APPLICATIONS OF SENSORY PERCEPTUAL METRICS TO SCREEN, TO TRACK CHANGES IN, AND TO DIFFERENTIATE CLINICAL POPULATIONS

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ABSTRACT

RICHARD NGUYEN: Applications of sensory perceptual metrics to screen, to track changes in, and to differentiate clinical populations.
(Under the direction of Mark A. Tommerdahl, Ph.D.)

In order to overcome limitations in current neurological screening methods, a portable, non-invasive, vibrotactile mechanical stimulator was developed to rapidly and quantitatively analyze various features of central information processing. Understanding the neurobiological processes involved in somatosensory perception of particular types of tactile stimulation, the general hypothesis on which these studies are based is that any systemic changes in central information processing can be attributed to variations observed in sensory perceptual metrics. These evaluations were designed to allow investigation into fundamental neurobiological mechanisms involved in cortical interactions and brain functionality. The uniqueness of each of the protocols has thus far demonstrated significant sensitivity to detecting alterations in various types of central information processing. This research explores the application of the method within young adult clinical populations—migraine, alcoholism, and concussion—which can benefit from additional or improved assessments. Analysis of the results revealed that sensory perceptual metrics could screen, track changes in, and differentiate these clinical populations. Future work consists of further developing dual-site protocols and exploring multi-site and bilateral protocols to study adjacent or near-adjacent, as well as cross-hemispheric, cortical interactions, respectively. The ultimate goal of these studies is to develop and establish a quantifiable method of analyzing brain functionality that can be considered as either an alternative or complement to current diagnostic or screening evaluations.

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2AFC	Two-Alternative Forced-Choice Tracking Algorithm
AD	Amplitude Discrimination (ADs: simple; ADssa: single-site adaptation)
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ASAP	Alcohol and Substance Abuse Program, Chapel Hill, North Carolina
AUDIT	Alcohol Use Disorders Identification Test
BES	Gormally Binge Eating Scale
CANTAB	Cambridge Neuropsychological Test Automated Battery
CATI	Computer-Assisted Telephone Interview
CM	Cortical Metrics
CNS	Central Nervous System
CSD	Cortical Spreading Depression
CT	Computed Tomography
D#	Digit Number (D2=index, D3=middle, D4=ring, D5=little)
DT	Detection Threshold (DTs: static, DTd: dynamic)
DRC	Dental Research Center
DPM	Drinks per Month
DSM-V	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalography
EM	Episodic Migraine
FH	Family History
FM	Fibromyalgia
fMRI	Functional Magnetic Resonance Imaging

GABA	γ-aminobutyric acid
Hx	Previous History
IBS	Irritable Bowel Syndrome
ICDH-2	International Classification of Headache Disorders
ITI	Inter-trial Interval
k-NN	k-Nearest Neighbors Algorithm
MEG	Magnetic Encephalography
MMSE	Mini Mental State Examination
MRCP	Motor-Related Cortical Rotentials
mTBI	Mild Traumatic Brain Injury
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NMDA	N-methyl-D-aspartate
NS	Novelty Seeking
PCA	Principal Component Analysis
PET	Positron Emission Topography
PM&R	Physical Medicine and Rehabilitation
PNS	Peripheral Nervous System
RAPI	Rutgers Alcohol Problem Index
RI	Response Interval
RT	Reaction Time (RTs: simple, RTc: choice)
S#	Somatosensory Cortex (S1=primary, S2=secondary)
SCAT	Standardized Concussion Assessment Tool
SL	Sweet Liking

S/T	Standard/Test Amplitudes
SVM	Support Vector Machine
TLFB	Timeline Followback
TMD	Temporomandibular Disorder
TMS	Transcranial Magnetic Stimulation
TPQ	Tridimensional Personality Questionnaire
UNC-CH	University of North Carolina at Chapel Hill
VAS	Visual Analog Scale
VVS	Vulvar Vestibulitis Syndrome
WAIS	Wechsler Adult Intelligence Scale
WF	Weber Fraction

CHAPTER 1. INTRODUCTION

Problems with Current Methods of Neuropsychological Screening

The primary purpose of conducting neurological diagnostic tests and screening assessments is to understand brain functionality and to reveal information about the structural integrity of the brain. Various advanced screening methods have been developed and clinically implemented over the years to analyze cognitive function, but several problems exist in the current approaches. Two common types of minimally-invasive neurological screening methods, namely a variety of neuropsychological assessments and imaging techniques, are briefly reviewed for their efficacy and limitations, and the quantitative method used throughout this research is subsequently introduced as either an alternative or complement to these existing methods of evaluation (Neurological Diagnostic Tests and Procedures., 2005).

Full neuropsychological evaluations consist of a series of lengthy assessments which can potentially reveal information about various cognitive processes including intelligence, attention, learning and memory, executive function, personality traits, speed of sensory and motor processing, among other significant functional domains. Common diagnostic measures might include identifying signs and/or symptoms within the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) or implementing batteries of neurological tests such as the Cambridge Neuropsychological Test Automated Battery (CANTAB), the Mini Mental State Examination (MMSE), the Wechsler Adult Intelligence Scale (WAIS), and the Halstead-Reitan Neuropsychological Battery, among others. While these test batteries are capable of detecting

functional impairment in the absence of imaging biomarkers (Harvey, 2012), evaluations can last for several hours with many assessments being subjective with self-reporting of symptoms and estimated recollection of notable incidences of neurological dysfunction.

The use of various imaging modalities, while providing a useful, more quantitative method of analyzing the structural integrity and functional correlates of the brain, are costly, require a significant amount of time for data acquisition and analytical processing, and are limited in accessibility. Common imaging modalities include computed tomography (CT), positron emission topography (PET), electroencephalography (EEG), magnetic encephalography (MEG), and functional magnetic resonance imaging (fMRI) among others. Although each of the imaging techniques can reveal particular systemic or regional aspects associated with brain functionality, single modalities alone may be incapable of comprehensively analyzing the complex nature of certain types of neurological dysfunction in various clinical populations (Shenton, et al., 2012).

In order to overcome the limitations of current diagnostic tests and screening methods, a portable and non-invasive system was developed to analyze particular features of central information processing and to rapidly conduct quantitative sensory testing in a variety of clinical populations. A four-site mechanical stimulator was designed to optimally deliver non-painful vibrotactile stimuli to the fingertips and has been utilized to assess a number of neurosensory information processing characteristics in various subject populations. The protocols developed for testing are unique in that they have demonstrated significant sensitivity to detecting alterations in central nervous system (CNS) information processing. The general hypothesis for this research is that any systemic changes in central information processing can be attributed to variations observed in these sensory perceptual metrics.

In the following chapters, the rationale for the somatosensory testing is described and current literature claims are briefly summarized. Next, the experimental methods utilized for testing and data analysis are explained, and establishment of objective standards for healthy controls are defined. Finally, differences among measures are highlighted within three different clinical populations, and, after understanding their etiologies, the results are subsequently used to draw conclusions about various features of central information processing.

Sensory Perceptual Metrics

Quantitative sensory testing has been shown to be an effective, non-invasive, non-painful, alternative approach to measuring and analyzing brain functionality (Chong & Cros, 2004). In particular, the neurobiological dynamics involved in central information processing have been thoroughly investigated through the implementation of vibrotactile psychophysics and subsequent analysis and comparison of sensory perceptual metrics. This type of testing has been utilized to explore somatosensory pathways, target neurobiological processes, detect neuropathies, and associate cortical functionality with measurable aspects of behavior (Gandhi, Sesek, Tuckett, & Bamberg, 2011). Because the relationship between cortical mechanisms and sensory perception is particularly relevant with respect to clinical populations in which central information processing is impaired, the feasibility of implementing a battery of tests to evaluate various clinical populations is further explored in order to understand the particular neurological mechanisms involved in their etiologies (Puts, Edden, Wodka, Mostofsky, & Tommerdahl, 2013).

Somatosensory System

Somatosensation is an ideal sensory modality to analyze for neurological screening assessments of central information processing because the system is somatotopically organized, stimulation results in a high signal-to-noise ratio, and the system is uniquely integrated with pain pathways. The somatotopic organization allows for observations of cortico-cortical interactions among adjacent and/or near-adjacent cortical regions. Furthermore, ambivalent environmental noise can be easily controlled. Finally, the somatosensory system is highly integrated with pain processing, which is often an important aspect of clinical diagnosis. A key concept in this model is that changes in sensory perception occur in parallel with systemic cortical alterations, and sensory perceptual metrics can allow for a non-invasive, functional biopsy of the cerebral cortex. These benefits, among others, are advantageous in understanding timing as well as spatial representations of sensory perception.

The somatosensory system, like most sensory systems, primarily consists of two components: sensory receptors in the peripheral nervous system (PNS) and somatotopic representations of these receptors in the cerebral cortex of the central nervous system (CNS). While the presence and density of each type of receptor varies according to the specific location of the body, a high density of tactile mechanoreceptors are localized in the digits due to their involvement with manual interactions. Tactile cutaneous mechanoreceptors can detect and transmit sensations of touch, pressure, and vibration through slowly-adapting (SA) receptors (Merkel discs and Ruffini endings) and rapidly-adapting (RA) receptors (Meissner's and Pacinian corpuscles) (Abraira & Ginty, 2013; Roudaut, et al., 2012). When stimulated, the tactile mechanical sensations received from the digits are transduced into electrical signals which propagate through the dorsal horn of the spinal cord and transmit through rapidly conducting Aβ

projection fibers through the thalamus to the primary somatosensory cortex (S1), specifically to areas 1 and 3b, where the signal is processed into a percept (Abraira & Ginty, 2013; Roudaut, et al., 2012). Because the fingers contain a large density of mechanoreceptors, the digit tips were appropriately chosen for analysis of adjacent and/or near-adjacent cortical information processing.

Somatosensory studies have progressed from implementing single-site stimulation in analyzing the effects of specific types of stimulation on cortical responses to utilizing dual-site stimulation to characterize the discriminative abilities among adjacent and/or near-adjacent spatial regions. The nature of the stimuli, being punctate or vibrotactile, as well as the combination of the digits being tested, have been shown to significantly affect the outcome of the resulting percept (Chiu, Tommerdahl, Whitsel, & Favorov, 2005; Favorov, Hester, Lao, & Tommerdahl, 2002; Friedman, Chen, & Roe, 2008). Results from animal studies have been compared with human experiments to form more accurate characterizations of the neurobiological mechanisms underlying somatosensory information processing (LaMotte & Mountcastle, 1975; Mountcastle, LaMotte, & Carli, 1972; Mountcastle, Talbot, Sakata, & Hyvärinen, 1969; Talbot, Darian-Smith, Kornhuber, & Mountcastle, 1968). While the animal studies have allowed the cortical mechanisms to be analyzed through electrophysiological and/or imaging techniques, the human studies have been capable of confirming these findings through sensory perceptual quantification.

CHAPTER 2. METHODS

Device

A portable, non-invasive, four-site mechanical stimulator (Cortical Metrics, CM-5), designed and fabricated to optimally deliver non-painful vibrotactile stimuli to the fingertips, was implemented in the following studies (Figure 2.1.). The independent, computer-controlled probe tips were able to deliver a wide range of vibrotactile stimulation of varying amplitudes (sinusoidal peak-to-peak displacements in μm), durations (ms), and frequencies (Hz). A number of protocols were developed to assess particular features of information processing in various populations (Holden, et al., 2012; Puts, Edden, Wodka, Mostofsky, & Tommerdahl, 2013; Tannan, Dennis, & Tommerdahl, 2005; Tannan, Dennis, Zhang, & Tommerdahl, 2007; Zhang, Tannan, Holden, Dennis, & Tommerdahl, 2008). These groups range from typically-developing individuals (Zhang, Francisco, Holden, Dennis, & Tommerdahl, 2011) to subjects with autism spectrum disorders (Tannan, Holden, Zhang, Baranek, & Tommerdahl, 2008; Tommerdahl, Tannan, Cascio, Baranek, & Whitsel, 2007; Tommerdahl, Tannan, Holden, & Baranek, 2008; Puts, Edden, Wodka, Mostofsky, & Tommerdahl, 2013) to patients with chronic pain conditions (Nebel, et al., 2010; Zhang, et al., 2011) as well as those with other neurological dysfunctions (Nelson, et al., 2012). These biologically-based and hypothesis-driven evaluations were designed to evoke interactions between adjacent and/or near-adjacent cortical regions with considerations to the unique advantages of the somatosensory system (see Somatosensory System). Subsequent analyses of the metrics and sensory thresholds have allowed investigation into the fundamental

systemic mechanistic changes which occur within and among cortical regions. The uniqueness of each of the protocols has thus far demonstrated significant sensitivity to alterations in central information processing.

Figure 2.1. Cortical Metrics Vibrotactile Stimulator.

Experimental Session

Following International Review Board approval and informed consent, over 200 subjects ranging from 18 to 70 years of age were recruited from the University of North Carolina at Chapel Hill (UNC-CH) to participate in the study. All subjects completed a survey on current medications and medical history prior to the experimental tests to exclude participants with any history of neurological impairment. The subjects were naïve to the study design and blinded to the issue under investigation.

During the experimental session, subjects were seated comfortably in a chair with the test (left) arm situated on an armrest attached to the head unit of the four-site vibrotactile stimulator. In these studies, vibrotactile flutter stimulation (25 Hz) were delivered via 5 mm Delrin probes on the glabrous tips of either, or both, the second (index, D2) and/or the third (middle, D3) digits

of the test hand. These digits were chosen as the test sites not only for convenience and comfort but also because of the wealth of neurophysiological data which supports the evaluation of these somatotopic regions in the non-human primate cerebral cortex (Chiu, Tommerdahl, Whitsel, & Favorov, 2005; Favorov, Hester, Lao, & Tommerdahl, 2002; Friedman, Chen, & Roe, 2008). A semi-automated procedure guided subjects through a series of assessments relating to the perception of the mechanical stimuli delivered (see Neurosensory Assessments). The right hand was placed on a two-button response device, and, throughout testing, subjects were instructed to press the left or right button when the correct response was perceived on the middle (D3) or index (D2) finger, respectively.

Visual cueing was provided through a computer monitor during each of the experimental runs. The cues indicated when the experimental stimuli were being delivered and when subjects were to respond. Training trials conducted prior to each task familiarized subjects with the tests, and correct responses on three consecutive training trials were required prior to the start of each assessment. For some tests, subjects were provided with performance feedback during data acquisition. Certain protocols implemented a two-alternative forced-choice (2AFC) paradigm to determine sensory perceptual thresholds (see Tracking Algorithm).

Sensory perceptual metrics were easily and rapidly obtained for each subject (1 to 3 minutes per test), and the battery of tests consisted of three classes of protocols: reaction times (RT), vibrotactile detection thresholds (DT), and amplitude discrimination thresholds (AD) (see Neurosensory Assessments). The battery, from start to finish, lasted between 10 and 20 minutes depending on subject performance on each task.

Neurosensory Assessments

Reaction Times: Simple and Choice

The reaction time tasks required subjects to quickly and accurately respond to a tap (Figure 2.2.A.). Previous studies indicate that reaction times are correlated with white matter integrity (Kerchner, et al., 2012; Tamnes, Fjell, Westlye, Ostby, & Walhovd, 2012), sensorimotor integration, and attentional aspects in addition to other neurological mechanisms (Puts, Edden, Wodka, Mostofsky, & Tommerdahl, 2013).

For the simple reaction time (RTs) task, a single tap (300 μm amplitude, 40 ms duration) was delivered to one digit. Subjects were subsequently instructed to quickly click the response device as soon as the tap was perceived.

For the choice reaction time (RTc) task, the single tap was delivered to one of two digits (D2 or D3), the location of which was randomly selected on a trial-by-trial basis. Subjects were subsequently instructed to quickly click the left or right side of the response device corresponding to the stimulated digit as soon as the tap was perceived.

A randomized delay ranging from 2 to 7 seconds occurred between each of the 20 trials. Response times and accuracies were recorded for each of the trials, and the mean reaction times were determined by excluding the two slowest and two quickest reaction times and averaging the remaining 16 reaction times.

Detection Thresholds: Static and Dynamic

The detection threshold tasks required subjects to respond to a vibrotactile stimulus by accurately identify the locus of stimulation (Figure 2.2.B.). Previous studies indicate that detection thresholds are correlated with white matter integrity and feed-forward inhibitory

mechanisms presumed to occur in somatosensory cortical input layer IV (Favorov & Kurson, 2011; Gabernet, Jadhav, Feldman, Carandini, & Scanziani, 2005) in addition to others (Puts, Edden, Wodka, Mostofsky, & Tommerdahl, 2013). Two types of detection thresholds were determined and have been previously defined as static and dynamic thresholds (Zhang, Francisco, Holden, Dennis, & Tommerdahl, 2011). Static thresholds (DTs) were those obtained using suprathreshold stimuli which were constant in amplitude during an individual trial (the minimum detectable constant-amplitude stimulus) while dynamic thresholds (DTd) were those obtained using subthreshold stimuli in which the amplitude was modulated at a defined rate during an individual trial (the minimum detectable increasing-amplitude stimulus).

The feed-forward inhibitory mechanisms for the dynamic threshold task may occur as the initial subthreshold stimulus gradually increases in amplitude the detectable level. Inhibitory neurons are thought to respond more to subthreshold afferent thalamocortical drive than excitatory neurons effectively sharpening receptive field properties through excitatory suppression and consequently raising the threshold at which excitatory neurons begin to respond to peripheral stimuli (Favorov & Kurson, 2011).

For the static detection threshold (DTs) task, a vibrotactile stimulus (initial parameters: 15 μm amplitude, 500 ms duration, 25 Hz flutter frequency) was delivered to one of the two digits (D2 or D3). Following each stimulus, subjects were prompted to select the digit on which they perceived a weak stimulus. Thresholds were determined over 20 trials using a two-alternative forced-choice (2AFC) tracking algorithm (see Tracking Algorithm).

For the dynamic threshold (DTd) task, after a delay period without stimulation (six randomized delay (D) conditions of 0, 0.5, 1, 1.5, 2, and 3 s), the device delivered a continuous stimulus beginning at 0 μm (25 Hz flutter frequency) to one of the two digits (D2 or D3). The

stimulus increased at a rate of 2 μm/s, and subjects were instructed to select the digit on which they first perceived the stimulus. The dynamic threshold task consisted of 7 trials (two trials with no delay), and the stimulus amplitude at the time of the response was recorded.

A fixed inter-trial interval (ITI) of 5 s occurred between each of the trials, and the stimulus location was randomly selected on a trial-by-trial basis. Detection thresholds were recorded for each of the trials, and the mean static thresholds were determined by averaging the last 5 test amplitudes recorded. The mean dynamic thresholds were determined by averaging the test amplitudes recorded across all trials.

