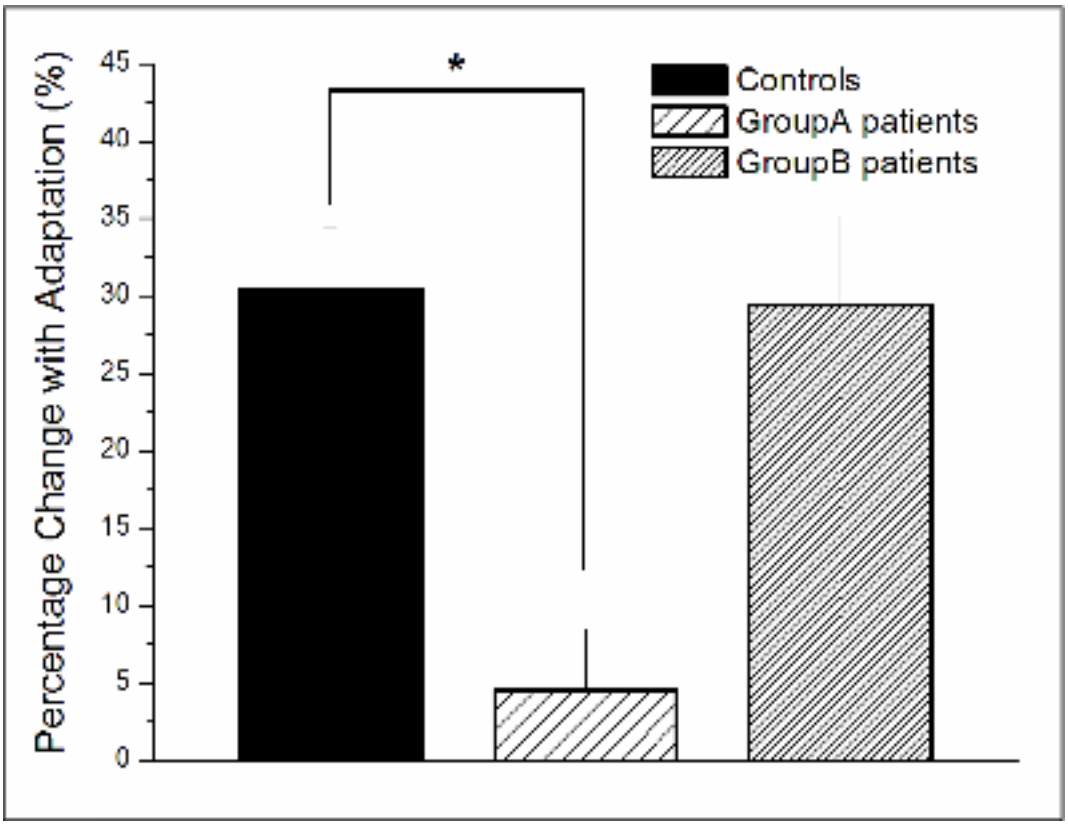

Figure 7.5: Percentage Change with Adaptation on Amplitude Discrimination
The WF obtained under the condition with adaptation was normalized to the unadapted condition on a subject-by-subject basis. Adaptation impaired the subject's amplitude discrimination capacity by nearly 30% for both the controls and the patients in Group B, while much less effect of adaption (3%) was observed in the patients in Group A.

In order to determine whether the differential effects of adaptation observed between groups were consistent within subjects, each subject's WF obtained under the adapted condition was normalized to the un-adapted condition. As shown in Fig. 7.5, The 1 sec conditioning stimulus significantly impaired amplitude discrimination capacity by nearly 30% for both the controls and the patients in Group B, while there was much less of an effect (3%) of adaptation observed in the patients in Group A ($p < 0.01$).

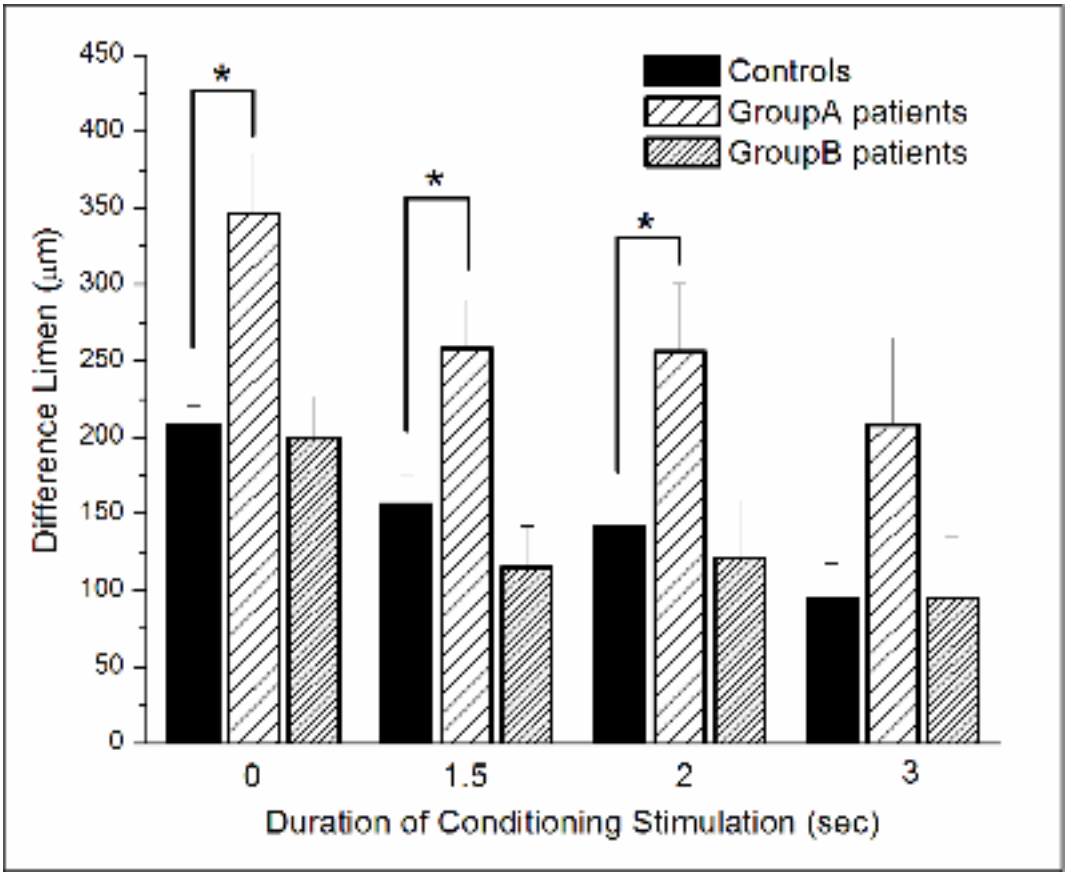

Figure 7.6: Comparison of the Group-Performance on Dynamic Tracking
Data obtained at the four different durations of dual-site conditioning stimulation (0, 1.5, 2 and 3 sec) for the controls and two sub-groups of patients with vulvodynia. Increasing the duration of the conditioning stimuli led to an improvement of performance. As the data obtained from patients in Group B deviated very little from that of controls, DLs obtained from patients in Group A were significantly higher compared to controls and showed only little effect with adaptation.

Dynamic Tracking with Adaptation

A dynamic amplitude discrimination protocol was employed which is able to effectively compare the degree to which a subject adapts to simultaneously delivered dual-site vibrotactile stimuli at different durations of conditioning stimulation. Fig. 7.6 summarizes the group-averaged performance with dual-site adaptation at the four different durations of conditioning stimulation (0, 1.5, 2, and 3 sec) for the controls and two sub-groups of patients with vulvodynia. The results show that increasing the duration of the conditioning stimuli delivered to both sites of skin led to an improvement of a subject's capacity to detect the difference in amplitude between the two stimuli. For example, after pre-exposure to 1.5 sec, 2 sec, or 3 sec

conditioning stimulus, control subjects were, on average, able to attain a DL (156 μm, 141 μm, 94 μm) that was ~73%, ~66%, or ~42% of the DL (208 μm) obtained without adaptation. Compared to controls, two sub-groups of patients with vulvodynia have distinct performance differences. Specifically, the DLs were significantly higher in patients of Group A compared to controls (0 sec adaptation: $p < 0.01$; 1.5 sec adaptation: $p = 0.01$; 2 sec adaptation: $p < 0.01$; 3 sec adaptation: $p = 0.06$), but there was no significant difference between patients of Group B and controls in the DLs obtained under all the conditions. In summary, data obtained from patients in Group A showed little effect with conditioning stimulation while the data obtained from patients in Group B deviated very little from that of controls.

Discussion

In this study, sensory perceptual measures were obtained on 12 patients diagnosed with vulvodynia and 20 healthy control subjects. Five tests were performed to assess: (1) detection threshold on the fingertips; (2) amplitude discrimination capacity; (3) the effects of adaptation on tactile discrimination capacity. The results suggest that women with vulvodynia have — although not statistically significantly — lower tactile thresholds on the fingertips than do control subjects. Furthermore, as amplitude discrimination capacity was not significantly different between the controls and patients with vulvodynia, the impact of single site conditioning (or adaptation) on performance of the dual-site task demonstrated a remarkable difference. Specifically, the observations of the conditioned sensory measures revealed that the patients with vulvodynia were clustered into two distinct sub-groups. Group B had data that was very similar to that obtained from healthy control subjects, while Group A demonstrated a significantly reduced impact of adaptation on the sensory percept. The primary difference between the compositions of the two sub-groups is the duration or longevity of pain of the patients in each sub-group. Group B was composed of patients that reported pain for an average of 3.4 ±1.3 years, while Group A was composed of patients who reported pain for an average duration of 9.3 ± 1.4 years.

The reduction of the adaptation metric in patients with vulvodynia studied in this paper has not been previously reported. There have been few studies to date that have assessed the changes in perception that normally result from repetitive vibrotactile stimulation on the population of chronic pain patients, though Hollins and colleagues did report decreased effects of adaptation in subjects with tempomandibular disorders (Hollins et al. 1996). Neurophysiological studies have demonstrated that repetitive stimulation results in temporal changes of cortical activity, the most prominent of which is a reduction in cortical response with extended stimulus duration. At the single cell level, both visual and somatosensory cortical pyramidal neurons undergo prominent use-dependent modifications of their receptive fields and response properties with repetitive stimulation. These modifications can attain full development within a few tens of milliseconds of stimulus onset, and can disappear within seconds after the stimulus ends (visual cortical neurons (Bredfeldt and Ringach 2002; Celebrini et al. 1993; Das and Gilbert 1995; DeAngelis et al. 1995; Dinse and Kruger 1990; Pack and Born 2001; Pettet and Gilbert 1992; Ringach, Hawken, and Shapley 1997; Shevelev et al. 1998; Shevelev, Volgushev, and Sharaev 1992; Sugase et al. 1999); alternatively, for review of short-term cortical neuron dynamics in visual cortex (Kohn 2007); for review of short-term primary somatosensory cortical neuron dynamics (Tommerdahl et al. 1998; Tommerdahl, Favorov, and Whitsel 2005; Tommerdahl, Simons, et al. 2005; Tommerdahl, Whitsel, et al. 1996)). Optical imaging studies have also characterized the short-term dynamics of the population-level response of squirrel monkey contralateral primary somatosensory (SI) cortex using different amplitudes and durations of vibrotactile stimulation (Simons et al. 2007; Simons et al. 2005; Chiu et al. 2005). Guided by the scientific work mentioned above, our research group has designed a series of tactile sensory diagnostics which effectively assess the impact that adaptation has on perception (Folger et al. 2008; Francisco et al. 2008; Tannan, Simons, et al. 2007; Tommerdahl, Tannan, Cascio, et al. 2007; Zhang et al. 2009; Zhang et al. 2008). For example, the protocols employed in the current study directly measure the change in amplitude discrimination capacity that occurs with prior conditioning stimuli. Previous studies using this

measure demonstrated that a subject's ability to discriminate between two simultaneously delivered vibrotactile stimuli – differing only in amplitude and location – was very robust and repeatable across a large number of healthy subjects, but it was also very sensitive to varying conditions of conditioning stimuli. For instance, changing the duration of the conditioning stimulus delivered to one of the two sites before the amplitude discrimination task significantly altered a subject's ability to determine the actual difference between the two stimuli in a predictive and quantifiable fashion. As a result, these methods could be viewed as a reliable indicator of the influence of adapting stimuli on central nervous system response, as changes in the peripheral response are not significantly changed at these short stimulus durations. Centrally mediated adaptation is dependent on several factors (e.g., GABAergic and NMDA receptor mediated neurotransmission, neuron-glial interactions) which play significant roles in the way in which cortical information processing capacities of a number of clinically identified subject populations are impacted by their respective disorder. For example, conditioning stimuli do not have as pronounced an impact on the amplitude discriminative capacity of subjects with autism as it does with typically developing subjects (for discussion of GABA-deficiencies in autism, see (Francisco et al. 2008; Tannan, Simons, et al. 2007; Tommerdahl, Tannan, Cascio, et al. 2007; Tommerdahl et al. 2008; Tommerdahl, Tannan, Zachek, et al. 2007). Additionally, subjects administered a relatively small dose of an NMDA receptor antagonist (60 mg of dextromethorphan) also demonstrated a degraded adaptation metric (Folger et al. 2008).

Two aspects of the adaptation process were measured in this study. The first, the gain effects of adaptation, was derived from the amplitude discrimination task in which a conditioning stimulus was delivered on one of the two test sites. The effect of that conditioning stimulus was on the gain of the conditioned site — that site was now perceived to be much smaller and thus, a reduction in gain was manifested, and subsequently, subjects (normally) become worse at the task. The second facet of adaptation that was measured was a contrast effect, in which contrast between two stimuli improve after conditioning stimuli have been delivered to both of the test sites, and the subjects (normally) perform better after conditioning

than they do without. In this study, the data obtained from the vulvodynia subjects clustered into two distinct sub-groups consistently with both of these aspects of adaptation. The patients in Group B performed very similar as healthy controls did, and the performance of the patients in Group A showed a significantly reduced impact of conditioning stimulation on the sensory percept. However, other sensory measures obtained in the absence of conditioning stimuli — such as threshold detection and amplitude discriminative capacity — demonstrated no statistically significant difference between the two sub-groups. The primary difference between the compositions of the two sub-groups of note is the duration that patients of the sub-groups have had pain, while average age of the two sub-groups was not significantly different. Considering the metrics of adaptation (measuring the effects of conditioning stimulation on sensory perception) could be a reliable indicator of systemic alterations on central nervous function, it is speculated that the performance difference between the two sub-groups of patients with vulvodynia observed in the current study might reflect the level of dysregulation of their central nervous system due to chronic vulvar pain.

The involvement of both peripheral and central mechanisms in the development and maintenance of vulvodynia has been supported by a series of studies (Giesecke et al. 2004; Pukall et al. 2002; Bergeron et al. 2001; Marinoff and Turner 1991; Bohm-Starke et al. 2001; Pukall et al. 2005; Gordon et al. 2003; Zolnoun et al. 2006). For example, it has been found that patients with vulvodynia have increased sensitivity to sensory stimulation at both genital regions and sites distant to it (Bohm-Starke et al. 2001; Giesecke et al. 2004; Pukall et al. 2002). This suggests that not only peripheral sensitization but also a generalized central abnormality is involved in vulvodynia and could be similar to that observed in patients with other pain syndromes, implying a widespread disturbance in the CNS (Pukall et al. 2005). The observation of increased tactile sensitivity of the skin area distant to the vulvar region — including the static thresholds of all vulvodynia subjects in this report — is consistent with altered central sensitization that develops with chronic pain.

All subjects, including controls, demonstrated a dynamic threshold that was higher than their static threshold. This noticeable difference in the threshold between the two tasks is consistent with previous reports (Morioka and Griffin 2002; Zhang et al. 2009). Although this could possibly be explained by the influence that psychophysical measurement methods have on tactile detection (Maeda and Griffin 1995; Morioka and Griffin 2002), we believe an alternate explanation is much more plausible. Mechanistically, this phenomenon could be the result of feed-forward inhibition that is generated by the initial sub-threshold stimulus that occurs when the threshold test is ramped from zero to the detectable level (Tommerdahl, Favorov, and Whitsel 2010). The significance of this is that this type of feed-forward inhibition takes place in somatosensory cortical input layer 4 (Favorov and Kursun 2011), in which local layer 4 inhibitory cells receive direct thalamocortical input and in turn suppress responses of neighboring layer 4 excitatory cells to their thalamocortical drive, thereby sharpening their RF properties (Douglas et al. 1995; Miller, Pinto, and Simons 2001; Bruno and Simons 2002; Alonso and Swadlow 2005; Sun, Huguenard, and Prince 2006; Cruikshank, Lewis, and Connors 2007). These inhibitory cells are more responsive to weak (near-threshold) afferent drive than are the excitatory layer 4 cells, and thus, sub-threshold or weak stimulus inputs will have the effect of raising the threshold at which excitatory layer 4 cells begin to respond to peripheral stimuli. Thus, though not statistically significant, the observation of the difference between the Group A and B patients in their dynamic thresholds is that the difference between the ratio of the respective dynamic and static thresholds are clearly evident, and suggestive of below normal feed-forward inhibition. If this alteration is, as we believe, sensitive to the time dependency of the GABAb receptor, then the measure itself might be an indicator that GABAb efficiency has been compromised in some individuals.

Our data on vulvodynia patients is consistent with existing constructs in the pain literature and supports the notion that the relative contribution of peripheral and central factors differ in subgroups of women with vulvodynia, and that clinical signs and symptoms alone are insufficient in identifying the underlying mechanism of pain as peripheral, central or

a combination of both. A wide range of therapies for vulvodynia have been proposed that include topical therapies, pharmacologic regimens, physical therapy, surgery, and cognitive behavioral therapy (Goldstein, Marinoff, and Haefner 2005). However, outcomes with these therapies vary widely. For example, as a commonly reported therapy for localized vestivular dysesthesia, vestibulectomy is most effective for a specific subset of patients, specifically women under 30 years old who have localized vulvar pain and provoked pain (Traas et al. 2006; Bornstein et al. 1997). These findings suggest that it's possible that this type of pain represents a localized nociceptor mechanism, while unprovoked and generalized pain could have a different mechanism. Our data suggest that women suffering vulvar pain for long duration or with unprovoked pain have more CNS involvement or dysregulation. The CNS involvement occur de novo (e.g., genetic polymorphism) or secondary to an intractable pain state; the latter is the likely mechanism by which women with provoked vulvodynia transition into unprovoked and/or chronic pain state. It is well documented that an intractable peripheral process can lead to neuroplastic changes (via central sensitization) at all levels of the CNS and "generalization of pain" (Traas et al. 2006; Bornstein et al. 1997).

The findings in this study are consistent with the idea that chronic pain, caused by vulvodynia, alters central sensitization that leads to changes in sensory information processing. These changes are manifested in lower sensory thresholds (or higher sensitivity) in sites without provoked pain — because of a change in the balance between excitation and inhibition (or glutamatergic and gabaergic neurotransmission). Lower thresholds are consistent with this imbalance; decreasing inhibition will result in less suppression of cortical activity. In other words, a simple stimulus on the skin will generate more cortical activity if altered central sensitization has resulted in decreased inhibition or increased excitation. However, threshold testing has not been considered as an efficient method in measuring altered central sensitization due to large inter-individual variability. And in order to show these small differences, group differences of repeated measurements are normally necessary. Alternatively, using a measure – such as an adaptation metric – in which the patient provides their own

individual baseline (i.e., the adaptation metric is derived on how amplitude discriminative capacity is impacted by conditioning) — could prove to be a more effective indicator of altered central sensitization that can be obtained reliably and efficiently (protocols employed in the current study can be obtained within 2-3 minutes). Sensory based measures of altered central sensitization appear to differentiate chronicity within subgroups of vulvodynia, and future studies will continue to investigate the changes in sensitization that appear to occur with the time course of the history of vulvodynia.

CHAPTER 8: SOMATOSENSORY INFORMATION PROCESSING IN THE AGING POPULATION[7]

Overview

While it is well known that skin physiology — and consequently sensitivity to peripheral stimuli — degrades with age, what is less appreciated is that centrally mediated mechanisms allow for maintenance of the same degree of functionality in processing these peripheral inputs and interacting with the external environment. In order to demonstrate this concept, we obtained observations of processing speed, sensitivity (thresholds), discriminative capacity and adaptation metrics on subjects ranging in age from 18 to 70. The results indicate that although reaction speed and sensory thresholds change with age, discriminative capacity and adaptation metrics do not. The significance of these findings is that similar metrics of adaptation have been demonstrated to change significantly when the central nervous system (CNS) is compromised. Such compromise has been demonstrated in subject populations with autism, chronic pain, acute NMDA receptor block, concussion, and with tactile-thermal interactions. If the metric of adaptation parallels cortical plasticity, the results of the current study suggest that the CNS in the aging population is still capable of plastic changes, and this cortical plasticity could be the mechanism that compensates for the degradations that are known to naturally occur with age. Thus, these quantitative measures — since they can be obtained efficiently and objectively, and appear to deviate from normative values significantly with systemic cortical alterations — could be useful indicators of cerebral cortical health.

---

[7] This chapter previous appeared in Frontiers in Aging Neuroscience. The original citation is as follows:
Zhang, Zheng, Eric M. Francisco, Jameson K. Holden, Robert G. Dennis, and Mark Tommerdahl. 2011. "Somatosensory Information Processing in the Aging Population." Frontiers in Aging Neuroscience 3 (December).

Introduction

There have been a number of significant findings related to both the anatomical and physiological degradation that occurs with normal aging. For example, structural and functional neuroimaging studies have consistently shown evidence of age-related reduction of cerebral cortical volume (Driscoll et al., 2009; Fjell et al., 2009; Raz et al., 2005; Resnick et al., 2003) and changes of white matter integrity in healthy older adults (Bartzokis et al., 2003; Gunning-Dixon and Raz, 2000; Gunning-Dixon et al., 2009). However, a number of researchers have noted that cognitive performance is relatively stable with normal aging (Morse, 1993; Van Petten et al., 2004; Wilson et al., 2002), although some metrics of sensory performance (e.g., thresholds) degrade (Gescheider et al., 1994; Lin et al., 2005; Verrillo, 1982; Verrillo et al., 2002). Dinse made the observation that restoration of function in the aging population is attainable due to the emergence of new processing strategies, and he attributed this to brain plasticity being operational in the aging population (Dinse, 2006). In a recent review, Greenwood put forth a hypothesis that with aging, although there is significant evidence of both anatomical and physiological decline, there is no, or even negative, correlation with cognitive performance. Greenwood largely attributes the undefined compensatory mechanism that allows for maintenance of cortical information processing capacity to cortical plasticity (Greenwood, 2007; Greenwood and Parasuraman, 2010).

