

1 Influence of experimental pain on the spatio-temporal activity of upper trapezius during
2 dynamic lifting – an investigation using Bayesian spatio-temporal ANOVA

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8

9 **Abstract**

10 High-density surface electromyography (HDsEMG) provides a detailed analysis of a
11 muscle's spatial distribution of activity. We applied a Bayesian spatio-temporal statistical
12 method to quantify how acute nociception and task repetition alters the upper trapezius
13 instantaneous spatial distribution of activity during dynamic muscular contractions. Ten
14 male adults performed repeated lifting of a 1 kg box between shelves positioned at hip and
15 shoulder heights with a cycle time of 3 s for 50 cycles under four conditions: baseline,
16 isotonic and hypertonic saline injections (nociception) to the right upper trapezius, and 15
17 minutes post injection. Activity of the right upper trapezius was measured using a 64-
18 channel surface electrode grid. Statistical inference was performed using Integrated Nested
19 Laplace Approximations (INLA), and significance was determined by a non-zero crossing
20 of the Bayesian 95% credible intervals (CrI). The maximal decrease in activity after
21 nociception was $-38.1\mu\text{V}$ [95% CrI -40.9 to -35.3] at 30% of the lift cycle when compared
22 to baseline. The maximal reduction in muscle activity between the early and later phases
23 of lifting in the presence of nociception was by $10.4\mu\text{V}$ [95% CrI 8.2 to 12.6]. A more
24 holistic understanding of muscle behaviour is achieved using spatio-temporal inference
25 than traditional reductionist methods.

26 **Keywords:** Pain, Electromyography, Motor control, Spatio-temporal, Bayesian

27

28 **1. Introduction**

29 High-density surface electromyography (HDsEMG) has been increasingly used to
30 study how pain (Falla et al., 2017), fatigue (Abboud et al., 2016), and repetitive task
31 execution (Samani et al., 2017) alter the spatial distribution of EMG amplitude. Changes in
32 the spatial distribution of EMG amplitude reflect a variety of physiological (mal) adaptations.
33 For example, the spatial distribution of intra-muscular activity may reflect the intrinsic
34 variation of motor neuron activity for load distribution (Martinez Valdes et al., 2018); a non-
35 uniform distribution of nociceptive input to motor neurons (Dideriksen et al., 2016); and a
36 strategy to sustain consistent force outputs (Falla and Farina, 2008a). Intra-muscular
37 coordination of the upper trapezius has been widely investigated, since this muscle is
38 commonly implicated in the development of musculoskeletal pain and fatigue syndromes
39 (Falla et al., 2017, Samani et al., 2017).

40 Excitation of nociceptors within the upper trapezius muscle via injection of
41 hypertonic saline, has been shown to shift the barycentre of muscle activity caudally (Falla et
42 al., 2009, Falla et al., 2017, Madeleine et al., 2006, Dideriksen et al., 2016). Whether motor
43 adaptations to a noxious stimulus is specific to the site of nociception remains unclear (Falla
44 et al., 2009, Gallina et al., 2018, Hug et al., 2013). For instance, a caudal shift in barycentre
45 of upper trapezius activity occurred regardless of the site of nociception within the muscle
46 (Falla et al., 2009, Dideriksen et al., 2016). At the vastus medialis, the region with the
47 greatest reduction in EMG amplitude was at the site of nociception (Gallina et al., 2018);
48 whereas Hug et al. (Hug et al., 2013) reported that the reduction in discharge rate of soleus
49 motor units was greatest in the region of nociception, but this was not observed in all
50 participants. It is evident from the topographical EMG amplitude maps of the two studies
51 (Falla et al., 2009, Gallina et al., 2018), that different sites of nociception could change the
52 spatial distribution of muscle activity differently. For example, a cranial injection to the upper

53 trapezius appear to reduce cranial muscle activity only, whilst a caudal injection to the same
54 muscle appear to reduce muscle activity (albeit non-symmetrically) in both the cranial and
55 caudal muscle regions (Falla et al., 2009).

