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Modulation of intracortical inhibition in response to acute psychosocial stress is impaired among individuals with chronic neck pain

Ryan J. Marker [a,1], Jennifer L. Stephenson [b,1], Benzi M. Kluger [c], Douglas Curran-Everett [d,e], Katrina S. Maluf [a,f,*]

[a] Rehabilitation Science Program, University of Colorado Anschutz Medical Campus, Aurora, CO, USA
[b] Clinical Science Program, University of Colorado Anschutz Medical Campus, Aurora, CO, USA
[c] Department of Neurology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA
[d] Division of Biostatistics and Bioinformatics, National Jewish Health, Denver, CO, USA
[e] Department of Biostatistics and Informatics, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, CO, USA
[f] Physical Therapy Program, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

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ABSTRACT

Objective: Psychosocial stress has been associated with a variety of chronic pain disorders although the mechanisms responsible for this relationship are unknown. The purpose of this study was to compare the excitability of intracortical and corticospinal pathways to the trapezius muscle in individuals with and without chronic neck pain during exposure to low and high levels of psychosocial stress.
Methods: Single and paired-pulse transcranial magnetic stimulation was used to assess motor evoked potentials (MEPs) and short-interval intracortical inhibition (SICI) during mental math performed in the presence and absence of social evaluative threat.
Results: All participants demonstrated higher amplitude MEPs in the high stress compared to the low stress condition ($p < 0.01$). Participants with chronic neck pain had significantly greater SICI than healthy participants in the low stress condition ($p = 0.03$). During exposure to the stressor, healthy participants showed an increase in SICI, whereas participants with neck pain showed no change (group difference for change in SICI, $p < 0.01$).
Conclusions: These findings suggest that individuals with chronic neck pain inhibit motor output to the trapezius in the presence of minor stressors, and are unable to compensate for additional stress-evoked increases in corticospinal excitability through further modulation of SICI. This observation has potential implications for the management of patients who have difficulty relaxing painful muscles during times of stress.

Introduction

Psychosocial stress, defined as a disruption in homeostasis caused by actual or perceived adverse emotional threats [1], is an established risk factor for a variety of chronic pain syndromes [2,3] including neck pain [4,5]. Despite the high prevalence of co-morbid stress and pain, the mechanisms responsible for this association are not clear. Stress and anxiety have known modulatory effects on both pain perception [6] and motor behavior [7,8]. Transcranial magnetic stimulation (TMS) studies have shown that anxiety can increase corticospinal excitability in pain-free individuals [9]. Similarly, a decrease in the responsiveness of $GABA_A$-mediated inhibitory circuits, assessed as short-interval intracortical inhibition (SICI), has been associated with anxiety-related personality traits [10]. The effects of psychosocial stress on excitability of motor pathways among individuals with chronic pain are currently unknown.

TMS studies have shown consistent evidence of reduced excitability of cortical neurons and corticospinal pathways to the muscle with experimentally induced acute pain in healthy adults [11–14]. Increased inhibition and reduced facilitation of intracortical motor circuits have also been observed during or shortly after resolution of acute pain [15], supporting central inhibition as one protective mechanism to restrict movement of painful areas within a muscle [16,17]. Neuromuscular adaptations to chronic pain, however, are less consistent. Corticospinal excitability is reduced in patients with chronic low back pain compared to healthy controls [18], whereas patients with chronic knee pain show increased excitability of corticospinal pathways [19]. Reductions in SICI have been demonstrated for patients with chronic regional pain syndrome [20,21], neuropathic pain [22,23], and fibromyalgia [24] compared to pain-free individuals. However, patients with chronic pain due to osteoarthritis show similar levels of SICI as healthy controls [22]. Patterns of muscle activation are also highly variable among patients with chronic pain, and often differ from those observed in response to experimental pain [25].

One possible explanation for the large variability in neural adaptations to chronic pain is the interaction between adaptations to pain and those associated with psychosocial stress. Therefore, the purpose

* Corresponding author at: Rehabilitation Science and Physical Therapy Programs, MS C244, Education 2 South, Bldg #L28, 13121 E. 17th Ave, Room 3108, Aurora, CO 80045, USA. Tel.: +1 303 724 9139; fax: +1 303 724 9016.
E-mail address: Katrina.Maluf@ucdenver.edu (K.S. Maluf).
[1] Both authors contributed equally to this work.

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of this study was to compare the excitability of intracortical and corticospinal pathways to the upper trapezius muscle in individuals with and without chronic neck pain during exposure to low and high levels of psychosocial stress. Based on previous studies showing consistent inhibition of motor output in response to experimentally evoked pain [11–15] and among patients with chronic spine pain [18], we hypothesized that individuals with chronic neck pain would exhibit greater intracortical inhibition and reduced corticospinal excitability compared to healthy controls in the low stress condition. During an acute increase in stress, however, we expected to observe a greater increase in corticospinal excitability and reduction in intracortical inhibition in the neck pain group.

Materials and methods

Participants

Participants with chronic neck pain and individuals without a history of chronic musculoskeletal pain were recruited through printed and electronic advertisements at a university medical campus and the surrounding community. All participants provided written informed consent in accordance with procedures approved by the Colorado Multiple Institutional Review Board, including additional protections for a partial waiver of consent required for the stress manipulation.

The neck pain group included participants with recurrent or persistent pain located between the superior nuchal line and the superior spine of the scapula for at least 1 year prior to enrollment, at least mild disability with a Neck Disability Index (NDI) score of $\geq$10% [26,27], and tender points in the upper trapezius confirmed by manual palpation. Participants were asked to refrain from taking pain medication for at least 24 h prior to the testing session. Individuals in the healthy control group reported a complete absence of neck pain in the year prior to enrollment, with no history of any neck pain lasting more than 12 weeks. These participants had no tender points in the upper trapezius confirmed by manual palpation on the day of testing.

