Cortical Metrics

Biological Basis for Cortical Metrics

Abstract

A large number of neurological disorders (neurodegenerative, neurodevelopmental or trauma induced) are difficult to diagnose or assess, thus limiting treatment efficacy. Existing solutions and products for this need are costly, extremely slow, often invasive, and in many cases fail to definitively (and quantitatively) diagnose or assess treatment. Our innovative low-cost sensory testing device non-invasively assesses the central nervous system (CNS) health status in minutes for numerous patient populations that are currently difficult to diagnose or assess. Based on pilot data (currently an ontological database of over 1500 subjects), the system can be used to enable clinicians to have a much better view of a patient's CNS health status. The diagnostic system delivers a battery of sensory based (tactile) tests that are conducted rapidly – much like an eye exam with verbal feedback – and are designed around the concept of measuring how much the CNS is impacted by a particular neurological disorder. Design and validation of the perceptual metrics was/is accomplished via correlative studies that compare non-invasive observations of human sensory percepts with non-human primate neurophysiological studies.

Introduction

There are countless reasons that a person's blood pressure could be high: hardening of the arteries, too much salt in the diet, kidney malfunction, obesity, etc., could all be one of many of the potential culprits that cause high blood pressure. The long list of things that could lead to high blood pressure would seemingly deter us from using it as a standard measure of health, since any of a number of factors could be what led to the deviation from normative values and thus, the measure seems somewhat nonspecific. However, it is generally regarded as a starting point for a physician to determine what, if any, action should be taken to return a patient to cardiovascular health.

Could such a non-invasive procedure exist for evaluating a patient's central nervous system (CNS)? Sensory perception relies on many facets of the CNS for a patient or subject to perform well on (or within a "normal" range). First, it requires that the peripheral nervous system (PNS) is, for the most part, intact. Second, transmission of the signal must reach the sensory cortex (in the case of the somatosensory system, via the spinal cord) with reasonably good fidelity. Third, processing within the cerebral cortex must be capable of spatially and temporally integrating information that it has received, and this typically requires multiple levels of processing – both in the primary sensory cortex as well as at cognitively higher levels.

The somatosensory system is ideally suited for the design of a CNS diagnostic system. First, the organization of the system is such that adjacent skin regions project to adjacent cortical regions (i.e., it is somatotopic). Second, ambient environmental noise in the system can be easily controlled (i.e., it is less likely that a patient will be exposed to distracting tactile input than auditory or visual input). Third, the somatosensory system is the only sensory system that is highly integrated with the pain system, and this is often an important aspect of a patient's diagnosis.

As a first step towards developing quantitative sensory testing methods that could non-invasively detect systemic alterations

Figure 1. CM4 vibrotactile stimulator.

in the CNS, we designed and fabricated a portable multi-site stimulator. The stimulator pictured at left (Figure 1; CM4 is fourth Cortical Metrics model) can be used to deliver vibrotactile stimuli to four digit tips (see inset to Figure 1). Typically, the mechanical stimuli that are delivered to the skin are sinusoidal in nature, and the stimulator is capable of delivering amplitudes in the range of 0 – 1000 microns and frequencies in the range of 0 – 200Hz. Stimuli can be delivered independently to each finger tip, and the temporal sequences of stimuli, as well as the amplitude, frequency, and duration, are computer controlled via USB interface. Prior models of the device and its design have been previously reported (Tannan et al, 2005a, 2007b).

In parallel with the development of the stimulator, we designed a number of unique sensory testing protocols aimed at extracting information exclusively about the CNS in an efficient and reliable manner. In this report, we describe the evolution of one of those measures. First, a description of how traditional clinical measures (e.g., tactile sensory detection thresholds) can be obtained is provided. These types of tests provide sensory information that is analogous to that normally obtained with a vision (e.g., eye chart exam) or hearing test. Second, we briefly describe the neurophysiological basis for comparing two simultaneously delivered stimuli, and sample data from this type of sensory test is also provided. Third, a description of how a measure can be impacted by an individual's ability to adapt to tactile stimuli (on the order of a second or less) and can be quantified is presented. In this section, we provide evidence that this type of metric – which we term as a "cortical metric" – has potential for providing clinicians with diagnostic information as well as a means for assessment of treatment efficacy for a number of neurological disorders. In this report, the biological basis of 5 different categories of cortical metrics will be described.

Categories of sensory based perceptual metrics:

1. *Feed forward inhibition*. Although it is difficult to reveal information about the CNS with threshold detection measures, it is possible to reveal the feed forward inhibition that is inherent in the system by comparing two independently obtained threshold detection measures by different methods. Comparison of a "static" threshold detection metric (described in Zhang et la, 2009) that determines the minimum supra-threshold stimulus that can be detected with a "dynamic" threshold metric in which a subthreshold stimulus is slowly grown into an above-threshold stimulus. The difference reveals the impact that sub-threshold stimulus evoked inhibition has.