56 Inconsistency in defining the nature of motor adaptations relative to the site of
57 noxious stimulation could be due to a myriad number of plausible surface EMG spatial
58 distribution patterns bringing about similar shifts in the barycentre. The sensitivity of
59 inferring a complex spatial EMG distribution from its barycentre may also depend on the
60 physical dimension and number of channels within the electrode grid. To understand the
61 spatial distribution of EMG amplitude driving a change in the position of the barycentre,
62 researchers have qualitatively drawn on observations from topographical EMG amplitude
63 maps.

64 It is also unclear if the effect of nociception on the spatial distribution within the upper
65 trapezius remains consistent during a repetitive dynamic task. Experimental pain induced a
66 caudal shift in the barycentre of the upper trapezius during an isometric contraction, and this
67 caudal shift persisted for the entire duration of the contraction (60 to 90s) (Falla et al., 2009,
68 Madeleine et al., 2006). Although Falla et al. (Falla et al., 2017) collected EMG data over 50
69 lifting repetitions, the authors did not investigate whether adaptations of the upper trapezius
70 during nociceptor excitation changed across repetitions of this dynamic motor task. However,
71 there is evidence from a pain-free cohort that repetitive dynamic movements resulted in a
72 significant lateral shift of the upper trapezius's barycentre of activity (Samani et al., 2017).
73 Knowing if motor adaptations to nociception is magnified or reduced by repeated
74 performance is fundamental towards understanding the mechanisms related to the
75 development of work-related neck-shoulder disorders.

76 HDsEMG data has a spatial component due to the two-dimensional coordinate system of
77 the electrode grid. Since muscle activity is assessed across time, there is also a temporal
78 component (Falla et al., 2017, Madeleine et al., 2006). Spatio-temporal HDsEMG has always
79 been summarized into discrete metrics, such as the barycentre. In the present study, a discrete
80 variable is one which has only magnitude and no space/time information. Although analysing
81 spatio-temporal data in a discrete form does not provide a comprehensive understanding of
82 physiological mechanisms, an advantage is that it allows for simpler statistical inference
83 methods (e.g. Analysis of Variance [ANOVA]). However, performing statistical inference on
84 discrete HDsEMG data is not without problems. As the number of repeated tests increases,
85 either the inflation of the familywise Type I error rate gets severely inflated when no efforts
86 are made to control the familywise error rate, or the statistical power diminishes when an
87 attempt is made to control the familywise error rate.

88 In the present study, Bayesian spatio-temporal ANOVA (Wang et al., 2018, Yu et al.,
89 2018) was used to perform a secondary analysis on previously published data investigating
90 the influence of experimentally induced upper trapezius muscle pain on spatio-temporal
91 activity of the upper trapezius during a repeated lifting task (Falla et al., 2017). The aim of
92 the present study was to quantify the spatial distribution of upper trapezius activity that
93 accounts for the reported shifts in its barycentre of activity under nociception (Falla et al.,
94 2017). Three hypotheses are proposed: First, hypertonic saline injection to the cranial portion
95 of the upper trapezius would only reduce muscle activity in the cranial region of the muscle
96 (Falla et al., 2009). Second, the reduction in cranial muscle activity after hypertonic saline
97 injection would be symmetrical in the medial-lateral direction (Falla et al., 2017). Third,
98 hypertonic saline injection would reduce the activity of the lateral portion of the upper
99 trapezius more during the early than later phase of lifting (Samani et al., 2017) - findings not
100 observed in the original study (Falla et al., 2017).

101 **2. Methods**

102 2.1. Design, participants, task

103 This was a secondary analysis of a previously published study, where full details of the
104 experimental procedures have been previously reported (Falla et al., 2017). The study was
105 approved by the local Ethics Committee (#200538), conducted according to the Declaration
106 of Helsinki and all participants provided written informed consent prior to their study
107 inclusion. Ten healthy male volunteers with a mean (standard deviation [sd]) age, height and
108 weight of 26.2 (3.1) years old, 1.78 (0.06) m, and 71.3 (9.2) kg, respectively, participated and
109 all participants completed the study.