Recently, we have developed unique sensory based measures that quantify particular aspects of a subject's central information processing capacity (Folger et al., 2008; Francisco et al., 2008; Tannan et al., 2005a; 2005b; 2006; 2007a; 2007b; 2008; Tommerdahl et al., 2007a; 2007b; 2008; Zhang et al., 2008; 2009; 2011). One particular focus of these studies has been on obtaining measures of centrally mediated adaptation — a process that is a fundamental component of cortical plasticity and operates on multiple time scales (for review, see (Kohn, 2007)). If cortical plasticity is the mechanism by which cortical information processing capacity is maintained, and if adaptation does, in fact, parallel cortical plasticity, then we would predict that metrics of adaptation would remain constant with normal aging. In terms of adaptation, in

this study, we are most concerned with changes that occur in response to short duration (0.2-1 sec) repetitive stimulation.

The metrics that we collected across the age spectrum could be broadly defined in one of two categories: those that are peripherally biased and those that are predominantly centrally mediated. We predicted that the measures that are predominantly peripherally mediated would be most sensitive to the impact of aging while measures that are predominantly centrally mediated would be less impacted. The results demonstrate that the peripherally mediated measures, such as threshold detection, were — as previously reported by others — significantly impacted with increasing age. This is not surprising, as most of these measures are primarily related to skin physiology, and it is well established that sensory thresholds do increase with age. Centrally mediated measures, such as those that rely mechanistically on cortical information processing properties such as lateral inhibition and/or adaptation, however, did not change with age. We viewed this as being consistent with the idea that others (e.g., Dinse, 2006; Greenwood, 2007) have put forth that cortical plasticity is maintained in normal aging and compensates for both anatomical and physiological losses that have been shown to naturally occur with age.

Material and Methods

In this study, 120 healthy subjects from a wide age spectrum (18-70 years) were recruited from the students and employees of the University of North Carolina at Chapel Hill. The subjects were divided into six age groups, 20 subjects in each group. A survey about medication and medical history was filled out by each subject before experimental tests to exclude subjects with a history of neurological impairment. All the subjects were naïve both to the study design and issue under investigation. The study was performed in accordance with Declaration of Helsinki, all subjects gave their written informed consent, and the experimental procedures were reviewed and approved in advance by an institutional review board.

During an experimental session, the subject was seated comfortably in a chair with right arm resting on an arm rest attached to the head unit of a portable four-site vibrotactile

stimulator (Fig.1; CM4, Cortical Metrics, LLC). Vibrotactile stimulation was conducted via 5 mm diameter probes that come in contact with subject's digit 2 (index finger) and digit 3 (middle finger) of the right hand. The independent probe tips are computer controlled and capable of delivery of a wide range of vibrotactile stimulation of varying frequencies (measured in Hertz) and amplitudes (measured in micrometers, μm). Glabrous pads of digit 2 (D2) and digit 3 (D3) were chosen as the test sites for two reasons: (1) to allow the convenience of access and comfort of the subject, and (2) because of the wealth of neurophysiological information that exists for the corresponding somatotopic regions of cortex in primates. The subject's left hand was holding a two-button response device. During each test, the subject was instructed to press the left/right button when the correct stimulus was perceived on the index/middle finger, respectively.

Figure 8.1: Images of the Multi-Site Vibrotactile Stimulator
Stimulators are positioned by rotating each of the 4 independently positioned drums to maximize contact between fingers and the stimulator tips. During an experimental session, the subject was seated comfortably in a chair with the right arm resting on the arm rest attached to the head unit of the stimulator. Index and middle finger were positioned for D2 and D3 stimulation.

Visual cueing was provided with a computer monitor during the experimental runs. Specifically, an on-screen light panel indicated to the subject when the stimulus was on and

when the subject was to respond. An audiometer was used to make sure that no auditory cues were emitted from the stimulator during delivery of the stimuli. Practice trials were performed before each test which allowed the subjects to become familiar with the test, and correct response on 5 consecutive training trials were required before commencing with each test. The subject was not given performance feedback or knowledge of the results during data acquisition. Stimulus parameters are specified by test algorithms based on specific protocols and subjects' responses during those protocols.

In the current study, a series of metrics were employed to assess each subject's tactile information processing capacity. The total experiment — from start to finish — lasted approximately 30 minutes and consisted of the following 6 metrics: (1) simple reaction time (RT); (2) choice RT; (3) static detection threshold; (4) dynamic detection threshold; (5) amplitude discrimination between two concurrent stimuli; (6) amplitude discrimination after pre-exposure to a conditioning stimulus to one of the stimulus sites (single site adaptation). Exemplary use, technical description, and neurobiological basis of individual metrics have previously been described in detail (Folger et al., 2008; Francisco et al., 2008; Tannan et al., 2007a; 2007b; 2008; Tommerdahl et al., 2007a; Zhang et al., 2009). An overview of the procedures is provided below.

Reaction Times

Simple RT was measured for 14 times during an experimental run for each subject. The left panel of Fig. 8.2a shows the schematic of the protocol. During each trial a single tap (amplitude in 300 μm) was delivered to D2. The subject was instructed to press a response button as soon as the tap was felt. After subject's response, a delay between 2 sec and 7 sec was placed before the onset of the next trial. For each trial, the RT was recorded as the time interval between stimulation tap and subject's response. In total, fourteen simple RTs were obtained for each subject. During the course of data analysis, the 2 largest and 2 minimum RT values were excluded in order to eliminate the effects of anticipation and inattention. As a result, a subject's simple RT was calculated as the average of 10 RTs recorded.

Choice RT was measured using a 14-trial Two Alternative Forced Choice (2AFC) protocol. The right panel of Fig. 8.2a shows the schematic of the protocol. During each trial a single tap (amplitude in 300 μm) was delivered to either D2 or D3; the stimulus location was randomly selected on a trial-by-trial basis in order to minimize subject's inattention and distraction. The subject was instructed to select the skin site (D2 or D3) that received the tap as fast as possible by pressing the left or right button on the response box. The response accuracy was recorded for each trial. After excluding the 2 largest and 2 minimum values, the average response time of trials with correct response was considered as a subject's choice RT. The average performance accuracy of all the subjects is 95%.

Static detection threshold

Each subject's vibrotactile detection threshold was measured using a 20-trial 2AFC tracking protocol (for recent description with this experiment setup, see previous studies Zhang et al. 2009). The left panel of Fig. 8.2b displays the schematic of the protocol. During each trial a 25 Hz vibrotactile test stimulus (lasts 500ms) was delivered to either D2 or D3; the stimulus location was randomly selected on a trial-by-trial basis. Following each vibrotactile stimulus, the subject was prompted to select the skin site (D2 vs. D3) that perceived the stimulation. After a 5 sec delay — based on subject response — the stimulation was repeated until the completion of the 20 trials. The stimulus amplitude was started at 15 μm and was modified based on the subject's response in the preceding trial. During the initial 10 trials, a 1-up/1-down algorithm was used for the purposes of amplitude modification. For example, the stimulus amplitude was decreased by 1 μm if the subject's response in the preceding trial was correct. However, it was increased by 1 μm if the response was incorrect. After the initial 10 trials, the amplitude was varied using a 2-up/1-down algorithm (two correct/one incorrect subject response(s) resulted in a decrement/increment, respectively, in the amplitude of the stimulus). The rationale for using 1up/1down algorithm in the first 10 trials was to expedite determination of subject's vibrotactile discriminative range without affecting the results, and this approach has been

previously reported (Folger et al., 2008; Francisco et al., 2008; Tannan et al., 2006; 2007a; 2007b; 2008; Tommerdahl et al., 2007a; 2007b; 2008; Zhang et al., 2008; 2009; 2011).

Dynamic detection threshold

At the beginning of each trial (as shown in Fig. 8.2b, right panel), a delay period (D) which includes no stimulation was applied. Four conditions of delay (n sec) were employed, in separate trials: 0, 1.5, 2, and 3 sec. After the initial delay, a 25 Hz vibrotactile stimulus was delivered to either D2 or D3 (the stimulus location was randomly selected on a trial-by-trial basis). The amplitude of the stimulus was initiated from zero and increased in steps of 2 μm/ sec. The subject was instructed to indicate the skin site that received the stimulus as soon as the vibration was detected. The stimulus amplitude at the time of subject's response was recorded, and only the value with accurate response was used to calculate the subject's average dynamic detection threshold.

Amplitude discrimination at baseline

Each subject's amplitude discrimination capacity was assessed using a 2AFC tracking protocol that has been described and implemented in a number of previous studies (Folger et al., 2008; Francisco et al., 2008; Tannan et al., 2007a; 2007b; 2008; Tommerdahl et al., 2007a; Zhang et al., 2008; 2009; 2011). As shown in Fig. 8.2c left panel, during the 20-trial experimental run, a vibrotactile test stimulus (T) (25 Hz, amplitude between 105 and 200 μm) was delivered to one digit pad at the same time that a standard stimulus (S) (25 Hz, amplitude fixed at 100 μm) was applied to the other digit pad. The loci of the test and standard stimuli were randomly selected on a trial-by-trial basis. At the beginning of the experimental run, the test amplitude was 200 μm and the standard amplitude was 100 μm. The difference between the amplitudes of the test and standard stimuli was adjusted on the basis of the subject's response in the preceding trial, such that the difference was decreased/increased after a correct/incorrect response, respectively. The step size was held constant at 10 μm throughout the experimental run. The same tracking algorithm as that described for the tactile detection threshold protocol was employed to track the subject's ability to determine the most intense

stimulus between the test and standard stimuli (i.e., the subject's difference limen (DL) was determined).

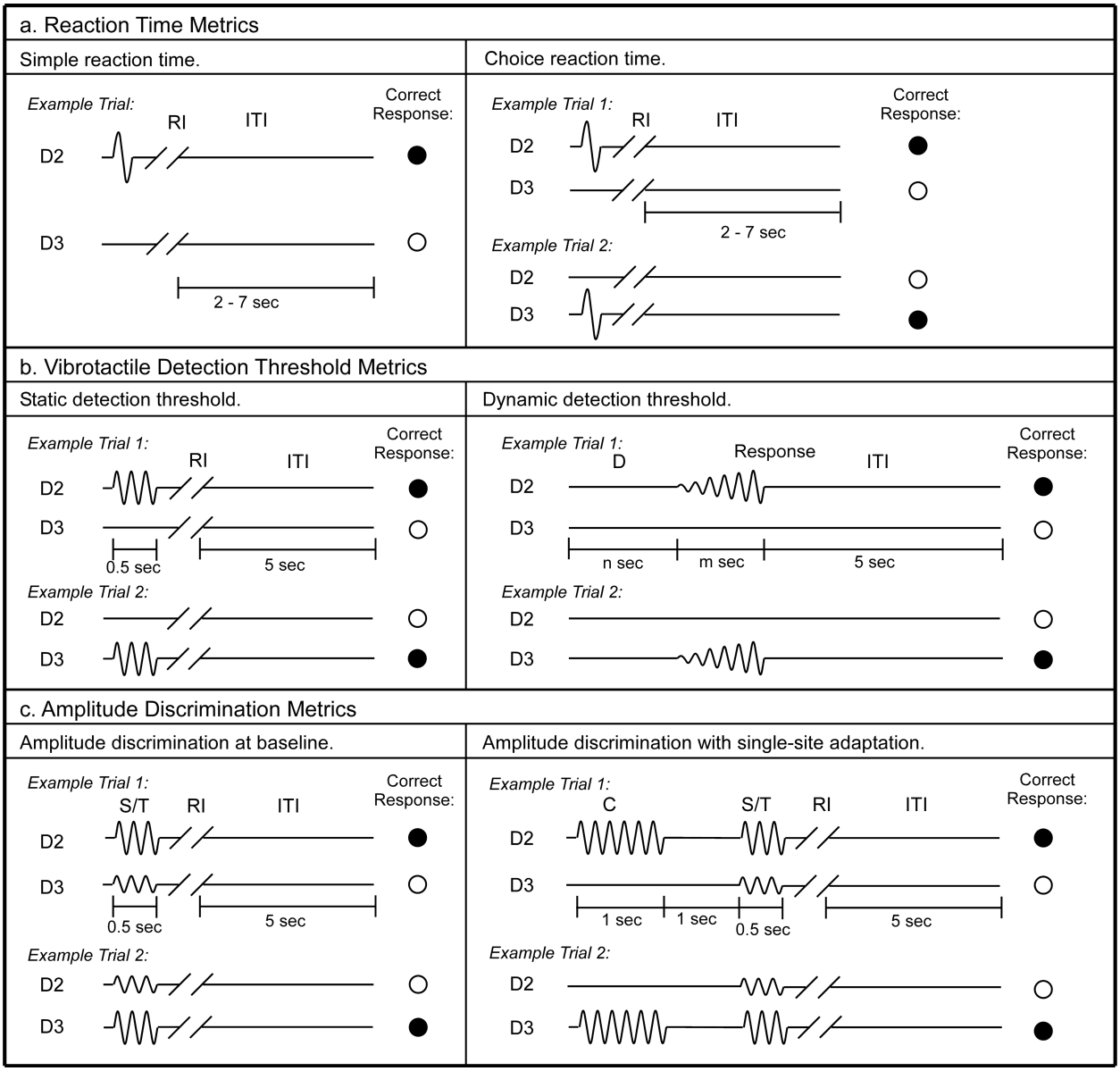

Figure 8.2: Schematics of the Protocols Used in this Study

Adaptation metric

Amplitude discrimination with single-site adaptation. In order to measure the effects that conditioning stimuli have on subsequent test stimuli, the previously described amplitude

discrimination protocol was modified such that delivery of the test and standard stimuli was preceded by a single conditioning stimulus to one of the two stimulus sites (as shown in Fig. 8.2c, right panel). Specifically, a 25 Hz 200 μm conditioning stimulus (C) was delivered 1 sec prior to the presentation of the test and standard stimuli (S/T). The duration of the conditioning stimulus was 1 sec, which was followed by a 1 sec delay before onset of the simultaneous delivery of the test and standard stimuli. The result of such a protocol modification is that the amplitude discrimination difference limen (DL) is typically significantly elevated after pre-exposure to a single-site conditioning stimulation (Folger et al., 2008; Tannan et al., 2007b; 2008; Zhang et al., 2009; 2011). When the conditioning stimulus is delivered to the same site as the test stimulus, the gain effect of adaptation (reducing the perceived intensity) can be quantified by comparison of the DL obtained in the adapted vs. non-adapted conditions (amplitude discrimination at baseline). The tracking algorithm used in the previously described protocol was employed.

Analysis

One way analysis of variance (ANOVA) and two-sample t-test were used to evaluate the difference of the subject's performance across different groups. Data are presented as means and standard errors (SE). A probability of less than 0.05 was considered statistically significant.

Results

In the current study, a series of sensory perceptual measures was performed on healthy control subjects of different ages (ranging from 18 to 70 years) that assessed: (1) reaction time; (2) vibrotactile detection threshold; (3) amplitude discrimination capacity; and (4) the impact of adaptation on amplitude discrimination capacity. The results indicate that although RT and sensory thresholds increased as a function of age, the subject's discriminative capacity and the effects of adaptation on performance remained constant across all the age groups tested.

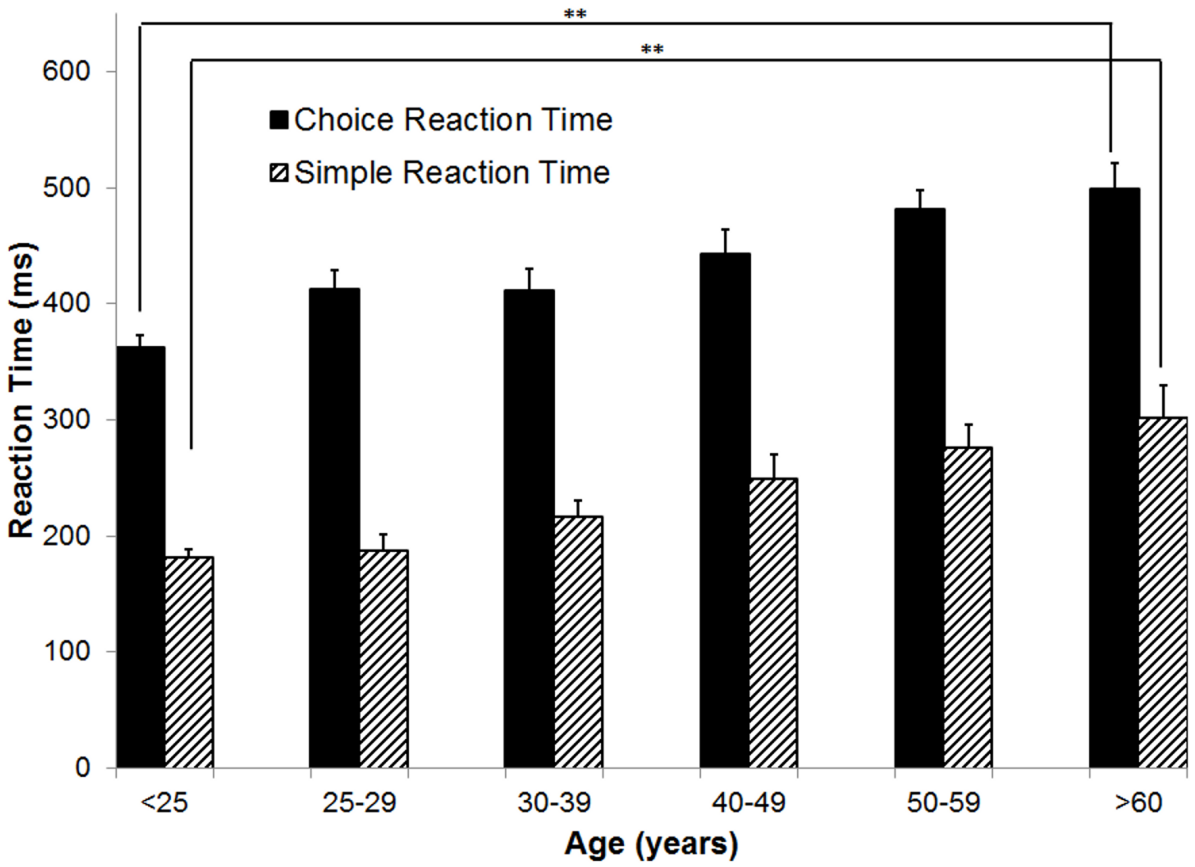

Figure 8.3: Summary of the Group-Averaged RTs for Six Age Groups
Significant differences in mean simple and choice RT were observed between the subject under 25 years and the subjects older than 60 years.

Reaction time increases with age. Fig. 8.3 summarizes the group-averaged RT of six age groups. Both choice and simple RTs progressively increase with advancing age. One way ANOVA was performed to compare the mean RT across six age groups, and there is evidence that there are significant differences in the means across groups ($p < 0.001$ for both simple and choice RT). Two-sample t-test was employed to compare the mean RT of the subjects under 25 years vs. the mean RT of the subject older than 60 years. There is a significant difference in the mean simple RTs (182 ms vs. 302 ms) and mean choice RTs (362 ms vs. 498 ms) with $p < 0.001$. The data suggests an age-related decrement in response speed. Note that for all the age groups, choice RT is always higher than simple RT. The difference between choice RT and simple RT might reflect the duration that it takes for a subject to identify a stimulus location. In Fig. 8.4,

the group-averaged RT values are plotted against age. Strong linear relationship (positive correlation) between RTs and age were observed, with R2=0.99 for simple RT and R2=0.95 for choice RT.

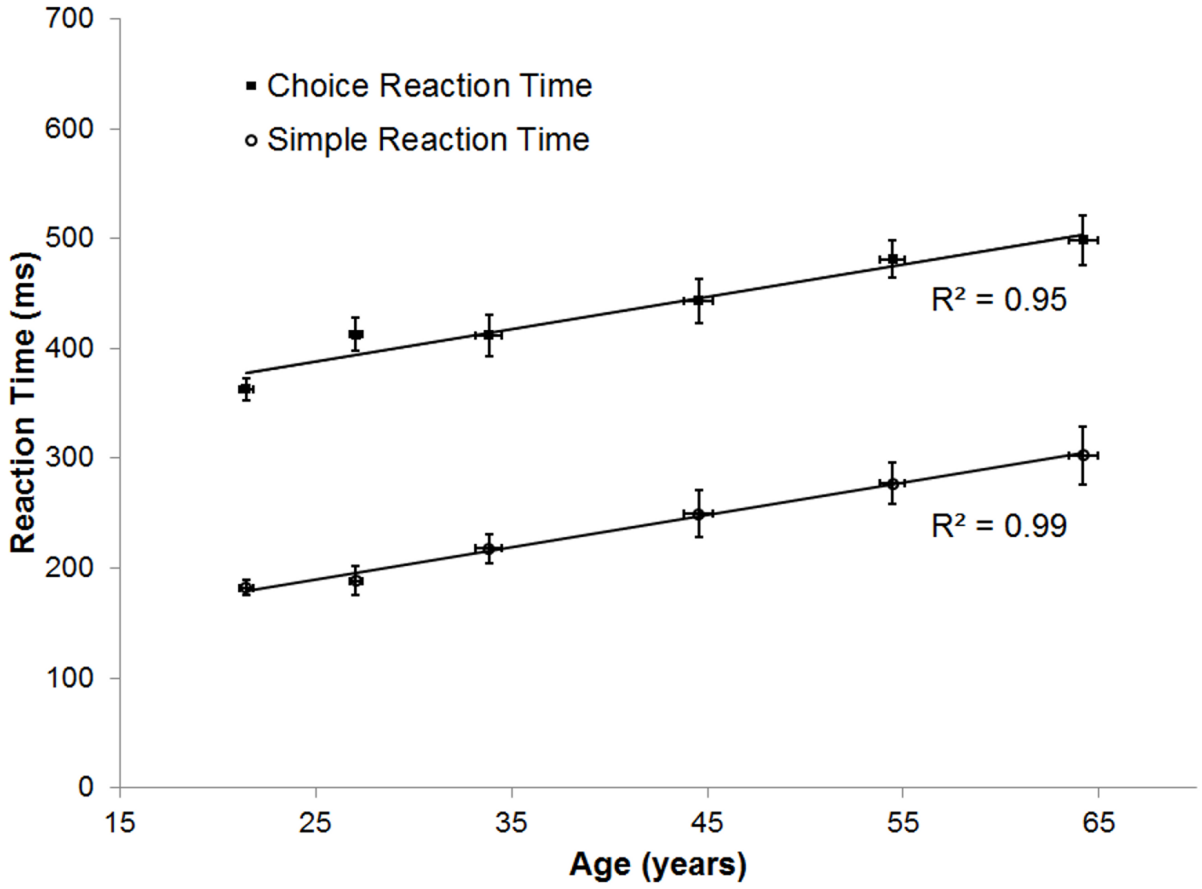

Figure 8.4: Summary of Group-Averaged RTs Plotted Against Mean Age
Strong liner relationship (positive correlation) between RTs and age were observed, with R^2=0.99 for simple RT and R^2=0.95 for choice RT.

In the current study, subjects performed each RT test for 14 times. In order to calculate the index of intra-individual variability, the standard deviation (SD) of repeated RT measures was normalized to the mean RT for each subject individually. The group-averaged index of intra-individual variability (%) on RT performance was calculated and plotted in Fig. 8.5. One way ANOVA was performed. It was found that there are evidence of significant differences in the means of intra-individual variability for simple RT performance ($p < 0.001$) across six age

groups, while no significant differences are found for choice RT performance ($p = 0.11$) across groups. Looking at the intra-individual variability for simple RT by itself, there is no significant differences in the means across age groups younger than 50 years ($p = 0.4$). However, two-sample t-test shows significant difference between mean of 40-49 years age group and mean of 50-59 years age group ($p < 0.05$). The data demonstrates that the group-averaged intra-individual variability remains relatively constant for the subjects younger than 50 years old, while the older subjects (>50 years) have significant higher intra-individual variability.