Amplitude Discrimination Thresholds: without and with Adaptation

The amplitude discrimination tasks required subjects to accurately identify one of two digits (D2 or D3) which received the larger of two simultaneously-delivered vibrotactile stimuli (Figure 2.2.C.). Amplitude discriminative capacity was defined as the minimal, or just-noticeable, difference in amplitudes of two mechanical sinusoidal vibratory stimuli in which an individual was able to successfully identify the stimulus of larger magnitude. Previous studies indicated that amplitude discrimination thresholds are correlated with lateral inhibitory mechanisms (Tannan, Dennis, & Tommerdahl, 2005), that they follow Weber's Law (Francisco, Tannan, Zhang, Holden, & Tommerdahl, 2008), and that pre-exposure to relatively brief periods of single-site conditioning stimulation significantly elevates discriminative thresholds (Tannan, Simons, Dennis, & Tommerdahl, 2007; Tannan, Whitsel, & Tommerdahl, 2006).

Sensory adaptation is an important fundamental neural mechanism involved in central information processing (Hollins, Goble, Whitsel, & Tommerdahl, 1989; Tannan, Simons, Dennis, & Tommerdahl, 2007; Tannan, Whitsel, & Tommerdahl, 2006). Impairments in the

ability to adapt to conditioning stimulation is suspected to be associated with disruption in the balance of excitation and inhibition (Heiss, Katz, Ganmor, & Lampl, 2008; Higley & Contreras, 2006), which can lead to inefficient neural coding (Reinagel, 2001). Neurophysiological studies have demonstrated that repetitive stimulation results in temporal changes in cortical activity, the most prominent of which is a reduction in cortical response with extended stimulus duration. At the single-cell level, somatosensory cortical pyramidal neurons have been shown to undergo prominent stimulus-dependent modifications of their receptive fields and their response properties with repetitive stimulation. These alterations can develop within milliseconds of stimulus onset and can diminish within seconds following stimulus termination (Kohn & Whitsel, Sensory cortical dynamics., 2002; Tommerdahl, et al., 1996; Tommerdahl, Delemos, Favorov, Metz, & Whitsel, 1998; Tommerdahl M. , Simons, Chiu, Favorov, & Whitsel, 2005; Tommerdahl M. , et al., 2005). At the neuronal population level, optical imaging studies have also characterized the short-term dynamics of the primary somatosensory (S1) cortical response using various amplitudes and durations of vibrotactile stimulation (Chiu, Tommerdahl, Whitsel, & Favorov, 2005; Simons, et al., 2005; Simons, Chiu, Favorov, Whitsel, & Tommerdahl, 2007). Previous studies led to the hypothesis that centrally-mediated adaptation is dependent on several factors including, but not limited to, the balance between inhibitory γ-aminobutyric acid (GABA) and excitatory N-methyl-D-aspartate (NMDA) receptor-mediated neurotransmission in addition to neuron-glial interactions. Reduced adaptation in a number of clinical populations have suggested imbalance in these mechanisms (Tannan, Holden, Zhang, Baranek, & Tommerdahl, 2008; Tommerdahl, Tannan, Cascio, Baranek, & Whitsel, 2007; Tommerdahl, Tannan, Holden, & Baranek, 2008). Furthermore, human studies showed that dextromethorphan (DXM), an

NMDA receptor antagonist, can also suppress the effects of sensory adaptation (Folger, Tannan, Zhang, Holden, & Tommerdahl, 2008).

For the simple amplitude discrimination (ADs) task, the device delivered simultaneous stimuli (initial stimulus parameters: 400 μm test, 200 μm standard, 25 Hz, 500 ms, 20 μm step size) to D2 and D3 over 20 trials. Thresholds were determined over 20 trials using a two-alternative forced-choice (2AFC) tracking algorithm (see Tracking Algorithm), and test amplitudes were recorded for all trials.

For the amplitude discrimination task in the presence of single-site adaptation (ADssa), the device delivered a vibrotactile conditioning stimulus (constant stimulus parameter: initial test amplitude in μm, 25 Hz, 1000 ms) one second prior to the delivery of the paired test and standard stimuli. The result of such a protocol modification is that the discriminative threshold, or difference limen (DL), is typically significantly elevated following pre-exposure to a single-site conditioning stimulation compared to the simple amplitude discrimination threshold (Tannan, Simons, Dennis, & Tommerdahl, 2007; Tannan, Whitsel, & Tommerdahl, 2006). Thresholds were determined over 20 trials using a two-alternative forced-choice (2AFC) tracking algorithm (see Tracking Algorithm), and test amplitudes were recorded for all trials.

A fixed inter-trial interval (ITI) of 5 s occurred between each of the trials, and the loci of the test and standard stimuli were randomly selected on a trial-by-trial basis. The magnitude of the test stimulus was always greater than that of the standard stimulus. The mean thresholds were determined by averaging the last 5 test amplitudes recorded in each task. The standard amplitude was subtracted from the mean thresholds to obtain difference limens (DL), and these DLs were then divided by the standard to obtain the Weber fraction (WF) for comparison across different standard amplitudes. When the conditioning stimulus is delivered at the same site as the test

stimulus, the gain effect of adaptation, or the reduction of the perceived intensity of the stimulus, can be quantified by comparing thresholds obtained in absence and in the presence of single-site adaptation stimulation.

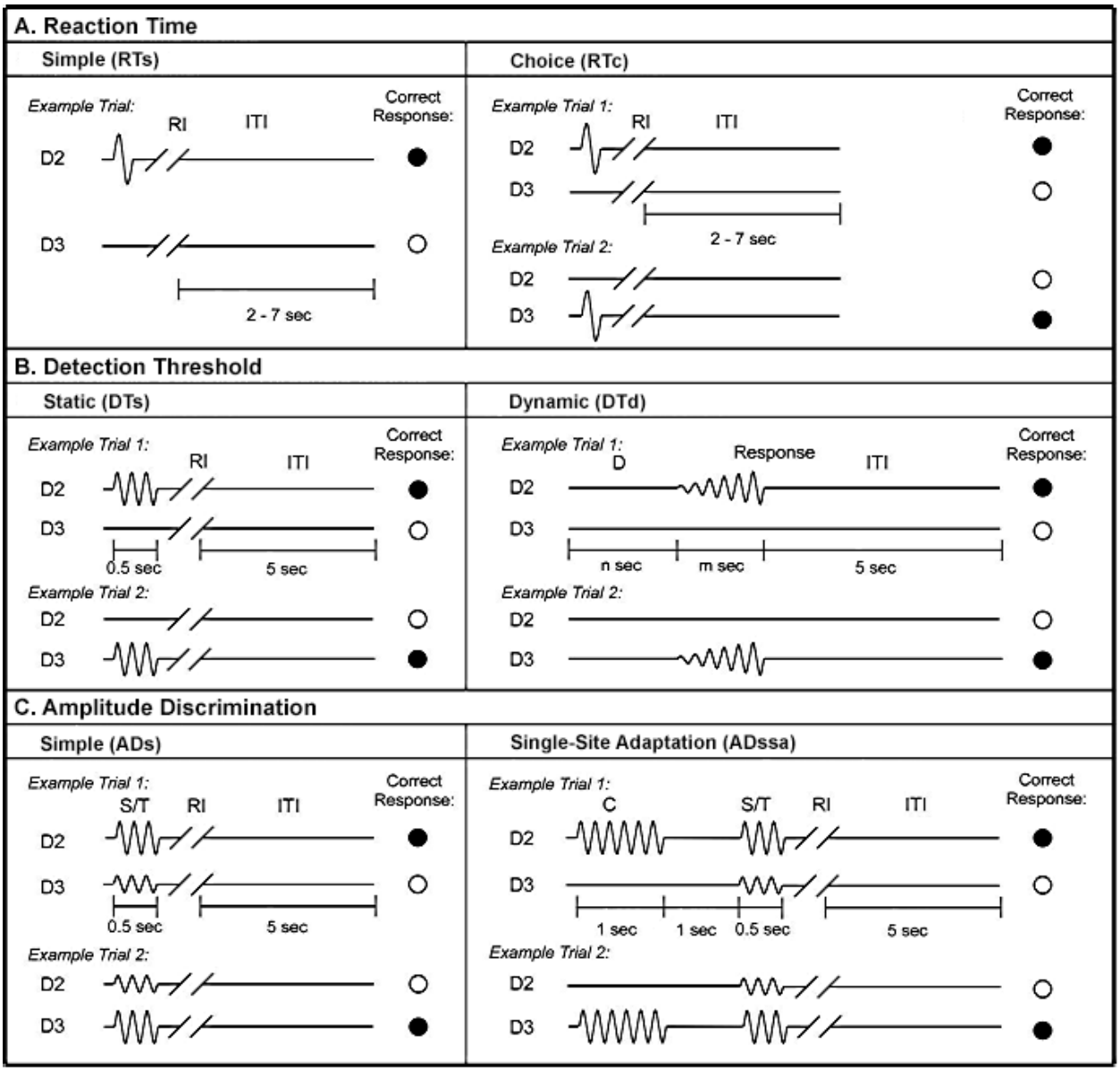

Figure 2.2. Schematic Diagrams of Experimental Protocols.

Tracking Algorithm

Thresholds (DTs, ADs, and ADssa) for each subject were obtained via a two-alternative forced-choice (2AFC) modified Georg von Békésy tracking algorithm (Green & Swets, 1966) (Figure 2.3.). Based on previous responses of the subjects, test stimulus amplitudes were modified until the completion of the protocols. During the first 10 trials, a 1-up/1-down algorithm was implemented for the purposes of rapid amplitude modification. Correct responses resulted in the lowering of the magnitude of the test stimulus while incorrect responses raised the amplitude of the test stimulus. In the remaining 10 trials, the amplitude was varied using a 2-up/1-down algorithm whereby two incorrect responses were required to raise the amplitude of the test stimulus. The rationale for implementing these algorithms was to initially expedite determination of vibrotactile discriminative range (Tannan, Dennis, Zhang, & Tommerdahl, 2007).

Data Analysis

Reaction times, detection thresholds, and Weber fractions were calculated for each subject, and metrics were averaged across each population by age. In order to normalize the results by each subject and analyze the effect of the secondary metric based on the primary metric (the effect of choice on reaction time, the effect of feed-forward inhibition on detection thresholds, and the effect of single-site adaptation on amplitude discrimination), the ratios of the metrics were also calculated. These calculations were arbitrarily converted to percentages where larger values implied that the secondary metric significantly affected performance compared to the primary metric.

Two-sample, one-tailed t-tests, were used to evaluate the difference in the performance of healthy control metrics on primary and secondary metrics across the age spectrum. The data are presented as means and standard errors of the means. A probability (p-value) of less than 0.05 was considered statistically significant.

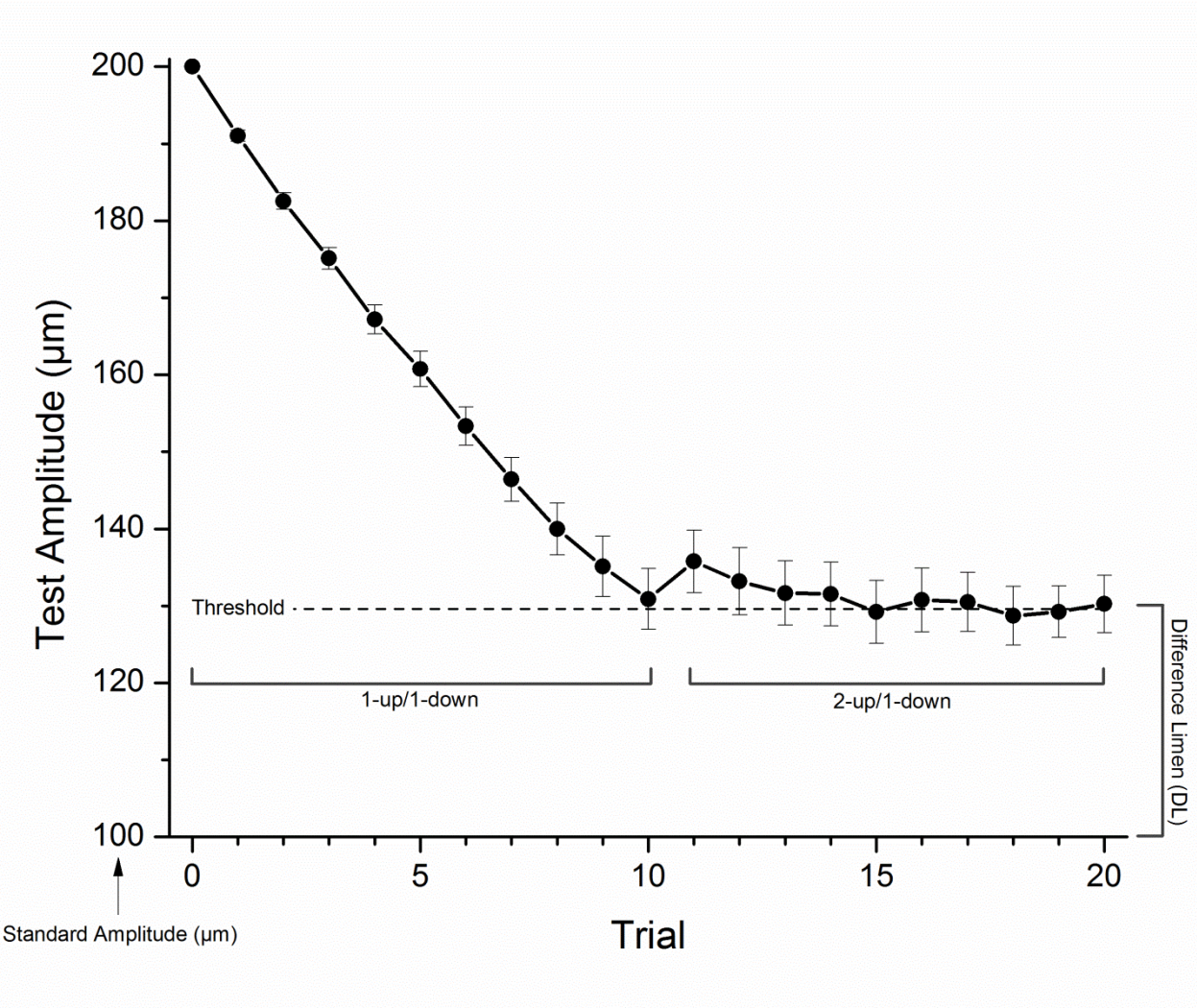

Figure 2.3. Tracking Algorithm for Amplitude Discrimination.

Summary of Control Metrics

Control data from previous studies were analyzed to provide a foundation with which to compare metrics obtained from clinical populations. The majority of subjects performed worse on secondary metrics than on primary metrics (RTc>RTs=92.73 %, DTd>DTs=93.33 %, and ADssa>ADs=76.22 %) across all classes of protocols (Table 2.1., Figure 2.3., ***p<<0.01). With increasing age, reaction times became significantly slower (Figure 2.3.A.) and detection thresholds became significantly higher (Figure 2.3.C.) while there was little effect of age on amplitude discrimination thresholds (Figure 2.3.E.). Furthermore, the ratio of the secondary metric to the primary metric was reduced with increasing age only for the detection threshold task suggesting progressive impairment in feed-forward inhibitory mechanisms (Figure 2.3.D., ***p=0.0006) while there was no significant change in the reaction time (Figure 2.3.B.) or amplitude discrimination tasks (Figure 2.3.F.) over increasing age. The results of the analysis were in accordance with previously-published data exploring the effect of age on sensory perceptual metrics (Zhang, Francisco, Holden, Dennis, & Tommerdahl, 2011).

These sensory perceptual metrics can be useful in assessing brain dysfunction as a database has been developed in order to establish standard cutoff thresholds for healthy performance. These data can be age-matched and compared to patient populations in order to evaluate brain functionality under the rationale that these populations undergo systemic alterations and plastic changes in central information processing. Understanding the average control values can reveal insight into defining healthy and unhealthy information processing. In order to avoid effects of age on the sensory perceptual metrics, the clinical applications focused on the young adult population defined to be subjects between 18 and 29 years of age (Table 2.1.).

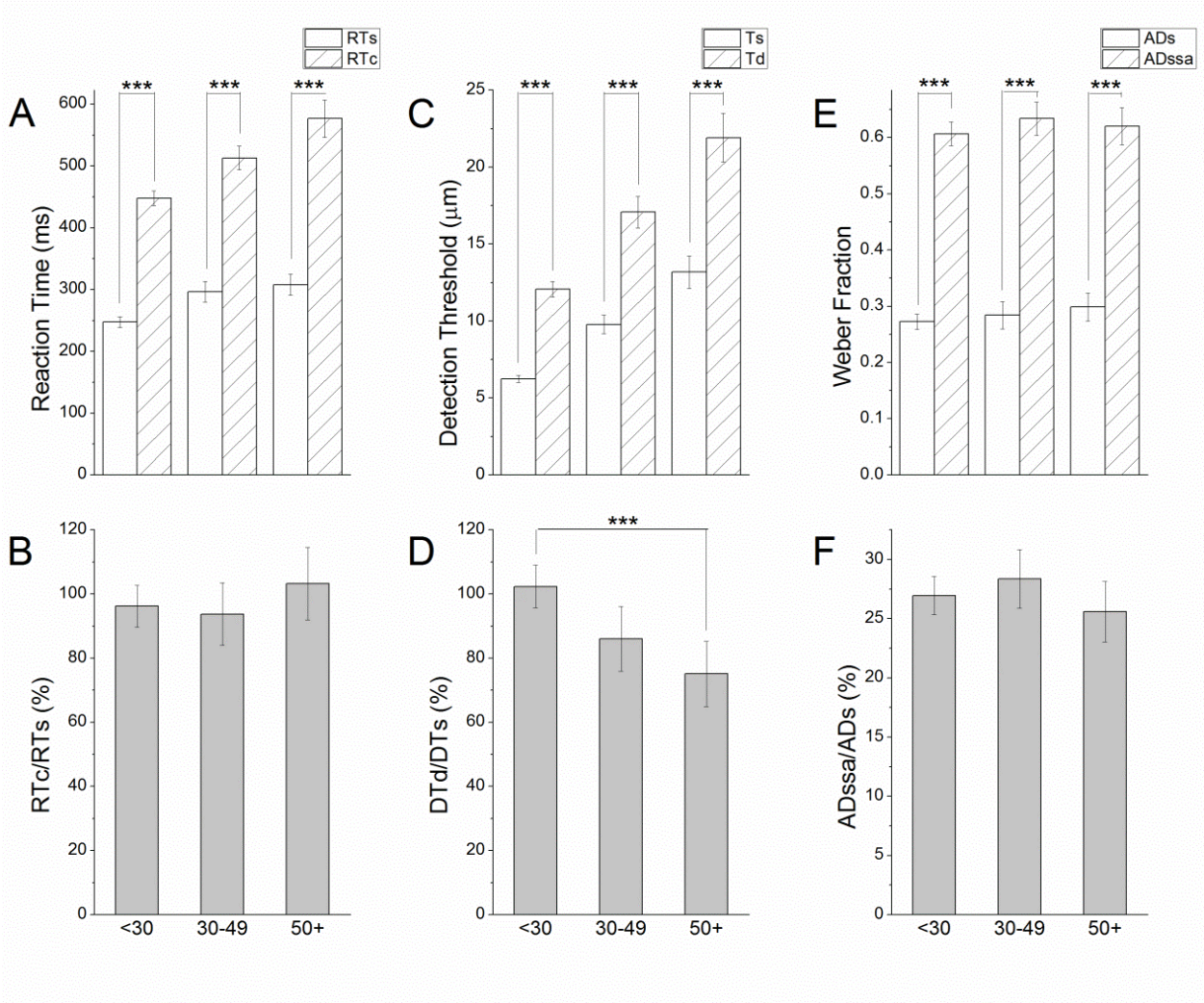

Figure 2.4. Summary of Control Metrics by Age.

