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Neurosensory assessments of migraine

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ABSTRACT

Headache medicine is primarily dependent on patients' subjective reports of pain, which are assessed at diagnosis and throughout the duration of treatment. There is a need for an objective, quantitative biological measurement of headache pain severity. In this study, quantitative sensory testing (QST) was conducted via multi-site vibrotactile stimulation in patients with migraine. The purpose was to investigate the sensitivity of the method and to determine if the metrics obtained from migraineurs could be differentiated from controls. Metrics reflecting sensory percepts of baseline measures of stimulus amplitude discrimination, temporal order judgment, and duration discrimination were significantly different. Additional measures previously demonstrated to be sensitive to alterations in centrally-mediated information processing features such as adaptation and synchronization were also significantly different from control values. In contrast, reaction times and vibrotactile detection thresholds of migraineurs failed to differentiate them from controls, indicating that the results are not due to peripheral neuropathy or some other primary afferent mechanism. The long-term objective of the study is to develop methods that can improve diagnosis and enable more accurate assessments of treatment efficacy in migraine.

1. Introduction

Headache medicine has few quantifiable biological markers for diagnosis. Screening is dependent primarily upon subjective patient reports of pain and impact of pain on mood and function, which are difficult to standardize among various clinical populations (Aurora et al., 2011; Diener et al., 2012; Headache Classification Subcommittee of the International Headache Society, 2004; Katsarava et al., 2012; Scott, 2011). In the case of primary headache disorders such as migraines, few objective tests are available to provide supplemental information to assess the burden of illness or track its change over time. This dependence on subjectivity remains true from diagnosis to evaluation of treatment efficacy to determine the level of disability. These qualitative reports may be biased by a number factors unrelated to

Abbreviations: AFC, two-alternative forced-choice; CATI, computer-assisted telephone interviewing; D2, digit 2; D3, digit 3; DD, duration discrimination; DL, difference limen; GABA, γ-aminobutyric acid; ICHD, International Classification of Headache Disorders; ISI, inter-stimulus interval; NMDA, N-methyl-d-aspartate; QST, quantitative sensory testing; SMA, supplementary motor area; TMS, transcranial magnetic stimulation; TOJ, temporal order judgment

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headache symptoms. Patients with prolonged migraines often underreport the severity of their symptoms, explaining that they have high pain tolerances or have become accustomed to their headaches. Others may exaggerate, or catastrophize, pain symptoms due to anxiety, depression, or other issues related to secondary pain or, potentially, malingering (Quartana et al., 2009). Thus, there is a compelling need for an objective, quantitative, biologically-based measurement of headaches that can track improvements or deteriorations in headache pain and/or chronification over time. Such quantitative metrics could significantly improve studies of underlying mechanisms, as these objective measures could be used for phenotyping in genetic studies and for quantitatively assessing impact of treatment in patient-centered studies.

Sensory assessments of headache have been explored in a number of previous studies. These studies used sensory testing with the rationale that headache patients are typically vulnerable to sensory stimuli such as light (photophobia), noise (phonophobia), and even odors (osmophobia) (Ambrosini and Schoenen, 2006). Sensory tests in various populations of headache patients showed altered sensory thresholds for certain forms of somatosensory stimuli as well as noxious stimuli (Karanovic et al., 2011; Ladda et al., 2006; Schwedt et al., 2011; Zappaterra et al., 2011). These alterations are supported by the observation of abnormal response patterns in the primary sensory cortices in relation to neuronal excitability and habituation in subjects with migraine (Ambrosini and Schoenen, 2006; Coppola et al., 2009, 2012; Schoenen, 1996). Based on these prior reports, we anticipate that sensory based metrics of central sensory information processing, which we have recently developed and demonstrated to be sensitive to acute conditions of concussion (Tommerdahl et al., 2010a, 2012; Francisco et al., 2012a), chronic pain conditions (Zhang et al., 2011a), neurodegenerative conditions (Nelson et al., 2012) and developmental conditions such as autism (Tannan et al., 2008; Francisco et al., 2011), will be significantly impacted in headache patients. Furthermore, this method of non-painful quantitative sensory testing allows analysis of metrics that cannot be gained by pain testing and may serve as an alternative and less aversive biomarker for pain processes.