110 Participants attended a single laboratory session and were required to lift a 1 kg box
111 between shelves positioned at hip and shoulder height, with a cycle time of 3 s for 50 cycles.
112 An acoustic signal from a digital metronome was provided to the subjects during the task to
113 standardize the duration of cycles. Subjects repeated the task four times: (1) baseline no
114 injection, (2) isotonic saline (0.9%) injection to the cranial portion of right upper trapezius,
115 (3) hypertonic saline (5.8%) injection to the same portion of the upper trapezius, and (4)
116 recovery (15 mins post hypertonic injection). The order of conditions was not randomized.
117 The rest interval between the repetitions was set to 15 minutes starting from the moment
118 when the pain caused by the injections disappeared. Subjects practiced the movement
119 sequence for ~1 min without the weight prior to data recording.

120 The experimental muscle pain was induced by injection (27G cannula) of 0.4 ml sterile
121 hypertonic saline (5.8%) into the upper division of the trapezius on the right side with the
122 subject seated. Isotonic saline (0.4 ml, 0.9 %) was used as a control injection in a similar
123 location. The location of the injection was defined as 15 mm cranial to the line between the
124 acromion and the spinous process of the seventh cervical vertebra. The bolus was injected

125 over a 10-s period. The isotonic saline injection was given first however participants were
126 blinded to each injection and were told that one or both might be painful.

127 2.2. HDsEMG

128 HDsEMG signals were recorded from the right upper trapezius using a 64-electrode
129 adhesive electrode grid (ELSCH64NM3, OT Bioelettronica, Torino, Italy) (Figure 1). The 64
130 electrodes were arranged in a 13 row by 5 column grid (1mm diameter, 8mm inter-electrode
131 distance), with an absent electrode in the upper right corner. The electrode grid was placed
132 with the fourth row along the line between the lateral edge of the acromion and C7, with the
133 lateral column 10 mm distant from the innervation zone (Falla et al., 2017). The injections
134 were performed lateral to the electrode grid (~ 10 mm) and corresponded to the 4th row of
135 the grid.

136 EMG signals were amplified 2000 times and sampled at 2048 Hz (EMGUSB2, OT
137 Bioelettronica, Torino, Italy). Four accelerometers were positioned on the box and the four
138 signals were averaged to produce a single signal, which was subsequently rectified and
139 filtered (low pass, 2nd order Butterworth at 10 Hz). A 50m/s² threshold on the filtered
140 accelerometer signal was used to identify the contact instants of the box with each of the 2
141 shelves, to obtain the beginning and end time points of a lifting repetition.

142 2.3. Signal processing

143 HDsEMG signals were filtered with a 2nd order Butterworth band-pass filter (10 – 400Hz).
144 Each lift cycle was discretized into ten 10% time epochs. Single differential channels were
145 extracted from each pair of electrodes in the horizontal direction, resulting in a 13 x 4 grid of
146 51 bipolar channels, with one missing channel on the upper right corner. The single
147 differential method was used to reduce the non-propagating components such as end of fibre
148 effects, which is a common procedure in surface EMG processing. RMS values from each

149 differential channel were calculated for each 10% epoch. This produced a 10 x 51 (time by
 150 channels) matrix of RMS values for each participant, condition, and each lifting repetition.
 151 Twelve participant-condition combinations had less than 50 repetitions of HDsEMG data,
 152 due to significant signal artefacts present within the accelerometer signals, precluding the
 153 identification of a lifting repetition. The minimum number of lifting repetitions available was
 154 39. Thirty-eight available repetitions were used from each participant and condition to allow
 155 pairwise difference in EMG signals to be computed (see below). Lifting repetitions were
 156 dichotomized into “early phase” (first 19 available repetitions) and “later phase” (second 19
 157 available repetitions).