Table 2.1. Summary of Control Metrics for Young Adults.

Protocol	Primary Metric	Secondary Metric	Neurobiological Process	N
Reaction Time	247.3±8.9 ms	447.7±11.9 ms (92.73 %, N=220*)	• White Matter Integrity • Sensorimotor Integration • Attention, Fatigue • Choice, Decision	N=101**
Detection Threshold	6.3±0.2 μm	12.1±0.5 μm (93.33 %, N=195*)	• White Matter Integrity • Feed-Forward Inhibition	N=119**
Amplitude Discrimination	27.3±1.3 %	60.7±2.1 % (76.22 %, N=286*)	• Lateral Inhibition • Short-Term Potentiation	N=139**

*all ages
**age <30 years old

CHAPTER 3. CLINICAL APPLICATIONS

Sensory perceptual metrics were assessed in young adults (ages 18 to 29 years) in three different clinical populations—migraines, alcoholism, and concussion—to analyze if particular measures were uniquely sensitive to changes in central information processing. Results from Section 3.1 and Section 3.2 were adapted from published work (Nguyen, et al., 2013a; Nguyen, et al., 2013b). The migraine population was analyzed as an extension of previous research regarding the effect of chronic pain conditions on these metrics (Nebel, et al., 2010; Zhang, et al., 2011). The effect of alcohol consumption on these metrics was also analyzed due to previous research supporting particular neurobiological mechanisms involved in modulating vibrotactile adaptation (Folger, Tannan, Zhang, Holden, & Tommerdahl, 2008). Lastly, the impact of mechanical injury on these metrics was assessed in order to determine if recovery could be tracked over time following concussions. The results are expected to show that, throughout these populations, systemic and focal effects on central information processing through endogenous neurological imbalance, chronic drug exposure, and mechanical injury, respectively, account for significant alterations in sensory perceptual metrics. Differences among these metrics are emphasized, and the combined results are used to differentiate these populations.

Section 3.1. Migraines

Background

Pain perception is a unique sensory experience involving complex associations among sensory stimuli and neuropsychological factors such as cognition and emotion. Peripheral nociceptors in the form of free nerve endings detect and transmit two forms of pain: sharp and aching. While sharp pain is quickly transmitted via Aδ fibers (5-30 m/s), aching pain is processed more slowly via C fibers (0.5-2 m/s) (Abraira & Ginty, 2013). These pain signals propagate through spinothalamic tracts where they are somatotopically processed in the primary (S1) and/or secondary (S2) somatosensory cortices (Omori, et al., 2013). Because pain perception can be modulated through central mechanisms, objective approaches to quantifying pain have been extensively studied in order to understand the neurobiological and psychological influences involved in the experience (Cruz-Almeida & Fillingim, 2014).

The presence of pain can affect the perception of non-painful somatosensory stimuli through touch gating, a phenomenon involving sensory interactions rather than resulting from attentional distraction (Apkarian, Stea, & Bolanowski, 1994; Harper & Hollins, 2012). In some instances, pain sensitivity can increase due to temporal summation, an NMDA receptor-dependent wind-up mechanism that occurs resulting from repetitive, frequency- and intensity-dependent stimulation over time (Herrero, Laird, & Lopez-Garcia, 2000). This mechanism may be responsible for hyperalgesia, where normally painful stimuli are perceived as increasingly painful, or allodynia where non-painful stimuli are perceived as painful (Sandkuhler, 2009). Chronic pain conditions may induce sensitization through cortical reorganization and/or descending modulations resulting in altered sensory thresholds and/or pain tolerances (Gustin, et al., 2012; Kyranou & Puntillo, 2012; Woolf, 2011)

Many chronic pain conditions are poorly understood, have few quantifiable biological markers for screening, and can involve a variety of differential or comorbid diagnoses inclusive of, but not limited to, migraines, fibromyalgia (FM), irritable bowel syndrome (IBS), temporal mandibular disorder (TMD), and vulvar vestibulitis syndrome (VVS) among others. Evaluations are primarily dependent on subjective reports of pain and subsequent impact on mood and/or function, all of which are difficult to objectively standardize among clinical populations. This dependence on subjectivity begins from diagnosis and continues throughout evaluation of treatment efficacy in order to determine the severity of impairment or disability. These qualitative reports may be biased by various factors that are unrelated to symptoms resulting in patients who might catastrophize symptoms due to anxiety, depression, or other issues related to secondary pain (Quartana, Campbell, & Edwards, 2009). Thus, there is a compelling need for a more objective measure of pain that can track deteriorations or improvements in, and/or chronification of, chronic pain symptoms over time.

In the case of primary headache disorders such as migraines, few objective tests are available to assess the burden of illness or track progression over time. This may be due to the fact that the causes of migraines are still poorly understood. The etiology of migraines is presumed to involve triggers such as cortical spreading depression, trigeminovascular activation, and/or sensitization mechanisms (Eikermann-Haerter & Ayata, 2010; Kojic & Stojanovic, 2013). More specifically, trigeminal activation is thought to trigger neuropeptide release subsequently leading to meningeal vasodilation and neuroinflammation. Signals are then transmitted through the brainstem into the cortex promoting waves of spontaneous depolarizations in the form of cortical spreading depression which can cause pain associated with migraines. Current treatments for migraines include pharmacotherapies targeting reduction of cortical hyper-excitability

(topiramate, divalproex) or modulation of trigeminovascular activation (propanalol, timolol, and onabotulinumtoxin A).

Sensory assessments of migraines have been previously explored with the rationale that many patients are particularly vulnerable to sensory stimuli such as light (photophobia), noise (phonophobia), and even odors (osmophobia) during attacks (Ambrosini & Schoenen, 2006). These alterations are supported by the observation of abnormal response patterns in the primary sensory cortices in relation to neuronal excitability and habituation mechanisms in subjects with migraine (Ambrosini & Schoenen, 2006; Coppola & Schoenen, 2012; Coppola, Pierelli, & Schoenen, 2009; Schoenen, 1996). The evaluations revealed altered sensory thresholds for certain forms of non-painful and painful somatosensory stimuli (Karanovic, Thabet, Wilson, & Wilkinson, 2011; Ladda, Straube, Förderreuther, Krause, & Eggert, 2006; Schwedt, Krauss, Frey, & Gereau IV, 2011; Zappaterra, Guerzoni, Cainazzo, Ferrari, & Pini, 2011). Based on previous research, alterations in central information processing due to migraines are expected to be reflected in sensory perceptual metrics, which have been demonstrated to be sensitive to evaluating chronic pain conditions (Nebel, et al., 2010; Zhang, et al., 2011), neurodegenerative conditions (Nelson, et al., 2012) and developmental conditions such as autism (Tannan, Holden, Zhang, Baranek, & Tommerdahl, 2008).

A battery of tests (see Neurosensory Assessments) was administered to young adults screened as healthy controls as well as those screened to have symptoms of episodic migraines (EM). These sensory perceptual metrics provided quantitative indices of brain function which were presumed to be associated with chronic pain conditions. In particular, discriminative sensory metrics for episodic migraineurs in the presence of conditioning stimulation were expected to differ from healthy controls due to neurological dysfunction brought about by

cortical spreading depression resulting in cortical hyper-excitability (Coppola & Schoenen, 2012), impairment of habituation mechanisms (Ambrosini & Schoenen, 2006; Coppola, Pierelli, & Schoenen, 2009; Schoenen, 1996), and/or sensitization (Nebel, et al., 2010; Zhang, et al., 2011). The results of this study demonstrated that certain metrics of central information processing were significantly altered in young adult episodic migraineurs. The long-term objective of the study was to develop methods that can improve diagnosis and can enable more accurate assessments of treatment efficacy for migraineurs. Such quantitative metrics could significantly improve the analysis of underlying mechanisms as these objective measures could be used for quantitatively assessing impact of treatment on patient-centered studies. Furthermore, this method of non-painful quantitative sensory testing allows analysis of metrics that cannot be gained by pain testing and that may serve as an alternative biomarker for pain processes.

Methods

Subjects

Following International Review Board approval and informed consent, 43 subjects ranging from 18 to 29 years of age were recruited from the Dental Research Center (DRC) at the University of North Carolina at Chapel Hill (UNC-CH) to participate in the study. These subjects included healthy controls (n=30) and episodic migraineurs (EM, n=13). All subjects completed a survey on current medications and medical history prior to the experimental tests to exclude participants with any history of neurological impairment other than chronic pain conditions. Subjects were permitted to withdraw from sensory testing due to fatigue prior to the completion of the battery. The subjects were naïve to the study design and blinded to the issue under investigation.

Screening Assessments

Subjects were screened via Computer-Assisted Telephone Interviews (CATI) resulting in a subset of the episodic migraineurs (n=7) being categorized with one or more comorbidities including FM, IBS, TMD, and/or VVS.

Neurosensory Assessments

Six sensory perceptual metrics were analyzed. The reaction times (RTs and RTc) and detection thresholds (DTs and DTd) were determined according to standard protocol parameters (see Neurosensory Assessments). The amplitude discrimination task was performed in the absence (ADs) and presence (ADssa) of single-site adaptation with standard amplitude of 400 μm and initial test amplitude of 800 μm.

Data Analysis

Two-sample, one-tailed t-tests, were used to evaluate the difference in the performance of the episodic migraine population as compared to control metrics. The data are presented as means and standard errors of the means. A probability (p-value) of less than 0.05 was considered statistically significant.

Results

Reaction times and detection thresholds in episodic migraineurs were similar to those in controls.

The mean simple reaction times were significantly quicker than choice reaction times for both the episodic migraineurs (361.2±36.7 ms versus 566.1±43.9 ms, ***p=0.0002, n=13, Figure 3.1.A) and for the controls (314.0±16.8 ms versus 536.0±25.1 ms, ***p<<0.01, n=30, Figure 3.1.A). Furthermore, both the simple and choice reaction times (p=0.13 and p=0.28, respectively), as well as the effect of choice on reaction times (85.5±13.5 % for controls versus 67.2±12.7 % for migraineurs, p=0.17, Figure 3.1.B) were similar across both populations.

The mean static detection thresholds were significantly lower than dynamic detection thresholds for both the episodic migraineurs (6.7±1.2 μm versus 10.7±0.8 μm, *p=0.02, Figure 3.1.C) and for the controls (5.8±0.3 μm versus 10.1±0.5 μm, ***p<<0.01, Figure 3.1.C). Furthermore, both the static and dynamic detection thresholds (p=0.23 and p=0.29, respectively), as well as the effect of feed-forward inhibition on detection thresholds (86.1±11.0 % for controls versus 105.7±30.7 % for migraineurs, p=0.28, Figure 3.1.D) were similar across both populations.

The effect of adaptation on amplitude discrimination was reduced for episodic migraineurs as compared to that in controls.

The mean Weber fractions for amplitude discrimination were significantly affected by single-site adaptation in controls (0.286±0.024 versus 0.491±0.051, ***p=0.0002, Figure 3.1.E) but not in episodic migraineurs (0.442±0.086 versus 0.503±0.114, p=0.29, Figure 3.1.E). Simple adaptation difference limens across both populations almost reached significance (p=0.05), but

adaptation conditions for amplitude discrimination (p=0.47) were similar across both populations (Figure 3.1.E). Additionally, while the mean effect of adaptation on amplitude discrimination was lower in episodic migraineurs versus controls, this effect was not statistically significant (16.5±4.0 % for controls vs 6.1±7.2 % for migraineurs, p=0.11, Figure 3.1.F).

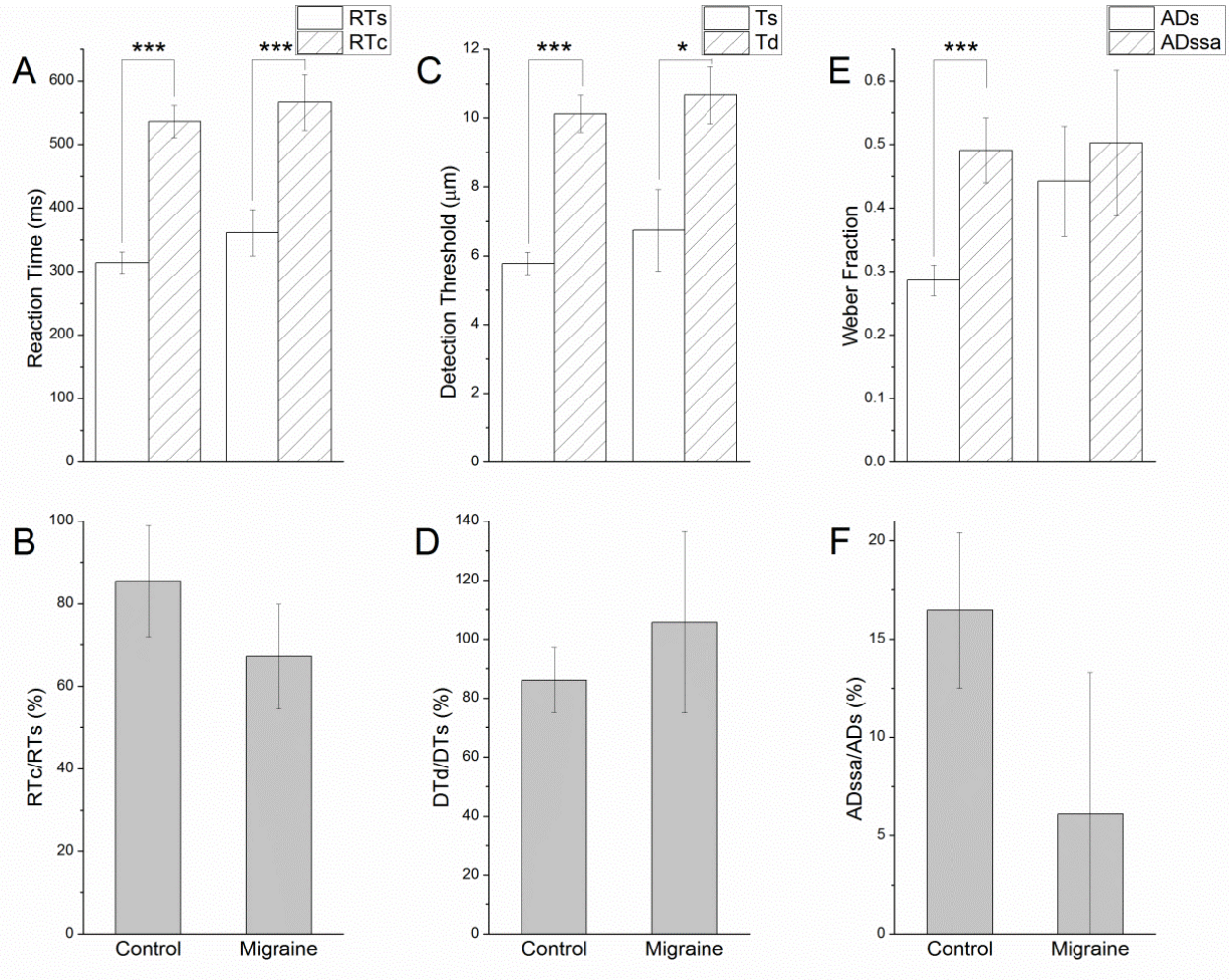

Figure 3.1. Sensory Perceptual Metrics of Episodic Migraineurs versus Controls.

Amplitude discrimination thresholds varied across other pain conditions.

Amplitude discrimination difference limens in the absence and presence of single-site adaptation were compared among healthy controls (n=80) and chronic pain subjects regardless of age (EM, n=47; FM, n=23; IBS, n=44; TMD, n=19; VVS, n=15) (Figure 3.2.). While subjects with FM and IBS responded to conditioning stimulation, subjects with EM, TMD, and VVS showed a reduced ability to adapt, which is in accordance with some previous findings (Zhang, et al., 2011).

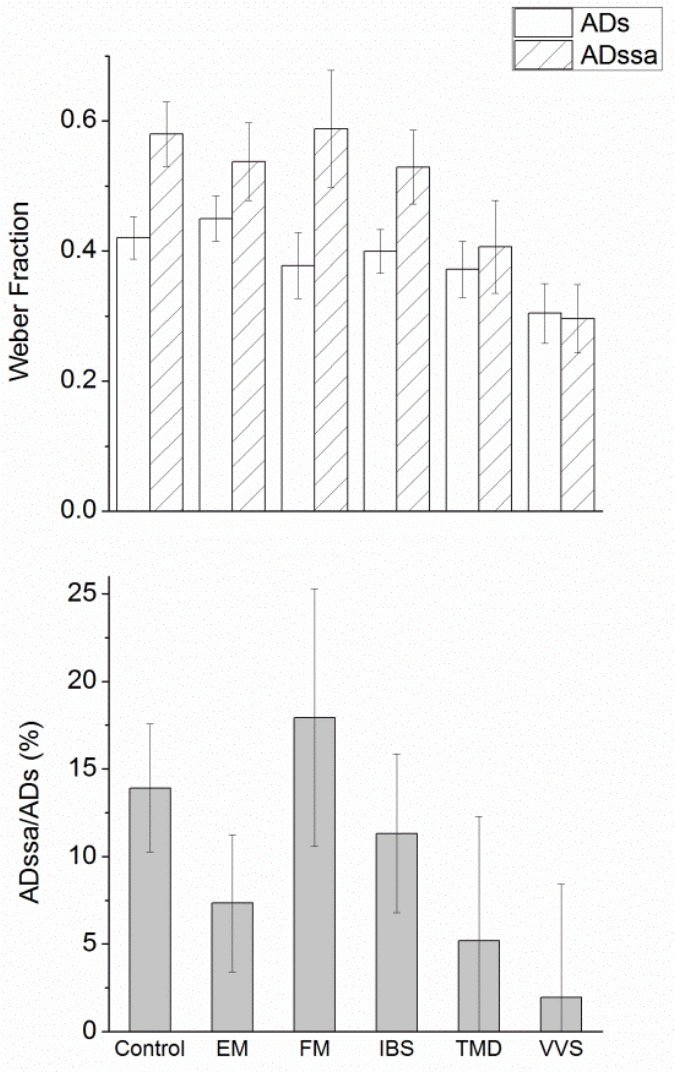

Figure 3.2. Amplitude Discrimination Thresholds across Other Pain Conditions.

Discussion

In this study, six sensory perceptual metrics were obtained in young adults screened for symptoms of episodic migraines. The results of the study demonstrated that, although reaction times and detection thresholds of episodic migraineurs did not significantly differ from controls, metrics reflecting lateral inhibitory mechanisms and the effect of adaptation on amplitude discriminative thresholds were significantly different from controls. Furthermore, differences in lateral inhibitory mechanisms and adaptation may vary across chronic pain conditions.