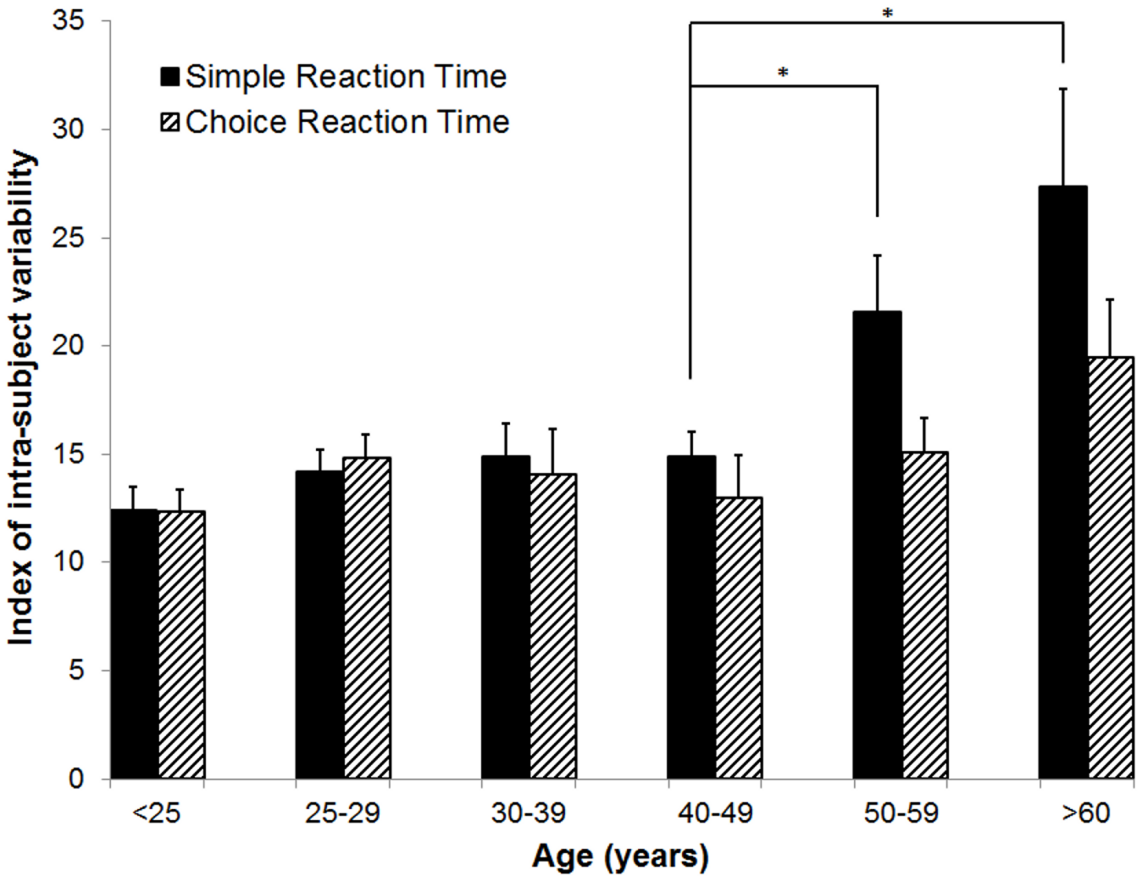

Figure 8.5: Variability in Reaction Times Across Six Age Groups
Looking at means of intra-individual variability for simple RT, there is no significant difference in the mean across groups that are younger than 50 years ($p = 0.4$). However, significant difference was found between mean of 40-49 years group and means of 50+ groups ($p < 0.05$). No significant difference was found for choice RT performance across groups ($p = 0.11$).

Figure 8.6: Summary of Group-Averaged Vibrotactile Detection Thresholds
Both static and dynamic detection threshold progressively rises with aging. All subjects demonstrated a dynamic threshold that was higher than their static threshold.

Vibrotactile detection threshold increases with age

The group-averaged detection thresholds were obtained with two different methods: a static testing paradigm and a dynamic testing paradigm. As shown in Fig. 8.6, the group averaged static threshold gradually increases with advancing age. Specifically, the averaged static threshold for the subjects who are older than 60 years is 13.95 μm which is about 8 μm larger than that of the subjects under 25 years old (5.42 μm). Since several studies have reported that psychophysical measurement methods had a significant influence on vibrotactile threshold (Maeda and Griffin, 1994; Morioka and Griffin, 2002), the threshold was also measured by a dynamic tracking protocol, in which a continuously increasing stimulus was delivered. Following the same trend as observed with static testing paradigm, the group

averaged dynamic threshold progressively rises with aging. In general, the data suggest an elevated tactile sensitivity for older subjects.

It is noteworthy that all subjects demonstrated a dynamic threshold that was higher than their static threshold. This noticeable difference in the threshold between the two tasks is consistent with previous reports (Morioka and Griffin, 2002; Zhang et al., 2009; 2011). One of the explanations could be linked to the fact that dynamic threshold is reaction time dependent, while static threshold is independent of reaction time. If this is simply the case, the difference between dynamic and static threshold should be equal to the product of choice RT and the speed of amplitude increment (2 μm/sec) during dynamic threshold measurement. Based on this assumption, we calculated the predicted dynamic thresholds using following equation:

*Predicted dynamic threshold = Observed static threshold + Choice RT * 2μm/sec*

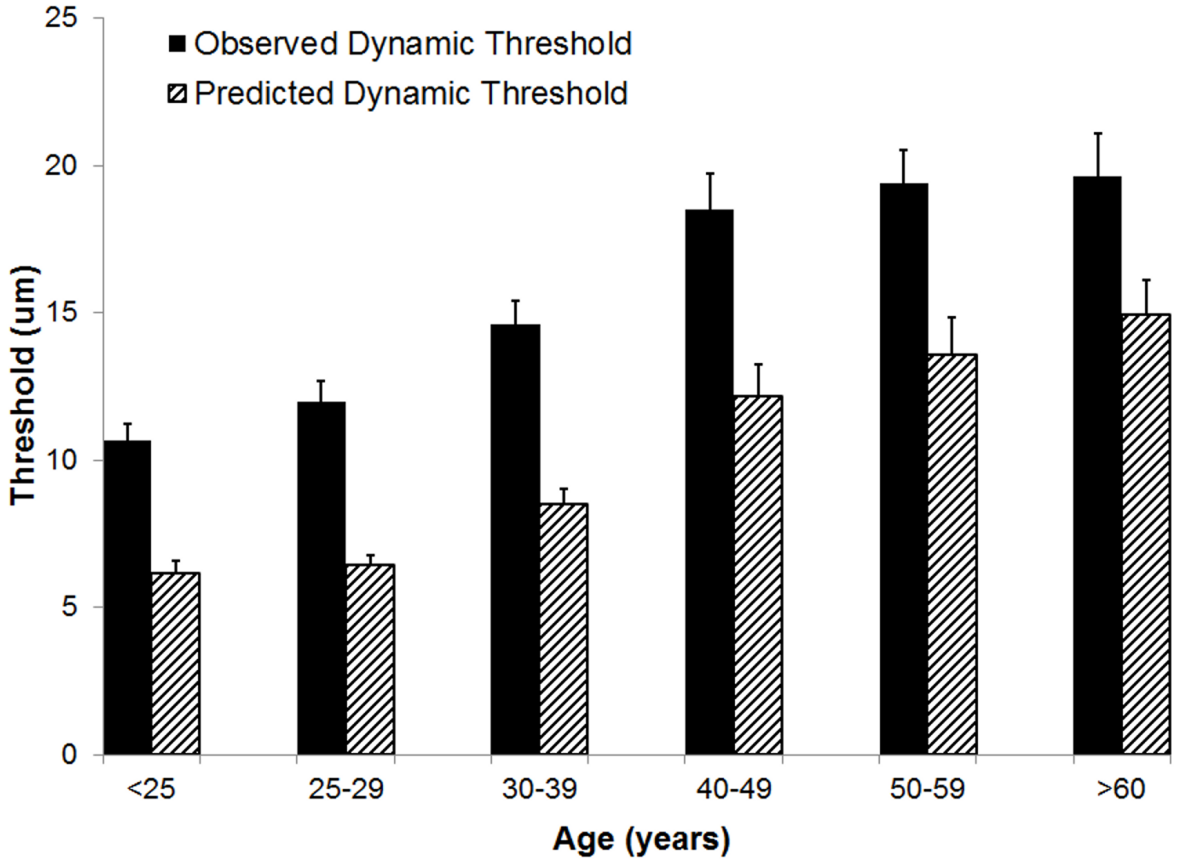

Figure 8.7: Comparison of the Predicted and Observed Dynamic Thresholds
The predicted values are always significantly smaller than the observed thresholds.

Fig. 8.7 compares the predicted and observed dynamic thresholds, and the predicted values are always significantly smaller than the observed thresholds, strongly suggesting that the difference between the two measures is not simply due to reaction time. Figure 8.8 is a direct comparison between the two threshold metrics for each age group (actually a ratio of dynamic/ static), and it emphasizes not only that the dynamic threshold is always greater than the static threshold, but that this ratio decreases with age. There is a significant difference between the youngest age group and the oldest age group ($p < 0.05$).

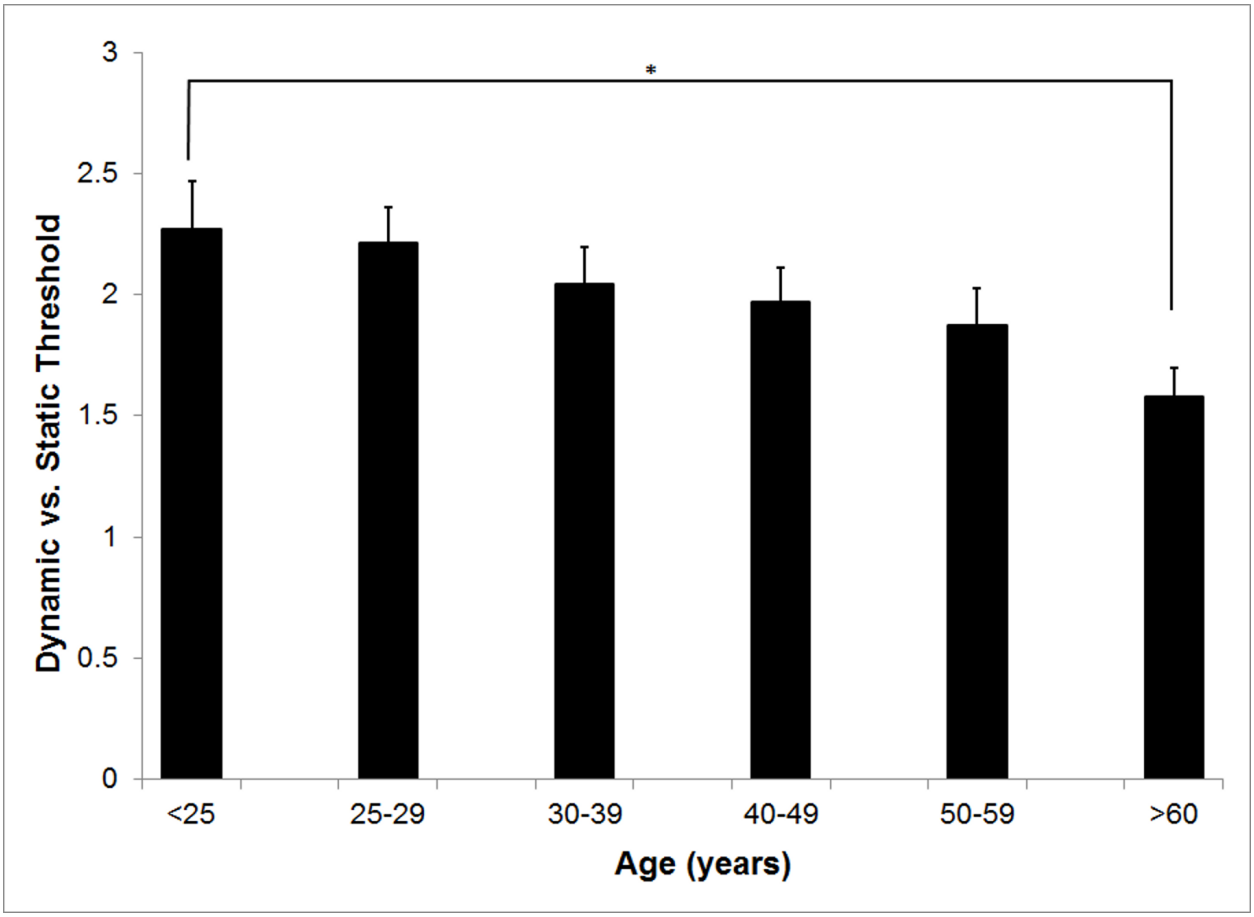

Figure 8.8: Ratio of Dynamic vs. Static Thresholds
Summary of ratio of dynamic vs. static detection threshold across six age groups. Not only the dynamic threshold is always greater than the static threshold, but the dynamic vs. static ratio decreases with age. There is a significant difference between the youngest age group and the oldest age group($p < 0.5$).

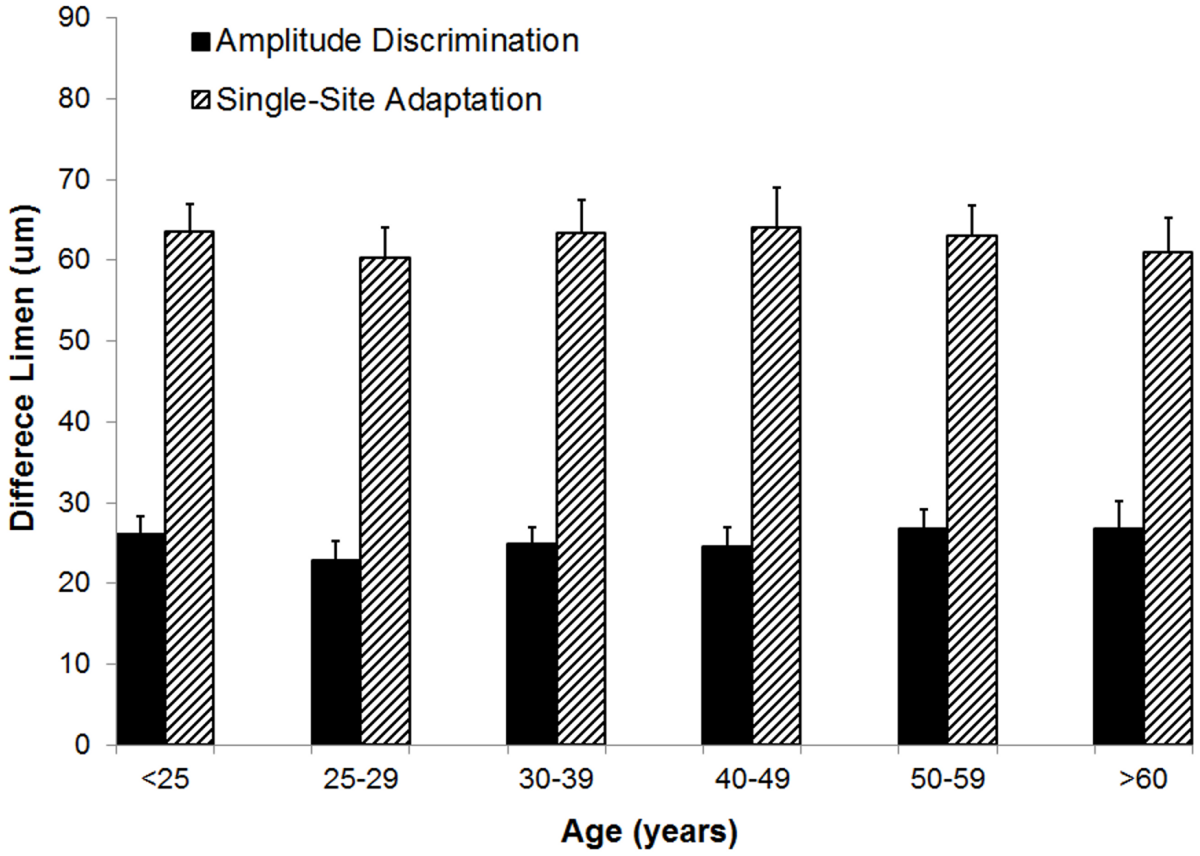

Figure 8.9: Differences in Amplitude Discrimination Across Ages
There is no significant difference in means across six age groups for both metric of amplitude discriminative capacity ($p = 0.85$) as well as adaptation metric ($p = 0.98$).

Amplitude discrimination capacity and the effects of adaptation were not altered with increases in age. Fig. 8.8 summarizes the group-averaged amplitude discrimination performance obtained during amplitude discrimination task with or without pre-exposure to a conditioning stimulus (adaptation). The data demonstrate that, in the absence of single site adaptation, subjects were able to discriminate between a 100 μm and nearly 125 μm stimulus equally well for all the age groups. On the other hand, the delivery of a conditioning stimulus to one of the two stimulus sites prior to the amplitude discrimination task significantly impacted the subject's amplitude discrimination capacity, and the effects of adaptation maintained well across all the age groups. This observed impairment of amplitude discrimination capability due to adaptation is consistent with the results of previous studies (Folger et al., 2008; Tannan et

al., 2007b; 2008; Zhang et al., 2009). One interpretation of this impairment is that a 1 sec conditioning stimulus reduces the perceived intensity of the subsequent test stimulus to the extent that a stimulus with amplitude of approximately 170 μm (compared to 125 μm without adaptation) was perceived as nearly the same in intensity as the 100 μm stimulus. One way ANOVA proves that there is no difference in means across six age groups for the amplitude discrimination task with adaptation ($p = 0.98$) or without adaptation ($p = 0.85$). To summarize the finding across the age spectrum, there is no significant difference in amplitude discrimination performance between subjects of different age groups in discriminative capacity with or without the presence of single-site conditioning stimuli. In other words, both the metric of amplitude discriminative capacity as well as the adaptation metric (the degree to which amplitude discriminative capacity changed with the conditioning stimulus) were maintained with increases in age.

Discussion

The present study evaluated the tactile information processing capacity of healthy human subjects across a wide age range (18 to 70 years). Six tests were performed to assess: (1) simple and choice RT; (2) vibrotactile detection thresholds; (3) amplitude discrimination capacity; (4) the effects of adaptation on amplitude discrimination capacity. While the results of peripherally mediated measures demonstrated significant increases in RT and detection threshold with age, the subjects' performance on the centrally mediated measures did not change. Specifically, the amplitude discrimination capacity and the impact of adaptation on performance were maintained with age. If adaptation is a metric that parallels cortical plasticity, the results of the current study suggest that the CNS in the aging population is still capable of plastic changes, and this cortical plasticity could be the mechanism that compensates for the degradations that are known to naturally occur with age.

Among many cognitive skills, speed of information processing is considered to be especially prone to aging effects. Prior studies have shown a significant increase in reaction time between 20 year olds and 60 year olds (Fozard et al., 1994; Ratcliff et al., 2001), and this

compares favorably with the results obtained in this study. In the current study, the subject's tactile information processing speed was assessed with two well established tasks: simple RT and choice RT tasks. We found that group-averaged RT was positively correlated with the average age for each group, with a correlation coefficient of 0.99 for simple RT and 0.95 for choice RT. Several studies have speculated the reasons for slowing reaction time with age, and factors other than simple speed of nerve transmission are most often cited. For example, human white matter integrity has been found to significantly correlate with information processing speed (Deary et al., 2006; Madden et al., 2009; Penke et al., 2010; Vernooij et al., 2009). Vernooij et al. (2009) conducted diffusion tensor imaging (DTI) scans and cognitive tasks in a sample of 860 older adults 61-92 years of age. It has been found that performance on tests that rely on processing speed degrades significantly with declining white matter integrity of the whole brain. Since many of these studies were performed on older healthy subjects without signs of mild cognitive impairment or dementia, the increase of RT might simply represent the effects of normal aging on basic cognitive function. In the context of the current study, we speculate that the increased mean RT could be the result of both decreased nerve transmission speed with age as well as the age-related decline in white matter integrity.

Increases in intra-individual variability on RT performance have been observed for older subjects compared with younger subjects. For example, it has been shown that inconsistency across trials on RT performance increases with age (Bunce et al., 2010; Gorus et al., 2008; Hultsch et al., 2000; 2002). In this report, we found that while the group-averaged intra-individual variability remains relatively constant for the subjects younger than 50 years old, the older subjects (>50 years) have significant higher intra-individual variability. In other words, older subjects showed greater inconsistency than younger subjects in response speed. Several studies have demonstrated that performance variability has the potential to be a good indicator of neurological disturbance and may be a good marker of preclinical status of dementia. For example, Bunce et al. (2010) found greater frontal white matter lesions were associated with higher intra-individual variability in choice RT in middle-aged healthy adults. Hultsch et al.

(2000) also demonstrated that performance variability was greater in patients with mild dementia than in healthy elderly subjects. As a result, measures of intra-individual variability may be a plausible behavioral indicator of aging-induced central neurological disturbances and may be able to serve as a valuable early marker of neurodegenerative disease.

Tactile detection threshold (a measure which determines the minimum stimulus intensity that can be perceived), has been documented to increase (due to decreased sensitivity) with age (Gescheider et al., 1994; Kenshalo, 1986; Lin et al., 2005; Thornbury and Mistretta, 1981; Verrillo, 1977, 1979, 1980). In the current study, the data is consistent with prior observations and shows degraded vibrotactile sensitivity (at 25 Hz) with increasing age. In order to determine if mechanisms involved in processing sub-threshold vs. threshold stimuli could be differentiated, tactile detection thresholds were collected using two different protocols. "Static" threshold is the minimum constant-amplitude stimulus detected, and "dynamic" threshold refers to the detection threshold measured with a stimulus that is increased from zero intensity to a detectable level (Zhang et al., 2009; 2011). It is noteworthy that all subjects demonstrated a dynamic threshold that was higher than their static threshold. This noticeable difference in the threshold between the two tasks is consistent with previous reports (Morioka and Griffin, 2002; Zhang et al., 2009; 2011). Since an argument could be made that the primary difference between the two measures is one of reaction time — dynamic threshold is reaction time dependent, while static threshold is independent of reaction time — we directly compared the actual results vs. results predicted based on this reaction time difference. As demonstrated in Fig. 8.6 of Results, the difference between the observations obtained by the two methods could not be explained by reaction time alone. An alternative possibility — and one that the authors have recently proposed (Favorov and Kursun, 2011; Tommerdahl et al., 2010; Zhang et al., 2011) — is that the difference between the two threshold metrics is impacted significantly by feed-forward inhibition that is generated by the initial sub-threshold stimulus that occurs when the dynamic threshold test is ramped from a null to a detectable level. Thus, the sub-threshold

stimulus delivered by the dynamic threshold test actually leads to the initial inhibition, or adaptation, that ultimately requires a larger stimulus to reach detectable levels.