This study administered a battery of sensory discrimination tests to subjects with diagnosis of migraine symptoms and to healthy control subjects. These methods provide indices of brain function that are sensitive to chronic clinical conditions such as autism and to acute alterations such as concussion. Within the headache population, sensory metrics are expected to differ from healthy controls due to neurological dysfunction such as cortical hyper-excitability (Coppola and Shoenen, 2012), impairment of habituation mechanisms (Ambrosini and Schoenen, 2006; Coppola et al., 2009, 2012; Schoenen, 1996) and adaptation to stimulation (e.g., Tannan et al., 2007; Folger et al., 2008; Zhang et al., 2011a, 2011b). The results of this study demonstrate that metrics of central brain processing are significantly altered in migraineurs. The long-term objective of the study is to develop methods that can improve diagnosis and enable more accurate assessments of treatment efficacy for migraineurs.

2. Results

2.1. *Reaction time performance and sensory threshold detection in the migraineurs is similar to that in the healthy control population.*

The mean simple reaction times (Fig. 1) for migraineurs (281.2±18.0 ms; $n=13$) were similar to those for age-matched healthy controls (271.8±24.9 ms; $n=13$) populations ($p=0.83$).

In comparing the two threshold detection tests (Fig. 2), the mean dynamic thresholds were higher than the mean static

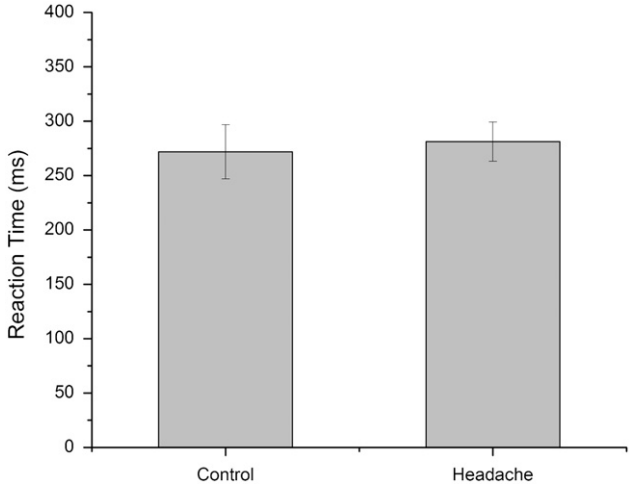

Fig. 1 – Average Reaction Times. The mean simple reaction times for headache patients ($n=13$) were similar to those for age-matched healthy control ($n=13$) populations ($p>0.05$).

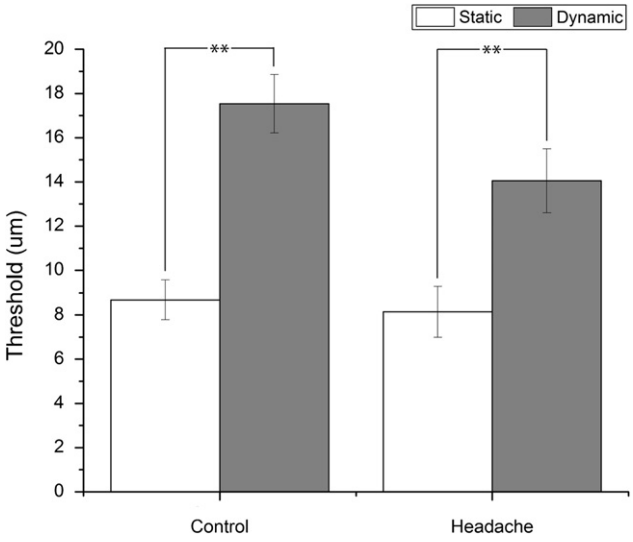

Fig. 2 – Average Static and Dynamic Thresholds. The mean static thresholds were lower than the mean dynamic thresholds in both the healthy controls ($n=17, 17$; $^{**}p \ll 0.01$) and in the migraine population ($n=17, 15$; $^{**}p<0.01$). Static and dynamic thresholds were not statistically significantly different between healthy controls and migraine patients ($p>0.05$ for both).

thresholds in both the healthy controls (17.5±1.3 μm versus 8.7±0.9 μm; $n=17$, 17; $^{**}p \ll 0.01$) and in migraineurs (14.1±1.4 μm versus 8.1±1.2 μm; $n=15$, 17; $^{**}p=0.003$). Static and dynamic thresholds of healthy controls and migraineurs were not statistically significantly different ($p=0.71$ and $p=0.09$, respectively).

2.2. *Amplitude discriminative capacity is reduced in migraineurs.*

The mean percent difference limens, or Weber fractions, for simple amplitude discrimination capacity for evaluating simultaneously delivered vibrotactile stimuli to D2 and D3 (Fig. 3) were significantly higher in migraineurs (less discriminative) than in the healthy age-matched controls (0.59±0.07% versus 0.30±0.06%; $n=23$, 23; $^{**}p=0.0032$).