There were no significant differences found between observations obtained from the episodic migraineurs and healthy control subjects on reaction time and detection threshold tasks which suggest that, for the subjects within this study, peripheral neuropathy may not appear to be a manifestation of migraine. While previous research has shown increased thresholds for thermal and mechanical noxious stimuli (an anti-nociceptive effect), there have been few reports analyzing differences in detection thresholds of non-noxious vibrotactile stimuli (Ladda, Straube, Förderreuther, Krause, & Eggert, 2006). Reduced dynamic thresholds relative to static thresholds have been previously observed in particular groups of women with vulvodynia (Zhang, et al., 2011). In a larger or more specific population of migraine patients, similar trends might be more evident, so future research must necessarily be conducted to verify if sensory thresholds are altered in this clinical population.

Previous reports have suggested that there may be dysfunction in the balance between excitatory and inhibitory neurotransmission with migraine (Cosentino, et al., 2011; Coppola & Schoenen, 2012), and this imbalance could be caused either by excessive excitation or by insufficient inhibition. Such systemic cortical hyper-excitability would predictably interfere with discrimination between two simultaneously-activated cortical areas such as in the amplitude

discrimination task. Previous studies have shown that suppressing inhibition with GABA receptor antagonists decreases the resolution of the activity evoked by two electrically-stimulated sites in sensorimotor cortical slice (Kohn, Metz, Quibrera, Tommerdahl, & Whitsel, 2000). Thus, amplitude discriminative capacity might prove to be a sensitive metric of cortical hyper-excitability for sufferers of episodic migraines.

Impairment of sensory habituation in migraineurs has been a promising biomarker for headache research and has shown to affect multiple sensory modalities (Ambrosini & Schoenen, 2006; Coppola, Pierelli, & Schoenen, 2009). In the young adult episodic migraine population, although amplitude discriminative capacity was relatively elevated in comparison to controls, the impact of the conditioning stimulation on the discriminative task was also reduced. These results indicate that the healthy controls adapted to the conditioning stimulus while the episodic migraineurs failed to do so. Previous studies support the concept that lack of habituation in migraineurs may be to be due to increased neuronal excitability or decreased inhibitory mechanisms while conflicting evidence suggest that lowered pre-activation levels may contribute to lack of habituation (Coppola, et al., 2005). The results of this study are more consistent with previous research analyzing the balance between excitatory and inhibitory neurotransmission in observing that migraineurs show a reduced adaptation metric, which is associated with short-term potentiation or habituation, in comparison to healthy control subjects (Ambrosini & Schoenen, 2006; Coppola & Schoenen, 2012; Coppola, Pierelli, & Schoenen, 2009; Schoenen, 1996).

Although the neurobiological mechanisms involved in migraine etiology are only partially understood, accumulating evidence suggests that structural, functional, and pharmacologic changes occur in the brains of migraineurs. Structural changes include subcortical

white matter lesions and iron deposits in the periaqueductal gray region (Kruit, van Buchem, Launer, Terwindt, & Ferrari, 2010). Functional alterations include focal areas of brain hypo-metabolism, cortical hyper-excitability, central sensitization, and dysfunction in thalamic gating to modulate sensory input (Brighina, Palermo, & Fierro, 2009; Coppola & Schoenen, 2012; Siniatchkin, et al., 2011). Previous studies also suggest involvement from pre- and post-synaptic mechanisms as well as glial interactions that may be associated with hyper-responsiveness and/or cortical spreading depression (Aurora, Kulthia, & Barrodale, 2011; Weir & Cader, 2011). Pharmacologic influences include paradoxical responses to opioids and changes in levels of excitatory amino acids in the anterior cingulate gyrus and insula (Bahra, Walsh, Menon, & Goadsby, 2003). The presence of such alterations in brain physiology suggests the potential for a biologically-based assessment to quantify and measure these differences with scores that could be characterized, validated, and tracked over time. The long-term objective of this work is to develop methods that can improve diagnosis and enable more accurate assessments of treatment efficacy for headache populations. Currently, there are no standardized methods for objective, quantitative tools to measure the impact that headache has on cortical information processing, or the degree to which treatments are effective. The non-invasive technique reported in this study has the potential to be utilized in a manner that could enable improvements in diagnosis and assessments of treatment efficacy.

Section 3.2. Alcoholism

Background

A number of studies have shown that chronic alcohol use can lead to sensory impairment and/or altered central processing. Sensory assessments of individuals with alcoholism, in particular assessments of vibration thresholds, thermal sensitivities, and pain tests, have provided useful metrics in detecting and describing alcoholic peripheral neuropathy (Hilz, Claus, Neundorfer, Zimmermann, & Beric, 1994; Hilz, et al., 1995; Jochum, Boettger, Burkhardt, Juckel, & Bar, 2010; Sosenko, et al., 1991; Yamitsky & Zaslansky, 1998). Impairment in central neural mechanisms in individuals with alcohol use disorders has also been demonstrated by analyzing sensory evoked potentials (Marco, Fuentemilla, & Grau, 2005).

Alcohol consumption among college students, a population which is particularly susceptible to moderate to heavy binge drinking (Grant, et al., 2004; Wechsler & Nelson, 2001; Wechsler, et al., 2002), has been shown to impair a variety of centrally-mediated functions of the nervous system inclusive of, but not limited to, spatial memory judgment and decision-making, mood and behavior, motor performance, learning, executive functioning, and rate of information processing (Courtney & Polich, 2009). These studies suggest that central information processing could be significantly impacted with long-term alcohol use by college-aged students.

A battery of tests (see Neurosensory Assessments) was administered to college students screened for alcohol consumption and related behaviors. This study serves as an extension of previous research exploring the role of adaptation mechanisms on sensory perception (Folger, Tannan, Zhang, Holden, & Tommerdahl, 2008). Standard screening methods of alcohol consumption (Timeline Followback, TLFB; Alcohol Use Disorders Identification Test, AUDIT; Rutgers Alcohol Problems Index, RAPI; Gormally Binge Eating Scale, BES; Tridimensional

Personality Questionnaire, TPQ; Family History, FH) and hedonic preferences to sucrose solutions (sweet liking phenotype, SL) were paired with sensory perceptual metrics in order to assess potential sensory information processing changes in college-aged students who consumed alcohol on a regular basis. Evaluations assessing hedonic responses to sucrose concentrations were conducted because the sweet liking phenotype is often associated with alcohol-related behavior (Garbutt, et al., 2009; Lange, Kampov-Polevoy, & Garbutt, 2010). The results of the study suggested that the sensory perceptual metrics which are presumed to predominantly be peripherally-mediated were relatively insensitive to change with increased alcohol use, while metrics centrally-mediated metrics were significantly altered with increased consumption.

Methods

Subjects

Following International Review Board approval and informed consent, 67 college students ranging from 18 to 26 years of age were recruited through electronic mail announcement from the Office of the Vice Chancellor of Student Affairs at the University of North Carolina at Chapel Hill (UNC-CH). These subjects included light (n=22), moderate (n=33), and heavy (n=12) drinkers screened for alcohol consumption via the Timeline Followback (TLFB) assessment and the Alcohol Use Disorders Identification Test (AUDIT). All subjects completed a survey on current medications and medical history prior to the experimental tests to exclude participants with any history of neurological impairment. The subjects were naïve to the study design and blinded to the issue under investigation.

Screening Assessments

Two screening assessments were implemented to determine the alcohol consumption of each of the subjects. The Timeline Followback (TLFB) method (Sobell, Sobell, Leo, & Cancilla, 1988) was administered to estimate alcohol consumption in a timeframe of one month (drinks per month, DPM). Alcohol consumption was defined by the product of the number of episodes in which subjects consumed alcohol per month and the drinks that they consumed per drinking day. The Alcohol Use Disorders Identification Test (AUDIT) (Schmidt, Barry, & Fleming, 1995) was a screening tool used to categorize the subjects according to risk for alcohol problems. Typically scores below 8 were considered low risk for alcohol problems while scores above 16 represented high risks for alcohol problems. According to these two screening tools, and considering the definition of moderate drinking by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the subjects were categorized as light (DPM<30 and AUDIT<8, n=22), moderate (DPM≤60 or AUDIT≥8, n=33), and heavy (DPM>60 and AUDIT≥8, n=12) drinkers.

Additional evaluations were also considered for comparison. The Rutgers Alcohol Problems Index (RAPI) (Neal, Corbin, & Fromme, 2006; White, Labouvie, & Papadaratsakis, 2005) was a tool used to assess drinking problems where scores less than 10 were considered low risk. Moreover, the Gormally Binge Eating Scale (BES) (Gormally, Black, Daston, & Rardin, 1982) was an evaluation used to assess binging characteristics in relation to substance abuse where scores less than 27 were considered low risk.

Sweet liking (SL) and novelty seeking (NS) phenotypes have been previously studied in the alcoholism population (Garbutt, et al., 2009; Lange, Kampov-Polevoy, & Garbutt, 2010). Sweet liking (SL) was determined via hedonic responses of pleasure towards varying sugar concentrations (0.05 to 0.8 M solutions) and was measured by utilizing visual analog scales

(VAS) of preference to unsweet or sweet solutions. The responses were subsequently categorized by the sign of their slopes, which were calculated as the change in hedonic response scale over the change in the sugar concentrations measured in units per concentration (M^{-1}). Negative hedonic response slopes were categorized as sweet dislikers (SL-) and positive slopes were categorized as sweet likers (SL+) regardless of the magnitude of the values. Novelty seeking (NS) was determined via one of three components (Novelty Seeking, NS; Harm Avoidance, HA; Reward Dependence, RD) of the Tridimensional Personality Questionnaire (TPQ) (Cloninger, 1987). Based on previous research, only the novelty seeking phenotype was considered for analysis, and the cutoff for determining low (NS-) versus high (NS+) novelty seeking characteristics was a score of 15.

Family history (FH) of alcoholism was also analyzed to provide further insight as to whether subjects with genetic predispositions of alcohol consumption correlated with performance on sensory perceptual metrics.

Neurosensory Assessments

Six sensory perceptual metrics were analyzed. The reaction times (RTs and RTc) and detection thresholds (DTs and DTd) were determined according to the previously-outlined protocol parameters (see Neurosensory Assessments). The amplitude discrimination task was performed in the absence (ADs) and presence (ADssa) of single-site adaptation with standard amplitude of 200 μm and initial test amplitude of 400 μm.

Data Analysis

Two-sample, one-tailed t-tests, were used to evaluate the difference in the performance of among groups with difference alcohol consumption behavior. The data are presented as means and standard errors of the means. A probability (p-value) of less than 0.05 was considered statistically significant.

Results

This population of college students reported alcohol consumption ranging from 0 to 144 drinks per month and AUDIT scores ranged from 0 to 28. The RAPI scores ranged from 0 to35, Gormally BES scores ranged from 16 to 52, and novelty seeking scores ranged from 3 to 29.

Reaction times and detection thresholds were not significantly impacted over increased alcohol consumption.

The mean simple reaction times were significantly quicker than choice reaction times (244.9±14.6 ms versus 415.4±14.3 ms, ***p<<0.01, Figure 3.3.A.) over increased alcohol consumption. While simple and choice reaction times were slower for moderate drinkers than for heavy drinkers (*p=0.017 and **p=0.008, respectively), the metrics were within normative values for controls, and there were no significant trends or differences comparing light drinkers to either moderate or heavy drinkers (Figure 3.3.A.). Furthermore, the effect of choice on simple reaction times did not differ with increased alcohol consumption (93.1±9.5 %, p>0.05, Figure 3.3.B.).

The mean static detection thresholds were significantly lower than dynamic detection thresholds (9.9±0.4 μm versus 15.9±0.6 μm, ***p<<0.01, Figure 3.3.C.) over increased alcohol

consumption. While dynamic detection thresholds were higher for moderate drinkers than for light drinkers (*p=0.017), the metrics were within normative values for controls, and there were no significant trends or differences comparing static and dynamic detection thresholds in heavy drinkers to either light or moderate drinkers (Figure 3.3.C.). Furthermore, the effect of feed-forward inhibition on detection thresholds did not differ with increased alcohol consumption (77.5±8.9 %, p>0.05, Figure 3.3.D.).

The effect of adaptation on amplitude discrimination was reduced over increased alcohol consumption.

The mean Weber fractions for amplitude discrimination were significantly affected by single-site adaptation for low (***p=0.00006) and moderate (***p=0.0001) drinkers, but conditioning stimulation failed to significantly affect thresholds for heavy drinkers (p=0.12, Figure 3.3.E.). While there was no significant difference in simple amplitude discrimination difference limens with increased alcohol consumption (35.9±2.9 %, p>0.05), thresholds in the presence of conditioning stimulation were significantly higher for light versus heavy drinkers (*p=0.015) (Figure 3.3.E.). Furthermore, the effect of single-site adaptation on amplitude discrimination significantly reduced for heavy versus light drinkers (**p=0.0097, Figure 3.3.F.).

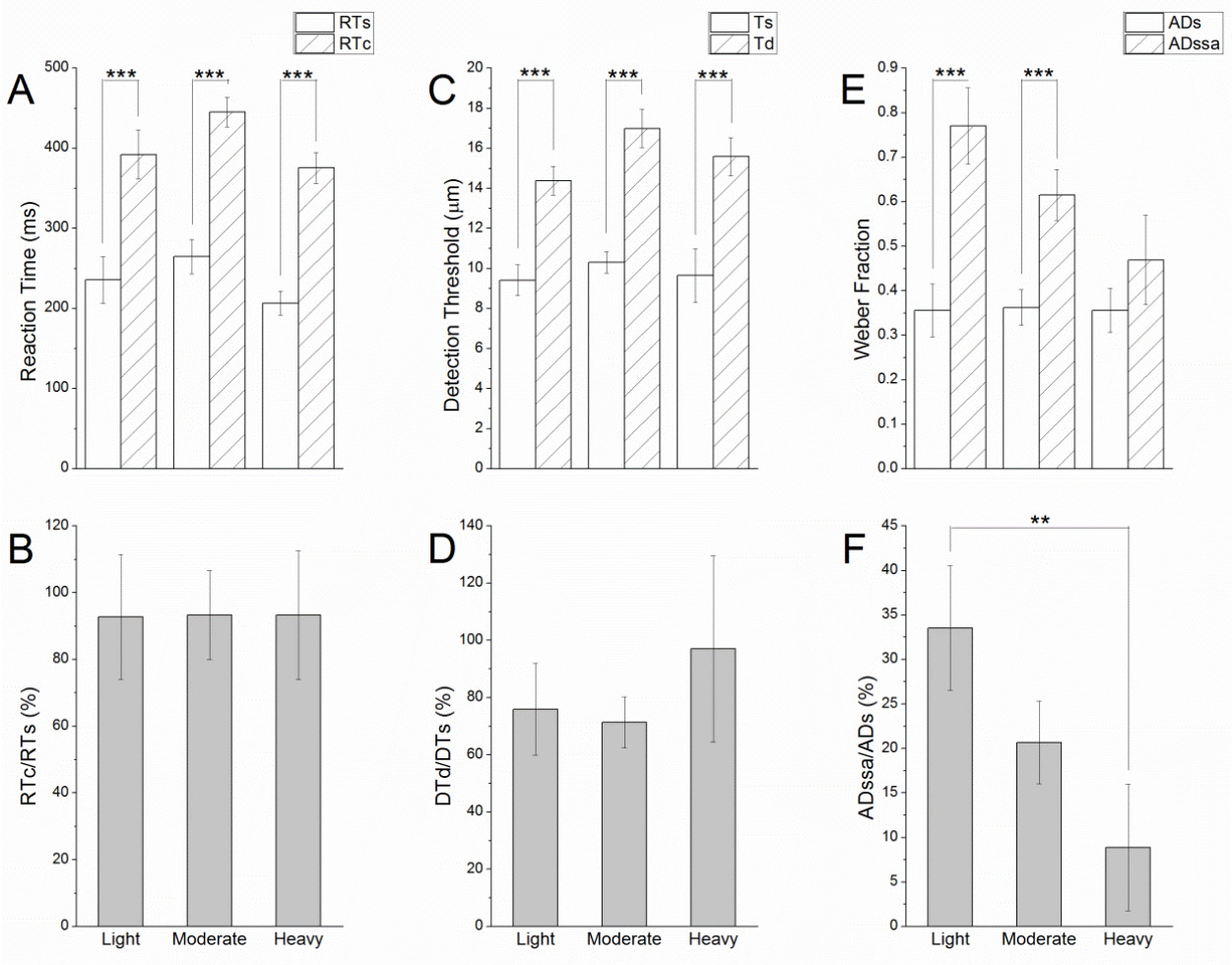

Figure 3.3. Sensory Perceptual Metrics over Alcohol Consumption.

Additional metrics provided insight into potential mechanisms involved in alcohol consumption behavior.

The RAPI categorized subjects according to low (n=44) versus high (n=23) risk of drinking problems while the Gormally BES divided subjects into having low (n=42) versus high (n=24) binging characteristics. While higher RAPI scores correlated with increased alcohol consumption (***p<<0.01, Figure 3.4.A.) and reduced effect of adaptation (*p=0.026, Figure 3.4.B.), the Gormally BES showed low predictive value for both consumption behavior and adaptation responses (Figure 3.4.C.,D.).

Subjects were also categorized according to novelty seeking and sweet liking phenotypes: NS-/SL- (n=8), NS-/SL+ (n=24), NS+/SL- (n=10), NS+/SL+ (n=24). Novelty seeking (NS+) correlated with higher alcohol consumption (***p=0.00043, Figure 3.4.E.) while only subjects with both novelty seeking and sweet liking traits (NS+/SL+) showed a reduced effect of adaptation when compared with those exhibiting neither phenotypic trait (NS-/SL-) (*p=0.032, Figure 3.4.F.).

Finally, family history (FH+, n=27) of alcohol consumption showed significantly higher alcohol consumption than those without history of alcoholism (FH-, n=40) (**p=0.007, Figure 3.4.G.) but did not predict responses to adaptation (Figure 3.4.H.).

