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The interactive effect of acute pain and motor learning acquisition on sensorimotor integration and motor learning outcomes

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Abstract

Previous work has demonstrated differential changes in early somatosensory evoked potentials (SEPs) when motor learning acquisition occurred in the presence of acute pain, however the learning task was insufficiently complex to determine how these underlying neurophysiological differences impacted learning acquisition and retention. In order to address this limitation, we have utilized a complex motor task in conjunction with SEPs. Two groups of twelve participants (N= 24) were randomly assigned to either a capsaicin (capsaicin cream) or control (inert lotion) group. SEP amplitudes were collected at baseline, post-application and following motor learning acquisition. Participants performed a motor acquisition task followed by a pain-free retention task within 24-48 hours. Following motor learning acquisition, the amplitude of the N20 SEP peak significantly increased ($p<0.05$) and the N24 SEP peak significantly decreased ($p<0.001$) for the control group while the N18 SEP peak significantly decreased ($p<0.01$) for the capsaicin group. The N30 SEP peak was significantly increased ($p<0.001$) following motor learning acquisition for both groups. The P25 SEP peak decreased significantly ($p<0.05$) following the application of capsaicin cream. Both groups improved in accuracy following motor learning acquisition ($p<0.001$). The capsaicin group outperformed the control group pre-motor learning acquisition ($p<0.05$), following motor learning acquisition ($p<0.05$), and approached significance at retention ($p=0.06$). Improved motor learning in the presence of capsaicin provides support for the enhancement of motor learning while in acute pain. In addition, the changes in SEP peak amplitudes suggests that early SEP changes reflect neurophysiological alterations accompanying both motor learning and mild acute pain.

New and noteworthy:

Enhanced learning was found when motor skill acquisition took place in the presence of acute capsaicin-induced experimental pain, indicating that pain does not always have negative effects on

motor learning, a finding relevant for rehabilitation and skill training. Differential changes in somatosensory evoked potentials (SEPs) were seen between those that performed the motor skill acquisition during pain vs control, indicating that SEPs may serve as markers for the early neuroplastic changes accompanying motor learning.

KEYWORDS

Somatosensory evoked potentials (SEP); motor learning; acute pain; sensorimotor integration (SMI)

INTRODUCTION

Within rehabilitation programs, the concurrent presentation of pain and motor deficits are ubiquitous. Typically, motor deficits are regarded as a consequence of movement related pain, however, there is evidence that pain affects motor control and has the ability to negatively influence the neuroplasticity associated with motor output (Hodges and Tucker 2011; Mercier and Leonard 2011; Bank et al. 2013). While the presence of acute pain during motor learning may interfere with skill acquisition (Flor 2003; Schweinhardt et al. 2006; Boudreau et al. 2007), our recent studies (Dancey et al. 2014; Dancey et al. 2016) demonstrated that motor learning acquisition improved in the presence of acute pain. A limitation of previous work (Dancey et al. 2014; Andrew et al. 2015; Dancey et al. 2016) is that learning saturation occurred with these typing tasks as baseline accuracy was high. If the learning task difficulty is not high enough, differences between groups may not be observed, and a type 2 error may be likely (Dancey et al. 2014; Dancey et al. 2016). To address this we developed and validated a more difficult motor tracing task. This tracing task has been used by Holland et al. (2015) who demonstrated continued motor learning acquisition throughout the training period with a significant consolidation of motor performance at retention and by Andrew et al. (2015) who showed that the tracing task was a more effective learning tool than a typing task. The application of a more complex motor tracing paradigm combined with electrophysiological and behavioural measures will allow us to examine the impact of acute pain on motor learning as well as the cortical, subcortical, and cerebellar regions involved.

Motor learning acquisition requires sensorimotor integration (SMI) which is the processing of somatosensory information received from the motor task and integrating this information with

the motor command in order to fine tune and improve motor task performance. Early somatosensory evoked potentials (SEPs) are electrical field potentials generated by different neuronal substrates within the peripheral and central nervous systems induced by electrical stimulation of somatosensory receptors and their axons (Mauguiere 1999). SEPs represent pre-cognitive sensory processing (Cruccu et al. 2008), and can be used to study the early neuroplastic consequences of the interactive effects of acute pain and motor learning acquisition. SEPs offer the highest temporal resolution available in non-invasive investigation (Walsh and Cowey 2000) and include peripheral (N9), spinal (N11,N13), subcortical (N18) and cortical (N20, P25, N24, N30) components for the upper limb. Recent work has found significant changes in spinal (N13) and cortical (N20, N24, P25, N30) SEP peaks following tracing (Andrew et al. 2015) and typing tasks (Dancey et al. 2016). Studies using experimental muscle pain (Rossi et al. 2003; Schabrun et al. 2013) and acute cutaneous pain (Dancey et al. 2016) have found decreases in early SEP amplitudes in healthy individuals. Additionally, we recently determined that following a motor learning acquisition typing task there was a significant increase in a cortical (N20) SEP peak for a control group that was not observed for a capsaicin-induced pain group and we hypothesized that acute pain may have negated a change that would have otherwise occurred (Dancey et al. 2016). It has been proposed that motor learning acquisition can reverse the effects of pain, and conversely that acute pain undermines the capacity for learning (Ferguson et al. 2012). There remains a gap in our understanding of whether early SEP peaks change in the presence of acute cutaneous pain in healthy humans and whether acute pain impacts SEP changes observed in response to a complex motor learning acquisition task, which will be addressed by the current study.

Another limitation of several previous studies is that they have not measured retention even though it is known that an offline or consolidation period is a critical process for learning (Boudreau et al. 2007; Dancey et al. 2014). A few studies have investigated the impact of capsaicin application on retention using a motor adaptation task during a locomotor (Bouffard et al. 2014) or an upper limb reaching task (Lamothe et al. 2014) and found that acute pain during motor learning acquisition had a negative impact on retention despite not having a negative impact on baseline performance measures (Lamothe et al. 2014) or acquisition (Bouffard et al. 2014). More recently, Bilodeau et al. (2015) investigated the effect of heat pain on motor learning of a finger tapping sequence task and found that acquisition and retention were not affected by the presence of pain during training. In addition, our recent work (Dancey et al. 2016) found improved retention for a local pain group as compared to a remote pain group. This provides support for improved motor learning retention with mild acute pain and we hypothesized that local acute pain increased attention to the body part utilized in motor learning acquisition (Dancey et al. 2016). Factors improving or decreasing motor learning acquisition are not necessarily predictive of motor retention (Richardson et al. 2006; Reis et al. 2009) and from a practical perspective, it is retention that indicates whether learning has been impacted positively or negatively. It is therefore important to investigate how retention is affected using a complex motor tracing paradigm.

The interactions between pain and motor control are complex and to date, few studies have investigated the effect of acute experimental pain on motor learning acquisition and retention in healthy humans. Inducing acute experimental pain in healthy participants is therefore instrumental in isolating the motor consequences of acute pain and the mechanisms and conditions under which motor learning in the presence of pain becomes either adaptive or maladaptive. We investigated the primary hypothesis that a novel motor learning acquisition task performed during

acute pain (capsaicin group) as compared with a control group would show differential changes in early SEP peaks. Our secondary hypothesis was that participants performing a novel motor learning acquisition task during acute pain would demonstrate improved accuracy pre-motor learning acquisition, post-motor learning acquisition and at retention when compared to a control group.

METHODS

Methods Overview:

Two groups of twelve participants, [14 males, 10 females; aged 19 – 27 (M 20.3 SD 2.5)], were recruited from the student population at the University of Ontario Institute of Technology. Each participant filled out a confidential health history in order to identify any exclusionary medical conditions which could impact normal somatosensation including, but not limited to: recent cervicothoracic injury, neurologic conditions, current use of neuroactive or pain medication, or currently suffering from a chronic pain condition.

