Alterations in central motor representation increase over time in individuals with rotator cuff tendinopathy

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Abstract

Objective: To investigate whether rotator cuff tendinopathy leads to changes in central motor representation of a rotator cuff muscle, and to assess whether such changes are related to pain intensity, pain duration, and physical disability.

Methods: Using transcranial magnetic stimulation, motor representation of infraspinatus muscle was assessed bilaterally in patients with unilateral rotator cuff tendinopathy.

Results: Active motor threshold is significantly larger for the affected shoulder comparatively to the unaffected shoulder (n = 39, p = 0.01), indicating decreased corticospinal excitability on the affected side compared to unaffected side. Further, results suggest that this asymmetry in corticospinal excitability is associated with duration of pain (n = 39; r = 0.45; p = 0.005), but not with pain intensity (n = 39; r = 0.03; p > 0.43). In contrast with findings in other populations with musculoskeletal pain, no significant inter-hemispheric asymmetry was observed in map location (n = 16; p-values P > 0.91), or in the amplitude of motor responses obtained at various stimulation intensities (n = 16; p > 0.83).

Conclusion: Chronicity of pain, but not its intensity, appears to be a factor related to lower excitability of infraspinatus representation.

Significance: These results support the view that while cortical reorganization correlates with magnitude of pain in neuropathic pain syndromes, it could be more related to chronicity in the case of musculoskeletal disorders.

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1. Introduction

Shoulder pain affects about 20% of the population and is second only to low back pain in prevalence of musculoskeletal (MSK) conditions (Pope et al., 1997; Picavet and Schouten, 2003). Disorders of rotator cuff (RC) tendons is the most common pathology of the shoulder, with RC tendinopathy accounting for 35% to 50% of rendered diagnoses (Chard et al., 1991; van der Windt et al., 1995). Clinical trials suggest that long-term outcomes of patients with RC disorders receiving rehabilitation are comparable to that of patients treated with surgery (Brox et al., 1999; Haahr and Andersen, 2006; Seitz et al., 2011). Regardless of treatment, more than a third of patients do not have a positive outcome as they...
continue to present pain and disability after the intervention (Seitz et al., 2011).

It has been recently hypothesized that reorganization of the somatosensory and motor cortices could explain part of the deficits associated with RC tendinopathy (Myers et al., 2006; Roy et al., 2009; van Vliet and Heneghan, 2006). This reorganization could also explain the chronicity of the symptoms and the lack of treatment effectiveness for one third of patients. Central changes underlying movement deficits associated with RC tendinopathy remain unclear. To our knowledge, they have never been directly tested in this population. However, changes in the central nervous system (CNS) have been documented in patients with other MSK disorders, primarily regarding the functional organization of the primary somatosensory and motor cortices (van Vliet and Heneghan, 2006; Boudreau et al., 2010). Consequently, understanding the involvement of CNS in MSK disorders is now considered as a key aspect to improve the management of patients with such disorders (Tsao et al., 2010; Tsao et al., 2008).

Current interventions for RC tendinopathy mainly target deficits at the joint level, such as altered posture (Gumina et al., 2008; Finley and Lee, 2003; Kalra et al., 2010; Kebaetse et al., 1999), muscular deficit (weakness/lack of endurance) (Ludewig and Cook, 2000; Wadsworth and Bullock-Saxton, 1997; Cools et al., 2003; Cools et al., 2004; Cools et al., 2007) and soft tissue tightness (Tauro and Paulson, 2008). However, if central (neural) changes are present in individuals with RC tendinopathy, then specific interventions, such as sensorimotor training, should be performed in order to reverse these changes and thereby decrease pain during arm movement. Reversal of central changes related to the peripheral lesion could be an important step towards recovering a normal level of shoulder function.

Given the high prevalence of RC tendinopathy, and continued pain symptoms in one third of the patients despite treatment, research to better understand the factors that may explain the persistence of pain in individuals with RC tendinopathy is needed in order to guide the development of more effective treatment approaches. The first objective of the current study was to investigate whether individuals with RC tendinopathy exhibit changes in the excitability and location of the cortical motor representation of a RC muscle. The second objective was to determine whether such central changes are related to clinical variables such as pain intensity, pain duration, and physical disability.

2. Methods

2.1. Participants

Thirty-nine participants (18 women, 21 men; mean age 46 ± 11 years) with unilateral RC tendinopathy were recruited (see Table 1 for participants’ characteristics). Participants were considered eligible if they were aged between 18 and 65, presented pain in one shoulder, and had at least one positive finding in each of these categories: 1) painful arc of movement during flexion or abduction; 2) positive Neer or Kennedy-Hawkins impingement signs; 3) pain on resisted lateral rotation, abduction or Jobe test. The diagnosis accuracy of these tests for RC tendinopathy has been shown (sensitivity & specificity ≥ 0.74, Positive likelihood ratio = 3–5) (Michener et al., 2009).