2. *Lateral Inhibition*. Simultaneously delivered vibrotactile stimuli to the two digit tips activate adjacent cortical regions. Parametric comparisions (e.g., differences in amplitude) of the stimuli delivered to the two sites yields insight into the subject's performance in GABAergic mediated lateral inhibitory interactions. Robustness of this measure is discussed in Francisco et al, 2008.

3. *Adaptation metrics.* Regardless of how well a subject performs a test, conditioning stimuli can be used to either confound or improve performance in that test. In healthy controls, the impact of such conditioning stimuli is robust (Tannan et al, 2007), yet in people with autism, it is not (Tannan et al, 2008).

4. *Functional connectivity*. How do adjacent, near-adjacent and remote cortical regions interact to coordinate

stimulus evoked activity? Utilizing one of these measures (Tommerdahl et al, 2007), we demonstrated distinct differences between controls and autism (Tommerdahl et al, 2008). Additionally, another measure of functional connectivity (described in Zhang et al, 2009) demonstrated high correlation with fcMRI (R2=0.80) and evenly split the cohort of 45 subjects into a bimodal distribution (in preparation for publication).

5. *Duration discrimination*. Based on the work of Simons et al, 2005 and 2007, in which we characterized the responses of the intrinsic signal (which is tightly coupled to glial activity; Lee et al, 2005) we devised a protocol to test interaction between the duration and the amplitude of a stimulus. The protocol has two parts: In the first part, a duration discrimination metric is obtained (i.e., how well can a subject tell the difference between a 500ms stimulus and one of another, longer duration but of equal amplitude). In the second part, the confound of changing the amplitude of one of the stimuli is introduced. In controls, the effect increasing the amplitude is to increase the percept of duration and this corresponds very well with the neurophysiological findings (normally by 30%). However, in concussion, there is no effect, and this correlates well with below normative glia activity known to impact this population (in preparation for publication). Thus, like many of our other protocols, subjects with some type of neurological compromise perform better on the given task than do controls.

1.Using sensory thresholds to determine a metric of feedforward inhibition

Tactile detection thresholds are typically collected by clinicians because sensitivity to a tactile stimulus generally increases with a neurological alteration. However, threshold measures are most useful if baselines are recorded – i.e., if a subject's threshold is acquired before something impacts his/her neurological health, then comparisons can be directly made. Without baseline measures, there can be a great deal of variability from one subject to another, primarily due to skin physiology (e.g., the callused hands of a manual laborer could result in higher than normal detection thresholds).

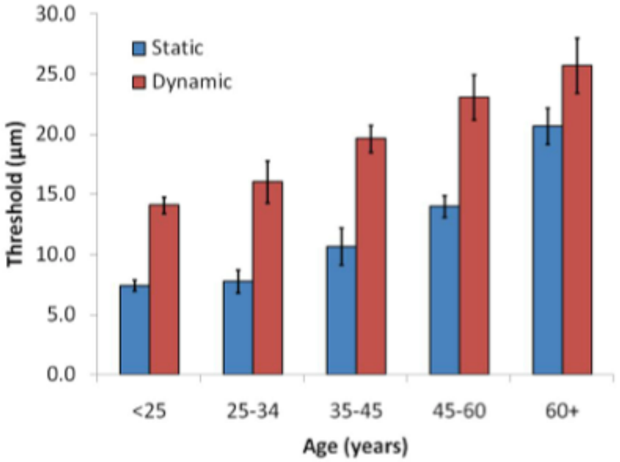


Figure 2. Tactile detection thresholds across an age spectrum. Note increase in threshold with increasing age.

Our approach to threshold detection is slightly altered from the traditional approach. The majority of published studies report thresholds using one stimulus site, and subjects generally indicate whether they feel "something" or "nothing". Utilization of two stimulus sites allows for the subject to be questioned as to where they thought the stimulus was, and ultimately generates a more accurate answer.

Our working hypothesis is that a centrally mediated measure will remain effectively constant across a subject population, provided that the CNS is healthy, although we would expect there to be a wide range in peripherally mediated measures. To demonstrate this concept, we examined thresholds across the healthy adult population. Due primarily to changes in skin physiology, detection thresholds go up (or sensitivity goes down) with age. Note in the graph in Figure 2 how threshold