Written informed consent was obtained for all participants and the study was approved by the University of Ontario Institute of Technology Research Ethics Board. This study was performed according to the principles set out by the Declaration of Helsinki for the use of humans in experimental studies.

Acute pain was induced by applying capsaicin cream and SMI was assessed by recording early SEPs in humans. The effect of acute pain on signal transmission was assessed by investigating changes in the amplitude of SEPs from baseline, at 20 minutes post-application, and then following the motor learning task (35 minutes from baseline) (See Figure 1 for a schematic illustration of the protocol). Prior to performing the motor learning acquisition task, participants in the capsaicin group received a topical application of capsaicin (0.075% Zostrix, New York, USA)

while the control group received a topical control skin lotion (Life Brand, Shopper's Drug Mart, Ontario, Canada). A 5 cm by 10 cm area was marked off on the lateral aspect of the dominant elbow and then the topical cream was applied to this 50 cm^2 area on the lateral aspect of the right elbow and was massaged into the skin.

[INSERT FIGURE 1 APPROXIMATELY HERE]

Outcome Measures

The outcome measures for this study included the amplitude (μV) of the early SEP peaks, motor learning accuracy, and pain (Numeric Pain Rating Score).

Motor learning task:

The motor learning tracing task was run through a custom Leap Motion software tool (Leap Motion, Inc., San Francisco, CA) and required participants to trace sequences of sinusoidal-pattern waves with varying frequency and amplitude using only their thumb on an external wireless touchpad (Logitech, Inc., Fremont, CA) and included a pre-motor learning acquisition test, a motor learning acquisition phase, a post-motor learning acquisition test and a retention test 24-48 hours later. The pre-motor learning acquisition, post-motor learning acquisition, and retention tests were approximately four minutes in duration while the motor learning acquisition phase (that occurred between the pre-motor learning acquisition and post-motor learning acquisition tests) was approximately 15 minutes in duration. The traces were formed by a series of dots and each trial consisted of 500 dots. Each tracing task was comprised of four pre-selected sinusoidal patterns of varying amplitude and frequency, as determined by a previous study (Holland et al. 2015). Motor error was determined by the software as the average distance of the participant's attempted trace from the presented sinusoidal wave. The training software captured the distance that the participant's cursor dot was from the 'perfect' trace and

recorded the average distance the cursor was from each dot as it passed the horizontal axis the participant was operating on. The motor error was determined as a percent that the participant's tracing cursor was from the original 'perfect' trace. Pre-motor learning acquisition, post-motor learning acquisition, and at retention, each of the versions, 1-4, were performed once; while for the motor learning acquisition phase each version was performed three times for a total of 12 traces. Combined flexion and adduction thumb movements were performed, which required the participants to sweep their thumb from left to right, utilizing the abductor pollicis brevis (APB) muscle.

Pain:

Subjective pain was quantified using a Numeric Pain Rating Scale (NPRS) in which participants graded the intensity of their pain from 0–10 (Dolphin and Crue Jr 1989). Participants in both groups were asked to rate their pain at baseline, post-application (5 minutes), post-application (20 minutes), following motor learning acquisition (35 minutes), and following the last round of SEP measurements (45 minutes) in order to ensure that they were in acute pain for the duration of the experiment.

Stimulation of median nerve to elicit SEPs

Stimuli consisted of electrical square pulses 0.1ms in duration delivered at frequencies of 2.47Hz through Ag/AgCl ECG conductive adhesive electrodes (MEDITRACE™ 130 by Ludlow Technical Products Canada Ltd., Massachusetts, USA) (impedance <5 kΩ) placed over the median nerve at the wrist of the right hand, with cathode proximal. Following the 5 minute 2.47 Hz session, stimuli were then delivered at a frequency of 4.98Hz for 15 minutes. SEPs were recorded at two different rates in order to record both the N24 and N30 SEP peaks. Using the slower rate of 2.47 Hz does not lead to SEP peak attenuation while the faster rate, 4.98 Hz attenuates the N30

SEP peak, allowing for the N24 SEP peak to be accurately identified (Fujii et al. 1994; Haavik and Murphy 2013). The stimulus intensity was increased until motor threshold was attained. Motor threshold was defined as the lowest stimulation intensity that evoked a visible muscle contraction of the APB muscle.

SEP recording parameters

SEP recoding electrodes (1.8m long Traditional Grass™ Lead, 10mm disc, 2mm hole gold cup EEG electrodes, Grass Technologies, An Astro-Med, Inc. Subsidiary, Massachusetts, USA) (impedance <5 kΩ) were placed according to the International Federation of Clinical Neurophysiologists (IFCN) recommendations using Grass Technologies EEG adhesive conducting paste (Type TEN20™). Recording electrodes were placed on the ipsilateral Erb's point, over C5 spinous process (Cv5), the anterior neck (tracheal cartilage), 2cm posterior to contralateral central C3/4 (a parietal site referred to as Cc'), and a frontal site (6cm anterior and 2cm contralateral to Cz) (Abbadie et al. 1997; Rossi et al. 2003). The C5 spinous process was referenced to the anterior neck (trachea) while all other electrodes were referenced to the ipsilateral earlobe. A 1.8288m Traditional Lead, 10mm disc, 2mm hole gold cup EEG electrode was also used as a ground, and was placed in the mouth of participants. SEPs were recorded at baseline, 20 minutes post-application, and then immediately following the motor tracing acquisition task (45 minutes from baseline).

The SEP signal was amplified (Gain 10,000), filtered (0.2-1000 Hz) and stored on a laboratory computer for later retrieval. A total of 1000 sweeps were averaged per stimulation rate using a purpose written Signal® configuration (Cambridge Electronic Design, England, UK). SEP peak amplitudes were measured according to the IFCN guidelines (Cruccu et al. 2008). We identified and analyzed the peak-to-peak amplitude (μV) and latencies of the following SEP

components: the peripheral N9, the spinal N11 and N13, the far-field N18, the parietal N20 and P25, and the frontal N24 and N30 SEP peaks. SEP amplitudes were measured from the averaged traces beginning at the peak of interest to the preceding or succeeding peak of opposite deflection, according to international recommendations (Nuwer et al. 1994) and previous studies in this field (Cheron and Borenstein 1987; Cheron and Borenstein 1991; Sonoo et al. 1991). SEP latencies were recorded from the time of stimulation onset to their maximal peak or trough for each of the SEP peaks.

Statistical Analysis

SEP peak amplitudes were normalized to baseline values to account for inter-participant baseline variability and to allow for between participant comparisons. The Shapiro-Wilk test for normality was run on each SEP peak. The main effect of interest was the interactive effect of pain and motor learning acquisition on SEP peak amplitudes which was tested using a repeated measures ANOVA with factors TIME (baseline versus post-motor learning acquisition) and GROUP (control versus capsaicin). In order to ensure that the observed interactions were due to the interaction of capsaicin and motor learning acquisition and not simply due to capsaicin application rather than the interactive effect, a separate repeated measures ANOVA with factors TIME (baseline versus post-application) and GROUP (control versus capsaicin) was performed on each SEP peak.

The Shapiro-Wilk test for normality was run on the accuracy data. To investigate and compare performance accuracy, a repeated measures ANOVA with factors TIME (pre-motor learning acquisition versus post-motor learning acquisition versus retention) and GROUP (control versus capsaicin) was performed on the accuracy data.

A Friedman test with pairwise comparisons was run on the capsaicin group NPRS ratings. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 19.0 (Armonk, NY: IBM Corp). Statistical significance was set at $p < 0.05$. Eta-squared was calculated in SPSS, as a measure of effect size with values of 0.01 representing a small effect size, 0.06 a medium effect size and 0.14 or greater, a large effect size (Fritz et al. 2012).