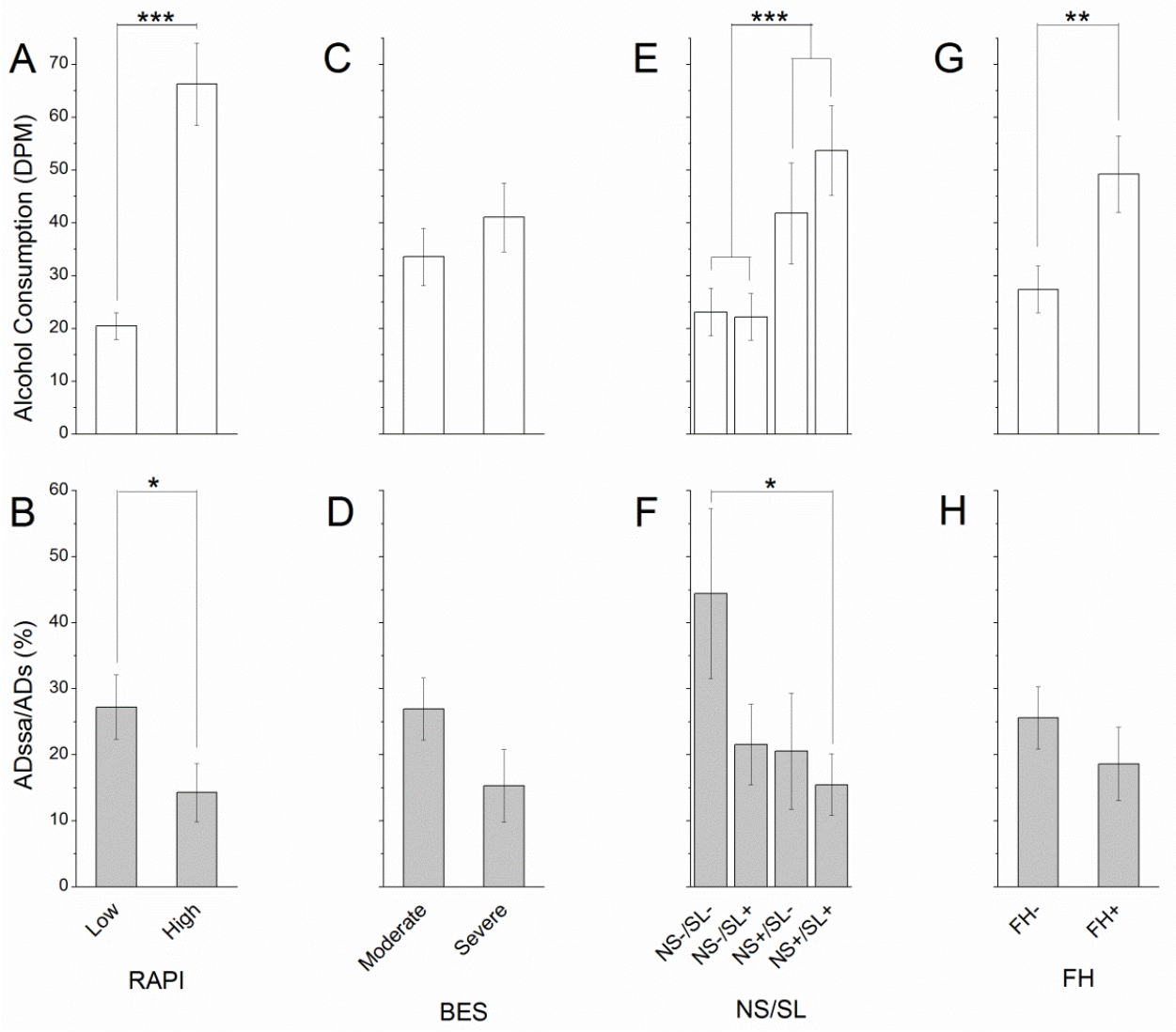

Figure 3.4. Additional Metrics Comparing Alcohol Consumption and Adaptation.

Discussion

In this study, six sensory perceptual metrics were obtained in college students who consumed alcohol. The results of the study demonstrated that, although reaction times and detection thresholds of did not significantly differ across ranges of alcohol consumption, metrics reflecting the effect of adaptation on amplitude discriminative thresholds were significantly reduced over increased reported alcohol consumption.

The observations from this study indicated that there were no significant changes in peripherally-mediated metrics across the spectrum of alcohol consumption even though previous studies have indicated that there are altered reaction times and sensory threshold measures with alcohol consumption (Schweizer & Vogel-Sprott, 2008; Tzambazis & Stough, 2000). Heavier alcohol consumption significantly reduced the impact of adaptation on the amplitude discrimination task, an impairment which has been shown to effect centrally-mediated neural mechanisms in this population (Marco, Fuentemilla, & Grau, 2005).

The mechanisms of adaptation are suspected to be impacted in alcoholism because chronic exposure to ethanol has been shown to affect GABA neurotransmission as well as NMDA receptor availability. Previous animal and human studies have showed that, at the level of neurotransmission, chronic exposure to ethanol increases the amount of pre-synaptic GABA neurotransmitter released and the post-synaptic response (Fleming, Manis, & Morrow, 2009; Valenzuela, 1997; Vengeliene, Celerier, Chaskiel, Penzo, & Spanagel, 2009). Furthermore, there is a redistribution and increase in NMDA receptor concentration and density by upregulation mechanisms with chronic ethanol exposure (Clapp, Gibson, Dell'acqua, & Hoffman, 2009; Chandrasekar, 2013). Other research has shown that chronic alcohol consumption can lead to white matter degradation, disrupt neurocircuitry, and induce neural plasticity which can alter

neurotransmission, particularly by increasing tonic inhibition (Cardenas, Studholme, Meyerhoff, Song, & Weiner, 2005; Crews, et al., 2005; Herting, Schwartz, Mitchell, & Nagel, 2010; Oscar-Berman & Marinkovic, 2007; Pfefferbaum, Rosenbloom, Fama, Sassoon, & Sullivan, 2010; Santhakumar, Wallner, & Otis, 2007; Sullivan & Pfefferbaum, 2005). Alterations in phasic and tonic components of information processing may also be affected by alcohol intoxication and drug tolerance as well as family history of these diseases (McBurney & Balaban, 2009). These changes are likely to reflect the neuroadaptational response to alcohol involving alterations in the healthy functional balance between inhibitory and excitatory mechanisms (Clapp, Gibson, Dell'acqua, & Hoffman, 2009; Fleming, Manis, & Morrow, 2009; Heiss, Katz, Ganmor, & Lampl, 2008; Higley & Contreras, 2006). This imbalance is supported by the use of anticonvulsants/sedatives such as topiramate, acamprosate, benzodiazepines, baclofen, gabapentin, and valproate to address the suspected cause of neurological dysfunction due to plastic changes which occur following chronic alcohol consumption.

While increased alcohol consumption may have resulted in the reduced adaptation capability through alterations in cortical plasticity, these changes may have been alternatively due to innate traits associated with motivation. The significance of modulating the reward response and reinforcing effects of alcohol addiction is supported by the use of pharmacotherapeutics such as naltrexone and disulfiram. In observing the impact of conditioning stimulation in relation to other phenotypic measures, the results suggested that alcohol-related problems, novelty seeking characteristics, and hedonic preferences, particularly associated with the motivational mechanisms of the dopaminergic and opioidergic systems, may be related to suppressed adaptation mechanisms. These results suggest that opioidergic, dopaminergic, GABAergic, and glutamatergic mechanisms may be involved not only in characterizing

behavioral phenotypes related to alcohol use disorders but also in the ability to adapt to conditioning stimulation (Johnson, 2010; Kranzler & Edenberg, 2010). Hedonic responses may correlate with varying levels of opioid activity which may be subsequently involved in GABAergic modulation (Davis, et al., 2009; Faure, Richard, & Berridge, 2010). Ultimately, these results may suggest that alcohol use disorders may be related to both the predisposed state of subjects, determined by characteristic phenotype, and exposure to alcohol. Together, these factors may amplify impulsive nature and motivation to increase frequency of consumption. However, the conclusions are limited in that they are not capable of differentiating whether these decreased discrimination or adaptation abilities are due to these inherent phenotypes or if heavy alcohol consumption results in cortical impairment.

Analyzing family history (FH) of alcoholism may provide further insight as to whether subjects with predispositions of heavy alcohol consumption are impaired in their sensory adaptation ability. There may be both genetic and environmental/epigenetic factors of substance abuse which can lead to cortical dysfunction such as decreased capability for sensory adaptation. Increased alcohol consumption in heavy drinkers may not necessarily result in lower adaptation responses based on genetic heritability of alcoholism. Heritable genetic factors may not necessarily predispose subjects to abuse alcohol, and the impulsive behavior may be dependent on experience thus supporting possible alterations in neurotransmission or structural morphology due to chronic alcohol consumption.

The causal mechanism in chronic alcoholism is still ambiguous. However, the screening data paired with the sensory perceptual metrics may suggest differences in phenotypic traits and neural compensation mechanisms (Werner, et al., 2009). Family history of alcohol use disorders has shown to be associated with hedonic preferences (Tremblay, Bona, & Kranzler, 2009), and

the results of this study showed variations in adaptation capabilities comparing sweet liking and sweet disliking subjects. Because the adaptation metric was significantly affected over increased alcohol consumption sparing any effects on reaction time and detection threshold measures, these tests may be sensitive in this particular population of college-aged students who engage in moderate to heavy drinking patterns. Further studies analyzing the relationship between alcohol consumption, hereditary factors, and other sensory perceptual metrics can be conducted in order to understand which of the factors are most significantly affected by substance abuse. These results are not only capable of evaluating the efficacy of current assessments (TLFB, AUDIT, and BES), but may also have diagnostic value. As a more rapid and more cost-effective alternative screening method, relationships among sensory metrics and current screening assessments may serve to provide clinicians a non-painful and non-invasive method of categorizing cortical dysfunction in a population of subjects with suspected or known alcohol or substance abuse.

Section 3.3. Concussion

Background

One of the most common mechanisms of acquiring brain injury involves injuries induced by mechanical force. These injuries may be caused by non-penetrating external blows to the head which may result in concussions or mild traumatic brain injury (mTBI). Previous studies have observed systemic changes (metabolic, hemodynamic, structural, and electrical) that occur within the brain over time immediately following concussions which could possibly lead to significant chronic repercussions. These alterations might induce a neurometabolic cascade leading to raised levels of calcium concentrations, spikes in glutamate (excitotoxicity), potassium ions, and glucose (hyperglycolysis), and subsequent decreases in cerebral blood flow possibly leading to neuronal apoptosis (Barkhoudarian, Hovda, & Giza, 2011; Giza & Hovda, 2001). Subsequent molecular imbalances have been suspected to result in spontaneous depolarizations and cortical spreading depression potentially due to changes in glial function and/or neuroinflammation (Torrente, et al., 2014).

Current methods of assessing the impact of concussions on brain functionality are limited in their ability to comprehensively characterize the multifaceted nature of mild traumatic brain injuries (Kubal, 2012; McLeod & Leach, 2012; Shenton, et al., 2012). Changes in brain functionality are difficult to objectively identify due to low sensitivity of imaging modalities to detect subtle systemic alterations, axonal injuries, and/or microhemorrhages. As a result, clinicians screen patients on the basis of clinical and cognitive metrics where non-specific symptoms may correlate with other diagnoses (Broglio, Macciocchi, & Ferrara, 2007). While the most commonly-reported symptoms may include headaches and dizziness, persistent post-

concussive symptoms may prolong cognitive, physiological, and clinical symptoms past three months post-injury leading to subsequent irritability, fatigue, sleep disturbances, nausea, blurred vision, sensory impairments, depression, anxiety, attention, concentration, memory, executive function, and speed of processing (Leddy, Sandhu, Sodhi, Baker, & Willer, 2012).

Sports-related risks of concussion are significantly high (75 % for male football, 50 % for female soccer) as college athletes may endure mechanical injury due to impact of at least 20 miles per hour per concussive blow. Furthermore, in an estimated 47 % of cases, athletes may fail to report any significant symptoms following concussive blows (Concussion Facts, 2012). Because successive concussions during the critical post-concussion recovery period can result in serious, if not fatal, brain dysfunction, there is an imperative need to develop more objective methods in order to more confidently assess return-to-play status for athletes.

A battery of tests (see Neurosensory Assessments) was administered to college athletes screened for concussions. The Standardized Concussion Assessment Tool (SCAT) was used analyze signs and symptoms of athletes following concussions, and these scores were paired with sensory perceptual metrics. Performance on sensory perceptual metrics was expected to be significantly be altered compared to baseline measures following injury as concussive blows may result induce neurological imbalance due to neuroinflammation and/or compromised systemic neuroprotection due to impaired glial function among other possible brain dysfunctions (Torrente, et al., 2014). The results of the study suggested that the sensory perceptual metrics can be used to track recovery in athletes following concussion.

Methods

Subjects

Following International Review Board approval and informed consent, 67 college student athletes ranging from 18 to 22 years of age were recruited. Controls represented baseline metrics (n=33) while concussed athletes (n=34) were screened via the Standardized Concussion Assessment Tool (SCAT). All subjects completed a survey on current medications and medical history prior to the experimental tests to exclude participants with any history of neurological impairment other than concussions. The subjects were naïve to the study design and blinded to the issue under investigation.

Screening Assessments

Athletes underwent various screening assessments. Athletic sport (basketball, football, lacrosse, soccer, wrestling), suspected location of concussion, and previous history of concussion (Hx) were determined for each athlete. The Standardized Concussion Assessment Tool (SCAT) was also used to score the athletes on signs and symptoms following a concussive blow. Concussed athletes were assessed each week, if possible, following mechanical injury in order to track progression of recovery, but not all subjects completed assessments each week. While some subjects were only tested once after their concussion, others may have skipped weeks in between testing.

Neurosensory Assessments

Five sensory perceptual metrics were analyzed. The simple reaction times (RTs) and detection thresholds (DTs and DTd) were determined according to the previously-outlined protocol parameters (see Neurosensory Assessments). The amplitude discrimination task was performed in the absence (ADs) and presence (ADssa) of single-site adaptation with standard amplitude of 200 µm and initial test amplitude of 400 µm.

Data Analysis

Multivariate principal component analysis (PCA) was used to combine performance metrics and generate unique profiles for each athlete. The transformation involved calculation of principal components to account for the largest possible variance in the data and to reduce the original number of variables. Quantitative performance of each subject on the battery of the five sensory tests were treated as localizing these subjects in an n-dimensional (n=5) cortical metrics space where each coordinate axis corresponded to one of the sensory perceptual metrics. These results were used to understand associations in test performance data collected in the concussed and baseline subject populations.

If subjects were assessed more than once within a week-long period, the first metric was considered for analysis. This method was conducted under the assumptions that significant changes in performance are negligible within one week and that recovery occurs at similar rates for all subjects. While these assumptions may be true for some subjects, they cannot necessarily account for performance for all subjects.

Results

Sensory perceptual metrics for control subjects were graphed on a scores plot with an area of interest defined within one standard deviation from the control mean (Figure 3.5.A.). Metrics for concussed subjects during their initial recorded assessment were also graphed on the scores plot. The majority of the baseline subjects (91 %) were within this control area while only a fraction of the concussed subjects (47 %) was greater than one standard deviation from the control mean (Figure 3.5.B.).

Previous history of concussion predicted worsened performance on sensory perceptual metrics.

Athletes without (Hx-, n=6) and with (Hx+, n=7) previous history of concussion were assessed each week following mechanical injury. The majority of Hx- athletes (67%) were within the control area, and subjects who were outside of this area tracked to healthy performance within one week (Figure 3.5.C.). A fraction of Hx+ athletes (67%) were greater than one standard deviation from the control mean, and subjects who were outside of this area tracked to healthy performance within, at most, three weeks (Figure 3.5.D.).

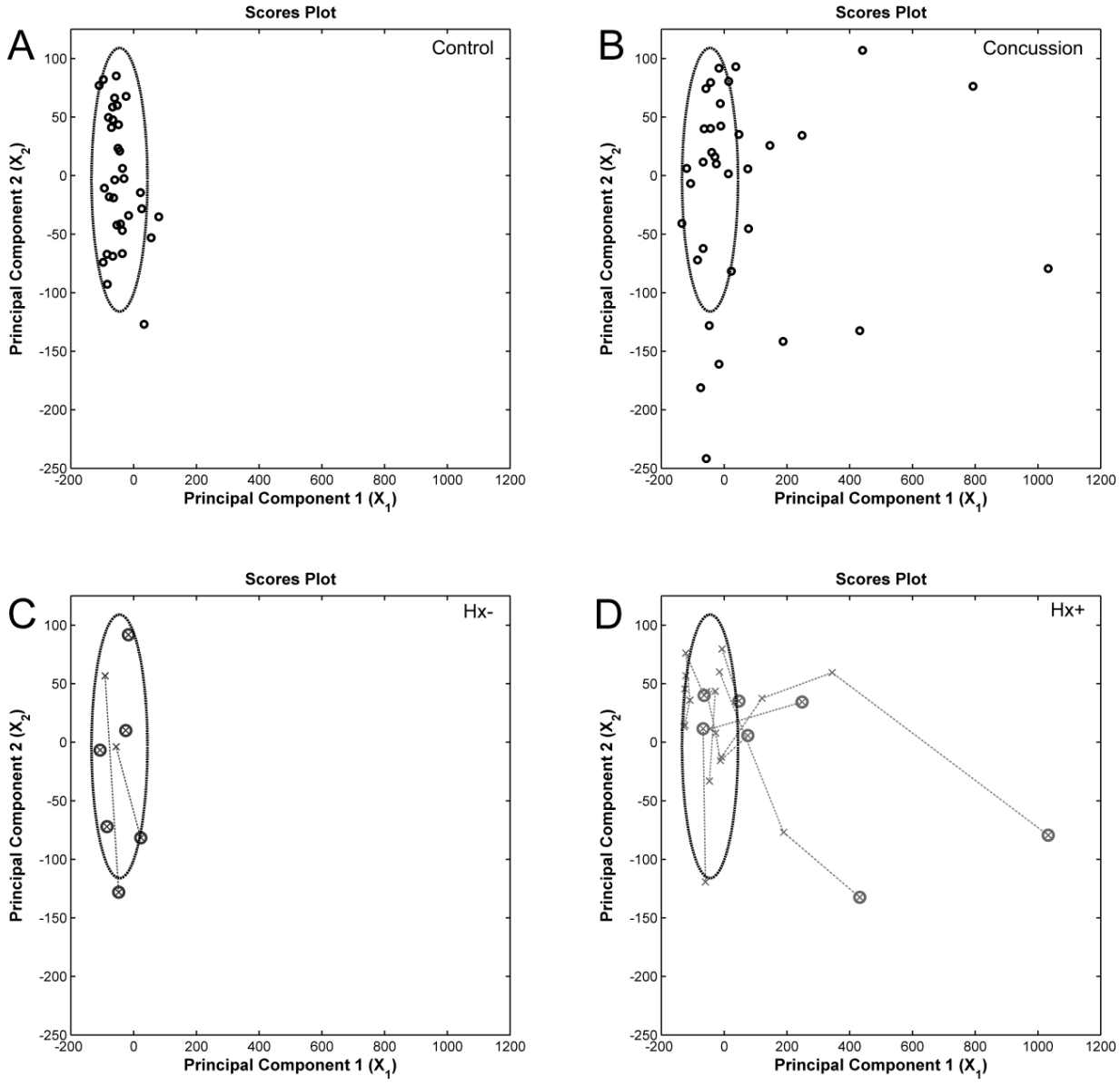

Figure 3.5. Principal Component Analysis for Concussed Athletes versus Controls.

Recovery following concussion was capable of being tracked over time.

Performance metrics for athletes were calculated in relation to the Euclidean distance from the control mean. These values positively correlated with SCAT scores (ranging from 0 to 66) for each athlete (R^2=0.64, Figure 3.6.A.). Because previous history of concussion was associated with higher severity of concussion symptoms, both evaluations were utilized to track recovery in athletes with (Hx+) and without (Hx-) previous history of concussion. Testing occurred for athletes approximately every week, and Hx- athletes showed slight but insignificant deviation from the control values while Hx+ athletes showed significantly higher SCAT scores (Figure 3.6.B.) and relatively further distances from the control mean (Figure 3.6.C.) within the first week following concussion. These metrics for both Hx- and Hx+ athletes were tracked up to 28 days following injury, and scores significantly approached healthy values by the fourth testing session (R^2=0.87 and R^2=0.86, respectively, Figure 3.6.B./C.).