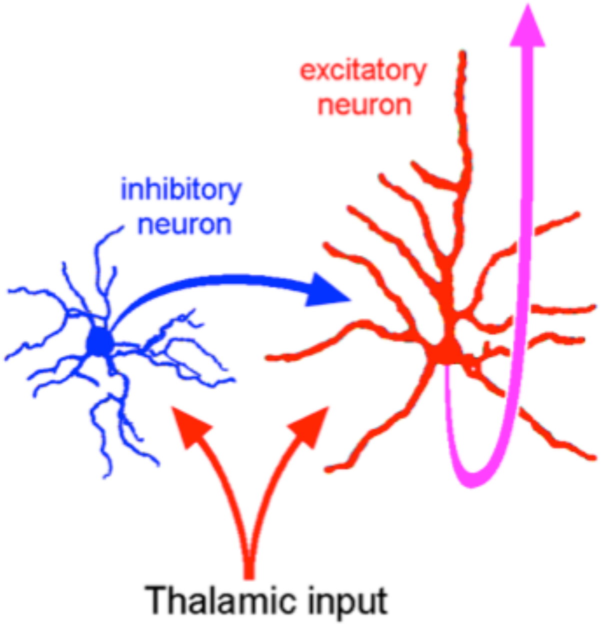
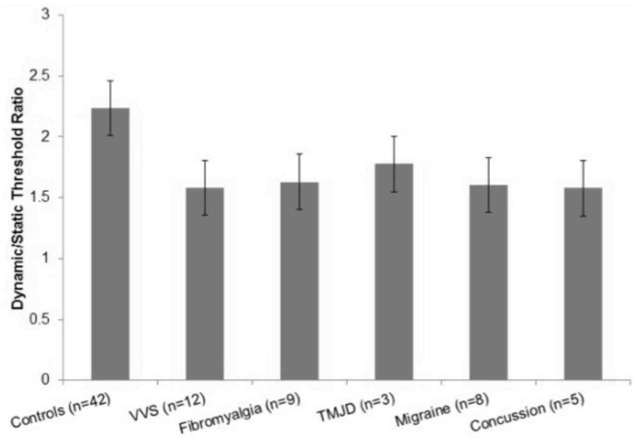


Figure 3. Feedforward model of inhibition.

goes up with age. Also note that two types of threshold measures are shown – a “static” threshold in which a two-forced choiced paradigm is used to track threshold and a “dynamic” threshold in which a subject has to detect a modulated stimulus (increasing in size from zero to

In our current feedforward model of dynamic threshold processing, we postulate that subthreshold inputs transmitted from the skin to cortex via thalamus result in activity driven inhibition. This inhibition subsequently raises the threshold, and the next stimulus – which is slightly larger than the previous stimulus – remains to be sub-threshold and in turn, causes another subsequent increase in inhibition. Eventually, the magnitude of the stimulus is increased enough to overcome the increased threshold. Deficiencies in the underlying mechanisms that support this feedforward inhibition would result in significant increases or decreases in the differences observed between static and dynamic thresholds. For example, in the Figure at left, note that subjects with compromised CNS health have a dynamic/static threshold ratio significantly lower than that obtained from healthy controls.



2.Biological basis of lateral inhibition metrics

A biopsy is often used to examine the viability of a biological tissue that is suspected to be diseased or injured. While this method is invasive, it is nevertheless quite effective as a means of putting one piece of a suspected tissue under a high degree of scrutiny. The underlying premise in that form of testing is that all pieces of the organ tissue have been afflicted by trauma, disease and/or injury in a similar manner. For this reason, we hypothesized that we could develop novel means to “non-invasively biopsy” the cerebral cortex of subjects/patients that have undergone some systemic neurological alteration. The techniques are based on strong correlations that have been observed (utilizing both human and animal studies in parallel) between cerebral cortical activity and perceptual measures that are evoked by tactile stimulation. Thus, the combinations of stimuli that are delivered to the skin generate sensory percepts that can be predominately accounted for within a relatively small region of cortex. Although this region of parietal cortex could be considered limited in scope, much of the basic cortical circuitry that is utilized throughout the entire cerebral cortex can be found in this “slice” and studying the interactions that take place in this slice can give explicit metrics about the functional connectivity that exists between adjacent and near-adjacent cortical regions. For example, comparison of the two images in Figure 4 that were evoked by the same conditions of electrical stimulation in the cortical slice demonstrate the difference that a small amount of GABA (gamma aminobutyric acid) antagonist (2 µM bicuculine) will have on the spatial distinction between the two near-adjacent cortical columns that have been activated (dark regions indicate areas of high neural activity; for more thorough experimental description, see Kohn et al, 2000). Similar experiments (both in vivo and in vitro) have shown that (1) GABA agonists improve the contrast between these cortical areas, (2) this contrast can also be improved with short-duration (1-5 sec) repetitive stimulation (a function of cerebral cortical neuroplasticity), (3) the improvements made by repetitive stimulation can be blocked with NMDA (N-methyl-d-aspartate) receptor antagonists, and (4) reversibly blocking glial activity will significantly impact the cortical response (for limited referral, see Whitsel et al, 1999).