RESULTS

A total of 24 participants were tested with 12 participants in the capsaicin group [8 females, 4 males; aged 18-27 (M 20.8 SD 3.3)] and 12 participants in the control group [6 females, 6 males; aged 18-24 (M 22.8 SD 2.0)].

Neurophysiological data: SEPs

The N9, N30, and P25 SEP peaks were normally distributed. For the N11, N24 SEP peaks only the capsaicin group (post-application) was non-normally distributed. For the N13, N20 SEP peaks only the control group (post-motor learning acquisition) was non-normally distributed. For the N18 SEP peak only the capsaicin group (post-motor learning acquisition) was non-normally distributed. All other categories were normal. When only one set of measurements in a repeated measures design are non-normally distributed, it is recommended to still run an ANOVA which is robust against departures from normality (Steiner 2008), as conclusions drawn from the ANOVA will be accurate. That is, type I and type II errors will not be inflated if the data are skewed and deviations in kurtosis will only affect power if the sample size is too low (Streiner 2008). Therefore we conducted a repeated measures ANOVA on all SEP peaks.

Cerebellum: P25, N18, N24

P25:

Following motor learning acquisition, there was no main effect of TIME on the P25 SEP

peak amplitude (p=0.96). Following the cream application, there was no main effect of TIME on P25 SEP peak amplitude (p =0.22), however, the interaction effect of TIME by GROUP was significant [F (2,23) = 5.12, $p<0.05$, $\eta^2=0.19$], with post-hoc ANOVA tests demonstrating that the capsaicin and control groups differed post-application [F(1,11) =5.93, $p<0.05$, $\eta^2=0.35$] with the capsaicin group P25 SEP peak decreasing significantly by 15.3% following the application of capsaicin cream [F(1,11)=5.05, $p<0.05$, $\eta^2=0.32$], while there was a non-significant 10.0% increase in the P25 SEP peak for the control group (p=0.28).

N18:

Following motor learning acquisition, there was a significant main effect of TIME [F (2,23) = 5.66, $p<0.05$, $\eta^2=0.21$], and a significant TIME by GROUP interaction effect [F (2,23) = 7.09, $p<0.05$, $\eta^2=0.25$]. Post hoc ANOVA tests demonstrated that the capsaicin and control groups differed following motor learning acquisition [F(1,11)=5.86 = $p<0.05$, $\eta^2=0.35$] with the capsaicin group SEP peak significantly decreasing by 18.5% following motor learning acquisition [F(1,11)=17.76, $p<0.01$, $\eta^2=0.62$] while the control group showed a non-significant 1.7 % increase in the N18 SEP peak (p=0.86). Following the application of the creams, there was no main effect of TIME on the N18 SEP peak amplitude (p = 0.59).

N24:

Following motor learning acquisition, there was a significant TIME effect [F (2,23) = 5.88, $p<0.05$, $\eta^2=0.21$], and a significant interaction effect of TIME by GROUP [F (2,23) = 98.92, $p<0.005$, $\eta^2=0.29$]. Post hoc ANOVA tests demonstrated that for the N24 SEP peak the capsaicin and control groups differed following motor learning acquisition [F(1,11)=8.14,$p<0.05$ $\eta^2=0.42$], with the control group N24 SEP peak decreasing significantly by 28.9% following motor learning acquisition [F(1,11)=52.47,$p<0.001$, $\eta^2=0.83$] while the capsaicin group showed a non-significant

3.0 % increase in the N24 SEP peak (p =0.80). Following the cream application, there was no main effect of TIME on N24 SEP peak amplitude (p = 0.19).

Primary Somatosensory area (SI): N20

Following motor learning acquisition there was a significant TIME effect [F (2,23) = 4.42, $p<0.05$, $\eta^2=0.17$], and a significant TIME by GROUP interaction effect [F (2,23) = 4.42, $p<0.05$, $\eta^2=0.35$]. Post hoc ANOVA tests demonstrated that the capsaicin and control groups differed following motor learning acquisition [$F(1,11)=14.02$ = $p<0.005$, $\eta^2=0.56$] with the control group N20 SEP peak significantly increasing by 48.9% following motor learning acquisition [$F(1,11)=11.32$, $p<0.05$, $\eta^2=0.51$] while there was a non-significant 11.5% decrease in the N20 SEP peak for the capsaicin group (p=0.29). Following the cream application for both groups, there was no main effect of TIME on N20 SEP peak amplitude (p =0.97).

Sensorimotor integration (SMI) and the Motor cortex (MI): N30

Following motor learning acquisition there was a significant main effect of TIME [F (2,23) = 23.84, $p<0.001$, $\eta^2=0.52$], while the interaction effect of TIME by GROUP was not significant (p =0.37). Following motor learning acquisition the N30 SEP peak increased by 23.8% for the control group and by 16.2% for the capsaicin group. Following the application of the creams, there was no main effect of TIME on the N30 SEP peak amplitude (p = 0.62).

For the N9, N11, and N13 SEP peaks no significant changes were seen for either group. There were no significant changes in latency data for any SEP peak in either the control group of the capsaicin group (See Table 2).

Figure 2 illustrates the raw data from a representational capsaicin participant indicating SEP peaks and Figure 3 illustrates the raw data from a representational control participant

indicating SEP peaks. The normalized averages for the SEP peaks are illustrated in Figures 4 A and 4 B. Table 1 indicates the mean amplitudes of significant SEP peaks and their associated p-values. Table 2 indicates the mean latencies of the SEP peaks.

[INSERT FIGURE 2 APPROXIMATELY HERE]

[INSERT FIGURE 3 APPROXIMATELY HERE]

[INSERT FIGURE 4 APPROXIMATELY HERE]

[INSERT TABLE 1 APPROXIMATELY HERE]

[INSERT TABLE 2 APPROXIMATELY HERE]

Behavioural data:

Accuracy

The Shapiro-Wilk test for normality demonstrated that both groups at all time points were normally distributed. The behavioural data demonstrates that motor learning occurred as both the control [$F(1,11)=79.193$, $p<0.001$, $\eta^2=0.88$] and capsaicin [$F(1,11)=12.42$,$p<0.001$, $\eta^2=0.51$] groups improved in accuracy. The interaction effect of TIME by GROUP was significant [$F(2,23)=6.28$, $p<0.05$, $\eta^2=0.51$], with post-hoc ANOVA testing demonstrating that both pre-motor learning acquisition (which occurred after the capsaicin cream had already been applied) [$F(2,23)=8.32$,$p<0.05$, $\eta^2=0.36$] and post-motor learning acquisition [$F(2,23)=9.49$, $p<0.05$, $\eta^2=0.58$] the capsaicin group was more accurate than the control group. For the retention session the capsaicin group outperformed the control group and this approached significance ($p=0.06$) (See Figure 5). Post-hoc ANOVA tests on the percent change in motor error demonstrate that there wasn't a significant difference between the groups following motor learning acquisition ($p=0.31$), however the groups differed significantly from each other at retention ($p=0.036$) with the

control group showing a 70.5% decrease in motor error and the capsaicin group a 46.0% decrease in motor error at retention relative to pre-motor learning acquisition values.

[INSERT FIGURE 5 APPROXIMATELY HERE]

Pain ratings:

The Friedman's test on the NPRS ratings demonstrated a significant effect for the capsaicin group [$\chi 2$ (df = 4, $p < 0.001$) = 39.4, η^2=0.69], with pairwise comparisons indicating that from baseline there was a significant increase in NPRS ratings 20 minutes post application ($p<0.001$), post motor learning acquisition ($p<0.001$), and post motor learning acquisition (45 minutes from baseline) ($p<0.05$). The increase 5 minutes post-application of the cream was not significant ($p=0.27$).The average NPRS ratings are illustrated in Figure 6. None of the participants in the control group reported any pain.