158 2.4. Outcome variables

159 There were six outcome variables, with the first three being:

$$\Delta EMG_{i=1,2,3}^{early} = EMG_{hypertonic} - EMG_{baseline,isotonic,recovery} \quad (1)$$

160 where $\Delta EMG_{i=1}^{early}$, $\Delta EMG_{i=2}^{early}$, $\Delta EMG_{i=3}^{early}$ represented the difference in the 10x51 matrix
 161 values of EMG RMS (μV) at each epoch between hypertonic saline injection vs baseline,
 162 hypertonic vs isotonic injections, and hypertonic injection vs recovery during the early lift
 163 phase, respectively. A negative $\Delta EMG_{i=1,2,3}^{early}$ indicated a reduction in EMG amplitude with the
 164 hypertonic saline injection, relative to its comparator. The other three outcomes were:

$$\Delta EMG_{phase}^{i=1,2,3} = \Delta EMG_{later}^{i=1,2,3} - \Delta EMG_{early}^{i=1,2,3} \quad (2)$$

165 where $\Delta EMG_{phase}^{i=1,2,3}$ represented the difference in the 10x51 matrix values of EMG RMS
 166 (μV) at each epoch between the later and early phase of lifting. If $\Delta EMG_{early}^{i=1,2,3}$ is negative,
 167 than a positive $\Delta EMG_{phase}^{i=1,2,3}$ indicates a greater reduction in EMG amplitude in the early than
 168 later phase.

169 2.5. Statistical inference

170 A two-way mixed-effects spatio-temporal ANOVA model with a random subject-intercept
171 of the form was fitted,

$$y_i = \eta(x_i) + b_{g_i} + e_i \text{ for } i = 1, \dots, n \quad (3)$$

172 where n is the total number of data points for all participant-condition combinations after
173 converting the data into a column vector, y_i is the ΔEMG in equations (1) and (2), $x_i =$
174 (t_i, s_i) is the fixed effect of lifting cycle (t_i) and spatial location of the electrode grid (s_i), g_i
175 is the subject indicator, b_{g_i} is the random effect such that $b_{g_i} \sim^{iid} N(0, \delta)$ with $\delta > 0$, and
176 $e_i \sim^{iid} N(0, \sigma^2)$ is the random error. t_i represents the 10 epochs of the lifting cycle, whilst s_i
177 represents the 51 bipolar channels. The predictor η can be further decomposed into main and
178 interaction effects as follows:

$$\eta(x_i) = \eta_1(t_i) + \eta_2(s_i) + \eta_{12}(t_i, s_i) \quad (4)$$

179 where η_1 is the main temporal effect of lifting cycle, η_2 is the main spatial effect of
180 electrode grid location, and η_{12} is the spatio-temporal interaction effect. We fitted model (3)
181 under a fully Bayesian framework. For the η_1 main temporal effect, a first order
182 autoregressive (AR1) prior was used (Wang et al., 2018). For the spatial effect η_2 , a
183 stochastic partial differential equation (SPDE) spatial prior was used. For the interaction
184 effect η_{12} , a separable spatio-temporal prior was used (Cameletti et al., 2013).

185 The resulting Bayesian mixed model can be efficiently estimated using integrated nested
186 Laplace approximations (INLA) (Wang et al., 2018). INLA provides accurate approximated
187 posterior distributions of all parameters (e.g. β coefficients) given the data, needed to make
188 fully Bayesian inference (i.e. posterior mean with credible intervals [CrI]). The technical
189 details of INLA can be found in the supplementary material. For the main and interaction

190 effects, we calculated the posterior joint probabilities for a change in any EMG channel
191 across the electrode grid to produce a topographical map of probabilities (Bolin and
192 Lindgren, 2015). The probability map provides useful visualization of the certainty of where
193 and when any EMG amplitude changes occur. To quantify the magnitude of EMG changes
194 on all spatial locations and across the lifting cycles, and to determine if these changes were
195 significant, the mean and 95% CrI was calculated. Significant changes were defined within a
196 Bayesian framework, by a non-zero crossing of the 95% CrI. We provide the data, code, and
197 results in a public repository (Liew et al., 2018).