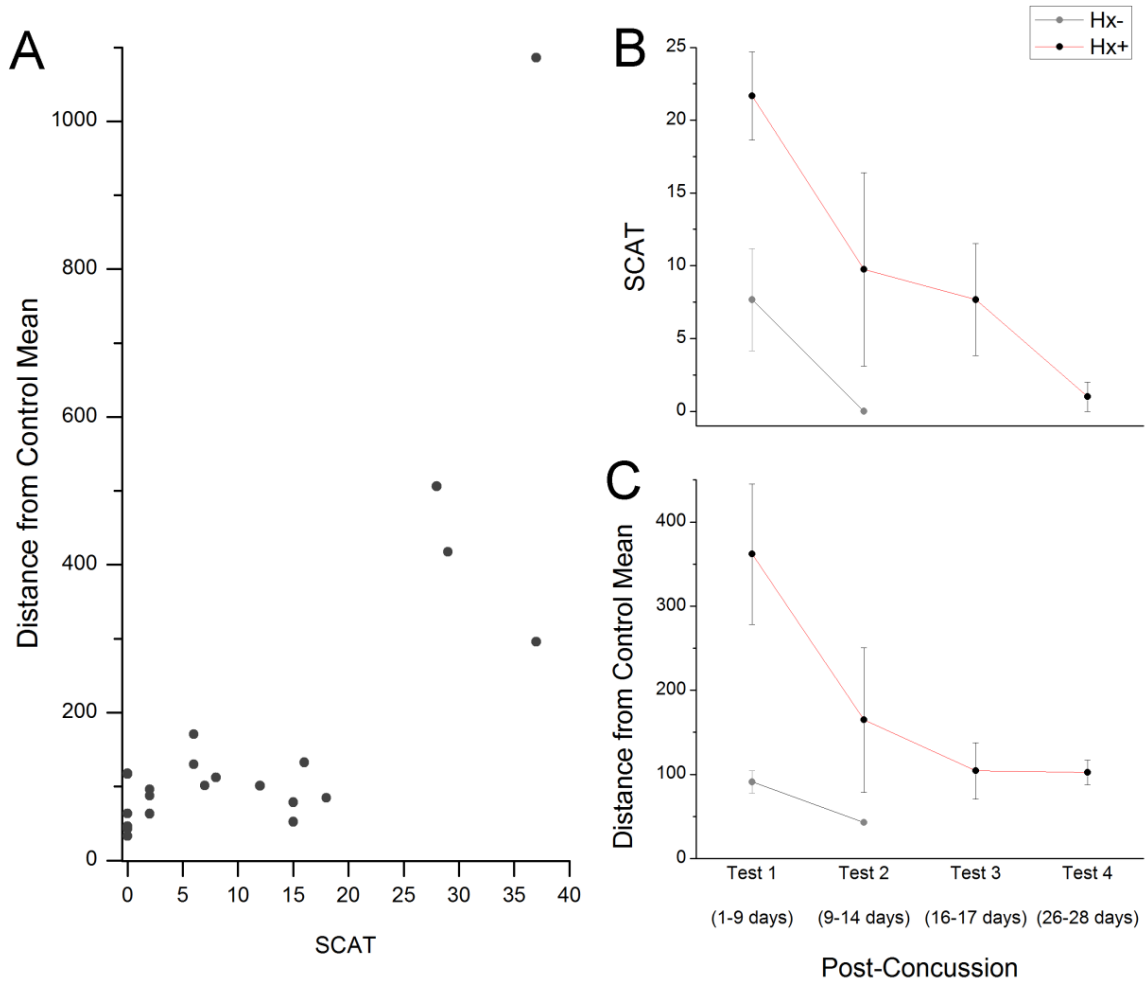

Figure 3.6. Sensory Perceptual Metrics and SCAT Scores Recover over Time.

Discussion

In this study, five sensory perceptual metrics were obtained in college athletes who experienced concussions. The results of the study demonstrated that, previous history of concussion was associated with worsened performance on sensory perceptual metrics within one week following concussion and that recovery following concussion was capable of being tracked over time.

The observations from this study indicated that athletes without previous history of concussion generally performed well on the sensory perceptual tasks. Their performance might suggest that initial concussions do not result in detectable changes in sensory perceptual metrics while subsequent concussions for those with previous history of concussion are more susceptible to significant and measurable brain dysfunction. Athletes with previous history of concussion performed significantly worse and required more recovery time (at least two weeks) to return to baseline metrics than those without previous history of concussion, and this would suggest that any other injuries occurring within this recovery timeframe would result in significant impairment in central information processing.

The majority of concussed athletes showed initial impairment on metrics followed by recovery over subsequent test days, but some subjects showed worsened performance many weeks following the concussion. Data analysis was conducted under the assumption that recovery occurs at similar rates for all subjects, and while these assumptions may be true for some subjects, they cannot necessarily account for performance for all athletes following concussion. These particular results implied that the neurometabolic cascade could lead to specific time-dependent impairments which may not occur immediately following concussion but instead days or weeks following the injury. Contributing factors might include raised levels

of calcium concentrations, spikes in glutamate (excitotoxicity), potassium ions, and glucose (hyperglycolysis), and/or subsequent decreases in cerebral blood flow possibly leading to neuronal apoptosis (Barkhoudarian, Hovda, & Giza, 2011; Giza & Hovda, 2001).

The successful implementation of multivariate analysis (PCA) showed that the technique could be an alternative method that is capable of generating unique profiles for subjects based on performance on sensory perceptual metrics and that this analysis could aid in understanding differences between individuals with healthy and impaired brain functionality. While not explicitly shown in the results, the analysis revealed that worsened performance for the concussed athletes was primarily attributed to slower reaction time measures. Performance on additional sensory perceptual metrics might reveal further separation of healthy versus unhealthy brain functionality based on severity, location, and/or timing of concussion injuries within this athlete population.

The potential utility of this work is highly significant as there are inherent limitations in the implementation of current methods for evaluating concussions (Chan, et al., 2012). There are no standardized, biologically-based, quantitative measures for the assessment of concussions. A simple, fast, non-invasive, cost-effective means for evaluating the impact of concussion on brain functionality that could be utilized by health care providers would have an overwhelming impact on return-to-play decisions. The advantage of the proposed methodology is that they system is easy to use and effective at both providing information about a subject that would allow for more informed decisions about diagnosis or treatment and provide a means for assessing treatment efficacy and recovery.

CHAPTER 4. DISCUSSION

Summary

Six sensory perceptual metrics were analyzed for young adults across three clinical populations: migraines, alcoholism, and concussion. The results for the effect of secondary metrics on primary metrics are summarized (Table 2.1.). While young adults within these populations seemed to perform well on detection threshold tasks showing no significant effect of feed-forward inhibitory mechanisms, concussed individuals showed impaired reaction time measures while migraineurs and alcoholism subjects performed worse on amplitude discrimination tasks in the presence of single-site adaptation. The results from the concussion population suggested that previous history of concussion predicted worsened performance on sensory perceptual tasks but also that improved performance following concussions implied that tracking of recovery over time was possible. Evolution of statistical analytical techniques toward multivariate analyses can allow for implementation of more advanced classification methods which could be useful for subject screening and/or diagnosis (see Machine Learning Algorithms for Classification).

Table 4.1. Comparison of Metrics in Control and Clinical Populations.

Population	Reaction Time	Detection Threshold	Amplitude Discrimination
Control	96.12±6.47	102.34±6.64	26.95±1.62
Migraine	67.17±12.72	105.67±30.74	6.12±7.18
Alcoholism	93.30±19.28	97.01±32.59	8.86±7.11
Concussion	57.82±12.67	96.83±14.62	15.50±5.53

Machine Learning Algorithms for Classification

Various machine learning algorithms can be implemented in order to classify subjects according to healthy versus impaired brain functionality. While principal component analysis (PCA) can be used to account for the largest possible data variance and variable reduction, additional data analytical methods can subsequently be implemented in order to be able to classify unknown variables which might aid in the future screening and diagnostic capabilities of sensory perceptual metrics. Two classification techniques are discussed to illustrate implementation of more advanced analytical methods.

k-Nearest Neighbors

k-Nearest Neighbors (k-NN) is a simple, unsupervised classification algorithm utilizing instance-based learning. Metrics were assigned to classes according to their proximity to their nearest neighbors training group. This algorithm was used in the concussion dataset to classify athletes with unknown history of concussion (n=17) evaluated for five sensory perceptual metrics (RTs, DTs, DTd, ADs, and ADssa). Because previous history of concussion was associated with worsened performance on sensory perceptual metrics (see Concussion: Results), those who were classified as Hx+ (23.8 %) were presumed to exhibit more severe symptoms compared to those who were classified as Hx- (76.2 %) (Figure 4.1.). Classified athletes were subsequently tracked over weeks following concussion, and while the majority of Hx- athletes (67 %) were within the control area (Figure 4.1.B.), a large fraction of the Hx+ athletes (83 %) were greater than one standard deviation from the control mean (Figure 4.1.C.). Implementation of this classification algorithm is useful in rapid categorization to predict healthy versus unhealthy subject performance.

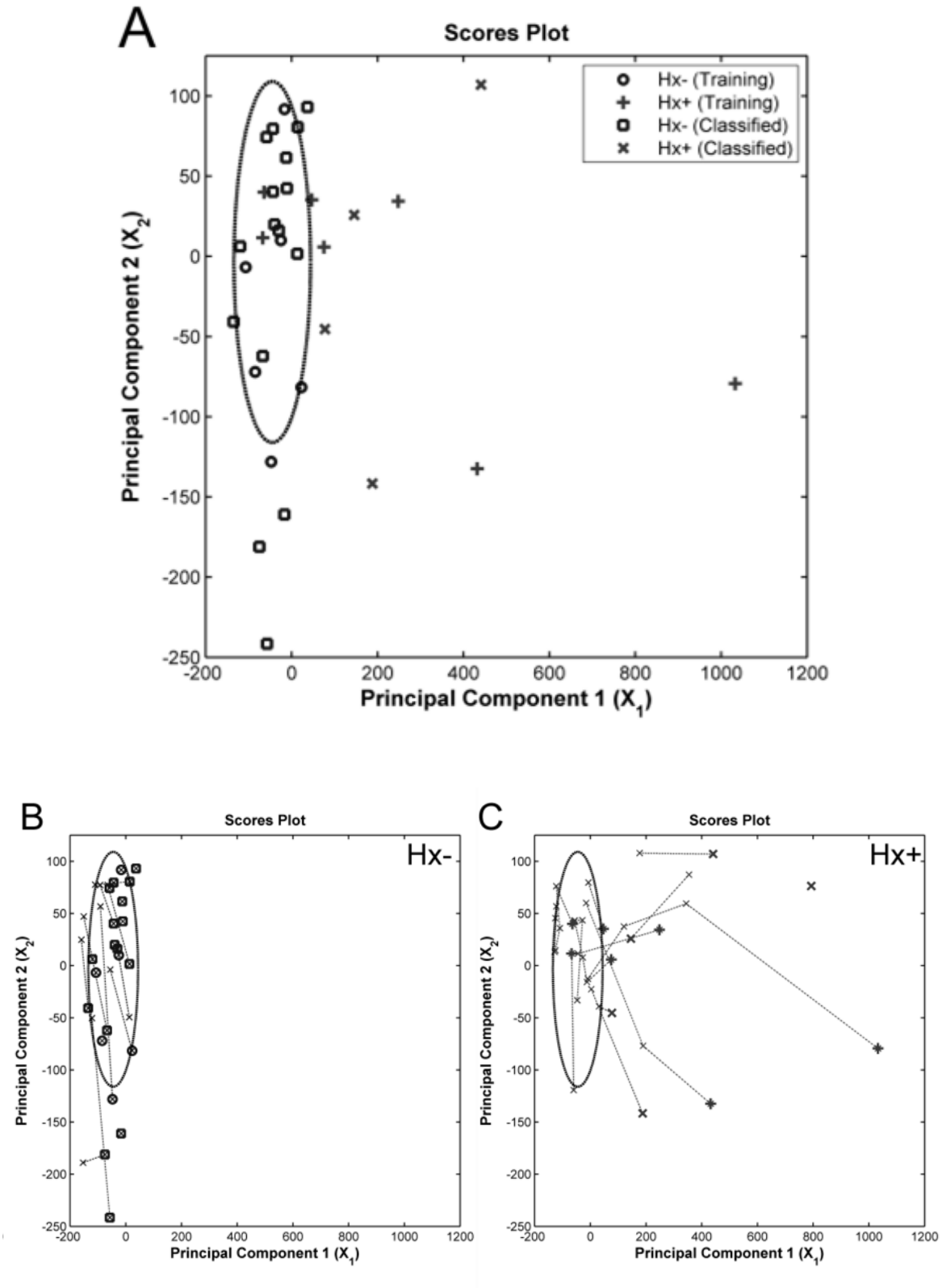

Figure 4.1. k-Nearest Neighbors Analysis for Classification.

Support Vector Machine

Principal component analysis (PCA) allowed generation of a control area defined within one standard deviation from the control mean from the three clinical populations (migraine controls, n=36; light drinkers, n=22; baseline metrics in athletes, n=33) evaluated for five sensory perceptual metrics (RTs, DTs, DTd, ADs, and ADssa). Further analysis illustrated qualitative differentiation among the clinical populations (episodic migraineurs, n=12; heavy drinkers, n=10; Hx+ concussed athletes, n=7) (Figure 4.2.A.). A supervised classification algorithm was subsequently utilized to determine if healthy and impaired brain functionality could be determined from this dataset.

The Support Vector Machine (SVM) method of analysis involved optimal placement of a hyperplane to separate distinct classes of data. The support vectors were generated from training samples which determined the orientation of the hyperplane. The data were evaluated by using the radial basis kernel function (σ=1) which expressed the similarity of two vectors as a function of the Euclidean distance between them.

The SVM classification was implemented in the young adult population. The training samples were extracted from the concussion population while the test samples were from the migraine and alcoholism populations. The classification resulted in an accuracy of 66.25 % (40.91 % sensitivity and 75.86 % specificity) with positive and negative predictive values of 39.13 % and 77.19 %, respectively. While these percentages reflected relatively low predictability in classification potential, this particular analysis involved only five sensory perceptual metrics and training samples were drawn specifically from the concussion population (Figure 4.2.B.). Additional metrics are expected to result in higher classification accuracy in determining healthy or impaired brain functionality (see Future Directions).

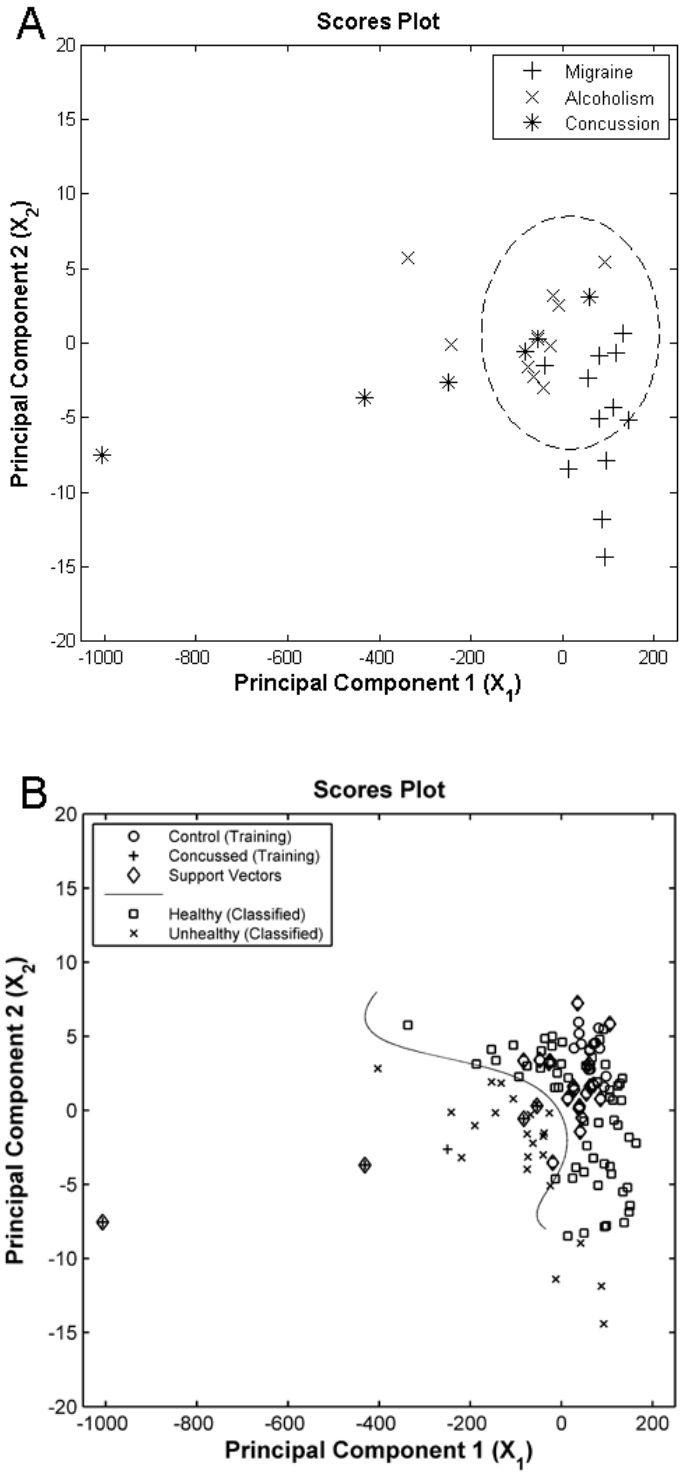

Figure 4.2. Support Vector Machine Analysis for Classification.

Limitations

Variability

While sensory perceptual metrics have been able to successfully detect impairments in central information processing based on subject performance on particular tasks (Figure 4.6.), assuredly categorizing subjects as healthy or impaired remains a challenge. Subject variability is a significant issue during testing and may be influenced by environment, attention and fatigue, training effects, and other related aspects. Furthermore, in some subject populations, malingering may occur where subjects purposefully attempt to perform poorly on the tasks. Many of these additional variables may affect classification of neurological function within healthy subject populations. Future studies must be conducted in order to analyze these particular effects on subject performance, and protocols can be optimized to minimize variability in these measures.

Severity, Comorbidities, and Medication History

The young adults in these studies may have been unable to exhibit more severe symptoms seen typically in these clinical populations. Many chronic migraineurs may show more severe symptoms at older ages. Additionally, different types of migraines (with or without aura, cluster, tension, and/or sinus headaches), location of pain, comorbid conditions, and medication history may contribute to variability in results. For the alcoholism population, considering the legal restrictions on alcohol consumption in the United States, measuring the effect of substance abuse at these ages may result in inconsistencies in self-reporting. Most chronic alcoholics are categorized by consumption around twice or three times more than the highest-consuming subjects in these studies, so metrics within this college-aged population are expected to differ

from those in adult populations due to the duration and/or severity of alcohol use or abuse. Additionally, assessments of other substances which may have been taken or medication history may also contribute to skewed results. Lastly, metrics in the college athlete population may be limited in that the severity of impact and location of mechanical injury may contribute to variable results on particular tasks. The type of sport played by the athletes might also contribute to higher susceptibility or risk of obtaining more severe concussive blows resulting in brain dysfunction.