[INSERT FIGURE 6 APPROXIMATELY HERE]

DISCUSSION

The results of our study support our hypothesis of differential changes in early cortical SEP peaks evoked following motor learning acquisition as we observed a decrease in the N18 SEP peak for the capsaicin group, whereas the control group had an increase in the N20 SEP peak and a decrease in the N24 SEP peak following motor learning acquisition. In addition, there was an increase in the N30 SEP peaks for both groups following motor learning acquisition and we found a significant decrease for the P25 SEP peak following the capsaicin intervention. There were significant differences in SEP peaks that represent activity in several pathways related to motor control including the SI (N20), cerebellum (N18, N24, P25), and MI (N30) and this highlights the role of these structures in motor learning acquisition and pain processing. Significant

improvements in accuracy were observed for both groups suggesting that motor learning acquisition had occurred. We observed significantly greater accuracy for the capsaicin group (who performed their initial pre-motor learning acquisition session in the presence of pain) when compared with the control group. In absolute terms, the capsaicin group continued to outperform the control group following motor learning acquisition, with a strong trend to at retention, however in relative terms, the control group actually experienced a greater percent learning following motor learning acquisition. This highlights the interactive effect of pain on the magnitude of the improvement. This is in line with our secondary hypothesis that participants performing a novel motor learning acquisition task during acute pain would demonstrate improved accuracy following motor learning acquisition when compared to a control group.

Neurophysiological Data:

Primary somatosensory area (SI): N20

The N20 reflects the earliest cortical processing within the SI (Mauguiere 1999) and is known to respond to contralateral tactile stimuli (Hlushchuk and Hari 2006). Our finding of a significant increase in the N20 SEP peaks for the control group following motor learning acquisition demonstrates the role of the SI in motor learning acquisition. This finding is in line with a recent study (Andrew et al. 2015) that demonstrated a significant increase in the N20 SEP peak following 10 minutes of tracing and 10 minutes of typing and it corroborates our previous work in which we found a significant increase in the N20 SEP peak for a control group following a typing task (Dancey et al. 2016). The task used for the Andrew et al. (2015) study and the current study is more complex than the typing tasks used in previous work (Dancey et al. 2014) that did not find an increase in the N20 SEP peak. The performance of a complex finger-tapping task results in additional areas of cortical activation, as measured by functional magnetic resonance

imaging (fMRI), when compared to a simpler task (Sadato et al. 1996) and the amount of overlapping cortical territories that are altered with learning is greater with fine rather than gross motor-skill training (Hluštík et al. 2004).

Cerebellum: P25, N18, N24

The P25 SEP peak amplitude was significantly decreased following capsaicin application. This peak reflects the process of invasion of the dendrites due to current spread from the cell body along the pyramidal cells of area 3b (Rossini et al. 1987) and therefore cerebellar-induced SEP alterations can be localized within the 3b area of the SI (Molinari et al. 2009). The decrease in the P25 SEP peak following capsaicin application is indicative of the role that the SI and the cerebellum plays in somatosensory processing. This finding is in line with our previous work (Dancey et al. 2014; Dancey et al. 2016) and with our finding of a significant decrease in the N18 SEP peak following motor learning acquisition for the capsaicin group. The N18 SEP peak originates in the brain stem, between the lower medulla and midbrain-pontine region (e.g. the dorsal column nuclei and/or the accessory inferior olives), reflects activity in the olivo-cerebellar pathways (Sonoo et al. 1991; Nuwer et al. 1994) and has the potential to show changes in cerebellar activity (Noel et al. 1996). Imaging studies have demonstrated significant increases in cerebellar activation with tasks requiring the discrimination of sensory information (Gao et al. 1996) and with the passive manipulation of a limb by an experimenter (Jueptner and Weiller 1998). In addition, previous research suggests that the cerebellum responds to noxious stimuli as most fMRI studies of pain show activation in the cerebellum (Apkarian et al. 2005; Borsook 2007). Our finding of a significant decrease in the P25 SEP peak following capsaicin application and a decrease in the N18 SEP peak for the capsaicin group following motor learning acquisition supports the role that the cerebellum plays in pain processing, sensorimotor processing, and motor

learning acquisition. This is interesting in light of the significant differences in the N20 and N24 SEP peaks following motor learning acquisition for the control group that was not observed for the capsaicin group. The N24 peak reflects activity in the pathway between the cerebellum and the SI and has the potential to show changes in cerebellar activity (Rossi et al. 2003). Source localization has identified the posterior wall of the central sulcus in area 3b of the SI as the site of N24 generation (Waberski et al. 1999). This area receives input from the cerebellar cortex and deep cerebellar nuclei (Molinari et al. 2009). We hypothesize that our finding of a significant decrease following motor learning acquisition for the N24 SEP peak is reflective of the role that cerebellar input plays in this cortical peak. Studies have shown that the cerebellum is associated with motor learning acquisition (Doyon and Ungerleider 2002; Manto and Bastian 2007; Molinari et al. 2007) as animal studies have shown that motor training is associated with increases in synapse number within the cerebellum (Black et al. 1990; Kleim 1994; Kleim et al. 1995) and plays an active role in motor adaption and the behavioral learning of unfamiliar tasks in humans (Doyon et al. 2003). The cerebellum modifies extra-cerebellar output through inhibition sourced from GABAergic neuron populations (Doyon et al. 2002). Imaging studies confirm that the cerebellum is active during motor sequence tasks (Doyon et al. 2002) and finger-tapping tasks (Olsson et al. 2008; Witt et al. 2008; Stoodley et al. 2012). The resulting increase in activation patterns can come with as little as 5-10 minutes (Classen et al. 1998) and are more pronounced if the task is novel (Sanes and Donoghue 2000). Our finding is consistent with the work of Baarbé et al. (2014) who demonstrated disinhibition of cerebellar projections to MI following a motor acquisition task and with a study in that found a significant decrease in the N24 SEP peak following motor learning acquisition (Andrew et al. 2015).

We hypothesize that acute pain may have negated the changes in cortical SEP peaks (N20 and N24) that occurs in the pain-free condition following motor learning acquisition. We hypothesize that the neuroplasticity associated with pain and motor learning acquisition share neural mechanisms and interact with each other (Ferguson et al. 2012). This corroborates previous research that demonstrated that performing an attention-demanding task attenuates the impact of negative stimuli (Morrow and Nolen-Hoeksema 1990; Erber and Tesser 1992; Glynn et al. 2002; Erthal et al. 2005) increases pressure pain thresholds in healthy participants (Volz et al. 2012) and suppresses the activity in limbic regions by frontal cortical regions (Drevets and Raichle 1998) . Pain fibers project to the SI and may produce inhibition of the MI via thalamocortical or cortico-cortical inhibitory inputs (Massion 1976).

Sensorimotor integration (SMI) and the motor cortex (MI): N30

Current evidence suggests that the frontal N30 peak reflects the activation within a complex supraspinal network linking the thalamus, premotor areas, basal ganglia and MI (Kanovsky et al. 2003; Cebolla et al. 2011) and is thought to reflect SMI (Rossi et al. 2003). Primate (Tanji and Wise 1981; Strick and Preston 1982), and human (Balzamo et al. 2004) intracortical recordings led to the hypothesis that the N30 SEP peak is generated at the MI. In contrast, there are topographic (Valeriani et al. 1998; Valeriani et al. 2000) and intracerebral (Barba et al. 2001; Barba et al. 2005) studies which support that this peak is generated in SI. Cebolla et al. (2011) determined that the N30 peak is generated by network activity in the MI as well as the premotor and prefrontal cortex through the use of swLORETA (standardized weighted Low Resolution Brain Electromagnetic Tomography). The amplitude of the N30 SEP peak was significantly increased following motor learning acquisition for both groups. Our finding of significant increases in the N30 peak following motor learning acquisition for both groups is consistent with previous work demonstrating significant changes in the N30 peak following

repetitive motor activity (Murphy et al. 2003; Haavik Taylor and Murphy 2007) and motor learning acquisition (Dancey et al. 2014; Andrew et al. 2015; Dancey et al. 2016).