One of the interesting findings of the current study is that although the subjects' vibrotactile detection threshold went up with age, their amplitude discrimination capacity was maintained. Specifically, subjects in all age groups demonstrated a similar ability to differentiate two supra-threshold stimuli that are delivered simultaneously to the skin. It should be noted that this amplitude discrimination task was conducted at supra-threshold levels (approximately 10x normative thresholds), and all subjects had approximately the same amplitude discriminative capacity at the amplitudes used. Thus, while the decline of tactile sensitivity is considered to be influenced predominantly by peripheral factors, we speculate that the ability to discriminate between two supra-threshold stimuli is more influenced by centrally mediated factors and would be only moderately influenced by changes in the periphery. This hypothesis was derived, in part, from studies which demonstrated that localized increases in the magnitude of the SI cortical response (Friedman et al., 2008; Simons et al., 2005; 2007) paralleled the changes in the ability of human subjects to distinguish between different intensities of skin stimulation (i.e., amplitude discrimination; Francisco et al. 2008).

To investigate potential changes in cortical plasticity with normal aging, the effect of single site adaptation on amplitude discrimination capacity was measured. Previous studies using this adaptation metric demonstrated that a conditioning stimulus delivered to one of the two sites before the amplitude discrimination task significantly altered a subject's ability to determine the actual difference between the two stimuli (Tannan et al., 2007b; 2008) by introducing a confound. In other words, the conditioning stimulus makes the subsequent stimulus, at the conditioned site, feel weaker and consequently, amplitude discriminative capacity is reduced. Neurophysiological studies have demonstrated that the effects of reduced intensity due to adapting stimulation are possibly attributable to a reduction in the responsivity of central neurons after prolonged or repetitive stimulation (Lee and Whitsel, 1992; Lee et al,

1992). When the single site adaptation measure is examined across a number of subject populations with compromised CNS - as may be the case with a neurodevelopmental disorder: autism (Tannan et al., 2008), acute pharmacological block (Folger et al., 2008) or a chronic pain condition (Zhang et al., 2011) — the adaptation metric is significantly diminished from that of the control population. These findings suggest that the method could be viewed as a potential indicator or marker of systemic cortical alterations, as adaptation, at this short duration time scale, is impacted by a number of factors (for discussion, see (Folger et al., 2008; Francisco et al., 2008; Tannan et al., 2007b; 2008; Tommerdahl et al., 2007a; 2010; Zhang et al., 2009; 2011)).

Evidence from a wide range of studies has demonstrated that while there are aspects of anatomical and functional degradation with age, the CNS is still capable of plastic changes. For instance, in a series of studies, Dinse and colleagues reported that experimental or environmental stimulations could induce use-dependent plasticity in older animal as well as human subjects at both cortical and behavioral level (Dinse, 2005, 2006; Dinse et al., 2006; Hilbig et al., 2002; Kalisch et al., 2008; 2009; Kattenstroth et al., 2010; Li and Dinse, 2002). Specifically, it has been found that aged rats exposed to an enriched environment showed complete recovery from the age-related enlargement of RFs of the hindpaw in somatosensory cortex typically found in animals housed in standard conditions (Hilbig et al., 2002). At the behavioral level, repetitive sensory stimulation procedures resulted in improvement of tactile acuity in elderly individuals, a phenomenon based on synaptic plasticity (Dinse, 2005; Dinse et al., 2006). In this study, we found that the effects of adaptation remain relatively constant across healthy populations regardless of age. Since adaptation is an important feature of cortical information processing that apparently remains intact with normal aging, it could be an important feature to assess in the aging population. Deviations from normative values could be an early indicator of neurodegenerative disease; studies directly addressing this issue are currently ongoing and will be reported in the near future.

FUTURE DIRECTIONS

Protocols

The novel tests used throughout this dissertation are exponentially quicker and potentially provide more insight into overall brain health. Through the use of confounds in chapter 4, we may have discovered a way to monitor glial status through a non-invasive tactile test that virtually anyone can perform. The dynamically changing stimuli seen in chapters 3, 5, 6,7, & 8, have given us insight into the role of feed forward inhibition and cortical plasticity in subjects with autism and VVS. In all likelihood, it is possible to measure even more specific interactions taking place in SI with the right test or the right combination of tests.

The protocols which use dynamically changing stimuli generally provide the same diagnostic information in a fraction of the time that it takes to run a classic 20 trial 2AFC protocol. These tests also give us the opportunity to provide conditioning or confounds, like “adaptation," without any real awareness to the subject. The chapters provided in this dissertation do a lot to describe how these tests work in relation to amplitude discrimination, at near threshold and super threshold amplitudes; but all these tests are performed at 40 Hz. A study using different frequency of vibration should be performed at a variety of amplitudes and rates of modulation in order to ascertain the impact that frequency has on the test. In preliminary testing, exponentially better performance was seen at higher frequencies (200 Hz) . Frequency confounds could also be used in this test to potential uncover a new protocol to test interactions between synchronization and spatial acuity. The tests with ramping stimuli generally were only ramped in one direction: in threshold testing the test stimulus began at 0 microns and ramped until perception and in the matching task they began at 0 microns and increased until the subject perceives a match. This potentially causes some bias to the

response and in studies of the “method of limits” generally the “limits” are studied in an ascending and descending fashion. These tests should more than likely be repeated with test amplitudes much higher in amplitude and then ramped down until the subject responds. This also creates a way to “mix-up” the tests quite easily but still get a robust measure of amplitude capacity, however, the impact of adaptation will be greater with the larger intensity stimuli.

A test of dynamically changing frequency would also be rather trivial to perform. In these tests, a standard stimulus should be delivered at a constant amplitude and constant frequency, while the other is ramped from 0 Hz with the same amplitude as the standard stimulus. The subject would respond when they felt the frequencies of the two stimuli match. The general outline of the study should look very similar to the one from chapter 3, the rate of frequency change should be varied as well as the standard frequency being used as a comparison. It is unlikely that amplitude strength would have a significant impact on this study, but different amplitudes should be tested to completely explore the method. Obviously the next step would be to apply amplitude confounds on the test or standard site and measure the impact on the subjects perception.

Our general goal for testing is to gather as much accurate information about a subjects brain health in as short a period as possible. The ramping stimuli do a lot to reduce the time of the test, but it still can exhibit problems. For instance, if extremely fast rates are being tested for extremely small amplitudes, the subject will commonly let the ramping stimulus increase to an amplitude higher than that of the standard amplitude, essentially creating a negative DL. This is usually explainable in terms of reaction time, but it is still not ideal for testing a subjects ability to match two stimuli. A new approach could be to allow the subject to control the increasing or decreasing amplitude of the test stimulus. Supplying the subject with control over the stimuli will reduce the common tendency for the subjects to respond prematurely, and most likely lengthen the test. Some control for the duration of the test will have to be designed; it may be appropriate to limit this by number of reversals (number of times they switch between increasing/decreasing) and not a randomly assigned cut off point to the test.

The easiest way to implement this with the current stimulator design is to allow one mouse button to increase the amplitude of the test stimulus, and the other button to decrease it. If the test stimulus is increased or decreased as a constantly changing stimulus, then the rates or amplitudes should be varied from trial to trial A new type of input device could also be used, such as a dial or a switch could be used to increase/decrease the stimuli in a slightly more intuitive manner. Regardless, the duration of the trial should be recorded, as well as the oscillation points the subject explores on the way to matching the stimuli.

The current version of the somatosensory stimulator can deliver 4 stimulation to 4 independent sites, but currently almost every test only uses 2 sites of stimulation. It seems that more efficient use of the 4 sites could provide faster testing. If 3/4 different amplitudes are delivered to 3/4 different sites, and the subject can correctly rank the intensity of the stimuli, this essentially provides 3 points of 2AFC in one trial. (That A<B<C<D, instead of A<B, B<C, and C<D delivered separately.)

Giving the subject the ability to rank their responses could provide similar gains in speed of testing. If the subjects could specify the ease of the current trial or their confidence in answering the question, after providing a correct response, this might allow for a few trials to be skipped. The skipping of trials would allow the subject to get to the more difficult trials sooner. These trials are the ones that correctly identify a subjects DL, and are the ones with the most diagnostic information.

Imaging

The data presented in a lot of these chapters is somewhat incomplete. The dynamic tests out lined in chapters 3, 5, 6, 7, & 8 show heterogeneity within subjects with VVS and autism, but the underlying cortical mechanisms behind this heterogeneity is not understood. The first step to gaining understanding of these tests is to do electrode and optical imaging studies in the somatosensory cortex of nonhuman primates. A simple electrode study with a ramping stimulus may be enough to completely understand the differences we are seeing. For the dynamic test heavily explained in chapter 3, we originally believed that the majority of the

separation between the two points could be explained by adaptational differences, that the standard stimulus (which was always constant) was actually being "adapted" to a point that it felt approximately 25% of its real amplitude (giving a DL of 75% as seen in some of the tests) but this seems unlikely after viewing the results of the 5 sec conditioning stimulus trials. The early estimates of congruency might be explained just by viewing a neurons response to a simple ramping stimulus, but if the mechanism behind the matching task is more related to synchronization than it might be necessary to have both the standard (not moving) stimulus and the test (ramping) stimulus simultaneously. If no differences can be observed using electrode recordings, then OIS imaging may prove useful in analyzing the difference between estimation of a constantly modulating stimulus from a static one.

The duration and amplitude confounds explored in chapter 4 can be explained using OIS data obtained from evoked potentials measured by Whitsel in 2003 and OIS performed by Simons in 2005 and 2007, but piecing together our understanding of these confounds from testing done at multiple different times on different types of animals is not ideal. It would be much more conclusive to have simultaneous electrode recordings and OIS imaging using parameters solely designed to elicit the difference seen with these confounds. A study by Lee in 2005 (Lee et al., 2005), showed that using fluoroacetate could separate the response observed in OIS from the firing of neurons, suggesting that OIS is not an accurate measure of neuron activation but possibly a measure of glial response. Studies like this should be further explored in order to completely explain the role of neurons and glia in the perception of amplitude and duration.

The preliminary data obtained in chapter 4 in subjects with concussion shows promising results for measuring concussion using somatosensory testing, this could me made much stronger by use of animal studies. Imaging and electrode recordings of animals with varying degrees of mTBI would elicit a better understanding of neuron-glial interactions in our tests but also potentially could reveal a better understanding of the neuroinflammatory response and how it impacts sensory perception.

Neuroinflammation

The concept of neuroinflammation is not as simple a topic as its name might imply. While at the base level "inflammation of the nervous system" does describe the general condition, it doesn't describe the major differences between neuroinflammation and inflammation in other parts of the body. The classical symptoms of inflammation are pain, heat, redness, and swelling; none of which are obviously present in neuroinflammation. Neuroinflammation refers to a complicated and not fully understood neurodegenerative condition used to describe the symptoms from patients with Alzheimer's, Parkinson's syndrome, Multiple Sclerosis, and those who suffer mild traumatic brain injury (mTBI). Neuroinflammation, like regular inflammation, is caused by the body's immune response to harmful stimuli, but in the case of neuroinflammation, this response kicks off a chain of events that leads to a chronic auto-immune disorder that can result in debilitating neurocognitive deficits. The nervous system can become inflamed in response to a variety of signals, including infection, traumatic brain injury, toxic metabolites, or autoimmunity. In the central nervous system, microglia are the principle immune cells that are activated in response to these cues. The CNS is typically an immunologically privileged site because peripheral immune cells are generally blocked by the blood brain barrier (BBB), a specialized structure composed of astrocytes and endothelial cells. Under many of these conditions, the BBB becomes compromised and allows infiltration of peripheral immune cells into the central nervous system. Once leukocytes migrate through the blood brain barrier, the effect can be toxic and promote widespread inflammation, perpetuating the body's immune response.

In order to setup a study to find a gold standard measure for neuroinflammation, we must first understand how neuroinflammation affects brain chemistry, in order to better track its existence and progress. There are two major changes that occur in the cortex in response to neuroinflammation that could be useful to use as biomarkers. The first is glial cells. Microglia, the main component of the CNS immune response, are responsible for the surveillance of the entire brain for signs of injury, to which they rapidly respond by migrating to the site,

confronting pathogens, and devouring damaged nerve-cell components to speed repair. Another item on the microglial resume is the “sculpting of neural circuits”: Microglia help prune away excessive or inappropriate brain-cell connections. Microglia actively survey their environment through, and change their cell morphology significantly in response to neural injury. Acute inflammation in the brain is typically characterized by rapid activation of microglia. During this period, there is no peripheral immune response. Over time, however, chronic inflammation causes the degradation of tissue and of the blood brain barrier. In response, microglia generate reactive oxygen species and release signals to recruit peripheral immune cells for an inflammatory response. The activation of microglia can trigger activation of nearby astrocytes. The activated astrocytes release various growth factors and undergo morphological changes, such as hindering axonal regeneration through formation of glial scar tissue.

A variety of proteins called cytokines play a large role in the brains inflammatory response. Cytokines can play a pro-inflammatory or anti-inflammatory role, depending on the type or even the time course. For example, TNF-α causes neurotoxicity at early stages of neuroinflammation, but contributes to tissue growth at later stages of inflammation. In the aged brain alone, without any evident disease such as Alzheimer’s, there are chronically increased levels of pro-inflammatory cytokines and reduced levels of anti-inflammatory cytokines. In the case of TBI, the release of cytokines may exacerbate the damage caused from the actual injury. A pro-inflammatory cytokine Il-1β causes DNA fragmentation and apoptosis, and together with TNF-α may cause damage to the blood brain barrier and infiltration of leukocytes. In TBI, the primary traumatic event results in delayed secondary injury due to the chemical and cellular changes made by the nervous system in response to the initial damage. Research demonstrates that neuroinflammation after TBI can have both harmful and favorable effects, and these likely vary in the acute and delayed phases after injury. The hallmark of Alzheimer's disease is the presence of amyloid plaques in the brain; it’s possible that an increase in inflammatory cytokines inhibit the activated microglia from phagocytosing amyloid-

beta, which could obviously lead to the formation of plaques over time (Ramesh et al. 2013; Lautner et al. 2011) .

There is obviously not a standard of measure for neuroinflammation currently in practice. In a clinical setting, the only way to assess a patient with neuroinflammation is by monitoring the symptoms exhibited by the disease's slow degenerative progression. In the case of Alzheimer's disease and TBI, the options for treatment are severely limited by the typically delayed diagnosis, much of the damage has been done before the disorder is recognized. There is evidence that such cognitive deficits can be improved through immediate rehabilitation and pharmacological intervention post TBI, but the lack of diagnostic methods makes it difficult to utilize these therapies. Much effort has been spent in research in identifying biomarkers for each of the disorders identified by neuroinflammation, and using experimental imaging techniques. A few researchers have had success identifying neuroinflammatory processes in the CNS; but none of this research has lead to a quantifiable measure of neuroinflammation that can be obtained in a clinical setting.

Most of the techniques to assess neuroinflammation being explored target two different biomarkers. The first is activated microglia. As described previously, it is believed that the activation of microglia, from a breakdown in the BBB or perhaps a different mechanism, causes a chain of events that cultivates widespread inflammation. If the activation of these microglia could be identified and possibly quantified, this would perhaps provide a fantastic early measure for neuroinflammation. Attempts to identify activated microglia are usually performed using complex imaging techniques; either Diffusion Tensor Imaging (DTI), MRI with special contrast agents (such as ultra-small particles of iron oxide or gadolinium chelates) (Wiart et al. 2007; Deddens et al., 2012), or Magnetic Resonance Spectroscopy (MRS). When microglial cells are activated, they also over-express the 18-kDa translocator protein TSPO; radioactive PET ligands are being tested experimentally that bind to TSPO, but as yet an agreement on which one can be used reliably in clinical practice has not been reached. Thus far,

microglial activation markers have generally failed to provide high enough diagnostic accuracy to be clinically useful as diagnostic tools on their own (Andreozzi, 2012).

The second target for assessing inflammation in the nervous system is the prevalence of cytokines. The real-time reverse transcription polymerase chain reaction (RT-PCR) is becoming widely used to quantify cytokines from cells, body fluids, tissues, or tissue biopsies. RT-PCR can be used to target the expression of numerous specific proteins linked to neuroinflammation, most studies focus on cytokines (TNF-α, IL-1β, IL-6, IL-1ra, TGF-β, IL-15, IFN-γ), chemokines (ccl5, cxcl1, cxcl2), and i-NOS measurements. RT-PCR is more powerful and more reliable than standard immunoassays or bioassays because the half-life of cytokines can be very short (~ 10 min) and levels of cytokines can be very low in the tissues actually affected (Giulietti et al., 2001).

One of the cardinal signs of neuroinflammation, a breakdown in the BBB, has been successfully imaged using nuclear imaging performed using SPECT agents, such as 99mTcO4, 99mTc-DTPA, and 201TI- and 67Ga-citrate, or PET agents, such as 68Ga-ethylenediaminetetraacetic acid. However, imaging BBB disruption isn't a true measurement of neuroinflammation, and more an indication of a downstream event.

A multi-parametric approach will have to be taken in order to discover a gold measure for neuroinflammation, some research seems to show little to no activated microglia in the brains of AD patients and focus more on the presence of amyloid-beta and specific cytokines. It could be that certain disorders affected by neuroinflammation are marked by increases in activated microglia and others by increases in pro-inflammatory cytokines; and in all likelihood these could be different in the early and late stages of each of the conditions.

Somatosensory testing can also be used to elucidate differences between populations with these neurodegenerative conditions. Neuroinflammation seems to greatly affect the integrity of white matter, and improvement in function may depend most on how well functional neural networks adapt to the injury. During previous imaging studies, researches have noted hyper-intensive increases in activated microglial in the somatosensory cortex; these

microglial and the impact they have on the white matter in the area should greatly impact subjects with neuroinflammation ability to perceive somatosensory stimuli. Certain types of sensory tests will be particularly robust at delineating a subject with neuroinflammation from a healthy control. These tests use illusory conditioning stimuli and the cortical phenomenon known as adaptation to greatly improve contrast in healthy controls with healthy white matter. The degradation that has occurred in the white matter of those suffering from neuroinflammation will suppress the impact of a conditioning stimulus. The tests which will be extremely useful are amplitude discrimination with adaptation, a duration discrimination trial with an illusory amplitude confound, dynamic threshold, and TOJ with and without confound, and possibly bilateral testing.

Amplitude discrimination with a conditioning stimulus (adaptation) has already been shown to reliably separate autistic subjects from healthy controls. Neuroinflammation and Autism are both identified by problems with white matter integrity, so it is likely that each will have trouble “adapting” in response to the conditioning stimulus delivered prior to the amplitude discrimination task. The performance differences to this task between autistic subjects and healthy controls is usually explained by decreased GABA levels in the autistic subjects, it is unclear if neuroinflammation subjects also have decreased GABA levels, but it's a safe assumption that the differences in white matter will cause significant differences from healthy controls.

The duration discrimination task involves running a simple duration discrimination task with one of the stimuli at a significantly higher amplitude. It is predicted from OIS imaging, that a significant increase in amplitude causes a significant increase in duration in the cortex to the stimuli. This allows another illusory test, where a normal healthy subject perceives the stimuli as being longer than it really is because of the impact of the increased amplitude on the duration perception. In subjects with compromised white matter (autistics), the impact of this test was compared to a duration discrimination task without any amplitude difference and very

little difference was seen (~10%); Healthy controls show an increase of almost 100%. It is likely that subjects with neuroinflammation will perform similarly.

Most studies have seen striking amounts of activated microglia centered on the corpus callosum but very few studies have looked at functional connectivity in the neuro-inflammed brain. A bilateral test could be useful to explore the impact that neuroinflammation has on functional connectivity, and determine the impact of neuroinflammation on the corpus callosum.

Somatosensory testing has many advantages over the imaging techniques being explored as measures for neuroinflammation now. The first, and most obvious is resolution. Resolution is of particular importance when attempting to quantify and/or classify neuroinflammation. Current imaging techniques claim they are able to detect activated microglia and other inflammatory cells, but there is a big difference between detecting the presence of certain types of cells and providing a metric of the current amount of neuroinflammation. Measuring the extent of the disease is of particular importance, as drug therapies will likely change based on the current stage of neuroinflammation. The current clinical measure for monitoring AD and TBI is basically measuring how far they have declined in cognitive function; once a biomarker is pinpointed, far more robust tests can be designed to target the actual mechanisms causing the decline. Having an understanding of how far the disease has progressed will prove much more beneficial than monitoring how far the patient has regressed. It is also extremely likely that the mechanisms at work in TBI, AD, etc are different from one another; making it unlikely one contrast agent and one method of imaging would be enough to quantify the amount or extent of neuroinflammation. The other major benefit to somatosensory testing is cost. Not only is the hardware exponentially cheaper than most imaging machines, it doesn't require an experienced technician to run it, and a radiologist is not required to diagnose the results.

For these reasons, it likely makes sense to run a multi-modal longitudinal study for each of the common neuroinflammation conditions. Keeping the groups separate, we may learn

what neural mechanisms separate the different varieties of neuroinflammation (which is not completely understood for AD, TBI, or Parkinson's). Groups of early diagnosis AD, recent TBI, early onset Parkinson's, and possibly subjects predisposed to mTBI injuries, such as athletes and military servicemen, should be recruited for participation in the study. Subjects with an extended history of disease or injury should most likely be excluded from testing. Advanced AD and Parkinson's patients could have difficulty completing the somatosensory portion of the testing due to lack of comprehension, memory, hallucinations, etc., and those suffering from mTBI/TBI from an injury in the distant past may no longer show signs of neuroinflammation. An age-matched control group with no history of concussion or neurological disorders should be recruited in parallel to the neuroinflammation subjects to insure the statistical significance of the measurements made in the neuro-inflammed group. The longitudinal study should ideally continue for as long as possible, but realistically a sampling period across 1-2 years should be sufficient to track changes in most of the groups. The goal for enrolling subjects pre-disposed to mTBI is that a baseline measurement could be recorded and the subjects departure from healthy controls could be much better understood. Any subjects recruited in this study that did not experience a concussion during the testing should be excluded from analysis (or possibly included in the control group if they meet all the criteria).

The overall goal of the study would be to document microglia activation using either MRS or PET (neither has been shown to definitively distinguish any specifics about microglial activation but research continues to focus on these two types of imaging for neuroinflammation) and cytokine presence using RT-PCR and correlate those measurements with clinical observations, demographics, and the results of somatosensory testing. The clinical observations will serve to monitor the subjects deterioration (or improvement) as their disease progresses, it is important to know which subjects are improving when analyzing data from the group as a whole; it may also help to give researchers a biological basis for the subjects clinical deteriorations/improvements. The data should be analyzed with special attention to each subject's affective disorder, although the goal here is to design a test for neuroinflammation,

these different conditions show a range of conditions and different symptoms across different time courses. It would be naive to think that each is measurable by exactly the same standard. The interactions between microglia and cytokines and their respective roles in neuroinflammation is not completely understood, it is likely that each contributes a different inflammatory effect and the combination and/or location of inflammation are responsible for the different types of neuroinflammation. Hopefully a study with enough measured parameters will be able to correlate differences between these populations.

