

The effect of experimental low back pain on lumbar muscle activity in people with a history of clinical low back pain - a muscle functional MRI study

Running head: Experimental LBP during remission of recurrent LBP

Danneels Lieven, Cagnie Barbara¹, D'hooge Roseline¹, De Deene Yves², Crombez Geert³,
Vanderstraeten Guy^{1,4}, Parlevliet Thierry⁵, Van Oosterwijck Jessica¹

¹ Department of Rehabilitation Sciences and Physiotherapy, Ghent University, Campus Heymans, De Pintelaan 185, B-9000 Ghent, Belgium

² Department of Radiotherapy and Experimental Cancer Research, Ghent University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium

³ Department of Experimental Clinical and Health Psychology, Ghent University, Henri Dunantlaan 2, B-9000 Ghent, Belgium

⁴ Department of Physical and Rehabilitation Medicine, Ghent University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium

⁵ Department of Physical Medicine and Orthopedic Surgery, Ghent University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium

Correspondence and reprint requests to Prof. Lieven Danneels, Ghent University Hospital, Dept. of Rehabilitation Sciences and Physical Therapy, De Pintelaan 185, 1B3, B-9000 Ghent, Belgium. Tel: +32 9 332 26 32, Fax: +32 9 332 38 11, E-mail: Lieven.Danneels@Ugent.be

1 ABSTRACT

2 In people with a history of low back pain (LBP), structural and functional alterations have
3 been observed at several peripheral and central levels of the sensorimotor pathway. These
4 existing alterations might interact with the way the sensorimotor system responds to pain. We
5 examined this assumption by evaluating the lumbar motor responses to experimental
6 nociceptive input of 15 participants during remission of unilateral recurrent LBP. Quantitative
7 T2-images (muscle functional MRI) were taken bilaterally of multifidus, erector spinae and
8 psoas at several segmental levels (L3 upper, L4 upper and lower endplate) and during several
9 conditions: 1) at rest, 2) upon trunk-extension exercise without pain, and 3) upon trunk-
10 extension exercise with experimental induced pain at the clinical pain-side (1.5ml
11 intramuscular hypertonic saline injections in erector spinae). Following experimental pain
12 induction, muscle activity levels similarly reduced for all 3 muscles, on both painful and non-
13 painful sides, and at multiple segmental levels ($p=0.038$). Pain intensity and localization from
14 experimental LBP were similar as during recalled clinical LBP episodes. In conclusion,
15 unilateral and unisegmental experimental LBP exerts a generalized and widespread decrease
16 in lumbar muscle activity during remission of recurrent LBP. This muscle response, is
17 consistent with previous observed patterns in healthy people subjected to the same
18 experimental pain paradigm. It is striking that similar inhibitory patterns in response to pain
19 could be observed, despite the presence of pre-existing alterations in the lumbar musculature
20 during remission of recurrent LBP. These results suggest that motor output can modify along
21 the course of recurrent LBP.

22 **Key words:** recurrent low back pain; experimental muscle pain; muscle functional magnetic
23 resonance imaging; lumbar paraspinal muscles; muscle recruitment

24 INTRODUCTION

25 Low back pain (LBP) is related to substantial reorganization of motor control strategies which
26 are assumed to protect from further injury or pain (Hodges et al. 2003, 2011). It is believed
27 that these motor alterations can persist after resolution of a LBP episode (Hides et al. 1996;
28 Hodges et al. 2011; Macdonald et al. 2009). Long-term persistence of altered recruitment
29 strategies has been hypothesized to have negative consequences for spinal health through
30 suboptimal load sharing, reduced spinal movement and/or reduced variability in muscle
31 recruitment strategies (Hodges et al. 2011). Therefore, further insight in the causal role of
32 LBP in relation to lumbar muscle dysfunction is important to administer appropriate
33 rehabilitation and prevent recurrence of LBP.

34

35 Experimental pain models have been applied to study the causal effect of peripheral
36 nociception on motor output (Graven-Nielsen et al. 2000, 2006). Previous studies have
37 demonstrated altered muscle behavior during experimental LBP in healthy people (Arendt-
38 Nielsen et al. 1996; Dickx et al. 2008, 2010; Hodges, et al. 2003; Kiesel et al. 2008; Zedka et
39 al. 1999), and its effects were also shown to be comparable to findings observed in clinical
40 LBP (Graven-Nielsen 2006). However, changes in motor output in relation to clinical LBP
41 not only depend upon peripheral nociceptive stimuli, but are the net resultant of a complex
42 interaction at multiple levels along the sensory, central and motor nervous system (Hodges et
43 al. 2003, 2011).

44 People with a history of clinical recurrent LBP have demonstrated several structural and
45 functional alterations which are situated at multiple peripheral and central levels along the
46 sensorimotor pathway. Compared to healthy controls, divergences in motor output during a
47 variety of lumbar tasks (D'Hooge et al. 2013; Jones et al. 2012; Macdonald et al. 2009, 2010

48 2011) and in lumbar muscle structure (D'Hooze et al. 2012; Hides et al. 1996) were present
49 subsequent to resolution of LBP. In addition, the cortical representation of specific lumbar
50 muscles appeared to be reorganized (Tsao et al. 2011), and changes at the proprioceptive level
51 (Brumagne et al. 2000) have been described, during remission of LBP. Applying an
52 experimental pain paradigm during remission of clinical LBP offers the possibility to
53 investigate whether and how existing alterations related to clinical LBP interact with muscle
54 behavior in response to acute pain.