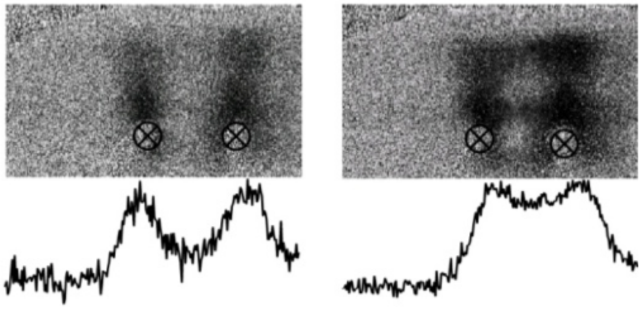


Figure 4. Top: images of activity evoked in sensorimotor cortical slice of the rat. Circled "X" denotes location of electrical stimulus. Bottom: Spatial histograms of above images.

The significance of Figure 4 is that delivery of two identical stimuli to the same cortical sites yield two distinctly different results under different experimental conditions. In the absence of a GABA antagonist, the two cortical regions are easily contrasted, as depicted by the cross-sectional histogram. With lower levels of GABA (in this case, due to the GABA antagonist), the contrast between the two stimulated sites is greatly reduced. Thus, this would predict that a subject, with diminished GABA levels (as is the case for a number of neurological disorders and/or traumas), would have more difficulty distinguishing the difference between two stimuli presented to skin sites that project to adjacent or near adjacent areas in the cortex than a subject without diminished or altered GABA levels.

To test the idea that comparison of two adjacent stimuli is relatively stable in healthy populations, an amplitude discrimination task in which both stimuli were delivered simultaneously to adjacent finger tips (D2 and D3) was performed on healthy subjects across a wide age spectrum. This measure was effectively constant across all age groups (see Figure 5). It should be noted that, in order to maximize signal to noise ratio, we conduct this amplitude discrimination task at supra-threshold levels. This allows us to deliver the same size stimuli to all subjects and thus, although threshold variation (discounting for subjects with very significant peripheral neuropathy) is in the range of 10-30 microns, all subjects are able to effectively compare stimuli that are 100 microns or greater.

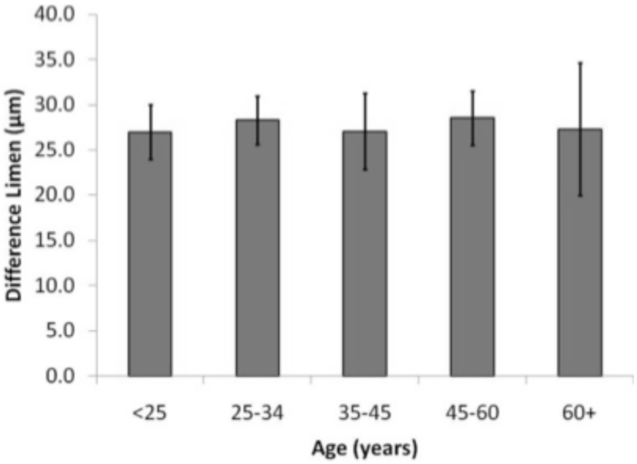
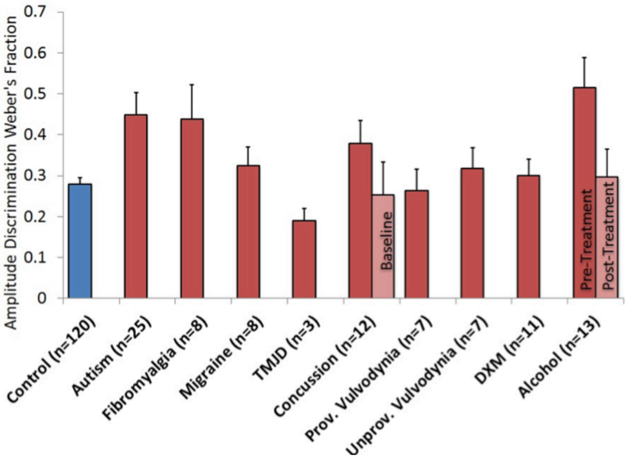


Figure 5. Average difference limens (DLs) recorded across the age spectrum. Note the absence of change with age as was the case in Figure 3.