Exclusion criteria were previous shoulder surgery, cervicobrachialgia or shoulder pain during neck movement, shoulder capsulitis (≥ 30% restriction of passive glenohumeral movement for two or more directions), clinical signs of a full thickness RC tear (dramatic weakness on resisted movement or positive Lag signs), pain or movement limitation at the unimpaired shoulder, current use of steroidal anti-inflammatory or opioids drugs, as well as contraindications for magnetic resonance imaging (MRI) or transcranial magnetic stimulation (TMS) (e.g. metallic or electronic implants, pregnancy, history of epilepsy, etc.) (Rossi et al., 2009). None of the subjects had a reported history of neurological deficit or systemic disease. This study was approved by the Ethics Committee of the Quebec Rehabilitation Institute. All participants gave their written consent after being informed of the nature and purpose of the study.

2.2. Experimental design

Each participant took part in two evaluation sessions within 7 days. During the first session, after the evaluation of eligibility criteria, participants completed a questionnaire on sociodemographic, symptomatic, and comorbidity. Hand dominance was determined using the revised Edinburgh Handedness Inventory (Oldfield, 1971). Then, the level of pain and disability of the shoulder was evaluated using the French Canadian version of the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire (Durand et al., 2005). The DASH is a 30-item self-reported questionnaire that addresses difficulty in performing various physical activities that require upper extremity function (21 items); symptoms of pain, activity-related pain, tingling, weakness, and stiffness (5 items); and impact of disability and symptoms on social activities, work, sleep, and psychological well-being (4 items) (Hudak et al., 1996). Response options are rated on a 5-item Likert scale. The final score range from 0 (no disability) to 100 (most severe disability).

Visual analog scales (VAS; 0 to 10) were also used to estimate participants’ reported pain level during the 48 h preceding the test at rest, during daily activities, and during nighttime. For the first 16 participants included in the study, a structural MRI of the brain was obtained in order to use a frameless stereotaxy neuronavigation system (Brainsight, Rogue Research, Canada) for cortical mapping. This system allows accurate and reliable positioning of the TMS coil. For the other 23 participants, frameless stereotaxy neuronavigation system was also used, but participants’ heads were coregistered with a standard MRI. In the following days, all the participants took part in a second evaluation session during which the motor cortex representation of a RC muscle was assessed bilaterally.

2.3. Cortical mapping

The infraspinatus has been selected as the target muscle for cortical mapping as it is a RC muscle for which the activation pattern has been shown to be altered during arm elevation in individuals with RC tendinopathy (Reddy et al., 2000). Furthermore, it is the only RC muscle for which the electromyographic (EMG) activity can be directly recorded using surface electrodes. Mapping was performed using a Bistim® stimulator (combined pulse mode) connected to a 70-mm figure-of-eight coil (Magstim Company Limited, United Kingdom). Stimuli were applied over grid sites spaced 1 cm apart and located over the upper limb representation of primary motor cortex (M1) in the contralateral hemisphere (using the neuronavigation system).