Behavioural Data

Significant increases in accuracy were observed for both groups, suggesting that motor learning acquisition had occurred. There was an effect of pain on the magnitude of improvement as the capsaicin group outperformed the control group significantly pre-motor learning acquisition, following motor learning acquisition, and approached significance at retention. Previous studies has shown motor learning deficits in association with acute experimental pain in both animal (Ferguson et al. 2006; Hook et al. 2008) and human models (Flor 2003; Schweinhardt et al. 2006; Boudreau et al. 2007). We observed an increase in learning accuracy pre-motor learning acquisition (performed in the presence of capsaicin) and following motor learning acquisition for the capsaicin group which is in line with our previous research (Dancey et al. 2014; Dancey et al. 2016). This work differed from our previous work (Dancey et al. 2014; Dancey et al. 2016) as the current study utilized a different task (tracing versus typing) that was more complex and had lower baseline accuracy. It is significant that in the studies showing an impaired acquisition of the task in the presence of pain, the motor task in itself evoked pain (Boudreau et al. 2007; Hook et al. 2008) and therefore impacted their ability to perform the motor learning acquisition task. The painful stimulation used in the present study and our previous work (Dancey et al. 2014; Dancey et al. 2016) and used by another study which demonstrated no impact of pain on motor learning acquisition and retention (Bilodeau et al. 2015) induced cutaneous pain unrelated to movement. This may help to explain why there was not an adverse effect of pain on motor learning acquisition outcomes as acute pain typically elicits motor responses that protect from further damage which may impair motor learning acquisition (Bank et al. 2013).

Our results suggest that there may be differing effects of pain on motor learning acquisition plasticity. Research indicates that the representation of muscles affected by pain are altered in the sensorimotor system and that the level of ongoing pain and the associated neuroplastic changes can be reversed by motor learning acquisition (Pleger et al. 2005). The re-establishment of sensorimotor representations and reduced pain following motor learning acquisition are also in line with the results of sensory discrimination training in phantom limb pain patients (Flor et al. 2001). There is an interdependence of sensory and motor systems and the effects of motor learning on pain may be due to cortico-thalamic loops, producing inhibition on sensory systems. Although it has been argued that pain may interfere with learning-induced motor plasticity (Boudreau et al. 2007), other studies indicate that pain may improve motor performance and learning acquisition (Dancey et al. 2014; Dancey et al. 2016) or have no effect if the quality of movement is maintained (Ingham et al. 2011; Bouffard et al. 2014).

Research demonstrates that neuroplasticity accompanying motor learning acquisition is mediated by changes in attention (McGaughy et al. 2002; Conner et al. 2003; Rosenkranz and Rothwell 2004; Stefan et al. 2004) as the learning of motor tasks depends on attentional resources (Nissen et al. 1987; Hazeltine et al. 1997). We hypothesize that improved motor learning acquisition outcomes for the capsaicin group is due to attention to the region of the body undergoing learning (McGaughy et al. 2002; Conner et al. 2003; Rosenkranz and Rothwell 2004; Stefan et al. 2004). Growing evidence demonstrates that affective processing is modulated by attention and cognitive regulation (Ochsner and Gross 2005) and that stress leads to a narrowing of attention (Callaway and Dembo 1958; Callaway 1959) decreasing the processing of task-irrelevant stimuli (Chajut and Algom 2003). Previous work has found that the application of tactile-proprioceptive noise improved sensorimotor performance (Mendez-Balbuena et al. 2012)

and that an intermediate level of input noise of one sensory modality (tactile noise) enhances the brain evoked response of another sensory modality (visual evoked potentials) (Mendez-Balbuena et al. 2015). In addition, Passmore (2014) had participants recreate the components of Morse code patterns and found that when paresthesia stimulation was present under transfer conditions, performance was significantly better than for the no-stimulation group. These results indicate that a secondary stimulus may draw increased attentional resources toward discerning the meaningful stimulus (Mendez-Balbuena et al. 2012; Passmore 2014; Mendez-Balbuena et al. 2015). Cognitive load studies confirm that under high load conditions, there is decreased activation in brain regions associated with emotion (amygdala) and increased activation in executive control areas (prefrontal cortex) (Erthal et al. 2005; Okon-Singer et al. 2007; Van Dillen et al. 2009).

CONCLUSION

This work provides supportive evidence for sensorimotor integration areas in motor learning acquisition as demonstrated by significant differences in the N30 SEP peaks amplitude following motor learning acquisition for both groups, and for the N20 and N24 SEP peaks (control group) and the N18 SEP peak (capsaicin group). A significant decrease in the P25 SEP peak was found following the application of capsaicin cream demonstrating the effect of acute pain on SEP peaks. As there were significant differences in SEP peaks that represent activity in the cerebellum (N18, N24, P25), an important direction for future work is to investigate changes in excitability between the cerebellum and MI following motor learning acquisition performed in the presence of pain using transcranial magnetic stimulation techniques that measure cerebellar inhibition (Baarbé et al. 2014) to see if pain changes excitability in the cerebellum to MI pathway. In addition, the findings of improved motor learning acquisition during acute pain may been caused through attentional mechanisms or through an increase in arousal during the painful stimulation, an

522 important direction for future work is the comparison of the effects of local versus remote acute
523 pain relative to the muscle(s) performing a complex motor learning acquisition task. In addition, as
524 pain can be viewed as a sensory perturbation that improves motor learning acquisition it would be
525 interesting to explore whether motor learning acquisition in the presence of tactile noise leads also
526 to significant differences in SEP peaks when compared with a control group. The results of this
527 study help to explain why activation of the motor system through therapeutic exercise (focusing on
528 movement) can assist in decreasing pain. As motor learning acquisition is accompanied by pain in
529 a variety of settings, the effect of pain on learning and neuroplasticity is important to consider to
530 ensure that therapeutic interventions lead to adaptive and not maladaptive changes.
531

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FIGURES AND TABLE CAPTIONS

Table 1: Significant SEP peak amplitudes and p-values.

Table 2: Average SEP latencies for each peak.

Figure 1: Schematic of the protocol.

Figure 2: raw data from a representational capsaicin participant. Note the significant differences for the P25 SEP peak ($p<0.05$) following capsaicin application and the N30 peaks ($p<0.001$)

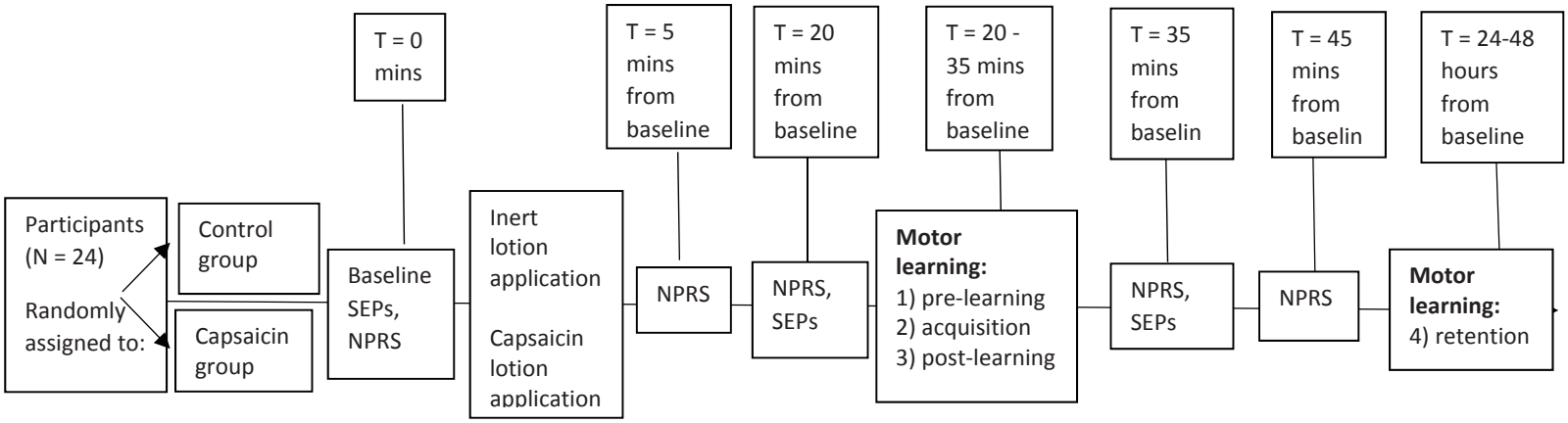
post-motor learning acquisition as indicated by asterisks.