Timing

For each of the populations, timing of symptoms, use, and injury are factors which must be considered in the migraine, alcoholism, and concussion populations, respectively. History of migraines, chronicity of occurrences (episodic versus chronic) as well as understanding migraine state (pre-ictal versus ictal versus post-ictal states) may reveal more information about the pain condition. For alcoholism subjects, drinking patterns concerning amount and timing (binging versus chronic drinking) may be factors that might result in variable susceptibility for brain dysfunction. Finally, understanding the number of occurrences of previous concussions, time periods between multiple concussions, and severity of mechanical injury over particular time periods may be helpful in revealing brain dysfunction associated with concussed athletes.

Future Directions

Dual-Site Protocols

Incorporating additional metrics for analysis can aid in further differentiation of subject populations. A variety of other protocols testing other aspects of neurobiological function have also been developed and tested in different populations (Table 4.2.). Additional protocols include temporal order judgment (TOJ) without and with synchronizing carrier stimulation (see Temporal Order Judgment), duration discrimination (DD) without and with confounding stimulation (see Duration Discrimination), and frequency discrimination among other tasks. The presence of illusory conditions on each of the tasks, similar to amplitude discrimination in the presence of single-site adaptation, showed that the majority of subjects performed worse on these protocols compared to in the absence of the sensory illusions (75.0 % for temporal order judgment with carrier stimulation and 66.7 % for duration discrimination with confounding stimulation). The implementation of these tests within a battery could result in greater separation of subject profiles according to neurobiological processes associated with each particular metric.

Table 4.2. Summary of Additional Sensory Perceptual Metrics.

Protocol	Mean±SD	N
Reaction Time Simple*	229.26±50.06 ms	355
Reaction Time Choice*	405.60±75.83 ms	48
% choice>simple	*93.5 %*	*123*
Static Threshold*	6.47±2.69 µm	86
Dynamic Threshold*	12.59±5.76 µm	103
% dynamic>static	*95.8 %*	*119*
Amplitude Discrimination	34.08±22.29 %	533
with Single-Site Adaptation	61.51±31.82 %	330
% adaptation>simple	*78.3 %*	*313*
Temporal Order Judgment	31.91±17.19 ms	271
with Carrier	45.33±19.68 ms	74
% carrier>simple	*75.0 %*	*56*
Duration Discrimination	67.75±30.81 ms	255
with Confound	94.38±51.47 ms	96
% confound>simple	*66.7 %*	*96*

* age <30 years old

Analysis of 14 different sensory perceptual metrics in the concussion population revealed that different athletes (F=football, S=soccer, W=wrestling) could be distinctly separated (Sport(Hx,SCAT), Figure 4.3.). These metrics included reaction times (2 RTs, RTc, and variance measures for each), detection thresholds (DTs and DTd), amplitude discrimination (ADs and ADssa), temporal order judgment (TOJs and TOJc, see Temporal Order Judgment), and duration discrimination (DDs and DDc, see Duration Discrimination). The athletes with previous history of concussion were also able to track toward healthy performance seen in those with no previous history of concussion. As a result, implementing additional metrics for testing may aid in further separation of subject populations.

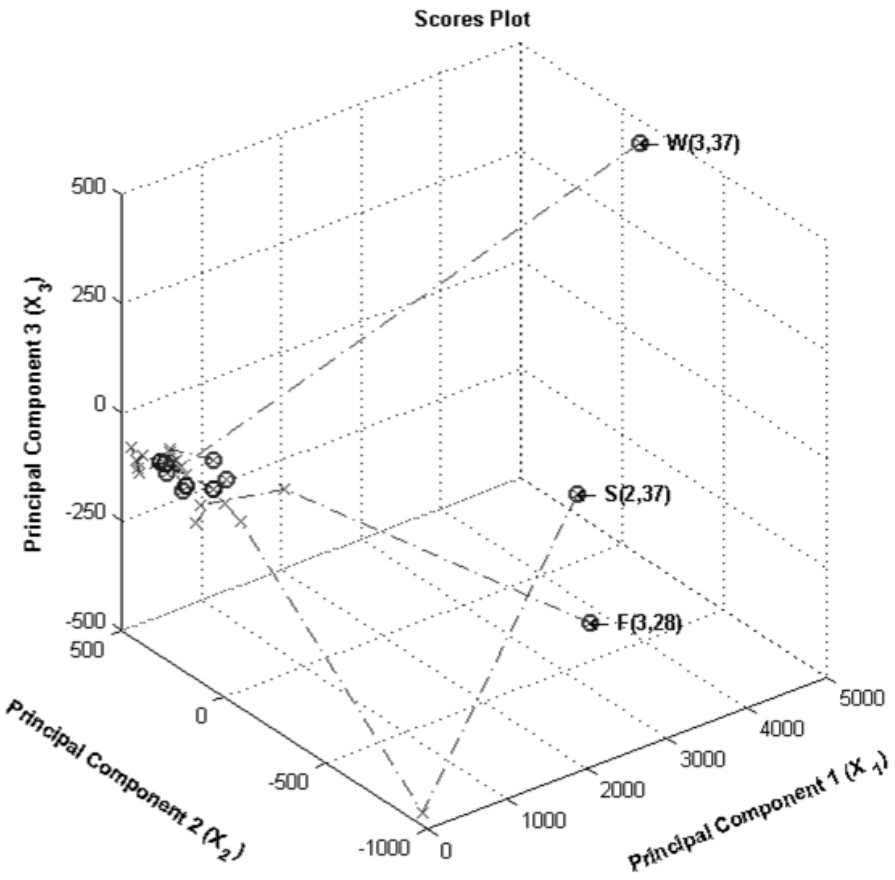

Figure 4.3. Principal Component Analysis with Additional Metrics for Concussed Athletes.

Quad-Site Protocols

Quad-Site simulation is a novel approach to analyzing central information processing because current studies have focused on paired digit stimulation. However, limitations in these dual-site stimulation assessments include failure to consider the contribution of the other adjacent and non-adjacent digits to the resulting percept. Novel protocols involving stimulation of multiple digits may reveal insight into adjacent and/or near-adjacent cortical interactions.

A finger agnosia protocol was assessed on healthy subjects (n=17) in order to demonstrate the capacity of the device to deliver vibrotactile stimuli at four independent sites as well as to evaluate the ability of subjects to recognize and identify stimulated digits in the absence and presence of conditioning stimuli at different amplitudes (Nguyen, et al., 2013c). These assessments showed that increased carrier amplitude stimulation resulted in significantly decreased percent accuracies of spatial localizations (Figure 4.4.A.). Because the conditioning stimuli at 100 μm resulted in the most significant percentage of incorrect responses when compared to task in the absence of conditioning stimuli, the number of inaccurate responses for each digit was quantified. These results suggested that subjects, on average, made the most inaccurate responses for the ring finger (D4) when compared with other digits while they were relatively better at identifying stimulation of the index finger (D2) (Figure 4.4.B.). These findings may imply potential interactions among adjacent and non-adjacent pairs of digits based on inaccurate responses. 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 (Hager-Ross & Schieber, 2000). In observing motor-related cortical potentials (MRCPs), the autonomous nature of D2 has been shown to be significantly high while D4 showed the most dependency on other digits (Slobounov, Johnston, Chiang, & Ray, 2002).

When stimulating all four digits simultaneously, the sensory percept is presumed to result from interactions among each of the digits (Nguyen, et al., 2013c). Excitatory or inhibitory interactions among adjacent and non-adjacent digits can ultimately affect the ability to discriminate differences in stimulus amplitudes. These results suggested that adjacent pairs of digits interacted more than non-adjacent pairs of digits (Figure 4.4.C.). 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, could contribute to bridging decades of neuroscientific research with human perceptual clinical and clinical research studies. One long term goal of the 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.

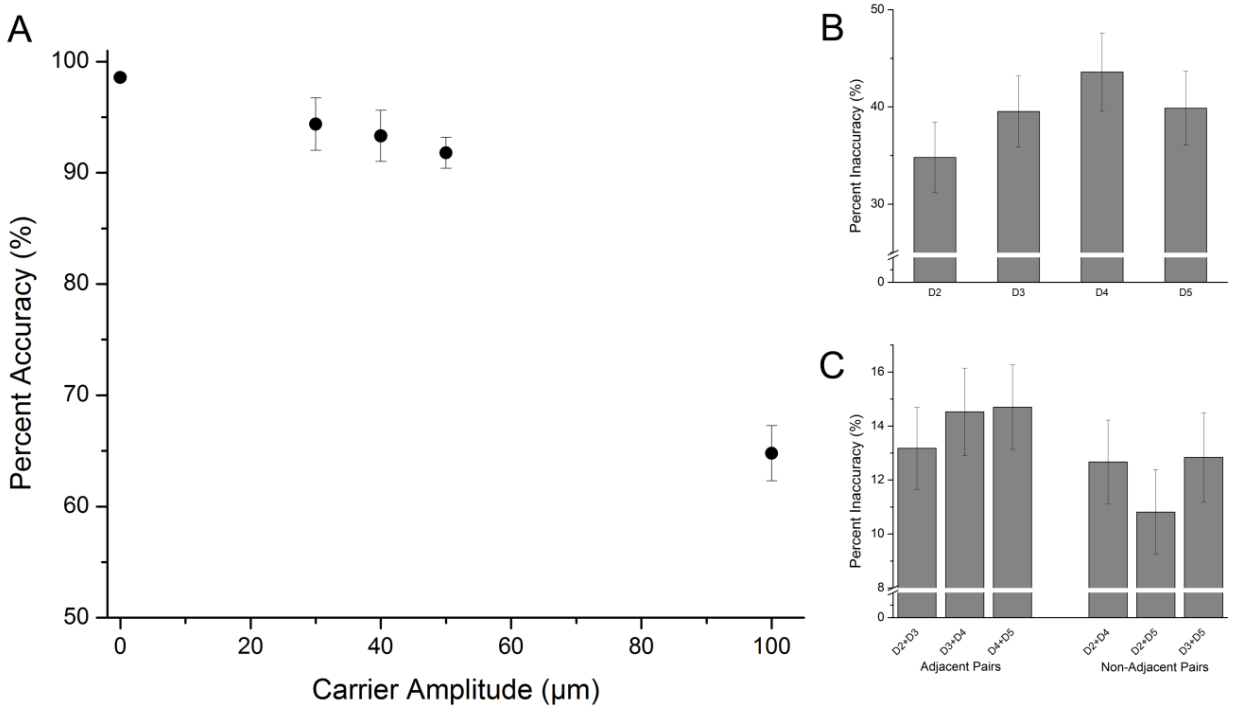

Figure 4.4. Quad-Site Stimulation on Spatial Localization and Amplitude Discrimination.

Bilateral Protocols

Bilateral simulation is an approach to analyzing central information processing and understanding the way in which sensory perceptual metrics are impacted across the body midline. A number of studies support both structural and functional associations between homologous regions across cortical hemispheres. Bilateral somatosensory integration is primarily mediated by callosal fibers which are involved in interconnections among the left and right cerebral hemispheres. These complex connections allow for interhemispheric modulation of information processing (Van der Knaap & Van der Ham, 2011). Animal models have revealed neuronal mechanisms involved in interhemispheric inhibiton (Palmer, et al., 2012; Wahl, et al., 2007) while human imaging studies have also revealed that stimulation of one hand leads to significant activation in the contralateral somatosensory cortex while inhibiting homologous regions in the ipsilateral somatosensory cortex (Tommerdahl M. , Simons, Chiu, Favorov, & Whitsel, 2005; Tommerdahl M. , et al., 2005; Zapallow, et al., 2013). While many of these studies claim that the secondary somatosensory cortex is primarily responsible for interhemispheric information transfer, recent studies have shown that bilateral processing may occur in early stages of processing in the caudal portion of the postcentral gyrus (Iwamura, Taoka, & Iriki, 2001; Ragert, Nierhaus, Cohen, & Villringer, 2011). Previous neurophysiological and sensory perceptual studies have shown that tactile localization and spatial acuity were affected by bilateral stimulation where interhemispheric interactions might account for mislocalizations and/or impaired discriminative performance.

The amplitude discrimination task was performed on control subjects (n=27) with standard amplitude of 200 μm and initial test amplitude of 400 μm (see Neurosensory Assessments) (Forshey, et al., accepted with revisions). This condition, in the absence of

unattended hand stimulation, was compared with several other conditions (dual-site equal-amplitude stimulation, dual-site unequal-amplitude stimulation, and single-site stimulation) whereby stimuli were delivered to the unattended (right) hand while amplitude discrimination capacity was determined for the attended (left) hand. Amplitude discrimination performance was compromised in conditions where unattended hand stimulation least matched that delivered to the attended hand while thresholds did not significantly change for tests in which unattended hand stimuli most matched that delivered to the attended hand (Table 4.3., Figure 4.5.).

Amplitude discriminative capacity was significantly worsened with equal-amplitude stimulation regardless of the amplitude applied to digits of the unattended hand (Table 4.3., Figure 4.5.). In these cases, the unattended hand stimulation suggested interhemispheric modulation of the stimulated digits of the attended hand subsequently resulting in worsened performance on the amplitude discrimination task. While this change in performance might be due to inhibitory modulation from stimulation of the unattended hand, perceptual differences might alternatively be due to a combination of inhibitory and/or excitatory mechanisms. Increasing the amplitude of the unattended hand stimulation failed to significantly alter discrimination performance in comparison to the lower amplitude condition. Subsequent tests with more specific types of unattended hand stimulation were performed to further reveal potential mechanisms (interhemispheric inhibition and/or excitation of homologous sites) involved in the attenuated performance.

Unequal-amplitude unattended hand stimulation differentially impacted amplitude discriminative capacity (Table 4.3., Figure 4.5.). In particular, the results suggested that mismatching stimulation resulted in a deterioration of amplitude discrimination performance while the matching condition indicated that similar patterns of stimulation on homologous sites

across hemispheres did not significantly affected discriminative capacity. However, the decrease in amplitude discriminative capacity in the mismatching condition suggested that one of several potential mechanisms may be involved in perceptual modulation, and thus degraded performance. The results implied that unattended hand stimulation may modulate sensory perception on the opposite hand through long range interhemispheric connections. The magnitude of the unattended hand stimuli may either potentiate or suppress attended hand perception depending on the particular pattern and loci of stimulation applied to the attended hand. For example, incongruent stimulation may reduce perceptual contrast due to increased activation of the locus where the standard stimulus is applied on the attended hand. In this case, the standard stimulus would be perceived as more intense, and therefore, the performance on the task may subsequently worsen. Alternatively, decreased activation of the locus where the test stimulus is applied on the attended hand may also worsen discriminative capacity in the same manner (the test stimulus would be perceived as less intense, and performance degrades). Lastly, there may be more complex mechanisms involved due to the lateral inhibitory mechanisms that exist among the unattended hand itself. The unattended hand percept may induce a perceptual rivalry which evokes tactile illusions and thus context-dependent differential performance on the amplitude discrimination task in the presence of unequal-amplitude unattended hand stimulation. The results of this portion of the study indicate that a mechanism other than inhibition contributes to tactile performance. In order to study the effects of unequal-amplitude digit stimulation in the absence of potential lateral inhibitory mechanisms in the unattended hand, single-site stimulations were applied to observe if there were any similar differential effects on amplitude discrimination performance.

The results from the single-site unattended hand stimulation at individual digits (D2 or D3) also resulted in differential performance on the amplitude discrimination task (Table 4.3., Figure 4.5.). Subjects performed worse when the pattern of stimulation on the unattended hand least matched that applied to the homologous site on the attended hand. In other words, when similar patterns of stimuli were applied to homologous sites, amplitude discrimination capacity was not significantly affected. This conclusion was based on the results which show that subjects generally perform worse in the incoherent conditions than in the coherent ones. Repetitive vibrotactile stimulation leads to distinct and stimulus parameter specific patterns of evoked activity in the primary somatosensory cortex, and if these patterns are perceptually relevant, then stimulus amplitude specificity could contribute to differential performance on the attended hand. The data show that the stimulus that is delivered on the unattended hand has a significant impact on task performance of the attended hand. The implications of this finding are that bimanual manipulations and explorations of objects are optimized when both homologous digits receive the same or similar input. Whether or not this similarity paradigm exists only for one parameter—in this study, amplitude—remains to be tested and future studies will investigate this interesting possibility.

Prior neurophysiological studies have shown that vibrotactile stimulation of the digits—as delivered in this study—result in am evoked response with single-site stimulation, and a positive response is evoked in both the contralateral and the ipsilateral hemispheres. However, when a second stimulus is introduced to the homologous skin site on the opposite side of the body, the responses evoked by the two stimuli are not summed. In other words, while positive responses are evoked by independently-delivered contralateral or ipsilateral stimuli, the combined response evoked by both stimuli in unison is reduced significantly—the sum is much

less than computational sum of the individually-evoked responses of the two stimuli. Combining those observations with those of the current study suggest that in some cases, magnitude of the evoked response does not necessarily correlate with task performance—if stimuli do not match, then perhaps some other factor—such as synchronization of cortical ensembles—plays a role in stimulus identification. One of the impacts of the change in stimulus conditions can be observed in S1—how much influence S2 has on the evoked response of S2 via these types of stimulus conditions would be difficult to assess. However, digit specificity was observed in the influence that different patterns of stimulation of the unattended hand had on task performance, and these observations suggest a strong S1 influence, since S2 receptive fields are much larger than those in S1 (are multi-digit). Both S1 and S2 play a role in the cortical network response that modulates the performance on tasks such as the ones deployed in this study, and ascertaining the independent roles of those cortical areas could only be teased out with additional experimentation, as the available literature simply does not currently provide sufficient information to address the questions posed by this study.

The results from these tests suggest that differential amplitude discriminative performance was associated with similarity between magnitudes of stimuli that were concurrently applied from on the unattended hand. In other words, the stimulus conditions where amplitude discrimination capacity was not significantly affected were when the unattended hand stimulations more closely matched the stimuli applied to the attended hand. The results of the three parts of the study suggested potential mechanisms involved in interhemispheric interactions. When stimuli were applied to the same homologous locus on both hands, if the stimulus magnitude on the unattended hand was greater than that on the attended hand, the percept of the attended hand stimulation suggested an increase in perceptual intensity

(excitatory). On the other hand, if the stimulus amplitude on the unattended hand was less than that applied to the attended hand, that percept was thought to decrease in perceptual intensity (inhibitory). These interactions were both dependent on the locus and pattern of stimulation applied to both hands. The findings suggested that each bilateral interaction was a context-dependent feature of the cortical network. Inhibitory and excitatory cortical circuits were dependent on each other in order to appropriately form balanced networks of activity. However, alterations in these networks might cause shifts in network balance. Interhemispheric interactions have been shown in studies where stimulus input evoked excitatory cortical responses to the contralateral hemisphere (Nihashi, et al., 2005; Zhu, Disbrown, Zumer, McGonigle, & Nagarajan, 2007), but there are also implications of inhibitory responses (Hlushchuk & Hari, 2006; Lipton, Fu, Branch, & Schroeder, 2006). Future neurophysiological studies will be required to determine the mechanisms involved in the digit specific interactions that were demonstrated in this report.