Pain

Pain is an enigma. It differs from the five classical senses: vision, hearing, touch, taste, and smell, because it is both a discriminative sensation and a behavioral motivator.

Understanding the complicated interactions between pain and sensitization begins with comprehension of the "Gate Control Theory." Brought forth in 1965 by Ronald Melzack and Patrick Wall (Melzack and Wall 1965), the Gate Control Theory proposes that a "nerve gate" exists in the dorsal horn of the spinal cord, which opens and closes based on specific input and essentially decides if a nociceptive signal being sent from the periphery is allowed to continue through to the cortex. Originally Melzack & Wall set out to explain why thoughts or emotions so easily impact the perception of pain, but they also found the physiological basis behind mechanoreceptor-induced analgesia. Analgesia (decreased responsiveness to noxious stimulation) can be triggered by input from a vibrotactile stimulus applied near the location of the noxious stimulus. You're probably familiar with the concept; if you were to slam your hand in the door, you will instinctively rub or shake it after the injury. You are activating your peripheral mechanoreceptors in an attempt to shut off the pain gate.

In 1994, Apkarian et al. (Apkarian, Stea, and Bolanowski 1994) showed that the opposite is true as well. Not only is pain diminished by touch, but touch is also impaired by the introduction of pain. Pain was introduced through contact heat and somatosensation was measured through vibrotactile detection thresholds and perceived magnitudes of supra threshold vibrations. The thresholds were statistically higher when the noxious stimulus was

evoked and perception of magnitude was significantly reduced. This became the foundation for "touch gating." Research on touch gating has confirmed similar tactile desensitization when applying electrical shock, by intradermal capsacin injection (Geber et al. 2008), and by injection of hypertonic saline into a muscle (Stohler et al. 2001). (Interestingly, research has shown that pain evoked by electrical shock is not reduced through local tactile stimulation (Watanabe 1999), that basically gate control theory doesn't apply to electrical stimulation.) The mechanisms behind touch gating are not as simple as those controlled under Gate Control Theory, it is unlikely controlled by simple "gates" in the spinal cord because tactile primary afferents ascend all the way to the brainstem. Ipsilateral heat-induced pain causes an elevation in tactile thresholds even when the noxious and non-noxious stimuli were not localized, and the effect seems to require that the painful stimulus only be within the somatosensory region defined in terms of dermatomal organization. Thus the effect is clearly related to somatotopic organization and is likely not peripherally mediated. The ability of pain to capture attention suggests that touch gating may just be an example of distraction, but the fact that pain increases tactile thresholds but not auditory thresholds argues that touch gating is specific to the somatosensory cortex. Most attempts to correlate pain intensity to the changes in tactile sensitivity have not been successful, meaning touch gating is not impacted by the habituation or perception of pain, and is likely not the result of distraction (Harper & Hollins 2012). It seems more than likely that touch gating is a centrally mediated phenomenon.

The effect that acute pain has on sensory percept is much better understood than the impact of chronic pain. This is partially due to the lack of understanding of chronic pain in general and also the variability seen with the chronic pain population; heterogeneity and diagnostic differences exist within even minor subsets of chronic pain. The gate control theory is not able to explain several chronic pain conditions, and as a result the theory has evolved to include brain mechanisms that may underlie some kinds of chronic pain. In the case of chronic pain, the pain the subjects are feeling is not a warning signal to give notice to physical injury or disease, the pain is the disease.

Studies of touch gating on subjects with chronic pain seem to show very conflicting results between different populations of chronic pain subjects. Hollins & Goble (1996) have shown increased thresholds in groups diagnosed with TMD both at baseline and when faced with a supra-threshold adaptation stimulus. They were even able to find significant correlation between the thresholds and the subject's perceived pain (higher thresholds for subjects with more muscle tenderness/higher perceived pain). Seltzer & Seltzer (1992) have also shown that two-point discrimination is impaired for a diverse group of chronic pain patients. In fibromyalgia, studies have found significantly decreased detection thresholds for touch, pressure, and of course, pain (the trademark of the condition). Patients with chronic cervicobrachialgia and persistent patellofemoral pain demonstrate systemic elevation of vibrotactile detection thresholds compared to healthy controls (Nebel et al. 2010). Similarly, provoking pain in patients with pathological pain (e.g., tennis elbow) increases tactile detection thresholds in the area of pain referral.

Similar studies in our lab have failed to show any statically significant detection threshold differences in subjects diagnosed with Vulvar vestibulitis syndrome (VVS) or migraines (Nguyen et al. 2013; Zhang et al. 2011). However, other differences have been uncovered. Similarly amplitude discrimination capacity was not significantly different between the controls and patients with vulvodynia, but the impact of single-site conditioning (or "adaptation") on performance of the dual-site task showed a remarkable difference within a subset of VVS patients. Those reporting pain for a longer duration of time were not significantly impacted by the adaptation stimulus while controls and those reporting pain for a relatively short period of time were impacted heavily. Subjects suffering from migraines showed results similar to those of long-term VVS, a conditioning stimulus delivered before amplitude discrimination had little to no impact on the subjects ability to perform the task. Migraneurs were also shown to have trouble with perception of timing and synchronization with particularly substandard performance to a duration discrimination task and a temporal order judgment task.

The heterogeneity and disparate differences within the chronic pain population is quite obvious after a review of the literature. Some of the results compiled are in alignment with our understanding of acute pain and tactile sensitization, while others cannot be understood with as simple a hypothesis as gate control theory or touch-gating. Goble and Hollins (1996) found that the subjects with more evoked pain (increased pain sensitivity) were also the subjects with higher thresholds (decreased tactile sensitivity). Increased pain sensitivity and altered vibrotactile sensitivity are two indicators of an underlying disturbance of somatosensory processing. It may be possible that the majority of chronic pain subjects suffer from increased periphery sensitivity while a generalized central abnormality is responsible for the unpredicted results. Although the clinical presentations of these conditions differ, there is increasing recognition that systematic assessment of somatosensory perception in these disorders would greatly aid diagnosis and evaluation of treatment efficacy.

There is one fundamental difference in these studies that might be worthwhile to explore. In the TMD studies by Goble & Hollins (1996), the subjects were stimulated on the jaw (locally to their pain) and higher than normal thresholds were observed, and it has been found that patients with vulvodynia have increased sensitivity to sensory stimulation at both genital regions and sites distant to it. However, in the studies performed in our lab (on VVS and migraneurs) the subjects were stimulated on digits 2 and 3 (not local to pain). In order to completely understand the periphery's role in chronic pain, these subjects should be tested locally to their pain.

The tests which are targeted at centrally mediated mechanisms (amp disc rim with adapt, TOJ, duration discrimination) yielded meaningful results for all the chronic pain subjects regardless of stimulus location. This shows the clear benefits of using these tests for quantification of chronic pain, as they will likely measure similarly whether local to chronic pain sites or not. It's likely that the relative contribution of peripheral and central factors differ in subgroups of chronic pain, and that clinical signs and symptoms alone are insufficient in identifying the underlying mechanism of pain as peripheral, central, or a combination of both.

REFERENCES

Abel, Sharon M. “Discrimination of Temporal Gaps.” The Journal of the Acoustical Society of America 52, no. 2B (August 12, 2005): 519–24. doi:10.1121/1.1913139.

Alary, Flamine, Rachel Goldstein, Marco Duquette, C. Elaine Chapman, Patrice Voss, and Franco Lepore. “Tactile Acuity in the Blind: A Psychophysical Study Using a Two-Dimensional Angle Discrimination Task.” Experimental Brain Research 187, no. 4 (2008): 587–94.

Allan, Lorraine G., and A. B. Kristofferson. “Psychophysical Theories of Duration Discrimination.” Perception & Psychophysics 16, no. 1 (January 1, 1974): 26–34. doi: 10.3758/BF03203244.

Allan, Lorraine G., A. B. Kristofferson, and E. W. Wiens. “Duration Discrimination of Brief Light Flashes.” Perception & Psychophysics 9, no. 3 (May 1, 1971): 327–34. doi:10.3758/ BF03212659.

Alonso, Jose-Manuel, and Harvey A. Swadlow. “Thalamocortical Specificity and the Synthesis of Sensory Cortical Receptive Fields.” Journal of Neurophysiology 94, no. 1 (2005): 26–32.

Andreozzi, Erica M. “The Development of Multimodal Imaging Probes for Visualizing Neuroinflammation in Alzheimer’s Disease and Traumatic Brain Injury.” UNIVERSITY OF CALIFORNIA, DAVIS, 2012. http://gradworks.umi.com/35/44/3544687.html.

Apkarian, A. Vania, Richard A. Stea, and Stanley J. Bolanowski. “Heat-Induced Pain Diminishes Vibrotactile Perception: A Touch Gate.” Somatosensory & Motor Research 11, no. 3 (1994): 259–67.

Arthurs, O. J., E. J. Williams, T. A. Carpenter, J. D. Pickard, and S. J. Boniface. “Linear Coupling between Functional Magnetic Resonance Imaging and Evoked Potential Amplitude in Human Somatosensory Cortex.” Neuroscience 101, no. 4 (2000): 803–6.

Artieda, J., M. A. Pastor, F. Lacruz, and J. A. Obeso. “Temporal Discrimination Is Abnormal in Parkinson’s Disease.” Brain 115, no. 1 (February 1, 1992): 199–210. doi:10.1093/brain/ 115.1.199.

Backes, W. H., W. H. Mess, V. van Kranen-Mastenbroek, and J. P. H. Reulen. “Somatosensory Cortex Responses to Median Nerve Stimulation: fMRI Effects of Current Amplitude and Selective Attention.” Clinical Neurophysiology 111, no. 10 (2000): 1738–44.

Bartzokis, George, Jeffrey L. Cummings, David Sultzer, Victor W. Henderson, Keith H. Nuechterlein, and Jim Mintz. “White Matter Structural Integrity in Healthy Aging Adults and Patients with Alzheimer Disease: A Magnetic Resonance Imaging Study.” Archives of Neurology 60, no. 3 (2003): 393–98.

Batson, Herbert Clifford. An Introduction to Statistics in the Medical Sciences. Burgess Pub. Co., 1956.

Belmonte, Matthew K., E. H. Cook, George M. Anderson, John LR Rubenstein, William T. Greenough, Andrea Beckel-Mitchener, Eric Courchesne, Lisa M. Boulanger, Susan B. Powell, and Pat R. Levitt. “Autism as a Disorder of Neural Information Processing: Directions for Research and Targets for Therapy*.” Molecular Psychiatry 9, no. 7 (2004): 646–63.

Bernstein, Hans-Gert, Johann Steiner, and Bernhard Bogerts. “Glial Cells in Schizophrenia: Pathophysiological Significance and Possible Consequences for Therapy.” Expert Review of Neurotherapeutics 9, no. 7 (July 2009): 1059–71. doi:10.1586/ern.09.59.

Bizo, Lewis A., Josey Y. M. Chu, Federico Sanabria, and Peter R. Killeen. “The Failure of Weber’s Law in Time Perception and Production.” Behavioural Processes 71, no. 2–3. Interval Timing: The Current Status (February 28, 2006): 201–10. doi:10.1016/j.beproc.2005.11.006.

Blakely, William Arthur. “The Discrimination of Short Empty Temporal Intervals.” University of Illinois at Urbana-Champaign, 1933.

Blatt, Gene J. “GABAergic Cerebellar System in Autism: A Neuropathological and Developmental Perspective.” International Review of Neurobiology 71 (2005): 167.

Bolanowski Jr, Stanley J., George A. Gescheider, Ronald T. Verrillo, and Christin M. Checkosky. “Four Channels Mediate the Mechanical Aspects of Touch.” The Journal of the Acoustical Society of America 84, no. 5 (1988): 1680–94.

Bolanowski, S. J., and R. T. Verrillo. “Temperature and Criterion Effects in a Somatosensory Subsystem: A Neurophysiological and Psychophysical Study.” Journal of Neurophysiology 48, no. 3 (1982): 836–55.

Boll, Thomas J. “Right and Left Cerebral Hemisphere Damage and Tactile Perception: Performance of the Ipsilateral and Contralateral Sides of the Body.” Neuropsychologia 12, no. 2 (1974): 235–38.

Bornstein, Jacob, Zeev Goldik, Zmira Stolar, Doron Zarfati, and Haim Abramovici. “Predicting the Outcome of Surgical Treatment of Vulvar Vestibulitis.” Obstetrics & Gynecology 89, no. 5, Part 1 (1997): 695–98.

Bredfeldt, Christine E., and D. L. Ringach. “Dynamics of Spatial Frequency Tuning in Macaque V1.” The Journal of Neuroscience 22, no. 5 (2002): 1976–84.

Brown, Caroline, Thomas Gruber, Jill Boucher, Gina Rippon, and Jon Brock. “Gamma Abnormalities during Perception of Illusory Figures in Autism.” Cortex 41, no. 3 (2005): 364–76.

Brumberg, JOSHUA C., DAVID J. Pinto, and DANIEL J. Simons. “Spatial Gradients and Inhibitory Summation in the Rat Whisker Barrel System.” Journal of Neurophysiology 76, no. 1 (1996): 130–40.

Bruno, Randy M., Vivek Khatri, Peter W. Land, and Daniel J. Simons. “Thalamocortical Angular Tuning Domains within Individual Barrels of Rat Somatosensory Cortex.” The Journal of Neuroscience 23, no. 29 (2003): 9565–74.

Bruno, Randy M., and Daniel J. Simons. “Feedforward Mechanisms of Excitatory and Inhibitory Cortical Receptive Fields.” The Journal of Neuroscience 22, no. 24 (2002): 10966–75.

Bunce, David, Kaarin J. Anstey, Nicolas Cherbuin, Richard Burns, Helen Christensen, Wei Wen, and Perminder S. Sachdev. “Cognitive Deficits Are Associated with Frontal and Temporal Lobe White Matter Lesions in Middle-Aged Adults Living in the Community.” PLoS One 5, no. 10 (2010): e13567.

Cannestra, Andrew F., Nader Pouratian, Marc H. Shomer, and Arthur W. Toga. “Refractory Periods Observed by Intrinsic Signal and Fluorescent Dye Imaging.” Journal of Neurophysiology 80, no. 3 (1998): 1522–32.

Casanova, Manuel F., Daniel Buxhoeveden, and Juan Gomez. “Disruption in the Inhibitory Architecture of the Cell Minicolumn: Implications for Autisim.” The Neuroscientist 9, no. 6 (2003): 496–507.

Casanova, Manuel F., Daniel P. Buxhoeveden, Andrew E. Switala, and Emil Roy. “Minicolumnar Pathology in Autism.” Neurology 58, no. 3 (2002): 428–32.

Castelli, Fulvia, Chris Frith, Francesca Happé, and Uta Frith. “Autism, Asperger Syndrome and Brain Mechanisms for the Attribution of Mental States to Animated Shapes.” Brain 125, no. 8 (2002): 1839–49.

Celebrini, Simona, Simon Thorpe, Yves Trotter, and Michel Imbert. “Dynamics of Orientation Coding in Area V1 of the Awake Primate.” Visual Neuroscience 10, no. 05 (1993): 811–25.

Chao, Hsiao-Tuan, Hongmei Chen, Rodney C. Samaco, Mingshan Xue, Maria Chahrour, Jong Yoo, Jeffrey L. Neul, Shiaoching Gong, Hui-Chen Lu, and Nathaniel Heintz. “Dysfunction in GABA Signalling Mediates Autism-like Stereotypies and Rett Syndrome Phenotypes.” Nature 468, no. 7321 (2010): 263–69.

Chen, Li M., Robert M. Friedman, and Anna W. Roe. “Optical Imaging of a Tactile Illusion in Area 3b of the Primary Somatosensory Cortex.” Science 302, no. 5646 (2003): 881–85.

Chen, Li M., Gregory H. Turner, Robert M. Friedman, Na Zhang, John C. Gore, Anna W. Roe, and Malcolm J. Avison. “High-Resolution Maps of Real and Illusory Tactile Activation in Primary Somatosensory Cortex in Individual Monkeys with Functional Magnetic Resonance Imaging and Optical Imaging.” The Journal of Neuroscience 27, no. 34 (2007): 9181–91.

Chen, Li Min, Robert Mark Friedman, and Anna Wang Roe. “Optical Imaging of Digit Topography in Individual Awake and Anesthetized Squirrel Monkeys.” Experimental Brain Research 196, no. 3 (July 1, 2009): 393–401. doi:10.1007/s00221-009-1861-y.

———. “Optical Imaging of SI Topography in Anesthetized and Awake Squirrel Monkeys.” The Journal of Neuroscience 25, no. 33 (2005): 7648–59.

Cherkassky, Vladimir L., Rajesh K. Kana, Timothy A. Keller, and Marcel Adam Just. “Functional Connectivity in a Baseline Resting-State Network in Autism.” Neuroreport 17 (2006): 1687–90.

Chiu, J. “Characterization of Minicolumnar Patterns in SI Cortex [Dissertation].” Chapel Hill: University of North Carolina at Chapel Hill, 2006.

Chiu, Joannellyn S., Mark Tommerdahl, Barry L. Whitsel, and Oleg V. Favorov. “Stimulus-Dependent Spatial Patterns of Response in SI Cortex.” BMC Neuroscience 6, no. 1 (2005): 47.

Chubbuck, J. G. “Small Motion Biological Stimulator.” Johns Hopkins APL Tech Digest 5 (1966): 18–23.

Clausen, Johs. “An Evaluation of Experimental Methods of Time Judgment.” Journal of Experimental Psychology 40, no. 6 (1950): 756.

Connor, C. E., S. S. Hsiao, J. R. Phillips, and K. O. Johnson. “Tactile Roughness: Neural Codes That Account for Psychophysical Magnitude Estimates.” The Journal of Neuroscience 10, no. 12 (1990): 3823–36.

Cornsweet, T. N., and H. M. Pinsker. “Luminance Discrimination of Brief Flashes under Various Conditions of Adaptation.” The Journal of Physiology 176, no. 2 (January 1965): 294–310.

Cornsweet, Tom N. “The Staircase-Method in Psychophysics.” The American Journal of Psychology, 1962, 485–91.

Craig, James C. “Vibrotactile Difference Thresholds for Intensity and the Effect of a Masking Stimulus.” Perception & Psychophysics 15, no. 1 (1974): 123–27.

Cruikshank, Scott J., Timothy J. Lewis, and Barry W. Connors. “Synaptic Basis for Intense Thalamocortical Activation of Feedforward Inhibitory Cells in Neocortex.” Nature Neuroscience 10, no. 4 (2007): 462–68.

Danby, Claire S., and Lynette J. Margesson. “Approach to the Diagnosis and Treatment of Vulvar Pain.” Dermatologic Therapy 23, no. 5 (2010): 485–504.

Das, A., and C. D. Gilbert. “Receptive Field Expansion in Adult Visual Cortex Is Linked to Dynamic Changes in Strength of Cortical Connections.” Journal of Neurophysiology 74, no. 2 (1995): 779–92.

DeAngelis, Gregory C., Akiyuki Anzai, Izumi Ohzawa, and Ralph D. Freeman. “Receptive Field Structure in the Visual Cortex: Does Selective Stimulation Induce Plasticity?” Proceedings of the National Academy of Sciences 92, no. 21 (1995): 9682–86.

Deary, I. J., M. E. Bastin, A. Pattie, J. D. Clayden, L. J. Whalley, J. M. Starr, and J. M. Wardlaw. “White Matter Integrity and Cognition in Childhood and Old Age.” Neurology 66, no. 4 (2006): 505–12.

Deddens, Lisette H., Geralda A.F. Van Tilborg, Willem J.M. Mulder, Helga E. De Vries, and Rick M. Dijkhuizen. “Imaging Neuroinflammation after Stroke: Current Status of Cellular and Molecular MRI Strategies.” Cerebrovascular Diseases 33, no. 4 (2012): 392–402. doi: 10.1159/000336116.

Delemos, Kimberly A., and Mark Hollins. “Adaptation-Induced Enhancement of Vibrotactile Amplitude Discrimination: The Role of Adapting Frequency.” The Journal of the Acoustical Society of America 99, no. 1 (1996): 508–16.

Dennis, R. G., and P. E. Kosnik. “Mesenchymal Cell Culture: Instrumentation and Methods for Evaluating Engineered Muscle.” Methods in Tissue Engineering, 2002, 307–16.

Densen, Michelle E. “Time Perception and Schizophrenia.” Perceptual and Motor Skills 44, no. 2 (1977): 436–38.

Derdikman, Dori, Rina Hildesheim, Ehud Ahissar, Amos Arieli, and Amiram Grinvald. “Imaging Spatiotemporal Dynamics of Surround Inhibition in the Barrels Somatosensory Cortex.” The Journal of Neuroscience 23, no. 8 (2003): 3100–3105.

Dinse, H. R. O., and K. Krüger. “Contribution of Area 19 to the Foreground-Background-Interaction of the Cat: An Analysis Based on Single Cell Recordings and Behavioural Experiments.” Experimental Brain Research 82, no. 1 (1990): 107–12.

Dinse, Hubert R. “Treating the Aging Brain: Cortical Reorganization and Behavior.” In Re-Engineering of the Damaged Brain and Spinal Cord, 79–84. Springer, 2005. http://link.springer.com/chapter/10.1007/3-211-27577-0_12.

Dinse, Hubert R., Nadine Kleibel, Tobias Kalisch, Patrick Ragert, Claudia Wilimzig, and Martin Tegenthoff. “Tactile Coactivation Resets Age-Related Decline of Human Tactile Discrimination.” Annals of Neurology 60, no. 1 (2006): 88–94.

Douglas, C. “Human Discrimination of Auditory Duration.” Journal of the Acoustical Society of America 34, no. 5 (1962): 582–93. doi:10.1121/1.1918172.

Douglas, Rodney J., Christof Koch, Misha Mahowald, K. A. Martin, and Humbert H. Suarez. “Recurrent Excitation in Neocortical Circuits.” Science 269, no. 5226 (1995): 981–85.

Driscoll, I., C. Davatzikos, Y. An, X. Wu, D. Shen, M. Kraut, and S. M. Resnick. “Longitudinal Pattern of Regional Brain Volume Change Differentiates Normal Aging from MCI.” Neurology 72, no. 22 (2009): 1906–13.

Ec, Hirsch, Hunot S, Damier P, and Faucheux B. “Glial Cells and Inflammation in Parkinson’s Disease: A Role in Neurodegeneration?” Annals of Neurology 44, no. 3 Suppl 1 (September 1998): S115–20.

Edelman, Gerald M., and Vernon B. Mountcastle. The Mindful Brain: Cortical Organization and the Group-Selective Theory of Higher Brain Function. Massachusetts Inst of Technology Pr, 1978. http://psycnet.apa.org/psycinfo/1979-25355-000.

Ehrlé, Nathalie, and Séverine Samson. “Auditory Discrimination of Anisochrony: Influence of the Tempo and Musical Backgrounds of Listeners.” Brain and Cognition 58, no. 1. Neuropsychology of Timing and Time Perception (June 2005): 133–47. doi:10.1016/j.bandc.2004.09.014.