Exclusion criteria for both groups included objective signs of structural pathology or neurologic impairment (e.g. radiculopathy), or a self-reported history of traumatic injury or surgery affecting the neck or shoulder region within 12 weeks of enrollment. Individuals with a history of widespread musculoskeletal pain were excluded. All participants were free from contraindications to TMS as outlined by the National Institute of Neurological Disorders and Stroke, denied any history of major cardiovascular, neurological, or psychiatric medical conditions, and were not taking centrally active medications. No participants reported a history of repetitive motor activity impairments.

Electromyography

Surface electromyography (EMG) was recorded from the dominant upper trapezius using bipolar Ag–AgCl surface electrodes. Electrodes were positioned with a 15 mm interelectrode distance and centered 20 mm lateral to the midpoint between C7 and the posterior lateral border of the acromion [28]. A reference electrode was placed over a bony portion of the ipsilateral clavicle. EMG data were amplified (1000×), band-pass filtered (13–1000 Hz LabLinc V, Coulbourn Instruments, Whitehall, PA; 10–500Hz, MP150, Biopac Systems Inc., Goleta, CA), and sampled at 2000 Hz (Micro 1401, Cambridge Electronic Design, Cambridge, UK). Data were collected during a 5–8 s time window surrounding the delivery of TMS stimuli to capture background levels of EMG and corresponding MEP.

Transcranial magnetic stimulation

TMS methods were performed and reported in accordance with Chipchase et al. [29], unless otherwise noted. TMS was applied over the contralateral motor cortex using a standard 70 mm figure-of-eight coil to stimulate the cortical representation of the dominant upper trapezius. Monophasic stimuli were generated using a Magstim Bistim^2 (The Magstim Company, Whitland, UK). The coil was held with the handle pointing posterolaterally at approximately a 45° angle to induce a posterior-to-anterior current in the motor cortex. Stimuli were applied in a grid pattern centered around the previously reported locus for the cortical representation of the upper trapezius muscle [30]. The optimal coil position for evoking motor responses in the upper trapezius muscle was identified individually for each participant as the position inducing the largest MEP during low-intensity muscle contraction. This position was recorded with Brainsight neuronavigation software (Rogue Research Inc., Montreal, QC), and remained constant across experimental conditions. Stimulation intensities and EMG recordings were controlled using Signal software (Cambridge Electronic Design, Cambridge, UK).

Resting motor threshold (RMT) was determined as the lowest stimulation intensity that evoked an MEP with peak-to-peak amplitude of at least 50 μV in 50% of trials in a relaxed muscle. Active motor threshold (AMT) was determined as the lowest stimulation intensity that evoked an MEP with a peak-to-peak amplitude of at least 100 μV in 50% of trials during low-intensity contraction of the upper trapezius [31]. Net excitability of the corticospinal tract was assessed by the amplitude of MEPs produced by a series of 8–12 single stimuli delivered at 120% RMT with the muscle at rest ($MEP_{120\%}$).

SICI was assessed with a series of 8–12 paired stimuli delivered with the muscle at rest according to the paired-pulse stimulation paradigm developed by Kujirai et al. [32]. A suprathreshold test stimulus (120% RMT, MEP_{UNCOND}) was preceded by a subthreshold conditioning stimulus (70% AMT, MEP_{COND}), with an inter-stimulus interval of 2.5 ms. A conditioning stimulus intensity of 70% AMT was selected to isolate inhibitory $GABA_A$ pathways, as conditioning stimuli at higher intensities may concurrently activate both inhibitory and facilitatory circuits [33]. Intensity of the test stimulus was calculated based on RMT in the baseline condition. To assess intracortical adjustments to a given input under different psychoemotional states that were expected to alter corticospinal excitability, the intensity of both the conditioning and test stimuli remained constant across low and high stress conditions. Previous research indicates that the population of interneurons recruited by the test stimulus is dependent on absolute stimulator intensity, regardless of changes in corticospinal excitability [34]. Therefore, a constant stimulation intensity allowed us to examine SICI for the same population of interneurons despite expected changes in the unconditioned MEP amplitude and motor threshold across stress conditions. These procedures contrast with recent recommendations to adjust the intensity of stimulation to maintain a constant MEP_{UNCOND} amplitude across experimental conditions [29]; therefore, a correlation analysis was performed to assess whether changes in SICI were associated with changes in MEP_{UNCOND} amplitude across stress conditions. A similar analysis was performed for changes in SICI and changes in RMT. These analyses allowed us to identify any contribution of changes in corticospinal excitability to changes in SICI assessed at the same absolute intensity across stress conditions. SICI was calculated as one minus the ratio between the amplitudes of the MEP_{COND} and MEP_{UNCOND} (illustrated in Fig. 1A). Thus, higher values of SICI indicated greater responsiveness of $GABA_A$-mediated inhibitory circuits within the motor cortex.

Perceived anxiety and physiologic arousal

Perceived anxiety was measured using the state anxiety portion of the Spielberger State-Trait Anxiety Inventory (STAI-S) [35]. Physiologic arousal was assessed based on cardiovascular responses collected with an automated monitor (Omron Healthcare, Inc., Bannockburn, IL) placed on the non-dominant arm to measure heart rate and blood pressure. Rate pressure product (RPP) was calculated as the product of systolic blood pressure and heart rate.