2.3. *The impact of pre-exposure of one stimulus site to repetitive conditioning stimulation on amplitude discrimination capacity is reduced in migraineurs.*

The single-site conditioning stimuli (Fig. 3) significantly raised the DL in healthy controls (0.60±0.07%; $n=23$; $^{**}p \ll 0.01$) but failed to do so in the migraine population (0.68±0.09%; $n=23$; $p=0.43$). Thus, the difference in the metrics between the simple and the adaptation conditions on the amplitude discrimination task was significantly greater in healthy controls versus migraineurs. Even though migraineurs performed poorly on the amplitude discrimination task, pre-exposure to single-site conditioning had a much less pronounced impact on that capacity than it did on controls who typically performed better on the amplitude discrimination task.

2.4. *Migraineurs perform worse on temporal order judgment (TOJ).*

The mean inter-stimulus interval for temporal order judgment in the absence of conditioning stimulation was significantly higher in the migraine population than in the healthy controls (83.4±13.9 ms versus 25.1±3.2 ms; $n=19$, 19; $^{**}p=0.00056$). While there was a significant decrease in temporal order judgment performance (Fig. 4) with the addition of conditioning stimulation in healthy age-matched controls, this trend was not observed in the migraine population. The presence of conditioning stimuli significantly raised the metric in healthy controls (84.7±13.4 ms; $n=19$; $^{**}p=0.00033$) but failed to do so for the migraine population (88.1±11.6 ms; $n=19$, $p=0.80$).

2.5. *Migraineurs are less affected by synchronized conditioning stimulation in the TOJ task.*

Although data obtained from healthy controls and migraine patients did not demonstrate a statistically significant difference ($p=0.85$) in temporal order judgment with synchronized conditioning stimuli (Fig. 4), the impact of conditioning on the controls' TOJ capacity was significantly greater than the impact observed for migraine patients on this task (ratio of TOJ in the presence and absence of conditioning stimuli on a subject by subject basis: 291.4±62.9% for controls and 71.9±41.3% for migraine patients; $^{**}p=0.0065$).

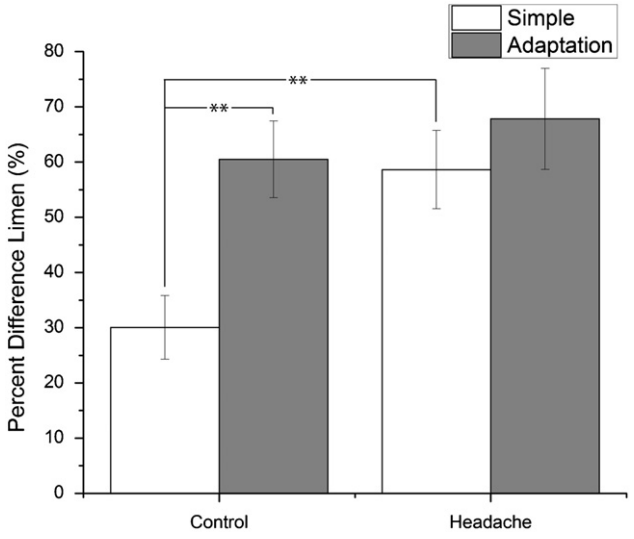

Fig. 3 – Absence and Presence of Conditioning Stimulation for Amplitude Discrimination. Amplitude discriminative capacity was significantly lower in the migraine population than in the healthy age-matched controls ($n=23$, 23; $^{*}p<0.01$). Additionally, there was a significant decrease in amplitude discrimination performance with pre-exposure to single-site conditioning stimuli delivered to one of the test sites in healthy controls ($^{**}p \ll 0.01$) that was not found in the migraine population ($p>0.05$).

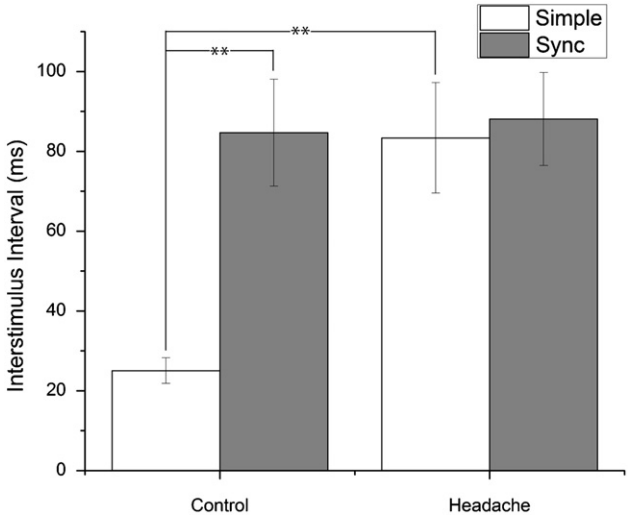

Fig. 4 – Absence and Presence of Synchronized Conditioning Stimulation for Temporal Order Judgment. The mean interstimulus interval for temporal order judgment in the absence of conditioning stimulation was significantly higher in the migraine population than in healthy age-matched controls ($n=19$, 19; $^{**}p<0.01$). The addition of conditioning stimulation to the TOJ task led to a significant decrease in TOJ performance in healthy controls ($^{**}p<0.01$) but not in the migraine population ($p>0.05$).