Ekblom, A, and P Hansson. “Effects of Conditioning Vibratory Stimulation on Pain Threshold of the Human Tooth.” Acta Physiologica Scandinavica 114, no. 4 (April 1982): 601–4. doi:10.1111/j.1748-1716.1982.tb07030.x.

Ekblom, Anders, and Per Hansson. “Extrasegmental Transcutaneous Electrical Nerve Stimulation and Mechanical Vibratory Stimulation as Compared to Placebo for the Relief of Acute Oro-Facial Pain.” Pain 23, no. 3 (1985): 223–29.

Favorov, Oleg V., and Mathew E. Diamond. “Demonstration of Discrete Place-Defined Columns—segregates—in the Cat SI.” Journal of Comparative Neurology 298, no. 1 (1990): 97–112.

Favorov, Oleg V., and Douglas G. Kelly. “Local Receptive Field Diversity within Cortical Neuronal Populations.” In Somesthesis and the Neurobiology of the Somatosensory Cortex, edited by Prof O. Franzén, Prof R. Johansson, and Prof L. Terenius, 395–408. Advances in Life Sciences. Birkhäuser Basel, 1996. http://link.springer.com/chapter/10.1007/978-3-0348-9016-8_33.

———. “Minicolumnar Organization within Somatosensory Cortical Segregates: I. Development of Afferent Connections.” Cerebral Cortex 4, no. 4 (1994): 408–27.

Favorov, Oleg V., and Olcay Kursun. “Neocortical Layer 4 as a Pluripotent Function Linearizer.” Journal of Neurophysiology 105, no. 3 (2011): 1342–60.

Favorov, Oleg, and Barry L. Whitsel. “Spatial Organization of the Peripheral Input to Area 1 Cell Columns. I. The Detection of ‘segregates.’” Brain Research Reviews 13, no. 1 (1988): 25–42.

Fjell, Anders M., Kristine B. Walhovd, Christine Fennema-Notestine, Linda K. McEvoy, Donald J. Hagler, Dominic Holland, James B. Brewer, and Anders M. Dale. “One-Year Brain Atrophy Evident in Healthy Aging.” The Journal of Neuroscience 29, no. 48 (2009): 15223–31.

Foeller, Elisabeth, Tansu Celikel, and Daniel E. Feldman. “Inhibitory Sharpening of Receptive Fields Contributes to Whisker Map Plasticity in Rat Somatosensory Cortex.” Journal of Neurophysiology 94, no. 6 (2005): 4387–4400.

Folger, Stephen E., Vinay Tannan, Zheng Zhang, Jameson K. Holden, and Mark Tommerdahl. “Effects of the N-Methyl-D-Aspartate Receptor Antagonist Dextromethorphan on Vibrotactile Adaptation.” BMC Neuroscience 9, no. 1 (2008): 87.

Fozard, James L., Max Vercruyssen, Sara L. Reynolds, P. A. Hancock, and Reginald E. Quilter. “Age Differences and Changes in Reaction Time: The Baltimore Longitudinal Study of Aging.” Journal of Gerontology 49, no. 4 (1994): P179–P189.

Francisco, E., J. Holden, Z. Zhang, O. Favorov, and M. Tommerdahl. “Rate Dependency of Vibrotactile Stimulus Modulation.” Brain Research 1415 (2011): 76–83.

Francisco, E., V. Tannan, Z. Zhang, J. Holden, and M. Tommerdahl. “Vibrotactile Amplitude Discrimination Capacity Parallels Magnitude Changes in Somatosensory Cortex and Follows Weber’s Law.” Experimental Brain Research 191, no. 1 (2008): 49–56.

Friedman, Robert M., Li Min Chen, and Anna W. Roe. “Responses of Areas 3b and 1 in Anesthetized Squirrel.” J Neurophysiol 100 (2008): 3185–96.

Gescheider, G A, J M Thorpe, J Goodarz, and S J Bolanowski. “The Effects of Skin Temperature on the Detection and Discrimination of Tactile Stimulation.” Somatosensory & Motor Research 14, no. 3 (1997): 181–88.

Gescheider, G. A., S. J. Bolanowski, and R. T. Verrillo. “Some Characteristics of Tactile Channels.” Behavioural Brain Research 148, no. 1 (2004): 35–40.

Gescheider, G. A., R. R. Edwards, E. A. Lackner, S. J. Bolanowski, and R. T. Verrillo. “The Effects of Aging on Information-Processing Channels in the Sense of Touch: III. Differential Sensitivity to Changes in Stimulus Intensity.” Somatosensory & Motor Research 13, no. 1 (1996): 73–80.

Gescheider, G. A., K. E. Santoro, James C. Makous, and S. J. Bolanowski. “Vibrotactile Forward Masking: Effects of the Amplitude and Duration of the Masking Stimulus.” The Journal of the Acoustical Society of America 98, no. 6 (1995): 3188–94.

Gescheider, George A., Stanley J. Bolanowski Jr, Ronald T. Verrillo, Dean J. Arpajian, and Timothy F. Ryan. “Vibrotactile Intensity Discrimination Measured by Three Methods.” The Journal of the Acoustical Society of America 87, no. 1 (1990): 330–38.

Gescheider, George A., S. J. Bolanowski, K. L. Hall, K. E. Hoffman, and R. T. Verrillo. “The Effects of Aging on Information-Processing Channels in the Sense of Touch: I. Absolute Sensitivity.” Somatosensory & Motor Research 11, no. 4 (1994): 345–57.

Gescheider, George A., Robert D. Frisina, and Ronald T. Verrillo. “Selective Adaptation of Vibrotactile Thresholds.” Sensory Processes, 1979. http://psycnet.apa.org/psycinfo/1981-02563-001.

Gescheider, George A., Jozef J. Zwislocki, and Alicia Rasmussen. “Effects of Stimulus Duration on the Amplitude Difference Limen for Vibrotaction.” The Journal of the Acoustical Society of America 100, no. 4 (1996): 2312–19.

Gescheider, Marian E. Berryhill. “Vibrotactile Temporal Summation: Probability Summation or Neural Integration?” Somatosensory & Motor Research 16, no. 3 (1999): 229–42.

Getty, David J. “Discrimination of Short Temporal Intervals: A Comparison of Two Models.” Perception & Psychophysics 18, no. 1 (January 1, 1975): 1–8. doi:10.3758/BF03199358.

Giesecke, Jutta, Barbara D. Reed, Hope K. Haefner, Thorsten Giesecke, Daniel J. Clauw, and Richard H. Gracely. “Quantitative Sensory Testing in Vulvodynia Patients and Increased Peripheral Pressure Pain Sensitivity.” Obstetrics & Gynecology 104, no. 1 (2004): 126–33.

Giovanni, Simone Di, Vilen Movsesyan, Farid Ahmed, Ibolja Cernak, Sergio Schinelli, Bogdan Stoica, and Alan I. Faden. “Cell Cycle Inhibition Provides Neuroprotection and Reduces Glial Proliferation and Scar Formation after Traumatic Brain Injury.” Proceedings of the National Academy of Sciences of the United States of America 102, no. 23 (June 7, 2005): 8333–38. doi:10.1073/pnas.0500989102.

Giulietti, Annapaula, Lut Overbergh, Dirk Valckx, Brigitte Decallonne, Roger Bouillon, and Chantal Mathieu. “An Overview of Real-Time Quantitative PCR: Applications to Quantify Cytokine Gene Expression.” Methods 25, no. 4 (December 2001): 386–401. doi:10.1006/meth.2001.1261.

Goble, Alan K., Amy A. Collins, and Roger W. Cholewiak. “Vibrotactile Threshold in Young and Old Observers: The Effects of Spatial Summation and the Presence of a Rigid Surround.” The Journal of the Acoustical Society of America 99, no. 4 (1996): 2256–69.

Goble, Alan K., and Mark Hollins. “Vibrotactile Adaptation Enhances Amplitude Discrimination.” The Journal of the Acoustical Society of America 93, no. 1 (1993): 418–24.

———. “Vibrotactile Adaptation Enhances Frequency Discrimination.” The Journal of the Acoustical Society of America 96, no. 2 (August 1, 1994): 771–80. doi:10.1121/1.410314.

Goldstein, Andrew T., Stanley C. Marinoff, and Hope K. Haefner. “Vulvodynia: Strategies for Treatment.” Clinical Obstetrics and Gynecology 48, no. 4 (2005): 769–85.

Goldstein, E. Sensation and Perception. Cengage Learning, 2013. http://books.google.com/books?hl=en&lr=&id=fZnklywcQLwC&oi=fnd&pg=PP1&dq=Sensation+and+perception.++Goldstein+2007&ots=PfLfaVrquP&sig=dpNXE2YMn3VQxCbrCCMxHe9PYwU.

Gorus, Ellen, Rudi De Raedt, Margareta Lambert, Jean-Claude Lemper, and Tony Mets. “Reaction Times and Performance Variability in Normal Aging, Mild Cognitive Impairment, and Alzheimer’s Disease.” Journal of Geriatric Psychiatry and Neurology 21, no. 3 (2008): 204–18.

Green, Barry G. “The Effect of Skin Temperature on Vibrotactile Sensitivity.” Perception & Psychophysics 21, no. 3 (1977): 243–48.

Green, Barry G., Susan J. Lederman, and Joseph C. Stevens. “The Effect of Skin Temperature on the Perception of Roughness.” Sensory Processes 3 (1979): 327–33.

Greenwood, P. M. “Functional Plasticity in Cognitive Aging: Review and Hypothesis.” Neuropsychology 21, no. 6 (2007): 657.

Greenwood, Pamela M., and Raja Parasuraman. “Neuronal and Cognitive Plasticity: A Neurocognitive Framework for Ameliorating Cognitive Aging.” Frontiers in Aging Neuroscience 2 (2010). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2999838/.

Grinvald, A. “Real-Time Optical Mapping of Neuronal Activity: From Single Growth Cones to the Intact Mammalian Brain.” Annual Review of Neuroscience 8, no. 1 (1985): 263–305.

Grinvald, Amiram, Ron D. Frostig, Ralph M. Siegel, and Eyal Bartfeld. “High-Resolution Optical Imaging of Functional Brain Architecture in the Awake Monkey.” Proceedings of the National Academy of Sciences 88, no. 24 (1991): 11559–63.

Grondin, Simon. “Unequal Weber Fractions for the Categorization of Brief Temporal Intervals.” Attention, Perception, & Psychophysics 72, no. 5 (July 1, 2010): 1422–30. doi:10.3758/APP.72.5.1422.

Grondin, Simon, Bastien Ouellet, and Marie-Ève Roussel. “About Optimal Timing and Stability of Weber Fraction for Duration Discrimination.” Acoustical Science and Technology 22, no. 5 (2001): 370–72.

Güçlü, Burak, and Stanley J. Bolanowski. “Modeling Population Responses of Rapidly-Adapting Mechanoreceptive Fibers.” Journal of Computational Neuroscience 12, no. 3 (2002): 201–18.

Güçlü, Burak, Emre Sevinc, and Resit Canbeyli. “Duration Discrimination by Musicians and Nonmusicians.” Psychological Reports 108, no. 3 (June 2011): 675–87.

Güçlü, Burak, Canan Tanidir, Nahit Motavalli Mukaddes, and Fatih Ünal. “Tactile Sensitivity of Normal and Autistic Children.” Somatosensory & Motor Research 24, no. 1–2 (2007): 21–33.

Gunning-Dixon, Faith M., Adam M. Brickman, Janice C. Cheng, and George S. Alexopoulos. “Aging of Cerebral White Matter: A Review of MRI Findings.” International Journal of Geriatric Psychiatry 24, no. 2 (2009): 109–17.

Gunning-Dixon, Faith M., and Naftali Raz. “The Cognitive Correlates of White Matter Abnormalities in Normal Aging: A Quantitative Review.” Neuropsychology 14, no. 2 (2000): 224.

Gunter, Jennifer. “Vulvodynia: New Thoughts on a Devastating Condition.” Obstetrical & Gynecological Survey 62, no. 12 (2007): 812–19.

Häger-Ross, Charlotte, and Marc H. Schieber. “Quantifying the Independence of Human Finger Movements: Comparisons of Digits, Hands, and Movement Frequencies.” The Journal of Neuroscience 20, no. 22 (2000): 8542–50.

Haist, Frank, Maha Adamo, Marissa Westerfield, Eric Courchesne, and Jeanne Townsend. “The Functional Neuroanatomy of Spatial Attention in Autism Spectrum Disorder.” Developmental Neuropsychology 27, no. 3 (2005): 425–58.

Halpern, Andrea R., and Christopher J. Darwin. “Duration Discrimination in a Series of Rhythmic Events.” Perception & Psychophysics 31, no. 1 (January 1, 1982): 86–89. doi:10.3758/BF03206204.

Hanna, Thomas E., Susanne M. von Gierke, and David M. Green. “Detection and Intensity Discrimination of a Sinusoid.” The Journal of the Acoustical Society of America 80, no. 5 (November 1, 1986): 1335–40. doi:10.1121/1.394385.

Hardan, Antonio Y., Ragy R. Girgis, Jason Adams, Andrew R. Gilbert, Matcheri S. Keshavan, and Nancy J. Minshew. “Abnormal Brain Size Effect on the Thalamus in Autism.” Psychiatry Research: Neuroimaging 147, no. 2 (2006): 145–51.

Hardan, Antonio Y., Ragy R. Girgis, Jason Adams, Andrew R. Gilbert, Nadine M. Melhem, Matcheri S. Keshavan, and Nancy J. Minshew. “Brief Report: Abnormal Association between the Thalamus and Brain Size in Asperger’s Disorder.” Journal of Autism and Developmental Disorders 38, no. 2 (2008): 390–94.

Harlow, Bernard L., Lauren A. Wise, and Elizabeth G. Stewart. “Prevalence and Predictors of Chronic Lower Genital Tract Discomfort.” American Journal of Obstetrics and Gynecology 185, no. 3 (2001): 545–50.

Harper, Daniel E, and Mark Hollins. “Is Touch Gating due to Sensory or Cognitive Interference?” Pain 153, no. 5 (May 2012): 1082–90. doi:10.1016/j.pain.2012.02.011.

Henry, Franklin M. “Discrimination of the Duration of a Sound.” Journal of Experimental Psychology 38, no. 6 (1948): 734–43. doi:10.1037/h0058552.

Herbert, M. R., D. A. Ziegler, C. K. Deutsch, L. M. O’brien, N. Lange, A. Bakardjiev, J. Hodgson, K. T. Adrien, S. Steele, and N. Makris. “Dissociations of Cerebral Cortex, Subcortical and Cerebral White Matter Volumes in Autistic Boys.” Brain 126, no. 5 (2003): 1182–92.

Hilbig, Heidegard, Hans-Jürgen Bidmon, Susanne Steingrüber, Heinrich Reinke, and Hubert R. Dinse. “Enriched Environmental Conditions Reverse Age-Dependent Gliosis and Losses of Neurofilaments and Extracellular Matrix Components but Do Not Alter Lipofuscin Accumulation in the Hindlimb Area of the Aging Rat Brain.” Journal of Chemical Neuroanatomy 23, no. 3 (2002): 199–209.

Hirsch, E. C., T. Breidert, E. Rousselet, S. Hunot, A. Hartmann, and P. P. Michel. “The Role of Glial Reaction and Inflammation in Parkinson’s Disease.” Annals of the New York Academy of Sciences 991, no. 1 (June 1, 2003): 214–28. doi:10.1111/j.1749-6632.2003.tb07478.x.

Holden, Jameson K., Eric M. Francisco, Zheng Zhang, Cristina Baric, and Mark Tommerdahl. “An Undergraduate Laboratory Exercise to Study Weber’s Law.” Journal of Undergraduate Neuroscience Education 9, no. 2 (2011): A71.

Hollander, Eric, Evdokia Anagnostou, William Chaplin, Katherine Esposito, M. Mehmet Haznedar, Elizabeth Licalzi, Stacey Wasserman, Latha Soorya, and Monte Buchsbaum. “Striatal Volume on Magnetic Resonance Imaging and Repetitive Behaviors in Autism.” Biological Psychiatry 58, no. 3 (2005): 226–32.

Hollins, Mark, Alan K. Goble, Barry L. Whitsel, and Mark Tommerdahl. “Time Course and Action Spectrum of Vibrotactile Adaptation.” Somatosensory & Motor Research 7, no. 2 (1990): 205–21.

Hollins, Mark, and Asgeir Sigurdsson. “Vibrotactile Amplitude and Frequency Discrimination in Temporomandibular Disorders.” Pain 75, no. 1 (1998): 59–67.

Hollins, Mark, Asgeir Sigurdsson, Lori Fillingim, and Alan K. Goble. “Vibrotactile Threshold Is Elevated in Temporomandibular Disorders.” Pain 67, no. 1 (1996): 89–96.

Hultsch, David F., Stuart WS MacDonald, and Roger A. Dixon. “Variability in Reaction Time Performance of Younger and Older Adults.” The Journals of Gerontology Series B: Psychological Sciences and Social Sciences 57, no. 2 (2002): P101–P115.

Hultsch, David F., Stuart WS MacDonald, Michael A. Hunter, Judi Levy-Bencheton, and Esther Strauss. “Intraindividual Variability in Cognitive Performance in Older Adults: Comparison of Adults with Mild Dementia, Adults with Arthritis, and Healthy Adults.” Neuropsychology 14, no. 4 (2000): 588.

Hussman, John P. “Letters to the Editor: Suppressed GABAergic Inhibition as a Common Factor in Suspected Etiologies of Autism.” Journal of Autism and Developmental Disorders 31, no. 2 (2001): 247–48.

Iguchi, Yoshinobu, Yoko Hoshi, Masato Tanosaki, Masato Taira, and Isao Hashimoto. “Selective Attention Regulates Spatial and Intensity Information Processing in the Human Primary Somatosensory Cortex.” Neuroreport 13, no. 17 (2002): 2335–39.

J. Bolanowski, GA Gescheider. “The Effects of Heat-Induced Pain on the Detectability, Discriminability, and Sensation Magnitude of Vibrotactile Stimuli.” Somatosensory & Motor Research 18, no. 1 (2001): 5–9.

J. Bolanowski, Lisa M. Maxfield. “The Effects of Stimulus Location on the Gating of Touch by Heat-and Cold-Induced Pain.” Somatosensory & Motor Research 17, no. 2 (2000): 195–204.

Johnson, James E., and Thomas P. Petzel. “Temporal Orientation and Time Estimation in Chronic Schizophrenics.” Journal of Clinical Psychology, 1971. http://psycnet.apa.org/psycinfo/1971-27201-001.

Johnson, K. O. “Reconstruction of Population Response to a Vibratory Stimulus in Quickly Adapting Mechanoreceptive Afferent Fiber Population Innervating Glabrous Skin of the Monkey.” Journal of Neurophysiology 37, no. 1 (1974): 48–72.

Johnson, Kenneth O., Steven S. Hsiao, and Takashi Yoshioka. “Book Review: Neural Coding and the Basic Law of Psychophysics.” The Neuroscientist 8, no. 2 (2002): 111–21.

Jones, E. G. “Anatomy of Cerebral Cortex: Columnar Input-Output Organization.” The Organization of the Cerebral Cortex, 1981, 199–235.

———. “Varieties and Distribution of Non-Pyramidal Cells in the Somatic Sensory Cortex of the Squirrel Monkey.” Journal of Comparative Neurology 160, no. 2 (1975): 205–67.

Juliano, Sharon L., Isabelle Dusart, and Marc Peschanski. “Somatic Activation of Thalamic Neurons Transplanted into Lesioned Somatosensory Thalamus.” Brain Research 478, no. 2 (1989): 356–60.

Just, Marcel Adam, Vladimir L. Cherkassky, Timothy A. Keller, Rajesh K. Kana, and Nancy J. Minshew. “Functional and Anatomical Cortical Underconnectivity in Autism: Evidence from an FMRI Study of an Executive Function Task and Corpus Callosum Morphometry.” Cerebral Cortex 17, no. 4 (2007): 951–61.

Kalisch, Tobias, Patrick Ragert, Peter Schwenkreis, Hubert R. Dinse, and Martin Tegenthoff. “Impaired Tactile Acuity in Old Age Is Accompanied by Enlarged Hand Representations in Somatosensory Cortex.” Cerebral Cortex 19, no. 7 (2009): 1530–38.

Kalisch, Tobias, Martin Tegenthoff, and Hubert R. Dinse. “Improvement of Sensorimotor Functions in Old Age by Passive Sensory Stimulation.” Clinical Interventions in Aging 3, no. 4 (2008): 673.

Kana, Rajesh K., Timothy A. Keller, Vladimir L. Cherkassky, Nancy J. Minshew, and Marcel Adam Just. “Sentence Comprehension in Autism: Thinking in Pictures with Decreased Functional Connectivity.” Brain 129, no. 9 (2006): 2484–93.

Kanner, Leo. “Autistic Disturbances of Affective Contact.” Nervous Child 2, no. 3 (1943): 217–50.

Kattenstroth, Jan-Christoph, Izabella Kolankowska, Tobias Kalisch, and Hubert R. Dinse. “Superior Sensory, Motor, and Cognitive Performance in Elderly Individuals with Multi-Year Dancing Activities.” Frontiers in Aging Neuroscience 2 (2010). http://www.ncbi.nlm.nih.gov/pmc/articles/pmc2917240/.

Kauppila, Timo, Parvaneh Mohammadian, Jesper Nielsen, Ole K. Andersen, and Lars Arendt-Nielsen. “Capsaicin-Induced Impairment of Tactile Spatial Discrimination Ability in Man: Indirect Evidence for Increased Receptive Fields in Human Nervous System.” Brain Research 797, no. 2 (1998): 361–67.

Kenshalo, Dan R. “Somesthetic Sensitivity in Young and Elderly Humans.” Journal of Gerontology 41, no. 6 (1986): 732–42.

Kenton, B., B. L. Crue, and E. J. A. Carregal. “Quantitative Measures of the Thermal Reactivity of Cutaneous Mechanoreceptors.” Neuroscience Letters 1, no. 6 (1975): 321–26.

Kenton, Bernard, Benjamin L. Crue, and Enrique JA Carregal. “The Role of Cutaneous Mechanoreceptors in Thermal Sensation and Pain.” Pain 2, no. 2 (1976): 119–40.

Khatri, Vivek, Jed A. Hartings, and Daniel J. Simons. “Adaptation in Thalamic Barreloid and Cortical Barrel Neurons to Periodic Whisker Deflections Varying in Frequency and Velocity.” Journal of Neurophysiology 92, no. 6 (2004): 3244–54.

Khatri, Vivek, and Daniel J. Simons. “Angularly Nonspecific Response Suppression in Rat Barrel Cortex.” Cerebral Cortex 17, no. 3 (2007): 599–609.

Kohn, A., C. Metz, M. Quibrera, M. A. Tommerdahl, and B. L. Whitsel. “Functional Neocortical Microcircuitry Demonstrated with Intrinsic Signal Optical Imaging< I> in Vitro</i>.” Neuroscience 95, no. 1 (1999): 51–62.