In order to validate the concept that amplitude discriminative capacity is directly related to SI cortical activity, we compared the results from our human perceptual studies to non-human primate imaging studies. This was accomplished by investigating the SI response to different amplitudes of vibrotactile stimulation utilizing the technique of optical intrinsic signal (OIS) imaging in nonhuman primates. We found that an increase in the amplitude of the stimulus corresponded with the increase in absorbance evoked within the region of SI cortex that receives its input from the stimulated skin field (Simons et al. 2005; Simons et al. 2007). The relationship between the maximal change in absorbance and stimulus amplitude was characterized by a near-linear function within the range of amplitudes studied (50-400 μm). Measurement of the spatial extent of the activated SI region, on the other hand, showed that higher amplitudes of stimulation did not produce a more extensive region of SI activation. Instead, as the amplitude was increased, average peak absorbance within an ~2 mm diameter SI region increased with the amplitude of stimulation, and the region of surrounding cortex underwent a prominent decrease (frequently to levels well below background) in absorbance. In order to directly compare the two principal findings of that study – the relationship of absorbance evoked by different amplitudes of stimulation and the apparent lack of correspondence of the spatial extent with amplitude of stimulation – we directly compared the DLs obtained from human sensory testing with those two entities. The results from those comparisons are shown in Figure 6 and demonstrate that there is a very strong correlation (R2 = 0.9971) between the DLs obtained at each standard amplitude and the neural activity evoked at each amplitude. On the other hand, a much weaker (not significant) correlation was observed between the spatial extent of the cortical response and the DLs obtained at the same amplitudes (R2 = 0.4542).

Thus far, in some populations, we see deviations from normative values in amplitude discriminative capacity, and we interpret this as the result of hyper-excitability, such as observed with a GABA antagonist shown in Figure 4: lower amounts of inhibition lead to difficulty in the subject being able to discriminate between two cortical areas.



3.Using repetitive stimulation to obtain adaptation metrics

Repetitive stimulation results in temporally defined changes of cortical activity, the most prominent of which is a reduction in cortical response with extended stimulus duration. At the single cell level, both visual and somatosensory cortical pyramidal neurons undergo prominent use-dependent modifications of their receptive fields and response properties with repetitive stimulation. These modifications can attain full development within a few tens of milliseconds of stimulus onset, and can disappear within seconds after the stimulus ends (visual cortical neurons: (Bredfeldt and Ringach, 2002; Celebrini et al., 1993; Das and Gilbert, 1995; DeAngelis et al., 1995; Dinse and Kruger, 1990; Pack and Born, 2001; Pettet and Gilbert, 1992; Ringach et al., 1997; Shevelev et al., 1998; Shevelev et al., 1992; Sugase et al., 1999); alternatively, for review of short term cortical neuron dynamics in visual cortex: (Kohn, 2007); for review of short-term primary somatosensory cortical neuron dynamics: (Kohn and Whitsel, 2002; Whitsel et al, 2002)). These rapid changes in cortical neurons are in striking contrast with the relative stability of primary afferent neurons (Whitsel et al, 2000).

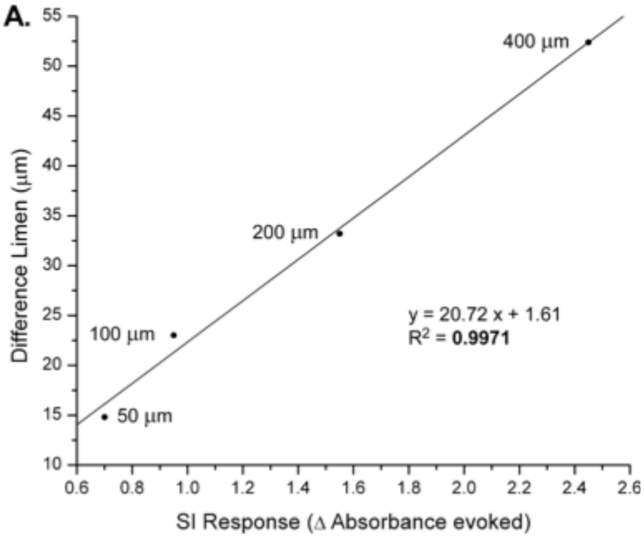


Figure 6. Correlation between human perceptual performance (DLs) and response recorded in SI evoked by same stimulus conditions in non-human primates. Modified from Francisco, et al, 2008.

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

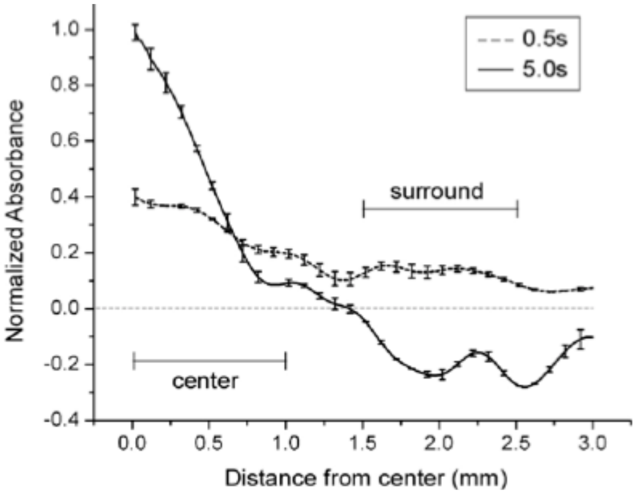


Figure 7. Radial histograms of SI cortical activity, measured via optical imaging. Data at center was at the maximally responding SI cortical territory to the 5 sec stimulus condition (modified from Simons et al, 2007).