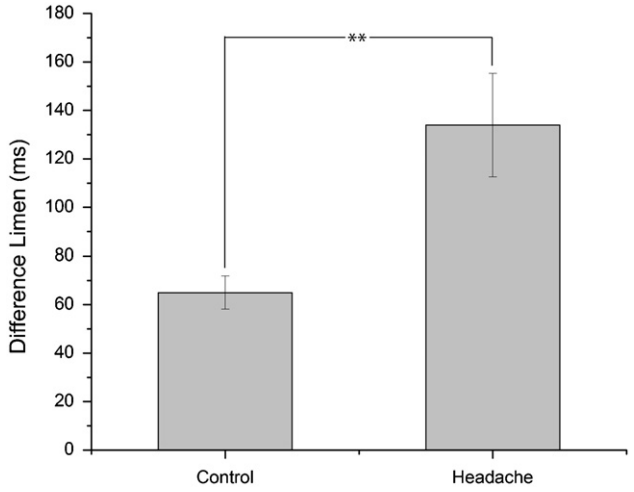

Fig. 5 – Average Duration Discrimination Thresholds. The mean difference limens for simple duration discrimination were significantly higher in the headache population than in the healthy age-matched controls ($n=23, 23$; $^{**}p<0.01$).

2.6. *Duration discrimination is significantly reduced in migraineurs compared with healthy controls.*

The mean difference limens for simple duration discrimination (Fig. 5) were significantly higher in migraineurs (less duration discrimination) than in the healthy age-matched controls (133.9 ± 21.4 ms versus 65.0 ± 6.9 ms; $n=23, 23$; $^{**}p=0.0048$).

3. Discussion

In this study, sensory perceptual metrics were obtained in patients with diagnosis of migraine symptoms. Five categories of evaluations were conducted to evaluate reaction time performance, sensory detection thresholds (static and dynamic), amplitude discrimination (with and without pre-exposure to single-site conditioning stimulation), temporal order judgment (with and without pre-exposure to synchronized conditioning stimulation), and duration discrimination. The results of the study demonstrated that although reaction times and vibrotactile detection thresholds of migraine patients did not differ from controls, metrics reflecting amplitude discriminative capacity, adaptation, temporal order judgment, and duration discriminative capacity were significantly different from healthy control metrics.

There were no significant differences found between observations obtained from the migraineurs and healthy control subjects on reaction time and tactile detection threshold tasks, and this strongly suggests that peripheral neuropathy does not appear to be a manifestation of migraine – at least for the subjects in this study. Decreased dynamic thresholds (relative to static thresholds) have been observed in previous studies in the pain population, in particular groups of women with vulvodynia (Zhang et al., 2011a). While previous research has shown increased thresholds for thermal and mechanical noxious stimuli (an antinociceptive effect), there have been few reports showing differences in tactile detection thresholds of non-noxious vibrotactile stimuli (Ladda et al., 2006). In this study, static and dynamic detection thresholds were evaluated since previous reports have shown differences in other populations of chronic pain patients (Zhang et al., 2011a). "Static" thresholds are the minimum constant-amplitude stimulus detected, while dynamic thresholds refer to the detection threshold measured with a stimulus that is increased from zero intensity to a detectable level (Zhang et al., 2011a, 2011b). Healthy control subjects generally demonstrated a dynamic threshold that is higher than their static threshold and this result is consistent with previous reports (Morioka and Griffin, 2002; Zhang et al., 2011a, 2011b). Although it could be argued that dynamic thresholds could be dependent on reaction time (or response to detecting the stimulus) and static thresholds are independent of reaction time, reaction time performance was similar in these two populations. Thus, the difference between the observations obtained by the two methods cannot be explained by reaction time alone. An alternative possibility, and one that has recently been proposed (Tommerdahl et al., 2010a; Favorov and Kursun, 2011; Zhang et al., 2011a, 2011b), is that the difference between the two threshold metrics is impacted significantly by feed-forward inhibitory mechanisms. These mechanisms are generated by the initial subthreshold stimulus that occurs when the threshold test gradually increases in amplitude from no stimulation to the detectable level. The significance of this is that this type of feed-forward inhibition occurs in the somatosensory cortical input layer 4 in which inhibitory cells receive direct thalamocortical input and, in turn, suppress responses of neighboring layer 4 excitatory cells to their thalamocortical drive, thereby sharpening their receptive field properties. These inhibitory cells are more responsive to weak (near-threshold) afferent drive than are the excitatory layer 4 cells, and thus, subthreshold or weak stimulus inputs will have the effect of raising the threshold at which excitatory layer 4 cells begin to respond to peripheral stimuli. While not statistically significant, the results of this study demonstrate a slight decrease in dynamic thresholds in the migraine group ($p=0.08$) which may compare similarly to reports of patients with other pain-related conditions (Zhang et al., 2011a). In a larger or more specific population of headache patients, this trend might be more evident, so future research is needed 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 in migraine (Cosentino et al., 2011; Coppola and Shoenen, 2012), and this imbalance could be caused by either excessive excitation or insufficient inhibition. Such systemic cortical hyper-excitability would predictably interfere with discrimination between two simultaneously activated cortical areas such as occurs with amplitude discrimination. For example, decreasing inhibition with GABA antagonists decreases the resolution of the activity evoked by two electrically-stimulated sites in sensorimotor cortical slice (Kohn et al., 2000). The measure of amplitude discriminative capacity has been shown to be a robust measure (Francisco et al., 2008) that changes little across the age spectrum for healthy controls (Zhang et al., 2011b), although it is altered for subjects with other types of systemic cortical alterations that are consistent with an