The significance of the finding in this report is that a relatively simple protocol, such as amplitude discrimination in the presence and absence of a confounding conditioning stimulus delivered to the unattended hand, could potentially be used to determine deficits in the connectivity across hemispheres. In other words, individuals with atrophied or damaged callosal connectivity would be predicted to outperform healthy individuals on a metric that compares amplitude discrimination capacity in the presence and absence of conditioning stimuli delivered to the unattended hand. Deficiencies in callosal connectivity have been demonstrated in a number of neurological disorders (aging deficits (Voineskos, Rajji, Lobaugh, Miranda, & Shenton, 2010; Zahr, Rohlfing, Pfefferbaum, & Sullivan, 2009), autism (Barnea-Goraly, et al., 2004; Hardan, et al., 2009), schizophrenia (Degreef, Lantos, Bogerts, Ashtari, & Lieberman,

1992; Lewis, Reveley, David, & Ron, 1988; Swayze, et al., 1990; Tibbo, Nopoulos, Arndt, & Andreasen, 1998; Wolf, Hose, Frasch, Walter, & Vasic, 2008), attention-deficit disorder (Hynd, et al., 1991)). Detection of these deficits utilizing simple and straightforward sensory testing methods could provide an efficient means for determining callosal abnormalities, but direct validation of this idea with parallel imaging studies needs to be conducted. Such studies are planned for the near future and we anticipate that differences in performance in perceptual tasks that integrate information across the body mid-line will parallel callosal health.

Table 4.3. Contralateral Stimulation on Amplitude Discimination.

	Attended Hand Stimulation (S/T µm)	Unattended Hand Stimulation (S/T µm)	Threshold (µm)
Amplitude Discrimination	200/[205-400] µm	0/0 µm	44.1±5.0
Equal Amplitude			
200 µm	200/[205-400] µm	200/200 µm	94.9±12.6***
400 µm	200/[205-400] µm	400/400 µm	81.7±10.2***
Unequal Amplitude			
Matching	200/[205-400] µm	200/400 µm	52.5±22.3
Mismatching	200/[205-400] µm	400/200 µm	129.1±14.0***
Single-Site			
Mismatching with Standard	200/[205-400] µm	0/200 µm	100.1±13.1***
Matching with Standard	200/[205-400] µm	200/0 µm	57.1±12.8
Matching with Test	200/[205-400] µm	0/400 µm	49.5±9.1
Mismatching with Test	200/[205-400] µm	400/0 µm	103.8±15.0**

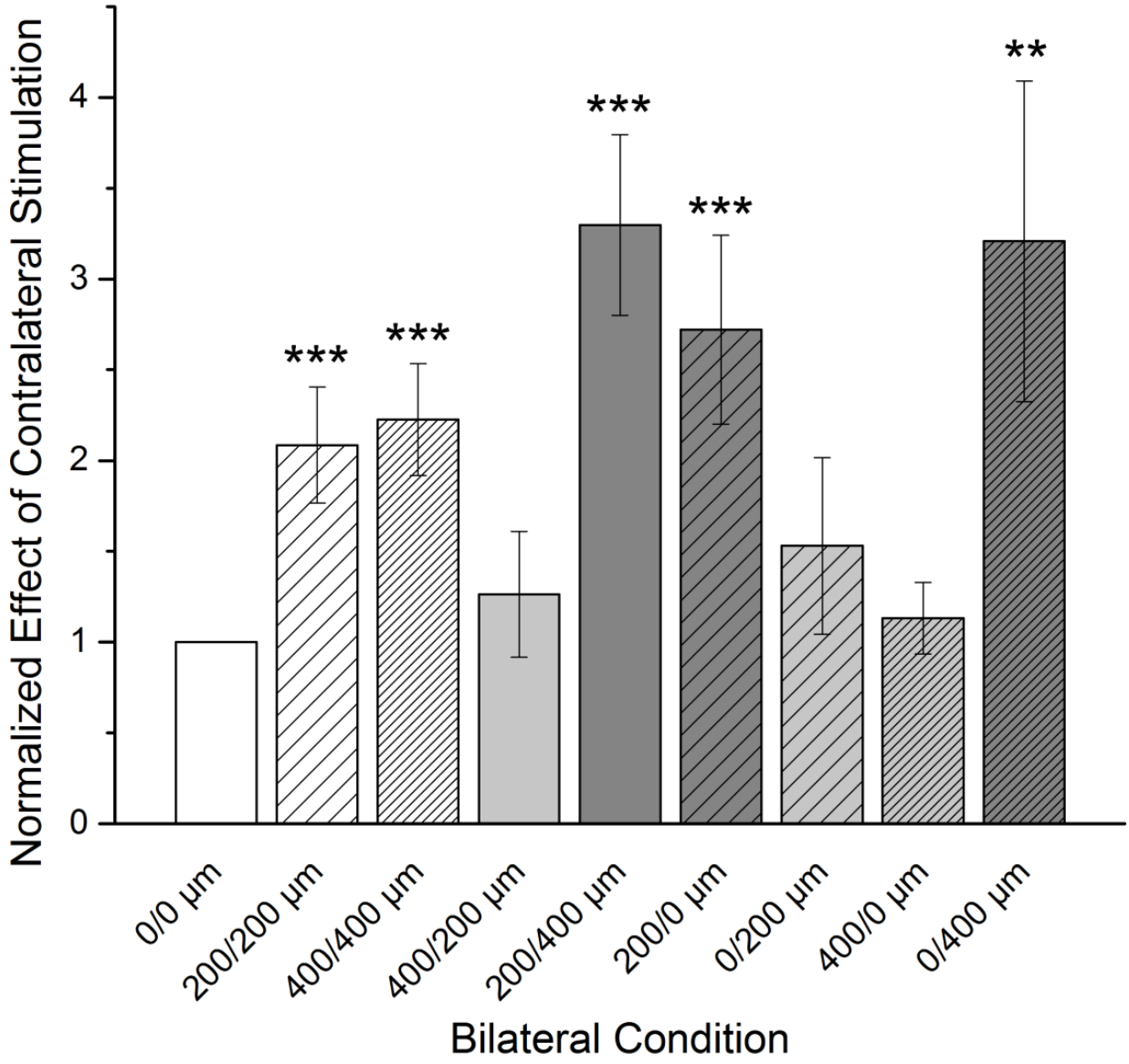

Figure 4.5. Contralateral Stimulation on Amplitude Discrimination.

Conclusions

Application of sensory perceptual metrics showed that these assessments can screen, track changes in, and differentiate these three clinical populations in young adults. Similar sensory perceptual metrics have been explored within other experimental systems allowing for further opportunities to expand the capabilities of this particular screening system. For example, the schizophrenia population has been thought to have impairments in sensory gating, and thus habituation (Potter, Summerfelt, Gold, & Buchanan, 2006), and the adaptation metric may show promise in detecting these types of dysfunctions. Furthermore, cross-hemispheric temporal order judgment has been explored in pain to reveal insights about spatial processing (Heed & Azanon, 2014), and this system possesses the capabilities to replicate and expound on these findings. Being able to optimize the system to provide a better, quicker, and more comprehensive battery of assessments than current methods is advantageous, and the technology has the ability to evolve. The goal of the research is to develop quicker and novel protocols to generate unique sensory profiles to be able to screen and categorize subjects according to their performance on the evaluations. Evaluating a large amount of subjects in different populations with the same protocols, various multiparametric approaches can be used to not only separate the populations but machine learning algorithms can be effectively implemented in order to categorize and predict neurological impairment in unclassified populations.

While concrete clinical diagnoses of subjects based on their sensory perceptual metrics is difficult to assert with high confidence due to the complex and multifaceted nature of many of these neurological disease states, the measures can provide insight into fundamental neurobiological mechanisms which may potentially be impaired. This approach of understanding particular features of information processing can be advantageous in finding nuanced

commonalities and subtle differences among certain systemic neurobiological manifestations. One particular example includes adaptation impairments in both the alcoholism and migraine populations, taken together with the fact that NMDA receptor antagonism blocks this mechanism, may suggest similarities in these populations through imbalanced excitatory and inhibitory neurotransmission. Research supports that chronic alcoholism results in hyperexcitability following withdrawal, which is a similar phenomenon seen in migraine excitotoxicity. As a result, understanding the neurobiological processes involved in these classes of protocol with the addition of understanding etiologies of particular neurological diseases can provide information about both the disease state as well as the fundamental biological mechanisms involved in healthy information processing.

Evaluation central information processing through this system is useful because control values have been established for many of the common tests, neurobiological correlates have been associated with the protocols, and the evaluations can take into account that the brain is plastic and that there is inherent variation within and among subject populations (Figure 4.6.). While there is plenty of room for system optimization, the published data in experimental and clinical populations suggest that this tool can provide insight into fundamental neurobiological processes and can thus be considered as a useful alternative or complement to current diagnostic or screening evaluations.

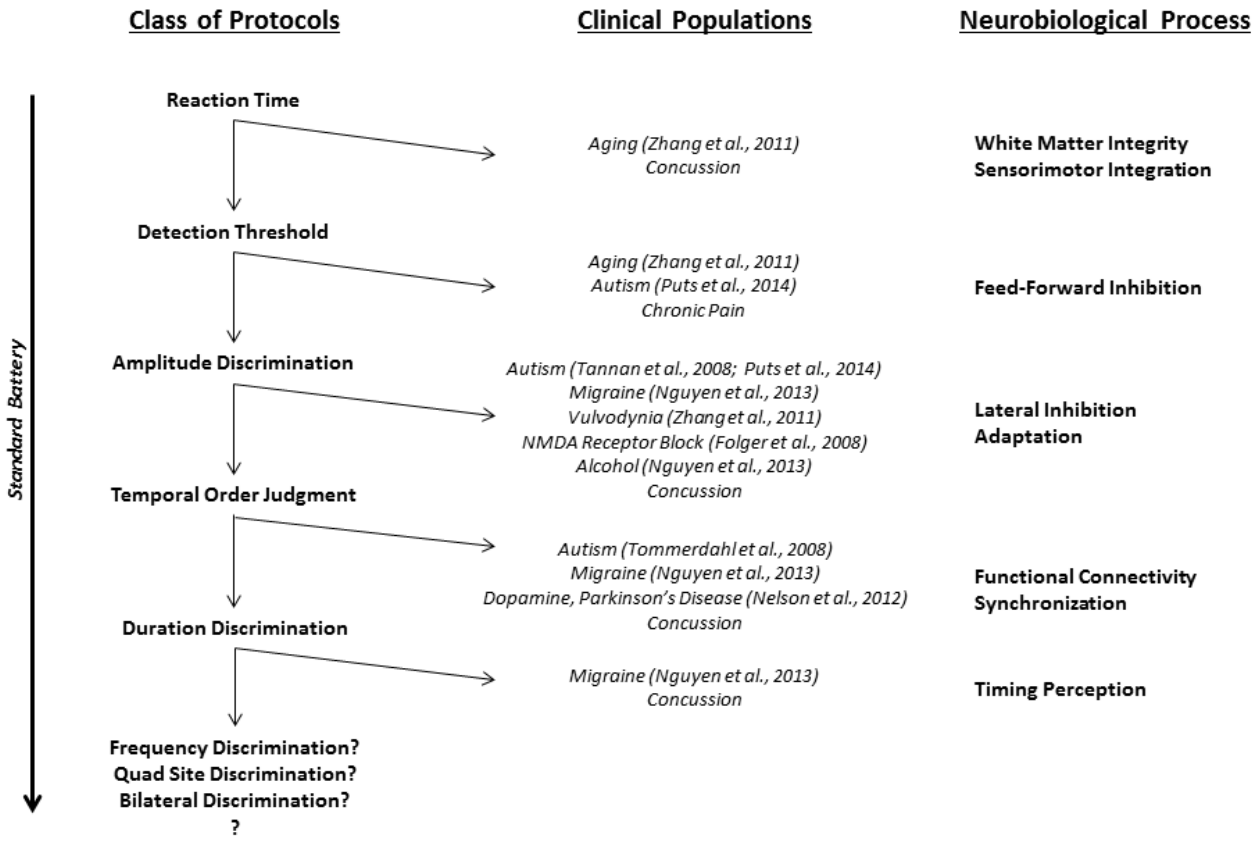

Figure 4.6. Classes of Protocols and Clinical Populations Assessed.

APPENDIX: ADDITIONAL PROTOCOLS

Temporal Order Judgment

The temporal order judgment tasks required subjects to accurately identify one of two digits (D2 or D3) which received the first of two sequential taps. Previous studies indicate that temporal order judgments are comparable across all sensory modalities (Hirsh & Sherrick, 1961) and are correlated with timing perception associated with various cortical regions including, but not limited to, the supplementary motor area, posterior parietal cortex, temporal parietal junction, and basal ganglia. This task was conducted in the absence and in the presence of concurrent, or synchronizing, stimulation. The stimulus-driven effect of the synchronized conditioning stimuli is suspected to be associated with coordinated activity of near-adjacent cortical ensembles in anterior parietal cortex. The delivery of the stimuli consequently impacts the topography of temporal perception by increasing functional connectivity between cortical regions resulting in impaired spatial discrimination (Tommerdahl, Tannan, Zachek, Holden, & Favorov, 2007). Additional evidence of synchronization is supported by transcranial magnetic stimulation (TMS) studies in where the effect of conditioning stimuli on the task was suppressed following TMS.

For the simple temporal order judgment task (TOJs), two sequential taps (initial stimulus parameters: 150 ms interstimulus interval (ISI), 200 μm amplitude, 40 ms duration), were delivered, one to each digit tip. Subjects were subsequently instructed to identify the digit which received the first stimulus.

For the temporal order judgment task in the presence of concurrent, or synchronizing, stimulation (TOJc), a carrier stimulus (25 Hz) was delivered for a minimum of 400 ms prior to the delivery of the first of the two sequential taps and lasted for the entire duration of the allotted interval (1 s) with the exception of the two 40 ms intervals during which the taps were being delivered. Subjects were subsequently instructed to identify the digit which received the first stimulus.

A fixed inter-trial interval (ITI) of 5 s occurred between each of the trials, and the locus of the digit which received the first of the two pulses was randomized on a trial-by-trial basis. Thresholds (interstimulus intervals, ISI) were determined over 20 trials using a two-alternative forced-choice (2AFC) tracking algorithm (see Tracking Algorithm), and ISIs were recorded for all trials. Correct responses resulted in shorter ISIs while incorrect responses resulted in longer ISIs.

The results show that increased carrier amplitude is positively correlated with longer interstimulus intervals on the temporal order judgment task (Figure A.1.). In other words, higher magnitude of concurrent conditioning stimuli effectively worsens performance on the temporal order judgment task due to synchronization and subsequent increased functional connectivity of cortical ensembles.

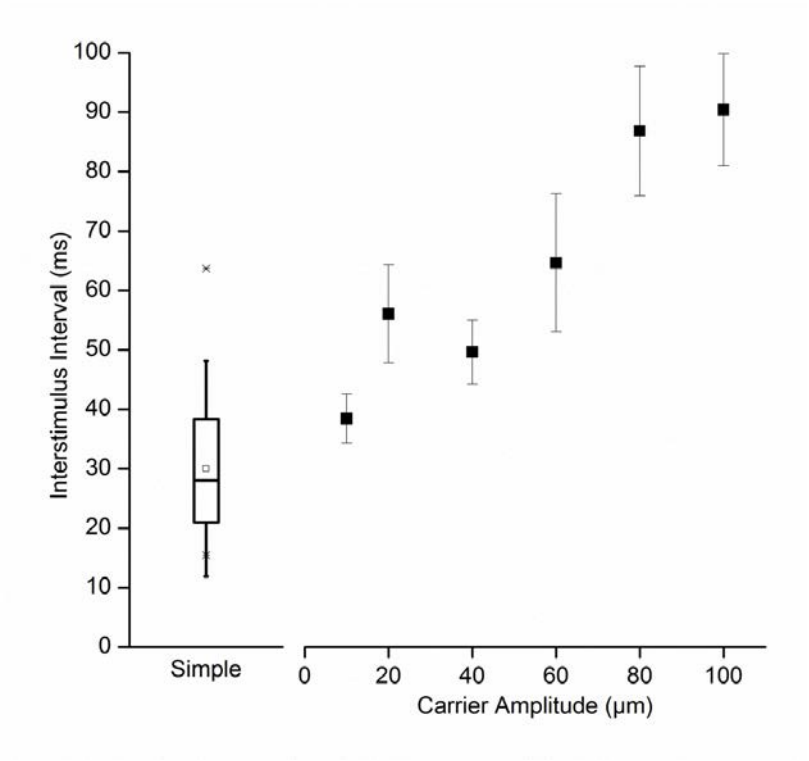

Figure A.1. Temporal Order Judgment.

Duration Discrimination

The duration discrimination tasks required subjects to accurately identify one of two digits (D2 or D3) which received the longer of two vibrations. Duration discriminative capacity is defined as the minimal difference in durations of two stimuli in which subjects can successfully identify the stimulus of larger duration. This task was conducted in the absence and in the presence of confounding stimulus. Duration discrimination capacity may be dependent on sensory exposure and development but is capable of being generalized across somatotopic location, hemisphere, as well as sensory modality. Various models suggest that timing perception may either involve multiple brain regions for shorter intervals (network state) or a centralized timing region for longer durations (internal clock). In particular, sub-second timing perception is hypothesized to reflect right prefrontal and posterior parietal cortical function among involvement of other cortical regions. The somatosensory cortex could also play a significant and direct role in duration discrimination, as increasing durations of repetitive vibrotactile stimulation lead to increases in the duration of the evoked response observed with intrinsic signal optical imaging. Interestingly, any impact on duration discrimination observed at the level of somatosensory cortex could be significantly altered by changes in neuron-glial interaction, the intrinsic signal in those studies has been demonstrated to be strongly correlated with glial activity.

For the simple duration discrimination task (DDs), two sequential vibrations (initial stimulus parameters: 750 ms test, 500 ms standard, 300 μm, 25 Hz, 25 ms step size), were delivered, one to each digit tip. Subjects were subsequently instructed to identify the digit which received the longer stimulus.

Fort the duration discrimination task in the presence of a confounding stimulus (DDc), the amplitude of the standard stimulus was 400 μm while that of the test stimulus remained at 300 μm. Subjects were subsequently instructed to identify the digit which received the longer stimulus.

A fixed inter-trial interval (ITI) of 5 s occurred between each of the trials, and the locus of the digit which received the longer of the two pulses was randomized on a trial-by-trial basis. The duration of the test stimulus was always greater than that of the standard stimulus. Thresholds (difference limens, DL) were determined over 20 trials using a two-alternative forced-choice (2AFC) tracking algorithm (see Tracking Algorithm), and DLs were recorded for all trials. Correct responses resulted in shorter test durations while incorrect responses resulted in longer test durations.

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