Motor evoked potentials (MEPs) were collected from the EMG recording of the infraspinatus muscle. After skin preparation, a pair of Ag/AgCl surface electrodes (1 cm² recording area) was placed over the infraspinatus muscle. The ground electrode was positioned over the ipsilateral acromion. Electrode placement over infraspinatus was based on Delagi & Perotto, i.e. 3–4 cm below and running parallel to the spine of the scapula, over the infraspinatus fossa (Delagi and Perotto, 1980). This arrangement has shown high levels of agreement between surface and intramuscular recordings (Johnson et al., 2011). EMG signals were amplified.
Participants’ characteristics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>All participants (n = 39)</th>
<th>Participants for motor mapping (n = 16)</th>
<th>Subgroups*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low chronicity &lt; 12 months (n = 21)</td>
</tr>
<tr>
<td>Age, years, X ± SD</td>
<td>46 ± 11</td>
<td>49 ± 10</td>
<td>45 ± 10</td>
</tr>
<tr>
<td>Gender - Female, n (%)</td>
<td>18 (46%)</td>
<td>8 (50%)</td>
<td>10 (48%)</td>
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<tr>
<td>Weight, kg, X ± SD</td>
<td>77 ± 17</td>
<td>77 ± 17</td>
<td>79 ± 20</td>
</tr>
<tr>
<td>Height, cm, X ± SD</td>
<td>169 ± 9</td>
<td>168 ± 9</td>
<td>169 ± 10</td>
</tr>
<tr>
<td>Dominance – Right handed, n (%)</td>
<td>34 (87%)</td>
<td>15 (94%)</td>
<td>18 (86%)</td>
</tr>
<tr>
<td>Dominant affected side, n (%)</td>
<td>25 (64%)</td>
<td>14 (70%)</td>
<td>13 (62%)</td>
</tr>
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<td>Symptoms duration, months, X ± SD</td>
<td>19 ± 21</td>
<td>24 ± 26</td>
<td>6 ± 4</td>
</tr>
<tr>
<td>DASH, /100, X±SD</td>
<td>29 ± 15</td>
<td>26 ± 16</td>
<td>30 ± 15</td>
</tr>
<tr>
<td>VAS - Pain at rest, /10, X±SD</td>
<td>2.0 ± 1.7</td>
<td>2.1 ± 1.9</td>
<td>1.8 ± 1.6</td>
</tr>
<tr>
<td>VAS - Pain during ADL, /10, X±SD</td>
<td>5.1 ± 2.2</td>
<td>4.6 ± 2.3</td>
<td>5.4 ± 1.9</td>
</tr>
<tr>
<td>VAS - Pain at night, /10, X±SD</td>
<td>3.8 ± 2.8</td>
<td>3.4 ± 3.0</td>
<td>4.4 ± 2.8</td>
</tr>
<tr>
<td>Medication¹, n (%)</td>
<td>5 (13%)</td>
<td>2 (13%)</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>2 (5%)</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

X: mean; SD: standard deviation; DASH: Disabilities of the Arm, Shoulder and Hand questionnaire (a higher score indicates higher disabilities); VAS: Visual Analogue Scale (a higher score indicates increased pain); ADL, Activity of Daily Living; NSAID, Nonsteroidal Antiinflammatory Drug.

* There were no statistical differences between the two subgroups for all variables (p > 0.05; independent t-tests or Chi-squared tests), except for symptoms duration.

¹ One participant (3%) took either pantoprazole, aldehyde, methocarbamol, buproprion, benzodiazepine, levothyroxine, nifedipine, atorvastatin, alfuzosin.

(1000x), bandpass filtered (20–1000 Hz), digitized at a sampling rate of 2000 Hz (Power1401 interface; Cambridge Electronic Design, Cambridge, United Kingdom) and stored on a computer for off-line analysis. Prior to the experiment, subjects performed isometric maximal voluntary contractions (MVC) in humeral lateral rotation with the shoulder at 0° of elevation and in neutral rotation. Two successive assessments were performed with an inter-assessment interval of 30 s. Maximal value over the two assessments was used to compute EMG targets for the experimental task (5 ± 1% of MVC). Visual feedback of actual EMG activity level and targeted level of contraction were provided in real-time on a computer screen placed in front of the subject. To ensure that the EMG level was maintained stable through the experiments, the EMG root mean square values obtained during a 50 ms time window preceding each TMS pulse was computed and recorded for off-line analyses (Armstrong et al., 1993). All TMS measurements were performed with the infraspinatus muscle slightly contracted (5% MVC) as, in the relaxed normal arm, responses elicited in proximal muscles are very small and require high intensities of stimulation (Rothwell et al., 1991). Therefore, participants were asked to actively maintain the arm elevated at 40° of humeral abduction in the frontal plane during TMS measurements, and to monitor their level of contraction on the computer screen in order to have a contraction of the infraspinatus between 4 and 6% of MVC (bars on the screen for the intervals and visual feedback of actual EMG activity level) (Fig. 1). Trials were repeated when the level of contraction was lower than 4% or higher than 6% of MVC. Resting and active cortical maps have been shown to be similar for hand muscles in healthy subjects when differences in motor thresholds are accounted for (Ngomo et al., 2011).

For all participants, the optimal location for stimulation of infraspinatus muscle (i.e. hotspot) was determined, as well as the active motor threshold (aMT) at this site. The hotspot was defined as the site at which MEPs are evoked with the lowest intensity of stimulation, while aMT was defined as the minimal TMS intensity that produced MEP amplitudes of at least 20% above background EMG in at least 50% of the trials (6 trials out of 12) at the hotspot.