55
56 To determine if people who have had clinical pain before respond to acute pain in the same
57 manner as healthy people, an established experimental low-back-pain paradigm will be
58 replicated in a participant sample with a history of clinical low back pain. Previously, lumbar
59 muscle activity has been investigated using muscle functional Magnetic Resonance Imaging
60 (mfMRI) in healthy people with and without experimental induced LBP (Dickx et al. 2008).
61 MfMRI is an innovative, post-exercise, evaluation method to assess the amount of metabolic
62 muscle activity by quantifying shifts in T2-relaxation times of muscle water upon exercise
63 (Cagnie et al. 2011; Meyer and Prior 2000). Published results in healthy people showed that
64 muscle activity during trunk-extension significantly decreased in multifidus (MF), erector
65 spinae (ES) and psoas (PS) at both body sides and multiple segmental levels, in response to
66 unilateral and unisegmental experimental pain (Dickx et al. 2008). The same study set-up, has
67 been used to demonstrate pre-existing dysfunctions in people in remission of recurrent LBP.
68 Specifically, this population showed increased MF activity during trunk-extension on both
69 body sides and at multiple levels compared to healthy controls, while no changes were evident
70 in ES or PS activity (D'Hooze et al. 2013).

71 Therefore, the aim of the current study was to investigate lumbar motor responses to
72 experimental nociceptive input in people with a pre-existing condition of the sensorimotor
73 system due to a previous clinical history of recurrent LBP.

74

75 MATERIALS AND METHODS

76 *Participants*

77 Fifteen people (6 males, 9 females) with a history of unilateral, non-specific, recurrent LBP
78 and aged between 20 and 55 years were recruited via advertisement from the local community
79 and university setting. Volunteers were included when having at least 2 previous LBP
80 episodes that interfered with daily functioning and/or required treatment (first onset LBP at
81 least 6 months before) of which at least 2 episodes took place in the past 12 months (Stanton
82 et al. 2010). An episode was defined as pain lasting for minimum 24 hours, preceded and
83 followed by at least 1 month without LBP (de Vet et al. 2002). Testing was scheduled at least
84 1 month after resolution of the last LBP episode. The characteristics of participants their LBP
85 history including duration since first onset of LBP (months), frequency of episodes per year,
86 mean duration of an episode (days), mean duration of the last experienced episode (days),
87 pain intensity (pain NRS 0-100), and disability during episodes (disability NRS 0-100), and
88 time since last episode (days) were determined using a custom-designed questionnaire and the
89 results are reported in Table 1.

90 Exclusion criteria were central, bilateral or side-variable localization of LBP; specific LBP;
91 participation in lumbar motor control training in the previous year; spine surgery; spinal
92 deformities; task-limiting medical conditions or contra-indications for MRI
93 (ferromagnetic/electronic implants that could be moved/affected by a magnetic field e.g.
94 pacemaker, aneurysm clip, etc.; claustrophobia; (possible) pregnancy).

95 All participants were informed of the study procedures, approved by the local Ethics
96 Committee, and provided written informed consent. The findings from this study sample have
97 not been published previously.

98

99 *General experimental design*

100 MRI-images were obtained under 3 consecutive conditions (Dickx et al. 2008): 1) at rest (T2-
101 rest) after 30min of supine lying, 2) immediately following exercise without pain (T2-
102 exercise), and 3) immediately following exercise performed with experimental pain (T2-
103 exercise+pain). Between the second and third condition, participants rested supine for 60min
104 to regain the resting metabolic state of the muscles (Cagnie et al. 2011).

105

106 *Exercise protocol*

107 Ten consecutive repetitions of a low-load, static-dynamic trunk extension were performed.
108 Participants were positioned prone on a variable angle chair in 45° of trunk flexion, with their
109 hands placed on the ipsilateral shoulders. One repetition consisted of extending the trunk in
110 line with the legs to a horizontal position (2sec), maintain the trunk horizontally (5sec), and
111 then lowering the trunk again (2sec) to the starting position. The exercise load was
112 individually adjusted to 40% of 1-RM (one repetition maximum). Because the calculated
113 weight of the exercise load was lower than the weight of the trunk, the body was assisted via a
114 load-pulley system. Details of the exercise protocol and methods for calculating the individual
115 exercise load are identical as described in previous studies (D'Hooge et al. 2013; Dickx et al.
116 2008, 2010). The individual 1-RM was indirectly determined, as described in those studies,
117 on a separate day which took place at least 7 days prior to the experiment.