198 **3. Results**

199 3.1. Comparing pairwise injection conditions during early lift phase

200 3.1.1. Main and interaction effects

201 There were significant spatial main and spatial-temporal interaction effects in EMG
202 changes. To clarify, a spatial main effect is the influence of different EMG channel locations
203 on EMG values (independent of lifting cycle); temporal main effect is the influence of
204 different lifting cycles on EMG values (independent of channel location); and spatio-
205 temporal interaction is the influence of different EMG channel locations at each lifting cycle
206 on the EMG values. At the spatial main effect level, there was a > 0.95 probability that EMG
207 changes were present between hypertonic saline injection and isotonic saline injection, and
208 recovery conditions largely in the cranial half of the electrode grid (Fig. 2). At the interaction
209 level, the period with the greatest number of spatial locations with > 0.95 probability of EMG
210 changes was at 30% lift cycle between hypertonic injection-baseline conditions, 30% lift
211 cycle between hypertonic-isotonic saline injections, and 30% between hypertonic injection-
212 recovery conditions (Fig. 3).

213 3.1.2. *Effect size of EMG RMS change (μV)*

214 The maximal decrease in EMG RMS within the electrode grid after hypertonic saline
215 injection was $-38.1\mu\text{V}$ [95% CrI -40.9 to -35.3] at 30% lift cycle when compared to baseline
216 (Fig. 4). The maximal decrease in EMG RMS within the electrode grid after hypertonic saline
217 injection was $-28.8\mu\text{V}$ [95% CrI -31.4 to -26.2] at 30% lift cycle when compared to recovery
218 (Fig. 4). The maximal increase in EMG RMS within the electrode grid after hypertonic saline
219 injection was $6.7\mu\text{V}$ [95% CrI 4.1 to -9.3] at 80% of the lift cycle and this was compared to
220 the recovery condition (Fig. 4).

221 3.2. *Influence of lift phase on the effects of hypertonic injection*

222 3.2.1. *Main and interaction effects*

223 There were significant spatial main and spatial-temporal interaction effects in EMG
224 changes between lifting phases. At the spatial main effect level, there was a > 0.95
225 probability that the effects of hypertonic saline injection changed between the early and later
226 lifting phases, independent of lifting cycle (Fig. 5). At the interaction level, the period with
227 the greatest number of spatial locations with > 0.95 probability of EMG changes happening
228 between lifting phases was at 80% lift cycle between hypertonic injection-baseline
229 conditions, 80% lift cycle between hypertonic-isotonic saline injections, and 40% lift cycle
230 between hypertonic injection-recovery conditions (Fig. 6).

231 3.2.2. *Effect size of EMG RMS change (μV)*

232 The reduction in EMG activity with hypertonic saline injection was predominantly greater
233 during the early than in the later lifting phase, although there were some spatial locations
234 where the reduction was less in the early than later lifting phase (Fig. 7). The maximal
235 difference in EMG RMS reduction within the electrode grid during the early phase after
236 hypertonic saline injection was $10.4\mu\text{V}$ [95% CrI 8.2 to 12.6] more than the later phase at

237 80% lift cycle when compared to baseline; and by $5.8\mu\text{V}$ [95% CrI 3.6 to 8.0] more than the
238 later phase at 20% lift cycle when compared to recovery (Fig. 7).

239 **4. Discussion**

240 The main aim of the present study was to quantify the spatial distribution of upper
241 trapezius activity under nociception that accounts for the reported shifts in its barycentre of
242 activity. The Bayesian spatio-temporal ANOVA method used presently revealed three new
243 findings which partially supported our hypotheses. First, an acute noxious stimulus to the
244 cranial upper trapezius reduced muscle activity within the same muscle region, and slightly
245 increased activity in the caudal-most portion of the muscle. Second, there was a greater
246 reduction of muscle activity detected on the medial compared to the lateral part of the
247 recording surface during acute nociception. Third, differences in the effects of acute
248 nociception between lifting phases predominantly lay in the cranial-caudal axis, rather than in
249 the medial-lateral axis.