The perceptual improvements in spatial discrimination that are normally observed with extended stimulus durations (e.g., Goble and Hollins, 1993; Tannan et al, 2005b, 2006) could be attributed to stimulus-evoked inhibition that surrounds areas of excitation. Single unit studies and imaging studies using voltage-sensitive dyes likewise have shown that excitation in the responding neuronal population is accompanied by the development of a surrounding field of inhibition (Brumberg et al., 1996; Derdikman et al., 2003; Foeller et al., 2005; Wirth and Luscher, 2004). Similarly, imaging studies that have used the OIS have shown that prolonged stimulation of a discrete skin site not only is associated with increased absorbance within the SI region representing the stimulated skin site, but also with decreases in absorbance in surrounding regions (Moore et al., 1999; Simons et al., 2005; Tommerdahl and Whitsel, 1996; Tommerdahl et al., 1999). Regions of decreased absorbance (increased reflectance) such as that described in Figure 7 are widely believed to be indicative of decreases in neuronal spike discharge activity (Grinvald, 1985; Grinvald et al., 1991), possibly resulting from stimulus-evoked inhibition at these locations. There is a great deal of evidence that the suppressed or below-background activity observed to suggest that stimulus-evoked inhibition is responsible for the improvements in discriminative performance that are normally observed with repetitive stimulation. Thus, we would anticipate that a task such as the aforementioned amplitude discrimination, would be sensitive to the duration of stimulation. Utilization of this scientific work has led us to more effectively develop sensory testing methods which detect deficiencies in specific clinical populations.

Randomly applying a conditioning stimulus to one of the two skin sites before the amplitude discrimination task significantly alters a subject's ability to determine the actual difference between the two stimuli, and the impact that the conditioning stimulus has is duration dependent (between 0.2 and 2 secs; Tannan et al, 2007). This finding suggested that the method could be viewed as a reliable indicator of the influence of adapting stimuli on central nervous system response, as changes in the peripheral response are not significantly changed at these short stimulus durations (for discussion, see Tannan et al., 2007a, 2008; Tommerdahl et al, 2007a, 2007b, 2008; Francisco et al, 2008; Zhang, et al, 2009). Simply stated, the reason that subjects get worse with conditioning stimulation to one of the stimulus sites is because the subsequent stimulus, which is used for comparison, now feels smaller than it really is. This creates an illusory effect which appears to be relatively constant across healthy populations regardless of age (see Figure 8).

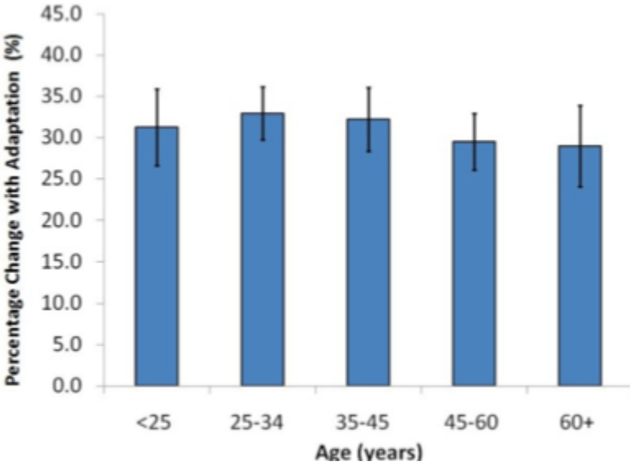


Figure 8. Change in amplitude discrimination DL after conditioning at a single stimulus site.

When this measure is examined across a number of subject populations, we do see significant deviations from control values. To summarize, the chart in Figure 9 demonstrates that this centrally mediated measure deviates from the control values for subjects with autism (Tannan et al, 2008), chronic pain (fibromyalgia, migraine, TMJD) and concussion. Ingestion of 60mg of dextromethorphan (DXM) also leads to a reduction in the impact of the adapting stimulus (Folger et al, 2008) as does chronic use of alcohol. Values that appear in the control range are post-recovery of concussion (3-7 days after concussion) and post-treatment of alcoholism (12 weeks of sobriety; initial measure was after 1 day of sobriety and BAC was zero). "Provoked VVS" is considered peripherally mediated (and exhibits near control values) while "unprovoked VVS" is a chronic pain condition which is thought to be centrally mediated (Zhang et al, 2011). The significance of the VVS study is that distinct differences in information processing capacity (or central sensitization) of the two groups was detected by utilizing sensory testing methods on a body region (the finger tips) that was not impacted by the subjects' affliction (pelvic pain). In other words, pelvic pain had little or no impact on subjects' thresholds, but it did have an impact on the subjects' centrally mediated neuroadaptation metrics.