118

119

120 *Muscle functional MRI*

121 MfMRI has been validated and proven complementary to surface-electromyography (EMG)
122 for assessing the amount of lumbar muscle activity during trunk-extension (Dickx et al.
123 2010). A 3-Tesla MRI-scanner (Magnetom Trio-Tim, Syngo MR VB13 software, SIEMENS
124 AG®, Erlangen Germany) was used for imaging. Participants laid supine, with a foam wedge
125 supporting the legs and ensuring a neutral spinal curvature. A flexible 6-element body-matrix
126 coil, centered on L4 ventrally, was combined with the standard phased-array spine coil
127 dorsally as a receiver-coil combination.

128 Three axial slices were planned from a sagittal localizing sequence with respect to vertebral
129 inclination along the upper endplate of L3 and L4, and the lower endplate of L4 (Figure 1A).

130 The lumbar MF, ES and PS were visualized.

131 T2-weighted images were acquired with a spin-echo multi-contrast sequence (SE_MC) with
132 the following parameters: repetition time (TR) 1000ms, echo train of 16 echoes ranging from
133 10.1 to 161.6ms with steps of 10.10ms, acquisition matrix 256*176mm², field of view (FOV)
134 340mm, voxel size 1.3*1.3*5.0mm³, scan-time 5min52s.

135

136 *Experimental pain*

137 Acute experimental LBP was induced by injecting a bolus of 1.5ml of hypertonic saline (5%
138 NaCl) in the lumbar ES (4cm lateral from the L4 spinous process, at a depth of 2.5cm) (Dickx
139 et al. 2008) of that side of the body in which participants had reported their natural unilateral
140 clinical recurrent LBP to occur. Thirty seconds after pain induction, participants verbally
141 rated the pain intensity induced by the injection of hypertonic saline using a pain numeric
142 rating scale (NRS). Scores from this scale ranged from 0 (no pain) to 100 (worst possible

143 pain). If the subject reported a score below 40/100, an additional bolus of 0.5ml was injected.
144 During the exercise, pain intensity was monitored by asking participant an NRS rate 1) before
145 the 1st repetition, 2) after the 5th repetition and 3) after the 10th repetition of trunk extension.
146 Upon completion of the experiment, pain localization was indicated on a pain diagram.

147

148 *Psychological exercise measures*

149 To not influence participants their pain experience they were informed that the injection of
150 hypertonic saline would induce pain, but no information was given regarding the expected
151 severity or localization of the induced pain. As participants had performed the trunk extension
152 exercises during the pre-screening, in order to determine their individual 1-RM, they were
153 familiar with these exercises which were repeated on the day of the experiments. Nonetheless,
154 before each exercise condition, fear of exercise performance was rated on a NRS from 0 (not
155 fearful at all) to 100 (extremely fearful). Similarly, fear of needle/injection and fear of
156 experimental pain were rated prior to the saline injection (Dickx et al. 2008). After each
157 exercise condition, experienced pain intensity during exercise (NRS, 0-100) and perceived
158 exertion (RPE) (Borg-scale, 15-20) (Borg 1982) were rated. Additionally, participant rated the
159 perceived similarity between experimental LBP and natural clinical LBP on a NRS from -100
160 (not similar at all) to +100 (completely identical) with 0 representing similar.

161

162 *Data analysis*

163 Images were analyzed using ImageJ (v. 1.41o, Java-based version of the public domain NIH
164 Image Software, USA; Research Services Branch). For each of the 3 conditions and
165 segmental levels, a quantitative T2-map was calculated using the MRI analysis T2-calculator,
166 with a T2-value (ms) assigned to each voxel. The first of 16 echoes was excluded for reasons

167 of better curve fitting (De Deene et al. 2000). Regions of interests (ROI's) were traced on the
168 T2-maps along the muscular borders of MF, ES and PS bilaterally (Figure 1B), excluding
169 visual fat, blood vessels or connective tissue. For each ROI, the mean T2-value was
170 calculated. Image processing was performed blinded to condition and pain-side. Then, T2-
171 shifts were calculated as the difference between T2-exercise (with and without pain) and T2-
172 rest.

173

174 *Statistical analysis*

175 Analyses were performed using SPSS (v19, IBM Statistics). Descriptive statistics (means and
176 standard deviation [SD]) were calculated for the participants' characteristics and T2-values.
177 Paired samples t-tests were used to compare fear, RPE and pain intensity between the exercise
178 condition with and without pain, and between pain intensity experienced from experimental
179 pain and pain intensity recalled from natural recurrent LBP episodes.

180 A general linear model (GLM) with repeated measures was used to examine T2-results. To
181 investigate which muscles were activated during the trunk-extension exercise, the difference
182 between the T2-rest and T2-exercise was tested for each muscle separately (because of
183 interaction effect for 'condition*muscle': $p=0.004$) with within-subject factors 'condition'
184 (T2-rest, T2-exercise), 'level' (L3 upper, L4 upper, L4 lower) and 'side' (painful side, non-
185 painful side). To investigate the effect of experimental LBP on T2-shift, within-subjects
186 factors were 'condition' (T2-shift exercise, T2-shift exercise+pain), 'muscle' (MF, ES, PS),
187 'level' (L3 upper, L4 upper, L4 lower) and 'side' (painful side, non-painful side).