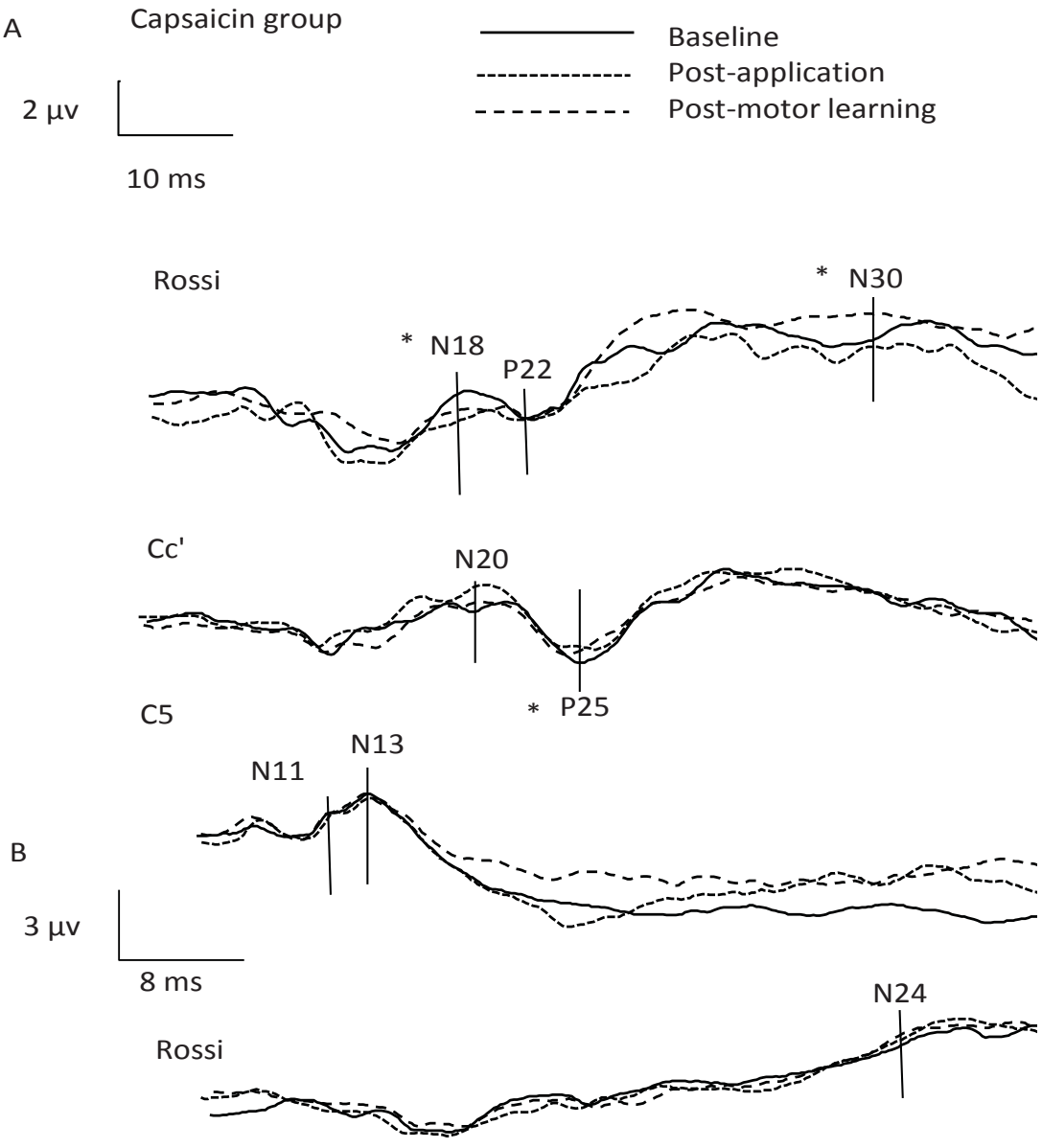
Figure 3: raw data from a representational control participant. Note the significant differences for the N20 ($p<0.05$), N24 ($p<0.001$), and N30 ($p<0.001$) SEP peaks post-motor learning acquisition as indicated by asterisks.

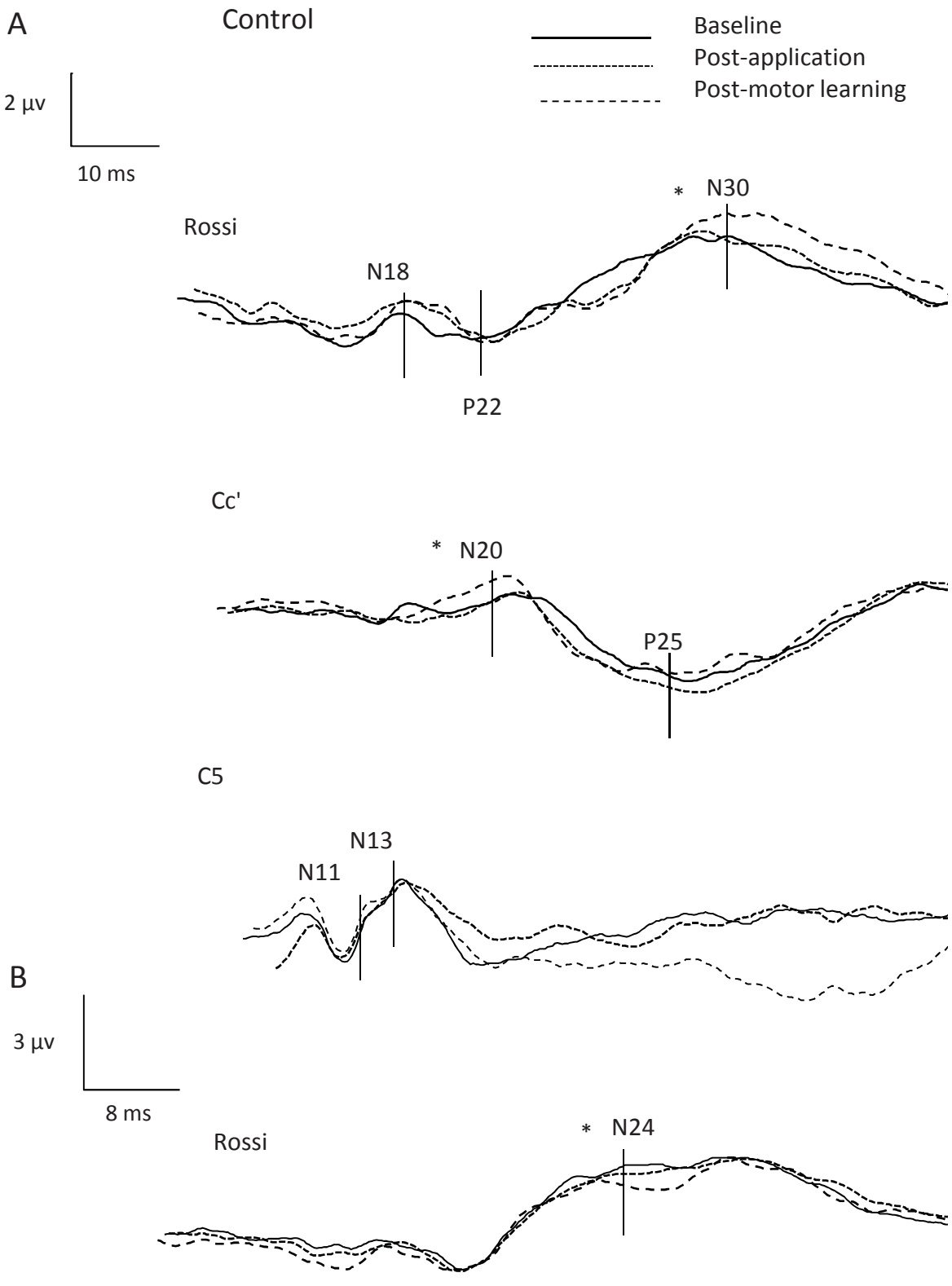
Figure 4: Bar-graph of averaged normalized SEP ratios showing capsaicin versus control groups post-application (A), and post-motor learning acquisition (B). A: No significant differences for the control group post-application while there was a significant decrease for the P25 SEP peak ($p<0.05$) for the capsaicin group post-application B: Following motor learning acquisition, significantly different changes from baseline are indicated by asterisks for the N20 ($p<0.05$), N24 ($p<0.001$), and N30 ($p<0.001$) SEP peaks for the control group and significantly different changes from baseline are indicated by asterisks for the N18 ($p<0.01$) and N30 ($p<0.001$) SEP peaks for the capsaicin group. Error bars represent the standard deviation.