250 The present study provides evidence that the intra-muscular adaptation to acute
251 nociception may be specific to the site of nociceptive stimulus (Gallina et al., 2018). Such an
252 adaptation may be aimed at mechanically unloading the painful muscle region (Gallina et al.,
253 2018). Location specific responses to acute nociception was observed in a previous study
254 (Gallina et al., 2018), but not others (Dideriksen et al., 2016, Falla et al., 2009). Dideriksen et
255 al. (Dideriksen et al., 2016) reported that the regional discharge rate of motor units of the
256 upper trapezius was similar regardless of nociception site. Dideriksen et al. (Dideriksen et al.,
257 2016) identified cranial motor units from the cranial six rows of the electrode grid, whilst
258 caudal motor units were identified from the caudal six rows. The smaller the spatial
259 separation of the motor units' sources, the more homogeneous will be their behaviour (Falla
260 et al., 2017). However, the spatial correlation between extracted motor units were not

261 considered during statistical inference, which may negatively influence the statistical model's
262 validity (Dideriksen et al., 2016).

263 This is the first study to quantify the influence of acute nociception on the instantaneous
264 spatial activity change of the upper trapezius. The periods of greatest reduction in amplitude
265 of the cranial region of the upper trapezius during acute nociception lay within periods when
266 the cranial region was most active (20% to 70% of lifting cycle). This may be an optimal
267 motor strategy to unload painful tissues as this represents a phase within the lifting cycle
268 when mechanical load on the muscle would be greatest. The influence of acute nociception
269 on a muscle's spatial distribution of activity appears to differ between dynamic and isometric
270 contractions. Sustained isometric contraction results in greater activity within the cranial
271 region of the upper trapezius (Madeleine et al., 2006, Falla et al., 2008). This increase in
272 muscle activity may augment tissue loading to the cranial region of the muscle. To reduce
273 pain associated with hypertonic saline injection, more activity should be reduced in the
274 cranial region of the upper trapezius as the contraction duration increases to mechanically
275 unload this region. This would mean observing a greater caudal shift in the upper trapezius
276 barycentre as isometric contraction duration increases in the presence of nociception. Instead,
277 previous studies observe that that caudal shift in the upper trapezius's barycentre remains
278 constant regardless of isometric contraction duration (Madeleine et al., 2006, Falla et al.,
279 2008).

280 The mechanisms explaining why nociception reduced muscle activity more when there
281 was higher versus lower baseline amplitude is unclear. It may be that pain intensity was
282 greatest between 20% to 70% of the lifting cycle, resulting in greater inhibition on the
283 motoneuron pool (Farina et al., 2004). However, subjective pain recordings within a
284 movement cycle in a repetitive dynamic task are difficult to collect. Alternatively, the
285 inhibition to the recruited motoneurons of the upper trapezius may remain invariant, but the

286 central excitability to the motorneurons may depend on the shoulder elevation angle. The
287 relationship between central excitability of a muscle and shoulder elevation angles, has been
288 shown for the infraspinatus (Lin et al., 2015), but not for the upper trapezius.

289 The medial-lateral coordinate of the upper trapezius's barycentre was reported to remain
290 invariant with acute nociception (Falla et al., 2017, Madeleine et al., 2006, Dideriksen et al.,
291 2016). The barycentre approach decomposes the shift in the centroid of muscle activity along
292 two Cardinal axes within the plane of the electrode grid. The present study observed greater
293 medial than lateral reductions of the EMG amplitude in the cranial two thirds of the upper
294 trapezius with acute nociception. This means that the shift in the centroid of muscle activity
295 under nociception would be caudal-laterally rather than purely within the longitudinal axis of
296 the grid.