imbalance in excitation and inhibition (Zhang et al., 2011a; 2011b). Thus, amplitude discriminative capacity could prove to be a sensitive metric of cortical hyper-excitability for migraine sufferers.

Impairment of sensory habituation in migraineurs has been a promising biomarker for headache research and has shown to affect multiple sensory modalities (Ambrosini and Schoenen, 2006; Coppola et al., 2009). Based on the principle that repetitive stimulation typically results in an overall decrease in the evoked cortical response (Cannestra et al., 1998; Kohn, 2007; Kohn and Whitsel, 2002; Tommerdahl et al., 2010b; Zhang et al., 2011b), we designed a simple method for evaluating the extent to which sensory percept is impacted by repetitive conditioning stimuli (previously reported in Folger et al., 2008; Francisco et al., 2011; Tannan et al., 2006, 2007, 2008; Tommerdahl et al., 1996, 2007a, 2010a; Zhang et al., 2009, 2011a, 2011b). The percent difference in the amplitude discriminative capacity of a subject between the absence (baseline condition) and presence of a repetitive conditioning stimulus at one of the test sites can be referred to as the adaptation metric. In the migraine population, although amplitude discriminative capacity is degraded in comparison to controls, the impact of the conditioning stimulation on that discriminative task is also reduced. These results indicate that the healthy control subjects experienced a change in their perception as a result of repetitive stimulation (or adapted, as controls in the above cited references also did), while the migraine population failed to do so.

Previous studies support the concept that lack of habituation in migraineurs may be due to increased neuronal excitability or decreased inhibitory mechanisms, while conflicting evidence suggest that decreased 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 showing that migraineurs show a reduced adaptation metric, which is associated with short-term desensitization or habituation, in comparison to healthy control subjects (Ambrosini and Schoenen, 2006; Coppola et al., 2009; Coppola and Shoenen, 2012; Schoenen, 1996).

Temporal order judgment thresholds are comparable across all sensory modalities (Hirsh and Sherrick, 1961) and timing perception has been shown to be associated with various cortical regions including, but not limited to, the supplementary motor area (SMA), posterior parietal cortex, temporal parietal junction, and basal ganglia (Davis et al., 2009; Lacruz et al., 1991; Pastor et al., 2004). The stimulus-driven effect of synchronized conditioning stimuli has been associated with the coordinated and synchronized activity of the near-adjacent cortical ensembles in anterior parietal cortex and consequently results in increased difficulty in perceptually distinguishing one cortical locus from the other (Tommerdahl et al., 2007b, 2008). As a result, healthy controls perform significantly worse on temporal order judgment in the presence of an illusory conditioning stimulus (Tommerdahl et al., 2007b, 2008). Functional connectivity between adjacent cortical regions typically leads to a reduction in performance on this task in healthy controls with the introduction of synchronized conditioning stimuli. The response is hypothesized to be the result of functional connectivity between adjacent and/or near-adjacent cortical ensembles, and the delivery of synchronized conditioning stimuli impacts the topography of temporal perception unless there is a systemic neurological deficit. This impact on the topography of temporal perception has been observed in in vivo studies of non-human primate (Francisco et al., 2012a, 2012b). The results of this study show that simple temporal order judgment capabilities are significantly worse than those of healthy controls. Furthermore, with the addition of illusory conditioning stimulation, the performance of the individual with migraine fails to differ from the simple condition. These results suggest deficits in fronto-striatal cortical function as well as dysfunction in functional connectivity among cortical ensembles in migraineurs.