188 Moreover, pearson correlation coefficients were calculated to investigate whether the decrease
189 in muscle activity (delta T2-shift) in the pain condition correlated with increased fear (delta
190 fear of exercise performance) or with changes in pain intensity (delta pain intensity).

191 Post-hoc comparisons were made when required and were adjusted using Bonferroni-
192 correction. Statistical significance was accepted at $\alpha=0.05$.

193

194 RESULTS

195 Mean T2-values in rest, exercise-without-pain and exercise-with-pain condition are presented
196 in Table 2.

197

198 *Effect of trunk-extension on T2-values*

199 T2-values were significantly higher in the exercise condition (without pain) compared to the
200 resting condition for MF ($p<0.001$) and ES ($p=0.003$), but not for PS ($p=0.281$) (Figure 2).

201 There were no differences in T2-values between the previously painful and non-painful side
202 (main effect 'side': MF $p=0.541$; ES $p=0.466$; PS $p=0.738$). There were no interaction effects
203 for condition with 'level' or 'side' ($p>0.05$).

204

205 *Effect of experimental LBP on T2-shift*

206 T2-shift was significantly lower in the exercise-with-pain compared to the exercise-without-
207 pain condition for all muscles (main effect 'condition' $p=0.038$) (Figure 3). For both
208 conditions, T2-shift was significantly higher in MF compared to ES ($p=0.041$) and compared
209 to PS ($p=0.002$), but was not significantly different between ES and PS ($p=0.244$) (main
210 effect 'muscle' $p=0.001$) (Figure 3). No main effects for 'level' ($p=0.638$) or 'side' ($p=0.525$),
211 and no interaction effects for condition with 'level' or 'side' were found ($p>0.05$).

212

213 *Psychological exercise measures*

214 Following saline injection, mean NRS pain intensity was 57 ± 18 before the 1st repetition,
215 56 ± 22 after the 5th repetition, and 54 ± 23 after the 10th repetition of trunk extension. Total pain
216 intensity experienced from experimental LBP during performance of the exercise
217 (NRS=52/100) was not different from self-reported pain intensity recalled from recurrent LBP
218 episodes (NRS= 57/100) ($p=0.391$).

219 Scores for fear of performance of the exercise, experienced pain and RPE (Table 3), were
220 significantly higher in the exercise-with-pain versus the exercise-without-pain condition.

221 Upon completion of the experiment pain diagrams were used to localize the experienced pain
222 elicited through pain induction. Interpretation of these diagrams revealed that 9 people
223 reported focal unilateral paraspinal pain as a consequence of the experimental pain induction,
224 from which 6 reported to have local pain during their natural episodes. The other 6
225 participants reported referred pain in the gluteal region, groin or posterior thigh (not below the
226 knee), all of these were among the 9 persons who experienced referred pain during their
227 natural episodes. None of the participants reported a more expanded region of pain.

228 The amount of inhibition in muscle activity was not correlated to the magnitude of pain
229 intensity ($r=0.103$, $p=0.749$). A trend towards significance ($r=0.533$, $r^2=0.284$, $p=0.074$)
230 indicated a weak association with muscle inhibition and fear of pain (delta NRS for fear of
231 exercise performance: mean=-31, range=-90 to 0).

232

233 DISCUSSION

234 This study investigated the effect of experimental nociception on lumbar muscle activity
235 during trunk-extension in people in remission of clinical recurrent LBP. During the
236 experimental pain condition, muscle activity significantly decreased for all 3 evaluated

237 muscles (MF, ES and PS), equally at the painful and non-painful side at all 3 segmental
238 levels.

239 This inhibitory response pattern was consistent with previously published results in healthy
240 controls which were obtained with an identical study set-up (Dickx et al. 2008). Similarly,
241 another study in healthy subjects reported decreased ES EMG activity during standing trunk
242 re-extension following experimental pain (Zedka et al. 1999). Studies evaluating ES EMG
243 activity during trunk extension in people with clinical (not experimental) LBP reported a
244 decrease (Shirado et al. 1995; Watson et al. 1997), others an increase (Descarreaux et al.
245 2007) or no difference (Lariviere 2000) compared to healthy controls. Apparently, comparing
246 changes in lumbar muscle activity between clinical LBP and healthy controls yielded more
247 variable results versus comparing muscle activity with and without experimental LBP. This
248 might be consistent with the proposition that alterations in motor output in clinical LBP do
249 not solely depend on muscular nociceptive mechanisms or other possible sources of spinal
250 nociception (e.g. disc, ligament, zygapophyseal joints, nerve root, etc.) (Deyo and Weinstein
251 2001), but also on other existing alterations along the sensorimotor system in relation to
252 clinical LBP.