297 The reductive effect of acute nociception on muscle activity was greater in the early, than
298 later lifting phases, which was most apparent in the cranial upper trapezius. Based on the
299 mechanical unloading hypothesis (Gallina et al., 2018), additional muscle activity to sustain
300 lifting ought to be recruited from the caudal upper trapezius, which has no noxious stimulus
301 induced. It appears that compensatory motor adaptations associated with repetitive task
302 performance and pain are competing in dynamic motor tasks. Speculatively, the caudal upper
303 trapezius may receive more inhibitory afferent input, due to the accumulation of local
304 extracellular potassium ions associated with prolonged contractions (Falla and Farina,
305 2008b). In addition, pain was decreasing from its maximum intensity in the later lifting phase
306 (Falla et al., 2017). Given the greater nociceptive afferent distribution to the cranial than
307 caudal region (Dideriksen et al., 2016), the reduction in pain intensity may preferentially
308 reduce the inhibitory afferent input to the former compared to the latter region of the upper
309 trapezius. It is unknown if compensatory neuromuscular adaptations associated with

310 repetitive task performance (including fatigue) and pain are competing in dynamic motor
311 tasks in clinical pain conditions.

312 This current work has several limitations. First, it was previously reported that acute
313 nociception resulted in a similar caudal shift of the barycentre of upper trapezius activity
314 between genders (Falla et al., 2008). Instead, the difference between genders lie in the
315 interaction between nociceptive stimulation and fatigue, on the neuromuscular adaption of the
316 upper trapezius (Falla et al., 2008). Given that only male participants were presently
317 investigated, the influence of task repetition on the intramuscular adaptations observed with
318 acute nociception should be generalized to female participants with caution.

319 Second, an injection was performed at a single location only in the present study. This
320 limits the ability to conclude if intramuscular adaptations to nociception are dependent on the
321 site of noxious stimulation within the upper trapezius. Nevertheless, the present study
322 provides a specific intramuscular “signature” of how the upper trapezius activity shifts
323 caudally relative to a specific site of nociception. Such knowledge, and indeed the proposed
324 statistical method, is essential for future study designs where multiple sites of injection are
325 used to investigate a muscle’s response to the site of nociceptive activity.

326 Third, changes in EMG amplitudes during dynamic contractions could be attributed to
327 alterations in muscle geometry (Farina et al., 2001). The influence of altered muscle
328 geometry on EMG activation cannot be eliminated but may be mitigated by averaging the
329 EMG signals across lifting cycles (Farina et al., 2001). By including subject-level random
330 effects into our statistical models, we simultaneously performed two procedures: (1)
331 estimating a weighted average effect of acute nociception on EMG alterations per participant,
332 and (2) using each participant’s weighted average effect to estimate the overall group-level
333 effect of acute nociception on the muscle’s activity.

334 5. Conclusions

335 Motor adaptations to acute nociception appears to be region-specific in the upper
336 trapezius, with a greater medial than lateral reduction in muscle activity. There also appears
337 to be competing motor adaptations induced by nociception and repetitive task performance.
338 Hence, mechanical unloading of painful tissues does not solely drive the motor adaptations
339 observed with acute nociception during low-load lifting. The methods used in the present
340 study provides a robust statistical inference method for spatio-temporal data, allowing a
341 richer mechanistic insight into the motor adaptations that occur in response to pain

342 **Acknowledgements**

343 None

344

345

346

Appendix

347 **Integrated nested Laplace approximation (INLA) method**

348 Rue et al. (Rue et al., 2009) developed INLA for approximate Bayesian inference as an
 349 alternative to traditional Markov chain Monte Carlo methods. The INLA framework can
 350 be briefly described as follows. First of all, $\mathbf{y} = (y_1, \dots, y_n)$ is a vector of observed
 351 variables and the mean μ_i (for observation y_i) is linked to the linear predictor η_i . The
 352 linear predictor can include terms such as fixed effect covariates and different types of
 353 random effects (e.g. spatial or temporal correlated effects, random intercepts, smoothing
 354 splines etc.). The vector of all latent effects will be denoted by \mathbf{x} , and it includes the linear
 355 predictor and the various random effects previously mentioned. In addition, the
 356 distribution of \mathbf{y} will depend on some vector of hyperparameters θ_1 .