Kohn, Adam. “Visual Adaptation: Physiology, Mechanisms, and Functional Benefits.” Journal of Neurophysiology 97, no. 5 (2007): 3155–64.

Kohn, Adam, and Barry L. Whitsel. “Sensory Cortical Dynamics.” Behavioural Brain Research 135, no. 1 (2002): 119–26.

Kosek, Eva, Jan Ekholm, and Per Hansson. “Modulation of Pressure Pain Thresholds during and Following Isometric Contraction in Patients with Fibromyalgia and in Healthy Controls.” Pain 64, no. 3 (1996): 415–23.

Koshino, Hideya, Patricia A. Carpenter, Nancy J. Minshew, Vladimir L. Cherkassky, Timothy A. Keller, and Marcel Adam Just. “Functional Connectivity in an fMRI Working Memory Task in High-Functioning Autism.” Neuroimage 24, no. 3 (2005): 810–21.

Kristofferson, A. B., and L. G. Allan. “Successiveness and Duration Discrimination.” Attention and Performance IV, 1973, 737–49.

Kwakye, Leslie D., Jennifer H. Foss-Feig, Carissa J. Cascio, Wendy L. Stone, and Mark T. Wallace. “Altered Auditory and Multisensory Temporal Processing in Autism Spectrum Disorders.” Frontiers in Integrative Neuroscience 4 (January 5, 2011). doi:10.3389/fnint.2010.00129.

L. Whitsel, EF Kelly. “Stability of Rapidly Adapting Afferent Entrainment vs Responsivity.” Somatosensory & Motor Research 17, no. 1 (2000): 13–31.

Laasonen, Marja, Jaana Tomma-Halme, Pekka Lahti-Nuuttila, Elisabet Service, and Veijo Virsu. “Rate of Information Segregation in Developmentally Dyslexic Children.” Brain and Language 75, no. 1 (2000): 66–81.

Lacruz, F., J. Artieda, M. A. Pastor, and J. A. Obeso. “The Anatomical Basis of Somaesthetic Temporal Discrimination in Humans.” Journal of Neurology, Neurosurgery & Psychiatry 54, no. 12 (1991): 1077–81.

LaMotte, R. H., and V. B. Mountcastle. “Capacities of Humans and Monkeys to Discriminate Vibratory Stimuli of Different Frequency and Amplitude: A Correlation between Neural Events and Psychological Measurements.” Journal of Neurophysiology 38, no. 3 (May 1, 1975): 539–59.

Langen, Marieke, Sarah Durston, Wouter G. Staal, Saskia JMC Palmen, and Herman van Engeland. “Caudate Nucleus Is Enlarged in High-Functioning Medication-Naive Subjects with Autism.” Biological Psychiatry 62, no. 3 (2007): 262–66.

Lapid, Einat, Rolf Ulrich, and Thomas Rammsayer. “On Estimating the Difference Limen in Duration Discrimination Tasks: A Comparison of the 2AFC and the Reminder Task.” Perception & Psychophysics 70, no. 2 (February 1, 2008): 291–305. doi:10.3758/PP.70.2.291.

Laskin, S. E., and W. A. Spencer. “Cutaneous Masking. I. Psychophysical Observations on Interactions of Multipoint Stimuli in Man.” Journal of Neurophysiology 42, no. 4 (1979): 1048–60.

Lautner, Ronald, Niklas Mattsson, Sch&#246, Michael Ll, Kristin Augutis, Kaj Blennow, Bob Olsson, and Henrik Zetterberg. “Biomarkers for Microglial Activation in Alzheimer's Disease.” International Journal of Alzheimer’s Disease 2011 (November 1, 2011). doi:10.4061/2011/939426.

Lavoie, Philippe, and Simon Grondin. “Information Processing Limitations as Revealed by Temporal Discrimination.” Brain and Cognition 54, no. 3 (April 2004): 198–200. doi:10.1016/j.bandc.2004.02.039.

Le Couteur, A., C. Lord, and M. Rutter. “The Autism Diagnostic interview–Revised (ADI-R).” Los Angeles, CA: Western Psychological Services, 2003.

Lee, Chang-Joong, and Barry L. Whitsel. “Mechanisms Underlying Somatosensory Cortical Dynamics: I. in Vivo Studies.” Cerebral Cortex 2, no. 2 (1992): 81–106.

Lee, Chang-Joong, Barry L. Whitsel, and Mark Tommerdahl. “Mechanisms Underlying Somatosensory Cortical Dynamics: II. In Vitro Studies.” Cerebral Cortex 2, no. 2 (1992): 107–33.

Lee, Jaekwang, M Tommerdahl, O V Favorov, and B L Whitsel. “Optically Recorded Response of the Superficial Dorsal Horn: Dissociation from Neuronal Activity, Sensitivity to Formalin-Evoked Skin Nociceptor Activation.” Journal of Neurophysiology 94, no. 1 (July 2005): 852–64. doi:10.1152/jn.00976.2004.

Lee, Jee Eun, Erin D. Bigler, Andrew L. Alexander, Mariana Lazar, Molly B. DuBray, Moo K. Chung, Michael Johnson, Jubel Morgan, Judith N. Miller, and William M. McMahon. “Diffusion Tensor Imaging of White Matter in the Superior Temporal Gyrus and Temporal Stem in Autism.” Neuroscience Letters 424, no. 2 (2007): 127–32.

Lhamon, William T., and Sanford Goldstone. “The Time Sense: Estimation of One Second Durations by Schizophrenic Patients.” Archives of Neurology and Psychiatry 76, no. 6 (1956): 625.

Li, Shu-Chen, and Hubert R. Dinse. “Aging of the Brain, Sensorimotor, and Cognitive Processes.” Neuroscience & Biobehavioral Reviews 26, no. 7 (2002): 729–32.

Lin, Yea-Huey, Song-Chou Hsieh, Chi-Chao Chao, Yang-Chyuan Chang, and Sung-Tsang Hsieh. “Influence of Aging on Thermal and Vibratory Thresholds of Quantitative Sensory Testing.” Journal of the Peripheral Nervous System 10, no. 3 (2005): 269–81.

Llinas, R., and M. Sugimori. “Electrophysiological Properties of in Vitro Purkinje Cell Dendrites in Mammalian Cerebellar Slices.” The Journal of Physiology 305, no. 1 (1980): 197–213.

Lord, Catherine, Susan Risi, Linda Lambrecht, Edwin H. Cook Jr, Bennett L. Leventhal, Pamela C. DiLavore, Andrew Pickles, and Michael Rutter. “The Autism Diagnostic Observation Schedule—Generic: A Standard Measure of Social and Communication Deficits Associated with the Spectrum of Autism.” Journal of Autism and Developmental Disorders 30, no. 3 (2000): 205–23.

Lund, J. S. “Spiny Stellate Neurons.” Cerebral Cortex 1 (1984): 255–308.

Lundeberg, T. “A Comparative Study of the Pain Alleviating Effect of Vibratory Stimulation, Transcutaneous Electrical Nerve Stimulation, Electroacupuncture and Placebo.” The American Journal of Chinese Medicine 12, no. 01n04 (1984): 72–79.

———. “Electrical Stimulation for the Relief of Pain.” Physiotherapy 70, no. 3 (1984): 98–100.

———. “Long-Term Results of Vibratory Stimulation as a Pain Relieving Measure for Chronic Pain.” Pain 20, no. 1 (1984): 13–23.

———. “The Pain Suppressive Effect of Vibratory Stimulation and Transcutaneous Electrical Nerve Stimulation (TENS) as Compared to Aspirin.” Brain Research 294, no. 2 (1984): 201–9.

———. “Vibratory Stimulation for the Alleviation of Pain.” The American Journal of Chinese Medicine 12, no. 01n04 (1984): 60–70.

Madden, David J., Ilana J. Bennett, and Allen W. Song. “Cerebral White Matter Integrity and Cognitive Aging: Contributions from Diffusion Tensor Imaging.” Neuropsychology Review 19, no. 4 (2009): 415–35.

Maeda, S., and M. J. Griffin. “A Comparison of Vibrotactile Thresholds on the Finger Obtained with Different Equipment.” Ergonomics 37, no. 8 (1994): 1391–1406.

———. “A Comparison of Vibrotactile Thresholds on the Finger Obtained with Different Measuring Algorithms.” In Proceedings of Hand-Arm Vibration Syndrome: Diagnostics and Quantitative Relationships to Exposure, Stockholm Workshop, 94:85–95, 1995.

Mayer, Cynthia L., Bertrand R. Huber, and Elaine Peskind. “Traumatic Brain Injury, Neuroinflammation, and Post-Traumatic Headaches.” Headache: The Journal of Head and Face Pain 53, no. 9 (October 1, 2013): 1523–30. doi:10.1111/head.12173.

McCasland, James S., and Thomas A. Woolsey. “High-Resolution 2-Deoxyglucose Mapping of Functional Cortical Columns in Mouse Barrel Cortex.” Journal of Comparative Neurology 278, no. 4 (1988): 555–69.

McGill, W. J., and J. P. Goldberg. “A Study of the near-Miss Involving Weber’s Law and Pure-Tone Intensity Discrimination.” Perception & Psychophysics 4, no. 2 (March 1, 1968): 105–9. doi:10.3758/BF03209518.

Melzack, Ronald, and Patrick D. Wall. “Pain Mechanisms: A New Theory.” Science 150, no. 3699 (November 19, 1965): 971–79. doi:10.1126/science.150.3699.971.

Miller, Kenneth D., David J. Pinto, and Daniel J. Simons. “Processing in Layer 4 of the Neocortical Circuit: New Insights from Visual and Somatosensory Cortex.” Current Opinion in Neurobiology 11, no. 4 (2001): 488–97.

Mioni, G., G. Mattalia, and F. Stablum. “Time Perception in Severe Traumatic Brain Injury Patients: A Study Comparing Different Methodologies.” Brain and Cognition 81, no. 3 (April 2013): 305–12. doi:10.1016/j.bandc.2012.12.005.

Mioni, Giovanna, Franca Stablum, and Anna Cantagallo. “Time Discrimination in Traumatic Brain Injury Patients.” Journal of Clinical and Experimental Neuropsychology 35, no. 1 (2013): 90–102. doi:10.1080/13803395.2012.755151.

Mondello, Stefania, Andreas Jeromin, Andras Buki, Ross Bullock, Endre Czeiter, Noemi Kovacs, Pal Barzo, et al. “Glial Neuronal Ratio: A Novel Index for Differentiating Injury Type in Patients with Severe Traumatic Brain Injury.” Journal of Neurotrauma 29, no. 6 (April 10, 2012): 1096–1104. doi:10.1089/neu.2011.2092.

Moore, Christopher I., Sacha B. Nelson, and Mriganka Sur. “Dynamics of Neuronal Processing in Rat Somatosensory Cortex.” Trends in Neurosciences 22, no. 11 (1999): 513–20.

Morioka, Miyuki, and Michael J. Griffin. “Dependence of Vibrotactile Thresholds on the Psychophysical Measurement Method.” International Archives of Occupational and Environmental Health 75, no. 1–2 (2002): 78–84.

Morse, Claire K. “Does Variability Increase with Age? An Archival Study of Cognitive Measures.” Psychology and Aging 8, no. 2 (1993): 156.

Mountcastle, Vernon B., Robert H. LaMotte, and Giancarlo Carli. “Detection Thresholds for Stimuli in Humans and Monkeys: Comparison with Threshold Events in Mechanoreceptive Afferent Nerve Fibers Innervating the Monkey Hand.” Journal of Neurophysiology, 1972. http://psycnet.apa.org/psycinfo/1973-26408-001.

Mountcastle, Vernon B., Gian F. Poggio, and Gerhard Werner. “The Relation of Thalamic Cell Response to Peripheral Stimuli Varied over an Intensive Continuum.” Journal of Neurophysiology 26, no. 5 (1963): 807–34.

Mountcastle, Vernon B., William H. Talbot, Hideo Sakata, and Juhani Hyvarinen. “Cortical Neuronal Mechanisms in Flutter-Vibration Studied in Unanesthetized Monkeys: Neuronal Periodicity and Frequency Discrimination.” Journal of Neurophysiology, 1969. http://doi.apa.org/?uid=1970-00278-001.

Nagarajan, Srikantan S., David T. Blake, Beverly A. Wright, Nancy Byl, and Michael M. Merzenich. “Practice-Related Improvements in Somatosensory Interval Discrimination Are Temporally Specific But Generalize across Skin Location, Hemisphere, and Modality.” The Journal of Neuroscience 18, no. 4 (February 15, 1998): 1559–70.

Nebel, Mary Beth, Stephen Folger, Mark Tommerdahl, Mark Hollins, Francis McGlone, and Gregory Essick. “Temporomandibular Disorder Modifies Cortical Response to Tactile Stimulation.” The Journal of Pain 11, no. 11 (November 2010): 1083–94. doi:10.1016/j.jpain.2010.02.021.

Nelson, Aimee J., W. Richard Staines, Simon J. Graham, and William E. McIlroy. “Activation in SI and SII; the Influence of Vibrotactile Amplitude during Passive and Task-Relevant Stimulation.” Cognitive Brain Research 19, no. 2 (2004): 174–84.

Nelson, Timothy S., Courtney L. Suhr, Alan Lai, Amy J. Halliday, Dean R. Freestone, Karen J. McLean, Anthony N. Burkitt, and Mark J. Cook. “Exploring the Tolerability of Spatiotemporally Complex Electrical Stimulation Paradigms.” Epilepsy Research 96, no. 3 (2011): 267–75.

Nguyen, R. H., S. Ford, A. H. Calhoun, J. K. Holden, R. H. Gracely, and M. Tommerdahl. “Neurosensory Assessments of Migraine.” Brain Research 1498 (March 1, 2013): 50–58. doi:10.1016/j.brainres.2012.12.043.

Nguyen, Richard H., Cody Gillen, J. C. Garbutt, Alexei Kampov-Polevoi, Jameson K. Holden, Eric M. Francisco, and Mark Tommerdahl. “Centrally-Mediated Sensory Information Processing Is Impacted with Increased Alcohol Consumption in College-Aged Individuals.” Brain Research 1492 (January 25, 2013): 53–62. doi:10.1016/j.brainres.2012.11.021.

O’Mara, S., MARK J. Rowe, and R_P Tarvin. “Neural Mechanisms in Vibrotactile Adaptation.” Journal of Neurophysiology 59, no. 2 (1988): 607–22.

O’Riordan, Michelle, and Filippo Passetti. “Discrimination in Autism within Different Sensory Modalities.” Journal of Autism and Developmental Disorders 36, no. 5 (2006): 665–75.

Ofek, Hadas, and Ruth Defrin. “The Characteristics of Chronic Central Pain after Traumatic Brain Injury.” Pain 131, no. 3 (2007): 330–40.

Pack, Christopher C., and Richard T. Born. “Temporal Dynamics of a Neural Solution to the Aperture Problem in Visual Area MT of Macaque Brain.” Nature 409, no. 6823 (2001): 1040–42.

Pantaleo, Tito, Roberto Duranti, and Fabrizio Bellini. “Effects of Vibratory Stimulation on Muscular Pain Threshold and Blink Response in Human Subjects.” Pain 24, no. 2 (1986): 239–50.

Pardo, Carlos A., Diana L. Vargas, and Andrew W. Zimmerman. “Immunity, Neuroglia and Neuroinflammation in Autism.” International Review of Psychiatry 17, no. 6 (January 2005): 485–95. doi:10.1080/02646830500381930.

Pastor, Maria A., Brian L. Day, Emiliano Macaluso, Karl J. Friston, and Richard S. J. Frackowiak. "The Functional Neuroanatomy of Temporal Discrimination." The Journal of Neuroscience 24, no. 10 (March 10, 2004): 2585–91. doi:10.1523/JNEUROSCI.4210-03.2004.

Penke, Lars, Susana Muñoz Maniega, Catherine Murray, Alan J. Gow, Maria C. Valdés Hernández, Jonathan D. Clayden, John M. Starr, Joanna M. Wardlaw, Mark E. Bastin, and Ian J. Deary. "A General Factor of Brain White Matter Integrity Predicts Information Processing Speed in Healthy Older People." The Journal of Neuroscience 30, no. 22 (2010): 7569–74.

Pertovaara, Antti. "Modification of Human Pain Threshold by Specific Tactile Receptors." Acta Physiologica Scandinavica 107, no. 4 (December 1, 1979): 339–41. doi:10.1111/j.1748-1716.1979.tb06485.x.

Peters, Alan, and Engin Yilmaz. "Neuronal Organization in Area 17 of Cat Visual Cortex." Cerebral Cortex 3, no. 1 (1993): 49–68.

Pettet, Mark W., and Charles D. Gilbert. "Dynamic Changes in Receptive-Field Size in Cat Primary Visual Cortex." Proceedings of the National Academy of Sciences 89, no. 17 (1992): 8366–70.

Pukall, Caroline F., Yitzchak M. Binik, Samir Khalifé, Rhonda Amsel, and Frances V. Abbott. "Vestibular Tactile and Pain Thresholds in Women with Vulvar Vestibulitis Syndrome." Pain 96, no. 1 (2002): 163–75.

Rakic, Pasko. "Specification of Cerebral Cortical Areas." Science 241, no. 4862 (1988): 170–76.

Ramesh, Geeta, Andrew G. MacLean, and Mario T. Philipp. "Cytokines and Chemokines at the Crossroads of Neuroinflammation, Neurodegeneration, and Neuropathic Pain." Mediators of Inflammation 2013 (August 12, 2013). doi:10.1155/2013/480739.

Rammsayer, Thomas, and Eckart Altenmüller. "Temporal Information Processing in Musicians and Nonmusicians," 2006. http://www.jstor.org/stable/10.1525/mp.2006.24.1.37.

Rammsayer, Thomas H. "Differences in Duration Discrimination of Filled and Empty Auditory Intervals as a Function of Base Duration." Attention, Perception, & Psychophysics 72, no. 6 (August 1, 2010): 1591–1600. doi:10.3758/APP.72.6.1591.

———. "THE EFFECTS OF SENSORY MODALITY AND TYPE OF TASK ON DISCRIMINATION OF DURATIONS RANGING FROM 400 TO 1,400 MILLISECONDS." Proceedings of Fechner Day 26, no. 1 (2010): 439–44.

———. "The Effects of Type of Interval, Sensory Modality, Base Duration, and Psychophysical Task on the Discrimination of Brief Time Intervals." Attention, Perception, & Psychophysics, n.d., 1–12. Accessed March 28, 2014. doi:10.3758/s13414-014-0655-x.

Rammsayer, Thomas H., and Susan D. Lima. "Duration Discrimination of Filled and Empty Auditory Intervals: Cognitive and Perceptual Factors." Perception & Psychophysics 50, no. 6 (November 1, 1991): 565–74. doi:10.3758/BF03207541.

Rammsayer, Thomas, and Rolf Ulrich. "The Greater Temporal Acuity in the Reminder Task than in the 2AFC Task Is Independent of Standard Duration and Sensory Modality." Canadian Journal of Experimental Psychology/Revue Canadienne de Psychologie Expérimentale 66, no. 1 (2012): 26–31. doi:10.1037/a0025349.

Ratcliff, Roger, Anjali Thapar, and Gail McKoon. “The Effects of Aging on Reaction Time in a Signal Detection Task.” Psychology and Aging 16, no. 2 (2001): 323.

Raz, Naftali, Ulman Lindenberger, Karen M. Rodrigue, Kristen M. Kennedy, Denise Head, Adrienne Williamson, Cheryl Dahle, Denis Gerstorf, and James D. Acker. “Regional Brain Changes in Aging Healthy Adults: General Trends, Individual Differences and Modifiers.” Cerebral Cortex 15, no. 11 (2005): 1676–89.

Reitan, R. M., and D. Wolfson. “The Halstead–Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation, 1993.” Reitan Neuropsychology Laboratory, Tucson, AZ, n.d.

Resnick, Susan M., Dzung L. Pham, Michael A. Kraut, Alan B. Zonderman, and Christos Davatzikos. “Longitudinal Magnetic Resonance Imaging Studies of Older Adults: A Shrinking Brain.” The Journal of Neuroscience 23, no. 8 (2003): 3295–3301.

Rinehart, Nicole J., Bruce J. Tonge, John L. Bradshaw, Robert Iansek, Peter G. Enticott, and Jenny McGinley. “Gait Function in High-Functioning Autism and Asperger’s Disorder.” European Child & Adolescent Psychiatry 15, no. 5 (2006): 256–64.

Ringach, Dario L., Michael J. Hawken, and Robert Shapley. “Dynamics of Orientation Tuning in Macaque Primary Visual Cortex.” Nature 387, no. 6630 (1997): 281–84.

Rocheron, Isabelle, Christian Lorenzi, Christian Füllgrabe, and Annie Dumont. “Temporal Envelope Perception in Dyslexic Children.” Neuroreport 13, no. 13 (2002): 1683–87.

Rojas, Donald, Eric Peterson, Erin Winterrowd, Martin Reite, Sally Rogers, and Jason Tregellas. “Regional Gray Matter Volumetric Changes in Autism Associated with Social and Repetitive Behavior Symptoms.” BMC Psychiatry 6, no. 1 (2006): 56.

Rothermundt, M, P Falkai, G Ponath, S Abel, H Bürkle, M Diedrich, G Hetzel, et al. “Glial Cell Dysfunction in Schizophrenia Indicated by Increased S100B in the CSF.” Molecular Psychiatry 9, no. 10 (October 2004): 897–99. doi:10.1038/sj.mp.4001548.

Rousseau, Robert, and Alfred B. Kristofferson. “The Discrimination of Bimodal Temporal Gaps.” Bulletin of the Psychonomic Society 1, no. 2 (February 1, 1973): 115–16. doi:10.3758/BF03334312.

Sagar, H. J., E. V. Sullivan, J. D. E. Gabrieli, S. Corkin, and J. H. Growdon. “Temporal Ordering and Short-Term Memory Deficits in Parkinson’s Disease.” Brain 111, no. 3 (June 1, 1988): 525–39. doi:10.1093/brain/111.3.525.

Sanger, Terence D., Daniel Tarsy, and Alvaro Pascual-Leone. “Abnormalities of Spatial and Temporal Sensory Discrimination in Writer’s Cramp.” Movement Disorders 16, no. 1 (2001): 94–99.

Schmitter-Edgecombe, Maureen, and Alicia D. Rueda. “Time Estimation and Episodic Memory Following Traumatic Brain Injury.” Journal of Clinical and Experimental Neuropsychology 30, no. 2 (2008): 212–23. doi:10.1080/13803390701363803.

Scholtyssek, Christine, Almut Kelber, and Guido Dehnhardt. “Brightness Discrimination in the Harbor Seal (< I> Phoca Vitulina</i>).” Vision Research 48, no. 1 (2008): 96–103.

———. “Brightness Discrimination in the Harbor Seal (Phoca Vitulina).” Vision Research 48, no. 1 (January 2008): 96–103. doi:10.1016/j.visres.2007.10.012.

Sears, Lonnie L., Cortney Vest, Somaia Mohamed, James Bailey, Bonnie J. Ranson, and Joseph Piven. “An MRI Study of the Basal Ganglia in Autism.” Progress in Neuro-Psychopharmacology and Biological Psychiatry 23, no. 4 (1999): 613–24.