253

254 It has been postulated previously that pain yields a generalized, widespread effect, affecting
255 recruitment of several muscles, sides and segmental levels (Ciubotariu et al. 2004; Dickx et al.
256 2008, 2010). In the present study, activity was reduced in all 3 measured muscles despite
257 administration of pain took place in ES only and synergistic activation of MF and ES but not
258 PS occurs during trunk-extension. Nevertheless, concurrent inhibition of all 3 muscles might
259 be attributed to the fact that deep stabilizing muscles are more likely to be affected by pain
260 compared to superficial torque-generating muscles (Hodges et al. 2003). Analogous to MF

261 and lumbar ES, evidence exists for the role of PS as a spinal stabilizer because of its
262 segmental connections (Hansen et al. 2006). These alterations in motor output in response to
263 pain have been postulated as an adaptive strategy, ultimately aiming to avoid further pain or
264 injury (Hodges et al. 2011). In addition, the trend towards a weak association between
265 inhibition of muscle activity and the increase in fear for exercise-performance during the pain
266 condition, might support the contemporary idea that unfavorable pain-related cognitions can
267 be involved in altering muscle recruitment patterns (Moseley and Hodges 2006).

268

269 Previously, several adaptations in motor output have been reported during remission of
270 recurrent LBP (D'Hooge et al. 2013; Jones et al. 2012; Macdonald et al. 2009, 2010, 2011). A
271 qualitative comparison of the systematic reduction in muscle activity following experimental
272 LBP in this study, with the previously published pattern of pre-existing alterations during
273 trunk-extension in remission of unilateral recurrent LBP (D'Hooge et al. 2013), demonstrates
274 contrasting findings. During LBP remission, participants exhibited higher MF activity
275 compared to healthy controls on both sides and segmental levels, without alterations for ES or
276 PS (D'Hooge et al. 2013). Since different muscles are affected to a different extent and in
277 opposite directions, the opposing patterns suggest that experimental LBP exerts a distinctive
278 effect on lumbar muscle activity, which is observed over and above the existing alterations in
279 lumbar muscle behavior during remission of recurrent LBP. Several factors might contribute
280 to the opposing muscle activity patterns. A key feature of LBP remission is the absence of
281 pain. Analogue to the restoration of recruitment strategies to a pre-pain state after
282 experimental LBP (Moseley and Hodges 2005), it could be hypothesized that the inhibitory
283 effects of nociception might have equally disappeared after resolution of clinical LBP. In
284 addition to pain, injury-related mechanisms have been reported in relation to localized and

285 selective changes in MF structure in acute clinical LBP (Hides et al. 1994) and following an
286 experimental lumbar injury procedure in pigs (Hodges et al. 2006). In order to maintain spinal
287 functioning during LBP remission, lumbar muscle behavior might be compensating for
288 structural spinal deficits (e.g. increased activity in MF) (Panjabi 2003).

289

290 The current study was unique in administering experimental LBP at the site of previous
291 clinical LBP, instead of in healthy controls. In this way, muscle recruitment was investigated
292 intra-individually with and without pain, while accounting for the individuals' sensorimotor
293 pathway and biopsychosocial background, which had been relevantly influenced by a history
294 of LBP. The novelty of the current results is situated in that the results from a healthy control
295 group were replicated in a clinical population. It is striking that, in people with a history of
296 LBP the motor pattern in response to pain was similar as in healthy people, despite having a
297 pre-existing condition of the sensorimotor system. This pattern resemblance might indicate
298 that acute pain exerts a stereotypical, inhibitory effect on motor output. As such, these results
299 bring us a step forward towards our understanding of sensorimotor adaptations in relation to
300 pain, as motor responses to pain were studied in a more representative, clinical study sample.

301

302 With regard to pain measures, experimental pain intensity and psychometric scores of fear
303 were of similar order compared to those previously reported in healthy controls (Arendt-
304 Nielsen et al. 1996; Dickx et al. 2008, 2010; Hodges et al. 2003; Kiesel et al. 2008).
305 Experimental pain intensity and localization were comparable to their usual clinical LBP. In
306 contrast, people with chronic widespread pain reported enlarged areas of referred pain and
307 hyperalgesia in response to experimental pain as a result of central sensitization (Graven-
308 Nielsen and Arendt-Nielsen 2008). Although the experimentally induced LBP was not

309 perceived as completely identical to natural clinical LBP, the similarity between experimental
310 and clinical pain was perceived within the positive range of the spectrum (NRS= +36 on scale
311 from -100 to +100). Taken together, this is to our knowledge the first intra-individual
312 evidence (cf. pain intensity and localization, perceived similarity) adding to the presumption
313 that intramuscular injection of hypertonic saline can closely mimic clinical pain
314 characteristics of acute LBP (Graven-Nielsen 2006). Nevertheless, recalling the intensity,
315 distribution and type of LBP may not be evident for each participant. Furthermore,
316 fundamental differences are situated within the perception of experimental compared to
317 clinical LBP, since the experimental nociceptive stimulus is known not to be damaging and is
318 controlled over a limited time-course (Graven-Nielsen 2006). These factors may reduce the
319 affective-emotional component of pain.

320

321 The results should be viewed within the scope of the methodology. MfMRI depicts muscle
322 activity post-exercise, hence other aspects of motor control, e.g. timing, cannot be considered.
323 Also, imaging focused on 3 deep lumbar muscles. Since muscle activity decreased in these
324 measured muscles, it is not known if redistribution of activity to other, superficial muscles
325 occurred or if exercise performance altered during pain. Despite the lack of biomechanical
326 data, movement velocity and range were controlled in a standardized way.