Additional evidence that this topography of temporal perception is impacted by the conditioning stimuli has been obtained by transcranial magnetic stimulation (TMS) (Lee et al., 2012). In these studies, TOJ is not impacted by continuous theta-burst repetitive TMS pulsed over somatosensory cortex, and individuals actually perform similarly on the TOJ task in the presence and absence of conditioning stimuli following TMS. Our interpretation of the data obtained in this study is that not only is TOJ performance in migraineurs worse—which is strongly implicated as a marker of dysfunction in the frontal lobe (Tommerdahl et al., 2008)—but that the functional linkage between adjacent and/or near-adjacent groups of cortical columns in somatosensory cortex is impaired. Alterations in local cortical circuitry might also lead to changes in systemic cortical functionality such as functional connectivity and synchronization. Such changes in connectivity may be associated with an imbalance between excitatory and inhibitory neurotransmission that many have predicted underlies the neocortical hyper-excitability and unstable cortical network activity characteristic of migraine episodes (Coppola and Shoenen, 2012). In other words, these disruptions in cortical network functionality may be due to an imbalance between GABA inhibitory neurotransmission and NMDA receptor-mediated excitatory neurotransmission and/or interactions between neurons and surrounding glia (for discussion, see Tommerdahl et al., 2007b, 2010b).

The impairment of sensory adaptation in patients with migraines may also be associated with altered metrics involving time perception. Previous studies have shown contradictory evidence, most likely due to different testing paradigms, of duration discrimination in patients with headaches. These studies found either no difference in time duration between patients with chronic headache and healthy controls or both under- or over-estimated time durations in patients (Anagnostou and Mitsikostas, 2005; Isler et al., 1987). The results of the present study support evidence that time perception is impaired in individuals with migraines, suggesting dysfunction in functional connectivity and neuron–glial interactions during sequential stimulation of two cortically-adjacent somatotopic receptive fields (Cosentino et al., 2011; Coppola and Shoenen, 2012).

Duration discrimination capacity seems to be dependent on sensory exposure and development but is capable of being generalized across somatotopic location and hemisphere, as well as sensory modality (Nagarajan et al., 1998). 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) (Eagleman et al., 2005). This study evaluated shorter

interval duration discriminations, and, in particular, sub-second timing perception, which is hypothesized to reflect right prefrontal and posterior parietal cortical function among involvement of other cortical regions (Gooch et al., 2011; Mauk and Buonoman, 2004; Smith et al., 2011). Interestingly, these same cortical regions have also shown involvement in neuroplasticity in pain perception mechanisms (Seifert and Maihöfner, 2011). The results indicate that headache patients show impairment of simple duration discrimination (Smith et al., 2011) or dysfunction of the aforementioned cortical regions resulting from headache pain. 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 (Simons et al., 2005, 2007). 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 these studies has been demonstrated to be strongly correlated with glial activity (Lee et al., 2005).

Although the neurobiological mechanisms involved in headache etiology are only partially understood, accumulating evidence suggests that structural, functional, and pharmacologic changes occur in the brains of headache patients. Structural changes include subcortical white matter lesions and iron deposits in the periaqueductal gray region (Kruit et al., 2010). Functional alterations include focal areas of brain hypo-metabolism, cortical hyper-excitability, central sensitization, and dysfunction in thalamic modulation sensory input (Brighina et al., 2009; Coppola and Shoenen, 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 et al., 2011; Weir and 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 et al., 2003). These alterations in brain physiology may provide a biologically-based assessment that quantifies and measures these differences with scores that can 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.

4. Experimental procedure

4.1. *Subjects*

Following Institutional Review Board approval and informed consent, 23 subjects ranging from 19 to 69 years of age (age=46.4±2.7 years; *m:f*=2:21) who were diagnosed with migraine were recruited into the study. Subjects were sub-categorized as having episodic migraine (with or without aura), and/or chronic migraine. Healthy age-matched control subjects were also recruited. Subjects completed a survey of current medications and medical history prior to the experimental tests to exclude participants with any history of neurological impairment other than migraines. Because subjects were permitted to withdraw from sensory testing due to fatigue prior to the completion of the battery, only a subset of patients completed all evaluations. All subjects were naive to the study design and blinded to the issue under investigation. In this study, all subjects were right handed and sensory assessments were obtained from stimuli applied to the left hand.