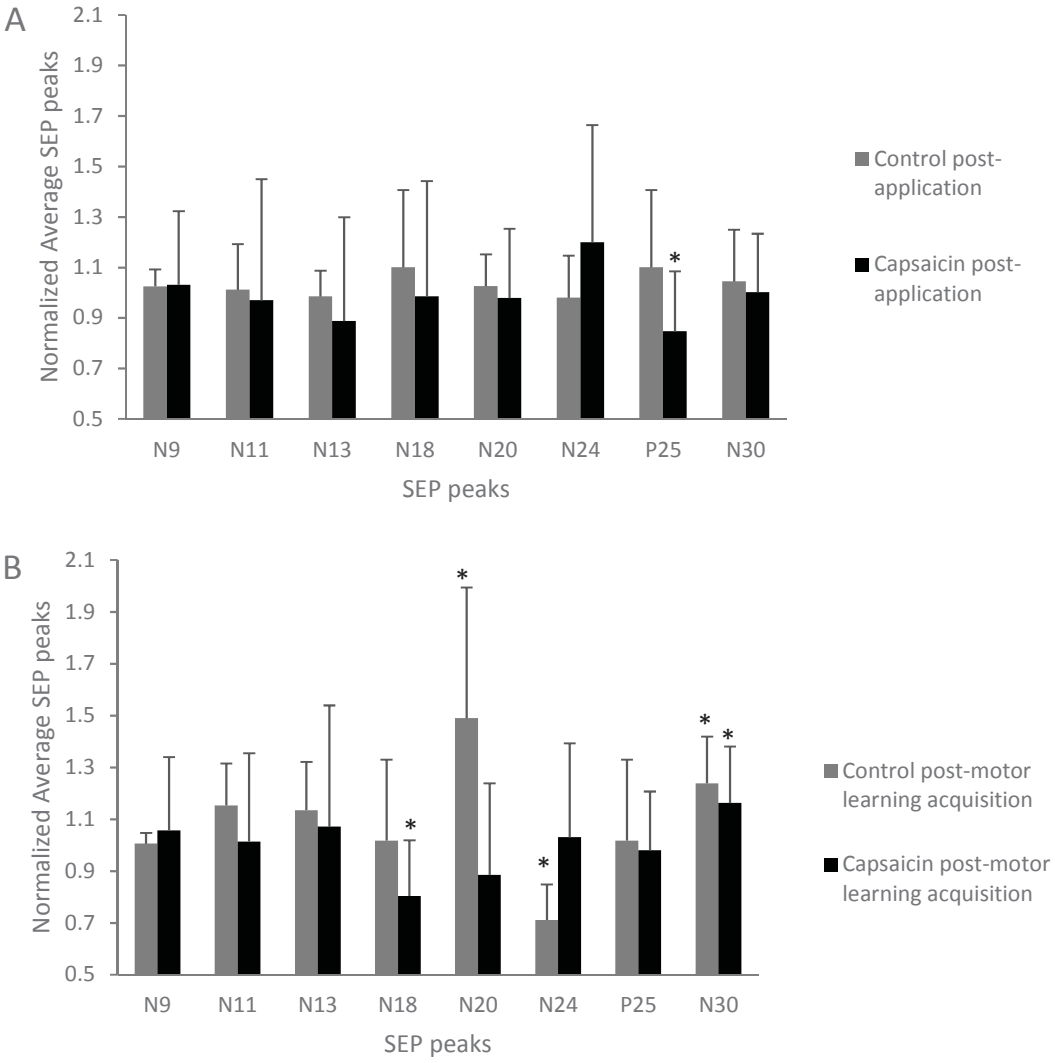
Figure 5: Bar-graph depicting the percent error by group. Both groups improved in accuracy following motor learning acquisition ($p<0.001$) as indicated by a double asterisk. The capsaicin group outperformed the control group pre-motor learning acquisition ($p<0.05$) and post-motor learning acquisition ($p<0.05$) as indicated by asterisks. Error bars represent the standard deviation.

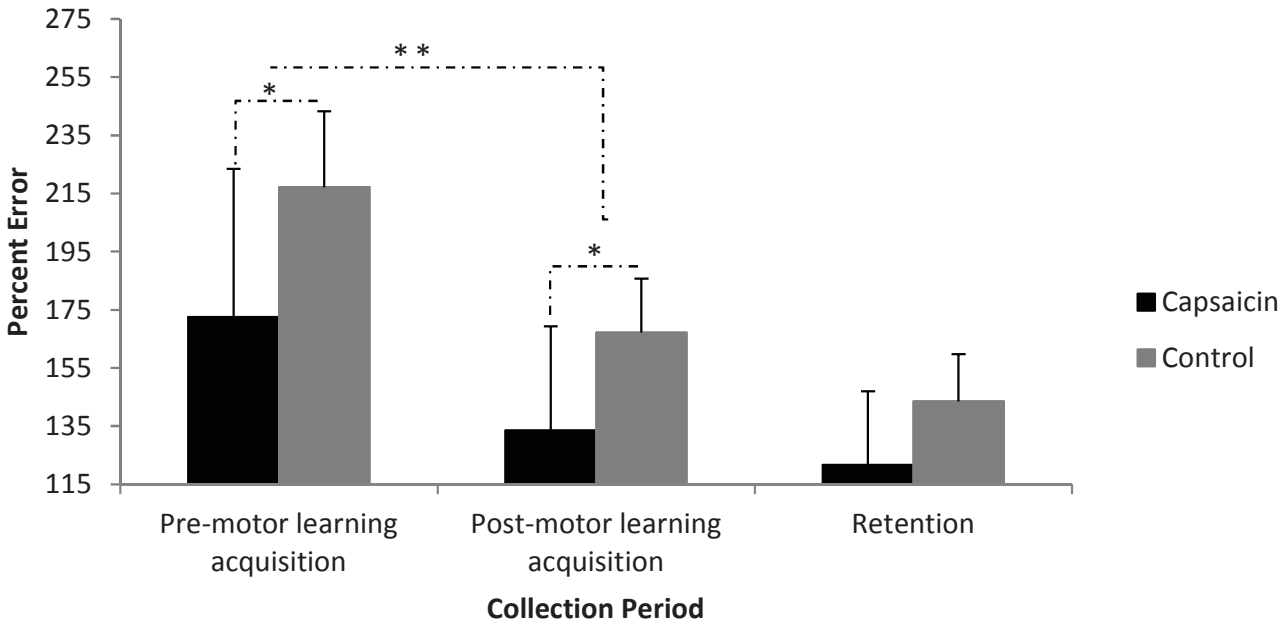
Figure 6: Bar-graph depicting averaged NPRS ratings of participants in the control and the capsaicin groups. Significant differences post application for the capsaicin group ($p<0.001$) relative to baseline are indicated by asterisks. Error bars represent the standard deviation. Error bars represent the standard deviation.