For the first 16 participants included in the study, motor mapping was also performed. Stimulations were applied at 110% of individual aMT. Six successive pulses separated by intervals of 4.5 to 5 s were delivered to each stimulated site. A site was considered as active if at least two MEPs were elicited. Non-active sites delimited the boundary of the map. Finally, stimulations were applied at four different intensities at the hotspot (100%, 110%, 120% and 140% of aMT) to assess the input–output relationship; the full input–output curve was not assessed, however. For all measurements, stimulation intensity was adjusted based on each hemisphere’s threshold. Therefore a difference in MEP amplitude could not solely reflect a change in threshold (Gagné et al., 2011). It was chosen not to map the entire motor representation of the infraspinatus for all participants given the time needed to perform such mapping bilaterally, and the lack of inter-hemisphere statistical difference or trend following the preliminary analysis of the first 16 participants.

2.4. Data pre-processing

TMS measures obtained included aMT for all participants (n = 39), as well as MEPs obtained with four intensities of stimulation (at 100%, 110%, 120% and 140% of aMT) and map center of gravity (CoG) for the first 16 participants. CoG was computed for the mediolateral (x) and anteroposterior (y) coordinates relative
to the vertex (expressed in mm) using the following formula: CoGx = Σ(x_i * MEP_i) / ΣMEP_i, and CoGy = Σ(y_i * MEP_i) / ΣMEP_i, where MEP_i represents the mean amplitude of the MEPs produced at one site (Wassermann et al., 1992).

2.5. Statistical analyses

Descriptive statistics were first calculated for all variables to summarize results. To verify whether there was asymmetry in the motor representation of the infraspinatus muscle between hemispheres, comparisons of aMT and CoG location were performed between affected (hemisphere opposite to the affected shoulder) and unaffected (hemisphere opposite to the unaffected shoulder) sides using paired t-tests. The presence of differences between sides in input–output relationship was assessed using 2 × 4 (side [affected/unaffected] x intensity [100, 110, 120, 140% aMT]) repeated measures ANOVA. When a significant inter-hemispheric difference appeared for a given TMS measure, background EMG levels in the pre-stimulation period were compared across sides (paired t-test) to verify that differences were not due to changes in background EMG activity.

Pearson product–moment correlation coefficients were calculated between TMS measures with an inter-hemispheric asymmetry and clinical variables including pain duration, pain intensity, and DASH score. Finally, given that a significant correlation was found between inter-hemispheric aMT asymmetry and symptoms duration, it was decided a posteriori to divide the 39 participants in two subgroups based on symptoms duration (low chronicity [< 12 months] and high chronicity [> than 12 months]) and to compare to two subgroups for inter-hemispheric aMT asymmetry using independent t-tests. In addition, for each subgroup, one-sample t-tests were performed to determine if the mean aMT asymmetry was significantly different from 0. All analyses were performed with SPSS 21.0 for Mac and the significance threshold was set at p < 0.05.

3. Results

3.1. Clinical variables

As shown in Table 1, mean pain duration was 19 ± 21 months. Average pain intensity (out of 10) was 2.0 ± 1.7 at rest, 5.1 ± 2.2 during daily activities, and 3.8 ± 2.8 during nighttime. The average DASH score (out of 100) was 29 ± 15.

3.2. TMS measures

A difference between sides was found for the aMT, aMT being significantly higher for the affected shoulder (39% of maximum stimulus output [MSO] ± 13%) comparatively to the unaffected shoulder (35% of MSO ± 10%) (p = 0.01; t = 2.71) (Fig. 2). A higher motor threshold indicates a decreased excitability on the affected side, as a higher intensity of stimulation is needed in order to evoke muscle responses. Note that no significant difference was found for either the absolute or normalized ( % of MVC) background EMG during aMT assessment (p > 0.41). Thus, it is unlikely that lower contraction levels on the affected side during TMS testing explain the asymmetry in aMT.

No significant difference was observed between the two hemispheres for the cortical map location (medialateral and anteroposterior CoG location; p-values > 0.91) (Fig. 3). Finally, no significant intensity x side interaction (p = 0.83) or main effect of the side (p = 0.20) was found for the MEP amplitudes, indicating similar input–output relationships for both sides once the differences in aMT were controlled for (Fig. 4). Unsurprisingly, a main effect of the intensity of stimulation was found (p < 0.001), reflecting the fact that larger MEPs were obtained at higher stimulation intensities.