4.2. *Sensory assessments*

A four-site mechanical stimulator (CM4; Cortical Metrics Model #4), designed to optimally deliver vibrotactile stimuli to the finger tips, was used in this study. This stimulator, most recently described in Holden et al., 2012, has been utilized to assess multiple sensory information processing characteristics in a number of subject populations (Folger et al., 2008; Francisco et al., 2008, 2012a; Tannan et al., 2005, 2007, 2008; Tommerdahl et al., 2007a, 2007b; Zhang et al., 2009, 2011a, 2011b). The prominent feature of these protocols that have demonstrated significant sensitivity to alterations in CNS processing is that they are independent of detection thresholds or skin sensitivity (Zhang et al., 2011b). In other words, changes in cortical information processing are responsible for the changes observed in these metrics.

During the experimental session, subjects were seated comfortably in a chair with the left arm situated on an armrest attached to the head unit of the four-site vibrotactile stimulator. The independent, computer-controlled probe tips can deliver a wide range of vibrotactile stimulation of varying amplitudes (sinusoidal peak-to-peak displacements in μm) and frequencies (Hz). In this study, vibrotactile flutter stimulation (25 Hz) was 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 left hand. These digits were chosen as test sites for convenience and comfort and also because of the wealth of neurophysiological data that supports the evaluation of the associated somatotopic regions in the non-human primate cerebral cortex. The right hand was placed on a two-button response device and subjects were instructed to press the left or right button when the correct stimulus was perceived on the middle or index finger, respectively.

A computer monitor provided visual cueing during each of the experimental runs. The cues indicated when the experimental stimuli would be delivered and when subjects were to respond. Training trials conducted prior to each task familiarized subjects with the test; correct responses on three consecutive training trials were required before the start of each assessment. Subjects were not provided with performance feedback or knowledge of the results during data acquisition. Stimulus parameters were specified interactively by test algorithms based on specific protocols and the responses of the subjects during those protocols.

A series of sensory perceptual measures were employed to assess tactile information processing ability. In sum, these tests lasted approximately thirty minutes and consisted of evaluations of reaction time (RT), vibrotactile threshold detection, amplitude discrimination (AD), temporal order judgment (TOJ), and duration discrimination (DD). The individual tests, some of which are described in previous reports (Folger et al., 2008; Francisco et al., 2008; Tannan et al., 2005, 2007, 2008; Tommerdahl et al., 2007a, 2007b; Zhang et al., 2009, 2011a, 2011b), are described below.

4.2.1. *Reaction time*

For the simple reaction time (RT) task, a single tap (300 μm, 40 ms) was delivered to D2 and subjects were instructed to respond by clicking the response device as soon as the tap was perceived. A randomized delay ranging from 2 to 7 s separated the trials. Response times were recorded for each of the 20 trials. This method was most recently reported in Zhang et al., 2011b.

4.2.2. *Threshold detection*

Two types of detection thresholds were collected and have been defined previously as "static" and "dynamic" thresholds (most recently described in Zhang et al., 2011a, 2011b). Static thresholds are those obtained using stimuli that do not change in amplitude during an individual trial, while dynamic thresholds are those obtained using stimuli in which the amplitude is constantly modulated at a defined rate during an individual trial.

For static threshold detection, the device delivered a vibromechanical stimulus (initial stimulus parameters: 15 μm, 1000 ms, 25 Hz) to either D2 or D3 over 20 trials using a two-alternative forced-choice (2AFC) modified von Békésy tracking protocol. The stimulus location was randomized on a trial-by-trial basis. Following each stimulus, subjects were prompted to select the digit on which they felt a weak stimulation. After a 5 s delay, based on the previous response of the subjects, the stimulus amplitude was modified until completion of the 20 trials. During the initial 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 stimulus while incorrect responses raised the amplitude of the stimulus. After the initial 10 trials, the amplitude was varied using a 2-up/1-down algorithm. The rationale for implementing these algorithms was to initially expedite determination of vibrotactile discriminative range and then account for response bias.

For the dynamic threshold task, after a delay period without stimulation, the device delivered a continuous stimulus beginning at 0 μm (25 Hz) to either D2 or D3. Stimulus location was randomly selected on a trial-by-trial basis. Six conditions of delay were employed in separate trials: 0, 0.5, 1, 1.5, 2, and 3 s. The stimulus increased at a rate of 2 μm/s, and subjects responded with the appropriate digit when they first perceived the stimulus. The dynamic threshold task consisted of 7 trials (two trials with zero second delay), and the stimulus amplitude at the time of the response was recorded.