357 The distribution of the vector of latent effects \mathbf{x} is assumed to be Gaussian Markov random
 358 field (GMRF). This GMRF will have a zero mean and precision matrix $\mathbf{Q}(\theta_2)$ (inverse of
 359 covariance matrix), with θ_2 a vector of hyperparameters. The vector of all hyperparameters
 360 in the model will be denoted by $\theta = (\theta_1, \theta_2)$.

361

362 The aim of the INLA methodology is to approximate the posterior marginals of the model
 363 effects (\mathbf{x}) and hyperparameters (θ). This is achieved by exploiting the computational
 364 properties of GMRF and the Laplace approximation for multidimensional integration.

365

366 The joint posterior distribution of the effects and hyperparameters can be expressed as:

$$\begin{aligned} \pi(\mathbf{x}, \theta | \mathbf{y}) &\propto \pi(\theta) \pi(\mathbf{x} | \theta) \prod_{i \in I} \pi(y_i | x_i, \theta) \\ &\propto \pi(\theta) |\mathbf{Q}(\theta)|^{\frac{1}{2}} \exp \left\{ -\frac{1}{2} \mathbf{x}^T \mathbf{Q}(\theta) \mathbf{x} + \sum_{i=1}^{n_y} \log(\pi(y_i | x_i, \theta)) \right\} \end{aligned}$$

367

368 Notation has been simplified by using $\mathbf{Q}(\theta)$ to represent the precision matrix of the latent
 369 effects. Also, $|\mathbf{Q}(\theta)|$ denotes the determinant of that precision matrix. n_y denotes the vector
 370 of values of the response variable.

371

372 The computation of the marginal distributions for the latent effects and hyperparameters
 373 can be done considering that

$$\pi(x_i | \mathbf{y}) = \int \pi(x_i | \theta, \mathbf{y}) \pi(\theta | \mathbf{y}) d\theta$$

374 and

$$\pi(\theta_j | \mathbf{y}) = \int \pi(\theta | \mathbf{y}) d\theta_{-j}$$

375 Note how in both expressions integration is done over the space of the hyperparameters
 376 and that a good approximation to the joint posterior distribution of the hyperparameters is
 377 required.

378 To approximate $\pi(\theta | \mathbf{y})$, we use the Laplace approximation:

$$\tilde{\pi}(\theta|\mathbf{y}) \propto \frac{\pi(\mathbf{x}, \theta | \mathbf{y})}{\tilde{\pi}_G(\mathbf{x}|\theta, \mathbf{y})} \Big|_{x=x^*(\theta)}$$

379 Where $\tilde{\pi}_G(\theta|\mathbf{y})$ is the Gaussian approximation to $\pi(\theta|\mathbf{y})$, and $x^*(\theta)$ is the mode of \mathbf{x} for
 380 a given configuration of θ .

381 Rue et al. (Rue et al., 2009) approximate $\pi(\mathbf{x}|\mathbf{y})$ using:

$$\tilde{\pi}(x_i|\mathbf{y}) = \sum_k \tilde{\pi}(x_i|\theta_k, \mathbf{y}) \times \tilde{\pi}(\theta_k|\mathbf{y}) \times \Delta_k$$

382 Here, Δ_k are the weights associated with a vector of values θ_k of the hyperparameters in a
 383 grid.

384 The approximation $\tilde{\pi}(\theta_k|\mathbf{y})$ can take different forms and be computed in different
 385 ways. Rue et al. (Rue et al., 2009) discuss how this approximation should be in order to
 386 reduce the numerical error.

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