327 Furthermore, the exercise conditions were performed in a fixed order (first without pain,
328 subsequently with pain) which introduces the possibility that sequential effects from the first
329 exercise bout might compromise the second bout. Several arguments however might indicate
330 that the effect of remaining fatigue would be minimal. The exercise was performed at low-
331 load intensity (confer RPE score between very light and fairly light). The resting period in
332 between the exercise bouts was prolonged to 60min, since it was not known if the standard

333 guidelines regarding recovery periods for T2-shifts on mfMRI (30-45min) (Cagnie et al.
334 2011) would equally apply to participants with musculoskeletal pain. Further, given that
335 trunk-extension does not increase T2-values to an equal extent in the 3 measured muscles
336 (T2-shift MF>ES>PS, Figure 3), it appears unlikely that T2-shift was homogeneously reduced
337 in all 3 muscles in the experimental pain condition (confer no interaction effect
338 muscle*condition $p=0.336$), if exercising muscles would not have recovered yet. Future
339 studies could incorporate repeated baseline T2-rest measures in between the 2 exercise
340 conditions to confirm that T2-shifts has recovered.

341 In addition, the current study did not control for possible mechanical effects from the
342 injection. In healthy people, the effects of injections with isotonic saline in the lumbar region
343 have been shown to be marginal compared to hypertonic saline (Hodges et al. 2003). Future
344 research could confirm whether this holds in participants with a history of clinical LBP.

345 The study was conducted on a small number of participants because of the invasive character
346 of the injections of hypertonic saline. The recruited numbers were in line with previous
347 studies in this population (Macdonald et al. 2009, 2010, 2011) and previous studies using
348 mfMRI (Dickx et al. 2008, 2010) and experimental pain inductions (Dickx et al. 2008, 2009).
349 Nevertheless, due to the small sample size, caution is warranted towards extrapolation of the
350 findings.

351 Finally, inclusion of a healthy control group would have allowed to directly compare the
352 response to experimental pain and not only in a qualitative manner (recruitment patterns) with
353 previous research, but also in a quantitative manner between participants with and without a
354 history of clinical LBP.

355

356 The current findings might have some implications and perspective for further research. For
357 now, it is assumed that adaptations fail to resolve following a LBP episode, resulting in
358 ongoing alterations in muscle behavior during remission of LBP (Hides et al. 1996; Hodges et
359 al. 2011; Macdonald et al. 2009). Since the current study shows immediate changes in muscle
360 activity in response to pain in people with a history of recurrent LBP, opposite to the patterns
361 observed during remission (=without pain), this might suggest that motor output can modify
362 along the course of LBP. This encourages the need for further research to unravel the
363 longitudinal course of muscle recruitment and the involved pathophysiological mechanisms
364 during and after episodes of recurrent LBP.

365

366 In conclusion, administration of experimental LBP in people with a history of recurrent LBP
367 effected a generalized, widespread inhibitory response in lumbar muscle activity during trunk
368 extension. This response was consistent with previously established inhibitory patterns in
369 healthy controls in response to acute pain, and appeared despite and in addition to the
370 presence of pre-existing dysfunctions during remission of recurrent LBP. The response was
371 opposite to the existing pattern of increased MF activity, which has been shown previously
372 during remission of recurrent LBP. These results might suggest a potential pathophysiological
373 role for pain in the modification of motor alterations along the course of recurrent LBP.

374 ACKNOWLEDGMENTS

375 The authors want to acknowledge and thank Dr. Nele Dickx, Eline Renard and Lauranne
376 Verschueren for assisting in data collection.

377

378

379 GRANTS

380 Roseline D'hooge is funded by a Phd fellowship from the Special Research Fund from Ghent
381 University. Barbara Cagnie is a postdoctoral fellow of the Fund for Scientific Research
382 (Research Foundation Flanders, FWO - Belgium). Jessica Van Oosterwijck is a postdoctoral
383 fellow funded by the Special Research Fund of Ghent University.