4.2.3. *Amplitude discrimination capacity*

Amplitude discriminative capacity is defined as the minimal difference in amplitudes of two mechanical sinusoidal vibratory stimuli for which an individual can successfully identify the stimulus of larger magnitude. For the amplitude discrimination (AD) 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. Discrimination capacity was assessed using a 2AFC tracking protocol that has been described and implemented in a number of previous studies (Folger et al., 2008; Francisco et al., 2008; Tannan et al., 2007, 2008; Tommerdahl et al., 2007a; Zhang et al., 2009, 2011a, 2011b). The magnitude of the test stimulus was always greater than that of the standard stimulus, but the loci of the stimuli were randomly varied on a trial-by-trial basis. Subjects were questioned as to which of the two digits received the higher magnitude stimulus. The difference between the amplitudes of the test and standard amplitudes was adjusted on the basis of the response such that correct responses lowered, while incorrect responses increased, the test amplitude on subsequent trials. The same tracking algorithm described previously for static threshold detection was employed to track the discriminative capacities of the subjects.

4.2.4. *Impact of single-site adaptation on amplitude discrimination capacity*

The measure that the impact of conditioning stimulation has on some aspect of amplitude discriminative capacity is often referred to as the "adaptation metric," which can be determined by measuring the impact of short duration conditioning stimuli on amplitude discriminative capacity. The effect of conditioning stimulation on subsequent test stimuli was analyzed by the addition of single-site adaptation, or pre-exposure to a conditioning stimulus prior to the simple AD task. Specifically, a vibrotactile conditioning stimulus (constant stimulus parameter: 400 μm, 25 Hz, 1 s) was delivered 1 s prior to the presentation of the pair of test and standard stimuli. The result of such a protocol modification is that the discriminative threshold, or difference limen (DL), is typically significantly elevated after pre-exposure to a single-site conditioning stimulation (Folger et al., 2008; Tannan et al., 2007, 2008; Zhang et al., 2009, 2011a, 2011b). When the conditioning stimulus is delivered to the same site as the test stimulus, the gain effect of adaptation, or reduction of the perceived intensity of the stimulus, can be quantified by comparison of the DLs obtained in the adapted versus non-adapted conditions. The same amplitude discrimination algorithm described previously was also employed to track the discriminative capabilities of the subjects. Each task consisted of 20 trials.

4.2.5. *Temporal order judgment*

For the temporal order judgment (TOJ) task, two sequential taps (200 μm, 40 ms) were delivered, one to each digit tip. These were initially temporally separated by an interstimulus interval (ISI) of 150 ms. The stimulus location that received the first of the two pulses was randomized on a trial-by-trial basis. Subjects were queried to select the digit that received the first stimulus.

Temporal order judgment was assessed both in the absence and in the presence of concurrent, or synchronizing, stimulation. For the latter case, a 25 Hz carrier stimulus was

delivered for a minimum of 400 ms prior to the delivery of the first of the two sequential pulses 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. For both cases, the temporal separation between the two pulses was adjusted on the basis of the previous response through employment of percentage tracking (15% step size) such that correct responses resulted in shorter ISIs while incorrect responses increased the ISIs. Each task consisted of 20 trials. These methods have been described in previous reports (Tommerdahl et al., 2007b, 2008).

4.2.6. *Duration discrimination capacity*

Duration discriminative capacity is defined as the minimal difference in durations of two stimuli for which an individual can successfully identify the stimulus of longer duration. For the duration discrimination (DD) task, sequential stimuli were delivered to D2 and D3 for 20 trials (initial stimulus parameters: 750 ms test, 500 ms standard, 300 μm, 25 Hz, 25 ms step size). Discrimination capacity was assessed using a 2AFC tracking protocol (in a manner similar to that described for amplitude discrimination capacity). The duration of the test stimulus was always greater than that of the standard stimulus, but the location of the stimulus of longer duration was randomly selected on a trial-by-trial basis. Subjects were asked to determine which of the two digits received the longer stimulus duration. The difference between the duration of the test and standard amplitudes was adjusted on the basis of subject response; correct responses resulted in shortening the test duration in subsequent trials while incorrect responses resulted in increasing the test duration in subsequent trials (total of 20 trials).

4.3. *Data analysis*

Statistical analytical techniques, specifically two-sample, two-tailed *t*-tests, were used to evaluate the difference in the performance of the migraine population as compared to healthy control metrics. Data are presented as means and standard errors of the means. A probability (*p*-value) of less than 0.05 was considered statistically significant.

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