Seltzer, Suzanne F., and Joseph L. Seltzer. “Tactual Sensitivity of Chronic Pain Patients to Non-Painful Stimuli.” Pain 27, no. 3 (December 1986): 291–95. doi: 10.1016/0304-3959(86)90156-9.

Seltzer, Suzanne F., Matthew Yarczower, Robert Woo, and Joseph L. Seltzer. “Laterality and Modality-Specific Effects of Chronic Pain.” Perception & Psychophysics 51, no. 5 (September 1, 1992): 500–503. doi:10.3758/BF03211645.

Sherer, Carolyn L., Jo Ann Clelland, Patricia O’Sullivan, Daniel M. Doleys, and Betty Canan. “The Effect of Two Sites of High Frequency Vibration on Cutaneous Pain Threshold.” Pain 25, no. 1 (April 1986): 133–38. doi:10.1016/0304-3959(86)90015-1.

Shevelev, I. A., U. T. Eysel, N. A. Lazareva, and G. A. Sharaev. “The Contribution of Intracortical Inhibition to Dynamics of Orientation Tuning in Cat Striate Cortex Neurons.” Neuroscience 84, no. 1 (1998): 11–23.

Shevelev, I. A., M. A. Volgushev, and G. A. Sharaev. “Dynamics of Responses of V1 Neurons Evoked by Stimulation of Different Zones of Receptive Field.” Neuroscience 51, no. 2 (1992): 445–50.

Simons, DANIEL J. “Response Properties of Vibrissa Units in Rat SI Somatosensory Neocortex.” J Neurophysiol 41, no. 3 (1978): 798–820.

Simons, S. B., J. Chiu, O. V. Favorov, B. L. Whitsel, and M. Tommerdahl. “Duration-Dependent Response of SI to Vibrotactile Stimulation in Squirrel Monkey.” Journal of Neurophysiology 97, no. 3 (March 1, 2007): 2121–29. doi:10.1152/jn.00513.2006.

Simons, Stephen B., Vinay Tannan, Joannellyn Chiu, Oleg V. Favorov, Barry L. Whitsel, and Mark Tommerdahl. “Amplitude-Dependency of Response of SI Cortex to Flutter Stimulation.” BMC Neuroscience 6, no. 1 (June 21, 2005): 43. doi:10.1186/1471-2202-6-43.

Slobounov, S., J. Johnston, H. Chiang, and W. J. Ray. “Motor-Related Cortical Potentials Accompanying Enslaving Effect in Single versus Combination of Fingers Force Production Tasks.” Clinical Neurophysiology 113, no. 9 (2002): 1444–53.

Smith, Matthew A., and Adam Kohn. “Spatial and Temporal Scales of Neuronal Correlation in Primary Visual Cortex.” The Journal of Neuroscience 28, no. 48 (2008): 12591–603.

Snowden, Robert J., and Oliver J. Braddick. “The Temporal Integration and Resolution of Velocity Signals.” Vision Research 31, no. 5 (1991): 907–14. doi: 10.1016/0042-6989(91)90156-Y.

Stevens, J. C., B. G. Green, and A. S. Krimsley. “Punctate Pressure Sensitivity: Effects of Skin Temperature.” Sensory Processes 1, no. 3 (1977): 238–43.

Stevens, Joseph C., and Barry G. Green. “Temperature–touch Interaction: Weber’s Phenomenon Revisited.” Sensory Processes, 1978. http://psycnet.apa.org/psycinfo/1980-22582-001.

Stevens, Joseph C., and Lawrence E. Marks. “Spatial Summation and the Dynamics of Warmth Sensation.” Perception & Psychophysics 9, no. 5 (1971): 391–98.

Stevens, Joseph C., Lawrence E. Marks, and Donald C. Simonson. “Regional Sensitivity and Spatial Summation in the Warmth Sense.” Physiology & Behavior 13, no. 6 (1974): 825–36.

Stillman, Jennifer A., Jozef J. Zwislocki, Minsheng Zhang, and Lisa K. Cefaratti. “Intensity Just-Noticeable Differences at Equal-Loudness Levels in Normal and Pathological Ears.” The Journal of the Acoustical Society of America 93, no. 1 (1993): 425–34.

———. “Intensity Just–noticeable Differences at Equal–loudness Levels in Normal and Pathological Ears.” The Journal of the Acoustical Society of America 93, no. 1 (January 1, 1993): 425–34. doi:10.1121/1.405622.

Stone, Herbert, and John J. Bosley. “Olfactory Discrimination and Weber’s Law.” Perceptual and Motor Skills 20, no. 2 (1965): 657–65.

Stott, Leland Hyrum. “The Discrimination of Short Tonal Durations.” University of Illinois at Urbana-Champaign, 1933.

Sugase, Yasuko, Shigeru Yamane, Shoogo Ueno, and Kenji Kawano. “Global and Fine Information Coded by Single Neurons in the Temporal Visual Cortex.” Nature 400, no. 6747 (1999): 869–73.

Sun, Qian-Quan, John R. Huguenard, and David A. Prince. “Barrel Cortex Microcircuits: Thalamocortical Feedforward Inhibition in Spiny Stellate Cells Is Mediated by a Small Number of Fast-Spiking Interneurons.” The Journal of Neuroscience 26, no. 4 (2006): 1219–30.

Takarae, Yukari, Nancy J. Minshew, Beatriz Luna, and John A. Sweeney. “Atypical Involvement of Frontostriatal Systems during Sensorimotor Control in Autism.” Psychiatry Research: Neuroimaging 156, no. 2 (2007): 117–27.

Tamás, Gábor, Andrea L\Horincz, Anna Simon, and János Szabadics. “Identified Sources and Targets of Slow Inhibition in the Neocortex.” Science 299, no. 5614 (2003): 1902–5.

Tannan, V., R. G. Dennis, and M. Tommerdahl. “Stimulus-Dependent Effects on Tactile Spatial Acuity.” Behavioral and Brain Functions 1, no. 1 (December 1, 2005): 1–11. doi: 10.1186/1744-9081-1-18.

Tannan, V., R. G. Dennis, Z. Zhang, and M. Tommerdahl. “A Portable Tactile Sensory Diagnostic Device.” Journal of Neuroscience Methods 164, no. 1 (August 15, 2007): 131–38. doi: 10.1016/j.jneumeth.2007.04.011.

Tannan, V., S. Simons, R. G. Dennis, and M. Tommerdahl. “Effects of Adaptation on the Capacity to Differentiate Simultaneously Delivered Dual-Site Vibrotactile Stimuli.” Brain Research 1186 (December 19, 2007): 164–70. doi:10.1016/j.brainres.2007.10.024.

Tannan, Vinay, R. Dennis, and M. Tommerdahl. “A Novel Device for Delivering Two-Site Vibrotactile Stimuli to the Skin.” Journal of Neuroscience Methods 147, no. 2 (2005): 75–81.

Tannan, Vinay, Jameson K. Holden, Zheng Zhang, Grace T. Baranek, and Mark A. Tommerdahl. “Perceptual Metrics of Individuals with Autism Provide Evidence for Disinhibition.” Autism Research 1, no. 4 (August 1, 2008): 223–30. doi:10.1002/aur.34.

Tannan, Vinay, Barry L. Whitsel, and Mark A. Tommerdahl. “Vibrotactile Adaptation Enhances Spatial Localization.” Brain Research 1102, no. 1 (August 2, 2006): 109–16. doi:10.1016/j.brainres.2006.05.037.

Teismann, Peter, Kim Tieu, Oren Cohen, Dong-Kug Choi, Du Chu Wu, Daniel Marks, Miquel Vila, Vernice Jackson-Lewis, and Serge Przedborski. “Pathogenic Role of Glial Cells in Parkinson’s Disease.” Movement Disorders 18, no. 2 (February 1, 2003): 121–29. doi:10.1002/mds.10332.

Thornbury, Julia M., and Charlotte M. Mistretta. “Tactile Sensitivity as a Function of Age.” Journal of Gerontology 36, no. 1 (1981): 34–39.

Tinazzi, Michele, Antonio Fiaschi, Emma Frasson, Mirta Fiorio, Feliciana Cortese, and Salvatore M. Aglioti. “Deficits of Temporal Discrimination in Dystonia Are Independent from the Spatial Distance between the Loci of Tactile Stimulation.” Movement Disorders 17, no. 2 (2002): 333–38.

Tinazzi, Michele, Emma Frasson, Laura Bertolasi, Antonio Fiaschi, and Salvatore Aglioti. “Temporal Discrimination of Somesthetic Stimuli Is Impaired in Dystonic Patients.” Neuroreport 10, no. 7 (1999): 1547–50.

Tommerdahl, M., K. A. Delemos, O. V. Favorov, C. B. Metz, C. J. Vierck Jr, and B. L. Whitsel. “Response of Anterior Parietal Cortex to Different Modes of Same-Site Skin Stimulation.” Journal of Neurophysiology 80, no. 6 (1998): 3272–83.

Tommerdahl, M., K. A. Delemos, C. J. Vierck Jr, O. V. Favorov, and B. L. Whitsel. “Anterior Parietal Cortical Response to Tactile and Skin-Heating Stimuli Applied to the Same Skin Site.” Journal of Neurophysiology 75, no. 6 (1996): 2662–70.

Tommerdahl, M., O. V. Favorov, and B. L. Whitsel. “Effects of High-Frequency Skin Stimulation on SI Cortex: Mechanisms and Functional Implications.” Somatosensory and Motor Research 22, no. 3 (2005): 151–70.

Tommerdahl, M., K. D. Hester, E. R. Felix, M. Hollins, O. V. Favorov, P. M. Quibrera, and B. L. Whitsel. “Human Vibrotactile Frequency Discriminative Capacity after Adaptation to 25 Hz or 200 Hz Stimulation.” Brain Research 1057, no. 1 (2005): 1–9.

Tommerdahl, M., V. Tannan, C. J. Cascio, G. T. Baranek, and B. L. Whitsel. “Vibrotactile Adaptation Fails to Enhance Spatial Localization in Adults with Autism.” Brain Research 1154 (June 18, 2007): 116–23. doi:10.1016/j.brainres.2007.04.032.

Tommerdahl, M., B. L. Whitsel, E. G. Cox, M. E. Diamond, and D. G. Kelly. “Analysis of the Periodicities in Somatosensory Cortical Activity Patterns.” In Society for Neuroscience Abstracts, 13:470, 1987.

Tommerdahl, M., B. L. Whitsel, O. V. Favorov, C. B. Metz, and B. L. O’Quinn. “Responses of Contralateral SI and SII in Cat to Same-Site Cutaneous Flutter versus Vibration.” Journal of Neurophysiology 82, no. 4 (1999): 1982–92.

Tommerdahl, M., B. L. Whitsel, C. J. Vierck, O. Favorov, S. Juliano, B. Cooper, C. Metz, and B. Nakhle. “Effects of Spinal Dorsal Column Transection on the Response of Monkey Anterior Parietal Cortex to Repetitive Skin Stimulation.” Cerebral Cortex 6, no. 2 (1996): 131–55.

Tommerdahl, Mark, Joannellyn Chiu, B. L. Whitsel, and O. Favorov. “Minicolumnar Patterns in the Global Cortical Response to Sensory Stimulation.” Neocortical Modularity and the Cell Minicolumn, 2005, 145–60.

Tommerdahl, Mark, O. Favorov, B. L. Whitsel, B. Nakhle, and Y. A. Gonchar. “Minicolumnar Activation Patterns in Cat and Monkey SI Cortex.” Cerebral Cortex 3, no. 5 (1993): 399–411.

Tommerdahl, Mark, Oleg V. Favorov, and Barry L. Whitsel. “Dynamic Representations of the Somatosensory Cortex.” Neuroscience & Biobehavioral Reviews 34, no. 2. Touch, Temperature, Pain/Itch and Pleasure (February 2010): 160–70. doi:10.1016/j.neubiorev.2009.08.009.

Tommerdahl, Mark, Oleg Favorov, and Barry L. Whitsel. “Optical Imaging of Intrinsic Signals in Somatosensory Cortex.” Behavioural Brain Research 135, no. 1 (2002): 83–91.

Tommerdahl, Mark, Stephen B. Simons, Joannellyn S. Chiu, Oleg Favorov, and Barry Whitsel. “Response of SI Cortex to Ipsilateral, Contralateral and Bilateral Flutter Stimulation in the Cat.” BMC Neuroscience 6, no. 1 (2005): 29.

Tommerdahl, Mark, Stephen B. Simons, Joannellyn S. Chiu, Oleg Favorov, and Barry L. Whitsel. “Ipsilateral Input Modifies the Primary Somatosensory Cortex Response to Contralateral Skin Flutter.” The Journal of Neuroscience 26, no. 22 (May 31, 2006): 5970–77. doi:10.1523/JNEUROSCI.5270-05.2006.

Tommerdahl, Mark, Vinay Tannan, Jameson K. Holden, and Grace T. Baranek. “Absence of Stimulus-Driven Synchronization Effects on Sensory Perception in Autism: Evidence for Local Underconnectivity?” Behavioral and Brain Functions 4, no. 1 (December 1, 2008): 1–9. doi:10.1186/1744-9081-4-19.

Tommerdahl, Mark, Vinay Tannan, Matt Zachek, Jameson K. Holden, and Oleg V. Favorov. “Effects of Stimulus-Driven Synchronization on Sensory Perception.” Behav Brain Funct 3 (2007): 61.

Torquati, Kathya, Vittorio Pizzella, Stefania Della Penna, Raffaella Franciotti, Claudio Babiloni, Paolo Maria Rossini, and Gian Luca Romani. “Comparison between SI and SII Responses as a Function of Stimulus Intensity.” Neuroreport 13, no. 6 (2002): 813–19.

Uhlhaas, Peter J., and Wolf Singer. “Neural Synchrony in Brain Disorders: Relevance for Cognitive Dysfunctions and Pathophysiology.” Neuron 52, no. 1 (2006): 155–68.

Van Petten, Cyma, Elena Plante, Patrick SR Davidson, Trudy Y. Kuo, Leslie Bajuscak, and Elizabeth L. Glisky. “Memory and Executive Function in Older Adults: Relationships with Temporal and Prefrontal Gray Matter Volumes and White Matter Hyperintensities.” Neuropsychologia 42, no. 10 (2004): 1313–35.

Vargas, Diana L., Caterina Nascimbene, Chitra Krishnan, Andrew W. Zimmerman, and Carlos A. Pardo. “Neuroglial Activation and Neuroinflammation in the Brain of Patients with Autism.” Annals of Neurology 57, no. 1 (January 1, 2005): 67–81. doi:10.1002/ana.20315.

Vernooij, Meike W., M. Arfan Ikram, Henri A. Vrooman, Piotr A. Wielopolski, Gabriel P. Krestin, Albert Hofman, Wiro J. Niessen, Aad Van der Lugt, and Monique MB Breteler. “White Matter Microstructural Integrity and Cognitive Function in a General Elderly Population.” Archives of General Psychiatry 66, no. 5 (2009): 545–53.

Verrillo, R. T. “Change in Vibrotactile Thresholds as a Function of Age.” Sensory Processes 3, no. 1 (1979): 49.

Verrillo, R. T., and G. A. Gescheider. “Effect of Prior Stimulation on Vibrotactile Thresholds.” Sensory Processes 1, no. 4 (1977): 292–300.

Verrillo, Ronald T. “Age Related Changes in the Sensitivity to Vibration.” Journal of Gerontology 35, no. 2 (1980): 185–93.

———. “Comparison of Child and Adult Vibrotactile Thresholds.” Bulletin of the Psychonomic Society 9, no. 3 (1977): 197–200.

———. “Effects of Aging on the Suprathreshold Responses to Vibration.” Perception & Psychophysics 32, no. 1 (1982): 61–68.

———. “Psychophysics of Vibrotactile Stimulation.” The Journal of the Acoustical Society of America 77, no. 1 (1985): 225–32.

Verrillo, Ronald T., and Stanley J. Bolanowski Jr. “The Effects of Skin Temperature on the Psychophysical Responses to Vibration on Glabrous and Hairy Skin.” The Journal of the Acoustical Society of America 80, no. 2 (1986): 528–32.

Verrillo, Ronald T., Stanley J. Bolanowski, and George A. Gescheider. “Effect of Aging on the Subjective Magnitude of Vibration.” Somatosensory & Motor Research 19, no. 3 (2002): 238–44.

Vierck Jr, Charles J., and Marshall B. Jones. “Influences of Low and High Frequency Oscillation upon Spatio-Tactile Resolution.” Physiology & Behavior 5, no. 12 (1970): 1431–35.

Villalobos, Michele E., Akiko Mizuno, Branelle C. Dahl, Nobuko Kemmotsu, and Ralph-Axel Müller. “Reduced Functional Connectivity between V1 and Inferior Frontal Cortex Associated with Visuomotor Performance in Autism.” Neuroimage 25, no. 3 (2005): 916–25.

Voelbel, Gerald T., Marsha E. Bates, Jennifer F. Buckman, Gahan Pandina, and Robert L. Hendren. “Caudate Nucleus Volume and Cognitive Performance: Are They Related in Childhood Psychopathology?” Biological Psychiatry 60, no. 9 (2006): 942–50.

Vriezen, Ellen R., and Morris Moscovitch. “Memory for Temporal Order and Conditional Associative-Learning in Patients with Parkinson’s Disease.” Neuropsychologia 28, no. 12 (1990): 1283–93. doi:10.1016/0028-3932(90)90044-O.

Wahl, Otto F., and David Sieg. “Time Estimation among Schizophrenics.” Perceptual and Motor Skills 50, no. 2 (1980): 535–41.

Watanabe, I, P Svensson, and L Arendt-Nielsen. “Influence of Segmental and Extra-Segmental Conditioning, Stimuli on Cortical Potentials Evoked by Painful Electrical Stimulation.” Somatosensory & Motor Research 16, no. 3 (1999): 243–50.

Weber, Ernst Heinrich. Tastsinn Und Gemeingefühl. Vol. 149. W. Engelmann, 1905. http://books.google.com/books?hl=en&lr=&id=HTMXAAAAYAAJ&oi=fnd&pg=PP4&dq=Der+Tastsinn+und+das+Gemeingefuhl&ots=fmJnbcC4oJ&sig=mfG3Bsz9t82hQ7cf-KRcpNUJRE0.

Wechsler, D. “WASI Manual.” San Antonio, Psychological Corporation, 1999.

Weinstein, Alvin D., Sanford Goldstone, and William K. Boardman. “The Effect of Recent and Remote Frames of Reference on Temporal Judgments of Schizophrenic Patients.” The Journal of Abnormal and Social Psychology 57, no. 2 (1958): 241.

Weitz, Joseph. “Vibratory Sensitivity as a Function of Skin Temperature.” Journal of Experimental Psychology 28, no. 1 (1941): 21.

Werner, Gerhard, and Vernon B. Mountcastle. “Neural Activity in Mechanoreceptive Cutaneous Afferents: Stimulus-Response Relations, Weber Functions, and Information Transmission.” Journal of Neurophysiology, 1965. http://psycnet.apa.org/psycinfo/1965-09565-001.

Whitsel, B. L., E. F. Kelly, M. Quibrera, M. Tommerdahl, Y. Li, O. V. Favorov, M. Xu, and C. B. Metz. “Time-Dependence of SI RA Neuron Response to Cutaneous Flutter Stimulation.” Somatosensory & Motor Research 20, no. 1 (2003): 45–69.

Whittington, M. A., R. D. Traub, N. Kopell, B. Ermentrout, and E. H. Buhl. “Inhibition-Based Rhythms: Experimental and Mathematical Observations on Network Dynamics.” International Journal of Psychophysiology 38, no. 3 (2000): 315–36.

Whittle, Paul. “Increments and Decrements: Luminance Discrimination.” Vision Research 26, no. 10 (1986): 1677–91. doi:10.1016/0042-6989(86)90055-6.

Wiart, Marlène, Nathalie Davoust, Jean-Baptiste Pialat, Virginie Desestret, Samir Moucharrafie, Tae-Hee Cho, Mireille Mutin, et al. “MRI Monitoring of Neuroinflammation in Mouse Focal Ischemia.” Stroke 38, no. 1 (January 1, 2007): 131–37. doi:10.1161/01.STR.0000252159.05702.00.

Wilson, Robert S., Laurel A. Beckett, Lisa L. Barnes, Julie A. Schneider, Julie Bach, Denis A. Evans, and David A. Bennett. “Individual Differences in Rates of Change in Cognitive Abilities of Older Persons.” Psychology and Aging 17, no. 2 (2002): 179.

Wilson, Tony W., Donald C. Rojas, Martin L. Reite, Peter D. Teale, and Sally J. Rogers. “Children and Adolescents with Autism Exhibit Reduced MEG Steady-State Gamma Responses.” Biological Psychiatry 62, no. 3 (2007): 192–97.

Wirth, Corina, and Hans-R. Lüscher. “Spatiotemporal Evolution of Excitation and Inhibition in the Rat Barrel Cortex Investigated with Multielectrode Arrays.” Journal of Neurophysiology 91, no. 4 (2004): 1635–47.

Wišcek, Roman, Stanis\law Pielka, Roman Rutowski, Jerzy Gosk, Krzysztof Skiba, and Pawe\l Reichert. “Evaluation of the Dynamics of Sensory Improvement in the Hand after Surgical Treatment of Carpal Tunnel Syndrome.” Neurologia I Neurochirurgia Polska 41, no. 6 (2007): 517–24.

Woolf, Clifford J., and Tim P. Doubell. “The Pathophysiology of Chronic Pain—increased Sensitivity to Low Threshold Aβ-Fibre Inputs.” Current Opinion in Neurobiology 4, no. 4 (1994): 525–34.

Zhang, Zheng, Eric M. Francisco, Jameson K. Holden, Robert G. Dennis, and Mark Tommerdahl. “Somatosensory Information Processing in the Aging Population.” Frontiers in Aging Neuroscience 3 (December 8, 2011). doi:10.3389/fnagi.2011.00018.

———. “The Impact of Non-Noxious Heat on Tactile Information Processing.” Brain Research 1302 (November 20, 2009): 97–105. doi:10.1016/j.brainres.2009.09.037.

Zhang, Zheng, Vinay Tannan, Jameson K. Holden, Robert G. Dennis, and Mark Tommerdahl. “A Quantitative Method for Determining Spatial Discriminative Capacity.” BioMedical Engineering OnLine 7, no. 1 (December 1, 2008): 1–8. doi:10.1186/1475-925X-7-12.

Zhang, Zheng, Denniz A. Zolnoun, Eric M. Francisco, Jameson K. Holden, Robert G. Dennis, and Mark Tommerdahl. “Altered Central Sensitization in Subgroups of Women with Vulvodynia.” The Clinical Journal of Pain 27, no. 9 (November 2011): 755–63. doi: 10.1097/AJP.0b013e31821c98ec.

Zolnoun, Denniz, Katherine Hartmann, Georgine Lamvu, Suzie As-Sanie, William Maixner, and John Steege. “A Conceptual Model for the Pathophysiology of Vulvar Vestibulitis Syndrome.” Obstetrical & Gynecological Survey 61, no. 6 (2006): 395–401.