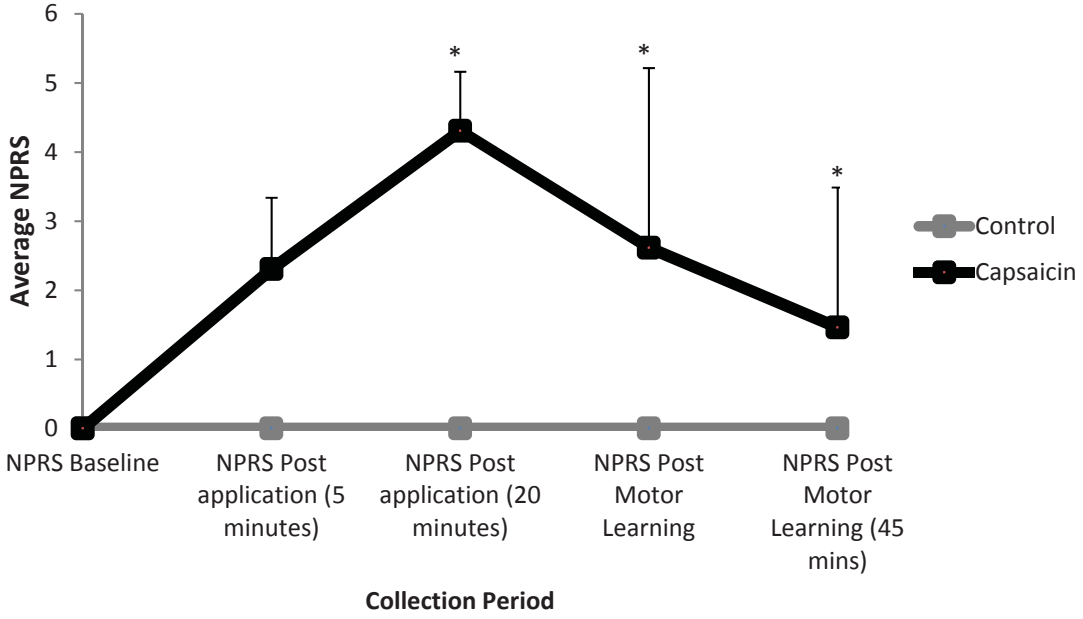

Participants (N = 24)
Randomly assigned to:
Control group
Capsaicin group
T = 0 mins
Baseline SEPs, NPRS
Inert lotion application
Capsaicin lotion application
T = 5 mins from baseline
NPRS
T = 20 mins from baseline
NPRS, SEPs
T = 20 - 35 mins from baseline
Motor learning:
1) pre-learning
2) acquisition
3) post-learning
T = 35 mins from baselin
NPRS, SEPs
T = 45 mins from baselin
NPRS
T = 24-48 hours from baseline
Motor learning:
4) retention


A
Capsaicin group
Baseline
Post-application
Post-motor learning
2 µv
10 ms
Rossi
* N30
* N18
P22
Cc'
N20
* P25
C5
N13
N11
B
3 µv
8 ms
N24
Rossi


A
Control
Baseline
Post-application
Post-motor learning
2 µv
10 ms
Rossi
N18
P22
* N30
Cc'
* N20
P25
C5
N13
N11
B
3 µv
8 ms
Rossi
* N24


A
2.1
1.9
1.7
1.5
1.3
1.1
0.9
0.7
0.5
Normalized Average SEP peaks
N9
N11
N13
N18
N20
N24
P25
N30
SEP peaks
*
Control post-application
Capsaicin post-application
B
2.1
1.9
1.7
1.5
1.3
1.1
0.9
0.7
0.5
Normalized Average SEP peaks
N9
N11
N13
N18
N20
N24
P25
N30
SEP peaks
*
*
*
*
*
Control post-motor learning acquisition
Capsaicin post-motor learning acquisition


275
255
235
215
195
175
155
135
115
Percent Error
* *
*
*
Pre-motor learning acquisition
Post-motor learning acquisition
Retention
Collection Period
Capsaicin
Control


6
5
4
3
2
1
0
Average NPRS
*
*
*
Control
Capsaicin
NPRS Baseline
NPRS Post application (5 minutes)
NPRS Post application (20 minutes)
NPRS Post Motor Learning
NPRS Post Motor Learning (45 mins)
Collection Period

SEP Peak	Group	Post-Application Mean	Post-application p-value	Post motor learning Mean	Post-motor learning p-value
P25	control	1.10 ± 0.31	0.28	1.02 ± 0.31	0.96
	capsaicin	**0.85 ± 0.24**	**P<0.05**	0.98 ± 0.23	0.96
N18	control	1.10 ± 0.31	0.59	1.02 ± 0.31	0.86
	capsaicin	0.99 ± 0.45	0.59	**0.80 ± 0.25**	**P<0.01**
N20	control	1.03 ± 0.13	0.97	**1.49 ± 0.50**	**P<0.05**
	capsaicin	0.98 ± 0.27	0.97	0.89 ± 0.35	0.29
N24	control	0.98 ± 0.17	0.19	0.71 ± 0.14	**P<0.001**
	capsaicin	1.20 ± 0.46	0.19	1.03 ± 0.36	0.80
N30	control	1.04 ± 0.20	0.62	1.24 ± 0.18	**P<0.001**
	capsaicin	1.00 ± 0.23	0.62	1.16 ± 0.22	**P<0.001**

Data are presented as mean ± SD

SEP peak	Control			Capsaicin		
	Pre-motor learning acquisition	Post application	Post-motor learning acquisition	Pre-motor learning acquisition	Post application	Post-motor learning acquisition
N9	10.1 ± 0.5	10.0 ± 0.6	10.2 ± 0.4	9.8 ± 0.6	9.7 ± 0.5	9.8 ± 0.7
N11	11.9 ± 0.7	12.0 ± 0.6	12.0 ± 0.5	11.6 ± 0.7	11.4 ± 0.7	11.5 ± 0.2
N13	13.2 ± 0.8	13.1 ± 0.7	13.3 ± 0.9	13.0 ± 0.6	13.1 ± 0.7	13.1 ± 0.4
N18	18.1 ± 0.4	18.3 ± 0.6	18.4 ± 0.4	17.8 ± 0.9	17.7 ± 1.1	17.4 ± 1.0
N20	20.1 ± 0.7	19.9 ± 0.6	20.4 ± 0.8	19.3 ± 0.9	19.2 ± 1.1	19.5 ± 1.0
N24	23.7 ± 0.6	23.5 ± 0.8	23.6 ± 0.7	24.1 ± 0.8	23.9 ± 0.9	23.8 ± 0.8
P25	24.9 ± 1.0	24.4 ± 1.3	25.0 ± 1.1	25.2 ± 0.8	25.5 ± 1.1	25.4 ± 0.7
N30	31.2 ± 0.8	31.4 ± 0.9	31.1 ± 1.1	30.4 ± 1.2	30.8 ± 1.1	30.5 ± 1.1

Data are presented as mean ± SD