384

385

386 DISCLOSURES

387 There are no conflicts of interests that may arise as a result of the research presented in this
388 manuscript.

389

390

391

392

393

394

395

396

397

398 REFERENCES

- 399 1. **Arendt-Nielsen L, Graven-Nielsen T, Svarrer H, & Svensson P.** The influence of
400 low back pain on muscle activity and coordination during gait: a clinical and
401 experimental study. *Pain* 64(2): 231-240, 1996
- 402 2. **Borg GA.** Psychophysical bases of perceived exertion. *Med Sci Sports Exer* 14(5):
403 377-381, 1982
- 404 3. **Brumagne S, Cordo P, Lysens R, Verschueren S, Swinnen S.** The role of paraspinal
405 muscle spindles in lumbosacral position sense in individuals with and without low
406 back pain. *Spine* 25(8): 989-994, 2000
- 407 4. **Cagnie B, Elliott JM, O'Leary S, D'Hooge R, Dickx N, Danneels, LA.** Muscle
408 functional MRI as an imaging tool to evaluate muscle activity. *J Orthop Sports Phys*
409 *Ther* 41(11): 896-903, 2011
- 410 5. **Ciubotariu A, Arendt-Nielsen L, Graven-Nielsen T.** The influence of muscle pain
411 and fatigue on the activity of synergistic muscles of the leg. *Eur J Appl Physiol* 91(5-
412 6): 604-614, 2004
- 413 6. **D'Hooge R, Cagnie B, Crombez G, Vanderstraeten G, Achten E, Danneels L.**
414 Lumbar muscle dysfunction in remission from unilateral non-specific low back pain -
415 evaluation with muscle functional MRI. *Clin J Pain* 29(3):187-94, 2013
- 416 7. **D'Hooge R, Cagnie B, Crombez G, Vanderstraeten G, Dolphens M, Danneels L.**
417 Increased Intramuscular fatty infiltration without differences in lumbar muscle cross-
418 sectional area during remission of unilateral recurrent low back pain. *Man Ther* 17:
419 584-8, 2012

- 420 8. **De Deene Y, De Wagter C, De Neve W, Achten E.** Artefacts in multi-echo T2
421 imaging for high-precision gel dosimetry: I. Analysis and compensation of eddy
422 currents. *Phys Med Biol* 45(7): 1807-1823, 2000
- 423 9. **de Vet HC, Heymans MW, Dunn KM, Pope DP, van der Beek AJ, Macfarlane**
424 **GJ, Bouter LM, Croft PR.** Episodes of low back pain: a proposal for uniform
425 definitions to be used in research. *Spine* 27(21): 2409-2416, 2002
- 426 10. **Descarreaux M, Lalonde C, Normand MC.** Isometric force parameters and trunk
427 muscle recruitment strategies in a population with low back pain. *J Manipulative*
428 *Physiol Ther* 30(2): 91-97, 2007
- 429 11. **Deyo RA, Weinstein JN.** Low back pain. *N Engl J Med* 344(5): 363-370, 2001
- 430 12. **Dickx N, Cagnie B, Achten E, Vandemaele P, Parlevliet T, Danneels L.** Changes in
431 lumbar muscle activity because of induced muscle pain evaluated by muscle
432 functional magnetic resonance imaging. *Spine* 33(26): E983-E989, 2008
- 433 13. **Dickx N, Cagnie B, Parlevliet T, Lavens A, Danneels L.** The effect of unilateral
434 muscle pain on recruitment of the lumbar multifidus during automatic contraction. An
435 experimental pain study. *Man Ther* 15(4): 364-369, 2010
- 436 14. **Dickx N, D'Hooge R, Cagnie B, Deschepper E, Verstraete K, Danneels L.**
437 Magnetic resonance imaging and electromyography to measure lumbar back muscle
438 activity. *Spine* 35(17): E836-E842, 2010
- 439 15. **Graven-Nielsen T.** Fundamentals of muscle pain, referred pain, and deep tissue
440 hyperalgesia. *Scand J Rheumatol Suppl* 122: 1-43, 2006
- 441 16. **Graven-Nielsen T, Arendt-Nielsen L.** Sensory and motor manifestations of muscle
442 pain. *Journal Musculoskeletal pain* 16 (1-2), 93-105, 2008

- 443 17. **Graven-Nielsen T, Svensson P, Arendt-Nielsen L.** Effect of muscle pain on motor
444 control: a human experimental approach. *Advances in Physiotherapy* 2, 26-38, 2000
- 445 18. **Hansen L, de Zee M, Rasmussen J, Andersen TB, Wong C, Simonsen EB.**
446 Anatomy and biomechanics of the back muscles in the lumbar spine with reference to
447 biomechanical modeling. *Spine* 31(17): 1888-1899, 2006
- 448 19. **Hides JA, Richardson CA, Jull GA.** Multifidus muscle recovery is not automatic
449 after resolution of acute, first-episode low back pain. *Spine* 21(23): 2763-2769, 1996
- 450 20. **Hides JA, Stokes MJ, Saide M, Jull GA, Cooper DH.** Evidence of lumbar
451 multifidus muscle wasting ipsilateral to symptoms in patients with acute/subacute low
452 back pain. *Spine* 19(2): 165-172, 1994
- 453 21. **Hodges PW, Holm AK, Hansson T, Holm S.** Rapid atrophy of the lumbar multifidus
454 follows experimental disc or nerve root injury. *Spine* 31(25): 2926-2933, 2006
- 455 22. **Hodges PW, Moseley GL.** Pain and motor control of the lumbopelvic region: effect
456 and possible mechanisms. *J Electromyogr Kinesiol* 13(4): 361-370, 2003
- 457 23. **Hodges PW, Moseley GL, Gabrielsson A, Gandevia SC.** Experimental muscle pain
458 changes feedforward postural responses of the trunk muscles. *Exp Brain Res* 151(2):
459 262-271, 2003
- 460 24. **Hodges PW, Tucker K.** Moving differently in pain: a new theory to explain the
461 adaptation to pain. *Pain* 152(3 Suppl): S90-S98, 2011
- 462 25. **Jones SL, Henry SM, Raasch CC, Hitt JR, Bunn JY.** Individuals with non-specific
463 low back pain use a trunk stiffening strategy to maintain upright posture. *J*
464 *Electromyogr Kinesiol* 22: 13-20 2012
- 465 26. **Kiesel KB, Uhl T, Underwood FB, Nitz AJ.** Rehabilitative ultrasound measurement
466 of select trunk muscle activation during induced pain. *Man Ther* 13(2): 132-138, 2008