At first glance, the above-described method appears fairly non-specific: virtually all the data obtained from subjects with

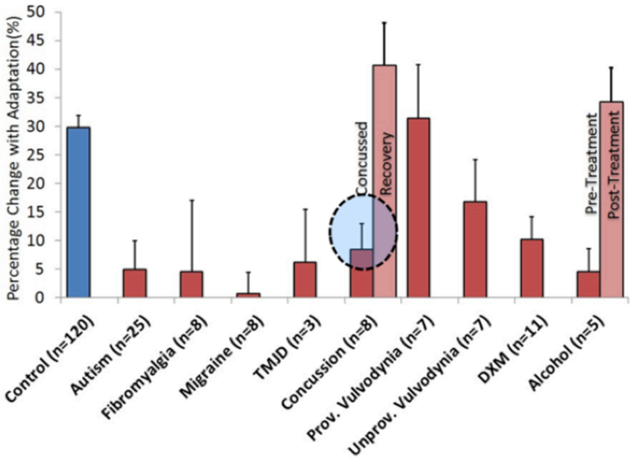
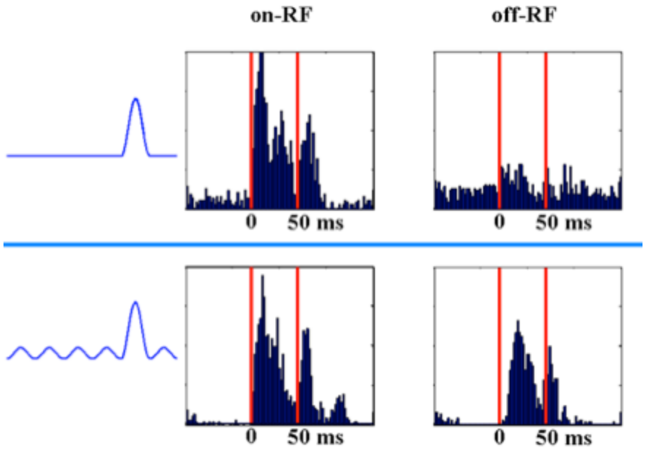


Figure 9. Neuroadaptation Metrics: Summary of adaptation metrics obtained from several different subject populations. Note that the amount that several subject populations adapt is much less than that of controls. The two exceptions are provoked VVS (peripherally mediated) and post-treatment of alcohol subjects (measures obtained after 12 weeks of sobriety). Thus, the impact of changes in centrally mediated mechanisms can be detected using a relatively fast vibrotactile methodology. Note that DXM refers to a post-ingestion of 60mg of dextromethorphan in control subjects. Data from control, autism and DXM subjects has been previously reported (Tannan et al, 2007b, 2008; Folger et al, 2008).

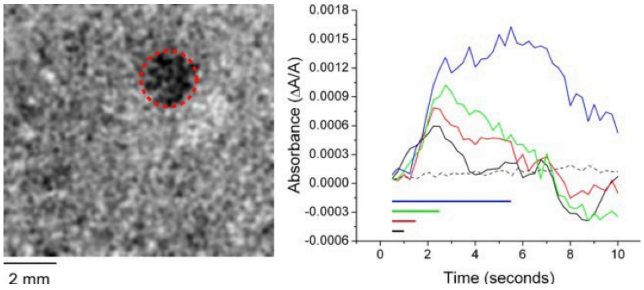
some type of centrally mediated neurological disorder impacted. Adaptation, which encompasses the ability to quickly adjust to one's environment, involves a number of mechanisms. The protocols that have been designed to obtain neuroadaptation metrics were optimized to enable objective evaluation of the neuronal communication between adjacent and near-adjacent regions within sensory cortex that is widely recognized to be essential to normal sensory function. In other words, this "functional connectivity" between two adjacent or near-adjacent cortical regions is indicative of overall CNS functional connectivity. The mechanisms required for this communication include neurotransmission mediated by the inhibitory neurotransmitter GABA and by NMDA receptors, and interactions / interdependencies between neurons and glial cells. These particular processes have been demonstrated to have a significant impact on centrally mediated cortical adaptation, and thus, this type of diagnostic test could prove useful as a quick (2-3 minutes), reliable and efficient means for assessing CNS health. Diagnostic tests aimed at extracting more specific information about functional connectivity have been and are continuing to be developed (Tommerdahl et al, 2007a; 2007b, 2008).

4.Biological basis of functional connectivity measures.