3.3. TMS measures and level of pain and disability

A significant correlation (r = 0.45; p = 0.005) was observed between asymmetry of aMT and pain duration. Subjects with more chronic pain exhibited larger inter-hemispheric asymmetry. Subgroup analyses showed that subjects with high chronicity (> than 12 months; mean asymmetry of 7% of MSO ± 9; n = 18) had significantly higher inter-hemispheric asymmetry (p = 0.021; t = 2.41) compared to subjects with low chronicity (< 12 months; mean asymmetry of 1% of MSO ± 5; n = 21). There were no other significant differences between the two subgroups for clinical variables such as age, pain intensity, and physical disability (Table 1). Mean aMT asymmetry of the high chronicity subgroup was significantly different from 0 (p = 0.006; t = 3.16), while the mean aMT asymmetry of the low chronicity subgroup was not (p = 0.336; t = 0.99). For the whole group, asymmetry in aMT was not significantly correlated (p-values > 0.43) with pain intensity (at rest [r = 0.03], during daily activities [r = -0.11], and during night time [r = -0.13]) or with physical disability (DASH score; r = -0.05). Similarly in the two subgroups, asymmetry in aMT was not correlated (p-values > 0.16) with pain intensity (at rest [r = 0.31], during daily activities [r < 0.21], and during night time [r < 0.12]) or physical disability (DASH score; r < 0.23).

4. Discussion

This study investigated whether individuals with unilateral RC tendinopathy exhibit changes in central motor representation of
the infraspinatus muscle, and whether these changes are related to shoulder pain intensity or duration as well as to physical disability. Our results show a significant inter-hemispheric asymmetry of infraspinatus aMT, indicating decreased corticospinal excitability on the affected side (hemisphere opposite to the affected shoulder) compared to the unaffected side (in the absence of a difference in the level of background EMG activity). Furthermore, chronicity of pain, but not its intensity, appears to be a factor related to the lower excitability of the infraspinatus representation. In a recent review, Moseley & Flor hypothesized that while cortical reorganization correlates with the magnitude of pain in neuropathic pain, results appear to be more related to chronicity in the case of MSK disorders (Moseley and Flor, 2012). To our knowledge, our study is the first to provide direct empirical evidence supporting that view in patients with MSK disorders.

The results related to the inter-hemispheric asymmetry are consistent with previous reports of alterations in corticospinal excitability for shoulder muscles in patients with other MSK shoulder disorders. Alexander et al. reported increased aMT of the trapezius muscle in subjects with non-traumatic shoulder instability compared to subjects without shoulder instability (Alexander, 2007). Berth et al. have evaluated the corticospinal excitability of the medial head of the deltoid muscle in individuals with full thickness RC tear (Berth et al., 2009). They reported that deltoid muscles displayed a bilateral (compared to control subjects) hyperexcitability at rest and hypoexcitability during voluntary activation. The latter study, however, presents important methodological limitations and should therefore be considered cautiously: motor threshold of a distal muscle was used to set the stimulation intensity for the deltoid muscle (leading to very small MEPs in the deltoid), and the level of background EMG was not properly controlled for.

TMS studies conducted in other types of MSK disorders have also shown alterations in corticospinal excitability, with some reporting reductions in excitability and others reporting increases (On et al., 2004; Strutton et al., 2003; Strutton et al., 2005). Some TMS studies looking specifically at the effect of immobilization have reported a significant decrease in corticospinal excitability (Facchini et al., 2002; Granert et al., 2011; Ngomo et al., 2012). A recent study has also shown decreased cortical thickness in M1 and primary somatosensory cortex as well as a decrease in fractional anisotropy in the corticospinal tract after two weeks of immobilization due to right upper extremity injury (Langer et al., 2012). According to this hypothesis, it could have been expected that the DASH score would correlate with the asymmetry. This was not the case. However, one needs to keep in mind that the DASH reflects the self-reported ability to perform certain activities, and not how frequently the affected upper extremity was used during daily life activities. The lack of quantitative measures of arm use is a limitation of the current study. A more direct and quantitative measure of the amount of use of the affected limb during everyday activities, for example using accelerometry, might reveal associations between the amount of use and the changes in corticospinal excitability.

Another potential limitation of this study is that 64% of participants were affected on their dominant side, raising some questions about the potential contribution of dominance to the observed asymmetry. However results from studies in healthy subjects do not support the view of such an inter-hemispheric asymmetry for either hand muscles or the infraspinatus muscle itself (Smith et al., 2011; Livingston et al., 2010; Ngomo et al., 2013). Moreover, potential effects related to dominance cannot account for the relationship observed between the asymmetry and the symptoms duration.

In conclusion, this study is the first to investigate central motor alterations in relation with RC tendinopathy. An interesting observation is that the chronicity of the pain, but not its intensity, appears to be a factor related to the lower excitability of the infraspinatus representation. Longitudinal studies are needed in order to better understand the role that such reorganization of motor representations may play in the chronicity of pain. For example, does the presence of central changes contribute to pain chronicity? Further studies will also be required in order to evaluate the
impact of rehabilitation and/or surgery on the central changes observed in this population.

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Conflict of interest

The authors declare that they have no competing interests and there is no conflict of interest.

References