- 467 27. **Lariviere C.** The comparison of trunk muscles EMG activation between subjects with
468 and without chronic low back pain during flexion-extension and lateral bending tasks.
469 *J Electromyogr Kinesiol* 10(2): 79-91, 2000
- 470 28. **Macdonald DA, Dawson AP, Hodges PW.** Behavior of the Lumbar Multifidus
471 During Lower Extremity Movements in People With Recurrent Low Back Pain
472 During Symptom Remission. *J Orthop Sports Phys Ther* 41: 155-64, 2011
- 473 29. **Macdonald DA, Moseley GL, Hodges PW.** Why do some patients keep hurting their
474 back? Evidence of ongoing back muscle dysfunction during remission from recurrent
475 back pain. *Pain* 142:183-8, 2009
- 476 30. **Macdonald DA, Moseley GL, Hodges PW.** People with recurrent low back pain
477 respond differently to trunk loading despite remission from symptoms. *Spine* 35(7):
478 818-824, 2010
- 479 31. **Meyer RA, Prior BM.** Functional magnetic resonance imaging of muscle. *Exerc*
480 *Sport Sci Rev* 28(2): 89-92, 2000
- 481 32. **Moseley GL, Hodges PW.** Are the changes in postural control associated with low
482 back pain caused by pain interference? *Clin J Pain* 21(4): 323-329, 2005
- 483 33. **Moseley GL, Hodges PW.** Reduced variability of postural strategy prevents
484 normalization of motor changes induced by back pain: a risk factor for chronic
485 trouble? *Behav Neurosci* 120(2): 474-476, 2006
- 486 34. **Panjabi MM.** Clinical spinal instability and low back pain. *J Electromyogr Kinesiol*
487 13(4): 371-379, 2003
- 488 35. **Shirado O, Ito T, Kaneda K, Strax TE.** Flexion-relaxation phenomenon in the back
489 muscles. A comparative study between healthy subjects and patients with chronic low
490 back pain. *Am J Phys Med Rehabil* 74(2): 139-144, 1995

- 491 36. **Stanton TR, Latimer J, Maher CG, Hancock MJ.** How do we define the condition
492 'recurrent low back pain'? A systematic review. *Eur Spine J* 19(4): 533-539, 2010
- 493 37. **Tsao H, Danneels LA, Hodges PW.** ISSLS prize winner: Smudging the motor brain
494 in young adults with recurrent low back pain. *Spine* 36(21): 1721-1727, 2011
- 495 38. **Watson PJ, Booker CK, Main CJ, Chen AC.** Surface electromyography in the
496 identification of chronic low back pain patients: the development of the flexion
497 relaxation ratio. *Clin Biomech* 12(3): 165-171, 1997
- 498 39. **Zedka M, Prochazka A, Knight B, Gillard D, Gauthier M.** Voluntary and reflex
499 control of human back muscles during induced pain. *J Physiol* 520 (2): 591-604, 199

500 FIGURE CAPTIONS

501 FIGURE 1 : Illustration of (A) sagittal localizer MRI scan of the lumbar spine indicating axial
502 slice positioning and (B) T2-weighted axial MRI image at the level of L4 upper endplate
503 demonstrating regions of interest bilaterally for multifidus, erector spinae and psoas.

504

505 FIGURE 2 : T2-values (in milliseconds, mean + SD; adjusted means for 'side' and 'level') in
506 the resting (T2-rest) and the exercise condition without pain (T2-exercise) for multifidus,
507 erector spinae and psoas.

508 Legends: * = $p < 0.05$

509

510 FIGURE 3 : T2-shifts (in milliseconds, mean + SD; adjusted means for 'side and 'level') for
511 the exercise in the non-pain (T2-shift Ex) and in the pain (T2-shift Ex+pain) condition for
512 multifidus, erector spinae and psoas.

513 Legends: * = $p < 0.05$

514

515

516

517

518

519 TABLE CAPTIONS

520 TABLE 1 : Means \pm SD for demographic and recurrent LBP characteristics of study
521 population

522 Legends: LBP = Low Back Pain; NRS = Numeric Rating Scale

523

524 TABLE 2 : Means \pm SD of T2 values (in milliseconds) in the resting condition (T2-rest), in
525 the exercise condition without pain (T2-exercise) and in the exercise condition with pain (T2-
526 exercise+pain) for each muscle (multifidus, erector spinae, psoas), level (L3 upper, L4 upper,
527 L4 lower endplate) and side (painful, non-painful)

528

529 TABLE 3 : Means \pm SD for psychometric exercise measures

530 Legends: LBP = Low Back Pain; NRS = Numeric Rating Scale; * = $p < 0.05$ between
531 exercise condition with and without pain