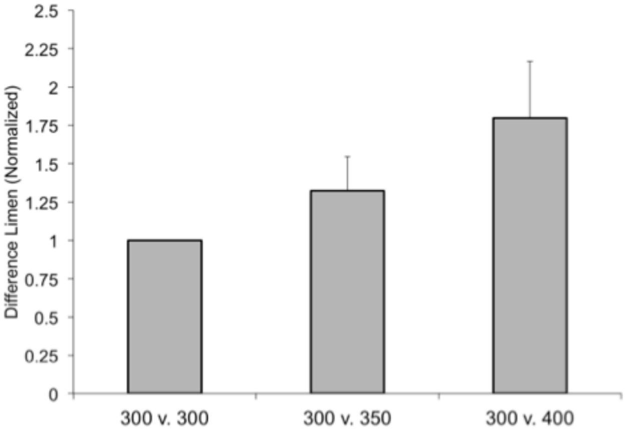


Consider the neural activity plots in the figure above. These were recorded from adjacent cortical regions – one projects to the tip of digit 2 (D2), the other to digit 3 (D3). When a simple pulse stimulus (top left) is applied to D2, the appropriate cortical region (labeled "on-RF") is activated, while the D3 ("off-RF") region remains relatively inactive. However, a conditioning stimulus, presented to both D2 and D3, has the effect of "functionally connecting" the two cortical regions. As evidence, note that post-conditioning (bottom panels), the pulse at D2 now evokes activity at both cortical regions. Prediction: Simultaneous and synchronized conditioning stimuli, delivered to adjacent digit tips, will result in the two corresponding cortical regions to become functionally linked, and a sensory percept differentiating the two digits will be impacted. Result: Subsequent sensory perceptual tests demonstrated this to be the case (Tommerdahl et al, 2007b). A second prediction of the neural data observation was that if the two regions were not able to functionally connect because of a neurological problem, then that same sensory percept would NOT be impacted. Subjects with autism exhibited lower than normal functional connectivity by actually performing better at this sensory test than did controls (Tommerdahl, et al, 2008). In pilot data of concussed subjects, there is a lack of synchronization, similar to that described in autism subjects. However, in the concussed subjects, this condition typically recovers in 7-10 days. Thus, disruption of functional connectivity appears to occur during this critical post-concussive phase – and it cannot be detected via any current methodology. Sensory perceptual metrics are much higher in resolution: these metrics are sensitive to cortical-cortical interactions that occur well within several hundred microns of cortical space, while the best resolution that modern imaging can observe is across millimeters of cortical space.

5.Biological basis of duration discrimination metrics



Pictured above (left panel) is an image of somatosensory cortex activity post vibrotactile stimulation. This is an absorbance image, and at the wavelength that it is recorded at, corresponds predominantly to glial swelling and extracellular K+. At right is the time course of the cortical response recorded within the red ring indicated in the image at the left. Note that the longer the stimulus (color coded horizontal bars inset in graph), the longer the trace. From a separate study, we also know that these traces are impacted by the strength or magnitude of the stimulus. In other words, increasing the amplitude of the stimulus results in a longer lasting stimulus. From this neurophysiological data (published in Simons et al, 2005, 2007), we hypothesized that comparison of the duration of two stimuli – delivered at different times – would be made more difficult if the amplitude of one of the stimuli were increased. The bar chart below demonstrates this particular finding. That is, as the amplitude of the shorter stimulus is increased, subjects have more difficulty telling the difference between the durations of two stimuli. However, pilot data suggests that some subjects that are neurologically compromised – in particular, those thought to have damage to white matter – do not perform worse at this task and actually outperform healthy control subjects when the amplitude confound is introduced.



Conclusions

A light-weight portable diagnostic sensory based testing device has been successfully designed and fabricated. Protocols designed to enable assessment of systemic alterations to CNS have been implemented and proof of concept has been established by applying the methods to multiple subject populations with a wide spectrum of neurological disorders (neurodevelopmental, neurodegenerative, pharmacological and trauma induced). The potential benefit of such a diagnostic device to the war fighter could be quite significant. Quantitative dosimetry of exposure to blast-related trauma would allow commanders to protect personnel from excessive exposure by reassignment as appropriate in each individual case. Personnel could be assessed for sub-clinical manifestations of TBI as a part of post-blast exposure screening & debriefing. If environmental and medical interventions are set in place, the system would allow quantitative tracking of the efficacy of treatment. Collateral benefits to society could include assessment of cumulative TBI and recovery during medical treatment related to sports injuries, vehicle trauma, developmental and aging disorders, behavioral and nutritional effects on cognitive function. New methods - such as those described in this report – could: enable development of standardized diagnostic criteria of the injury, advance the understanding of threshold of injury and the role of repeated exposure, and identify individual factors that may allow for risk prevention of subjects from over-exposure to such blast injuries. These methods could also provide a means for determination of baseline neuropsychological assessments for the study of the various groups at risk of TBI.

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