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Experimental knee-related pain enhances attentional interference on postural control

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1	$^7_{8}$ EXPERIMENTAL KNEE-RELATED PAIN ENHANCES ATTENTIONAL INTERFERENCE ON POSTURAL CONTROL		
2	9 10 Eneida Yuri Suda ¹ , Rogerio Pessoto Hirata ² *, Thorvaldur Palsson ² , Nicolas Vuillerme ³ , Isabel C N Sacco ¹ ,		
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32 Abstract

⁹ *Durpose*: To quantify how postural stability is modified during experimental pain while performing different
¹¹ *L*ognitively demanding tasks.
¹³ *Methods*: Sixteen healthy young adults participated in the experiment. Pain was induced by intramuscular
¹⁴ *Spiection of hypertonic saline solution (1mL, 6%) in both vastus medialis and vastus lateralis muscles (0.9% 16)*¹⁵ *Solution of hypertonic saline solution (1mL, 6%) in both vastus medialis and vastus lateralis muscles (0.9% 16)*¹⁶ *Solution of Pressure (CoP) was recorded before and immediately after injections, while performing 20*²¹ *Swo cognitive tasks: (i) counting forwards by adding one; (ii) counting backwards by subtracting three. CoP*²² *Solution of displacement, velocity in anterior-posterior (AP-velocity) and medial-lateral (ML-*²⁴ *Seleocity) directions, and CoP sample entropy in anterior-posterior and medial-lateral directions were 26*

42 ²Gisplayed as the difference between the values obtained after and before each injection and compared
 43 ²Between tasks and injections.

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44 3 (*Results*: CoP total area (-84.5 ± 145.5 vs. 28.9 ± 78.5 cm²) and ML-velocity (-1.71 ± 2.61 vs. 0.98 ± 1.93 cm/s) 31
45 3 (*Results*: CoP total area (-84.5 ± 145.5 vs. 28.9 ± 78.5 cm²) and ML-velocity (-1.71 ± 2.61 vs. 0.98 ± 1.93 cm/s) 31
45 3 (*Results*: CoP total area (-84.5 ± 145.5 cm²), ML-velocitor injection while counting forward (*P* < 0.05). CoP total area 33
46 3 (*A*12.8 ± 53.9 vs. -84.5 ± 145.5 cm²), ML-velocity (-0.34 ± 1.92 vs. -1.71 ± 2.61 cm/s) and AP-velocity (1.07 ± 35 36.35 vs. -0.39 ± 1.82 cm/s) increased while counting backwards vs. forwards after the painful injection (*P* < 37 38.05).
49 39 (*onclusion*: Pain interfered with postural stability according to the type of cognitive task performed, 41

 $\begin{array}{c} 41\\ 42\end{array}$ suggesting that pain may occupy cognitive resources, potentially resulting in poorer balance performance.

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52 4 Keywords: postural stability, center of pressure, attention, distraction, pain

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7 53 gist o f	fabbreviation	5
54 9		
55 10 11	ANOVA	Analysis of variance
56 12 13	au	Arbitrary units
57 14 15	СоР	Center of pressure
58 16 17	SaEn	Sample entropy
59 18 19	SD	Standard deviation
60 20 21	VAS	Visual analogue scale
⁶¹ 22	VM	Vastus medialis
²³ ⁶² 24	VL	Vastus lateralis
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Introduction

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Controlling of upright posture requires a significant amount of attention to constantly gather 1 for postural control (Morasso and Sanguineti 2002). Although the majority of postural control is regulated 14 68 15ia automatic neural processes (Bronstein and Buckwell 1997), higher cortical centers are significantly holved in processing sensory information to plan and execute the best motor strategy for postural control 70 1 9Winter 1995). In daily life, postural control is challenging as several tasks simultaneously compete for the 2.0 71 2 pognitive resources available (Woollacott and Shumway-Cook 2002), limited by the capacity of higher 72 25 enters to process sensory information (Kahneman 1973). Therefore, sharing attentional resources may 25ause impairments in the performance of daily living activities (Brauer et al. 2004). Evidence suggests that $^{26}_{\frac{\text{aFor example,}}{27}}$ competition for cognitive resources during tasks involving postural stability results in body $^{27}_{27}$ 2 $_{\text{Stability being prioritized over secondary tasks (Liston et al. 2014).}$

Dual tasks paradigms, where subjects perform an additional task during quiet standing, are employed 3 2 quantify the extent to which attention is associated with postural control. Decreases in postural sway 3 While performing a secondary task compared with control conditions have been reported (Andersson et al. 32002; Pellecchia 2003) whereby focusing the attention on standing as still as possible increased postural way compared with conditions without similar instructions (Vuillerme and Nafati 2007). Altogether, these $\frac{39}{40}$ esults suggest that postural control demands attention (Woollacott and Shumway-Cook 2002) and that 41_{42} Simultaneous cognitive loading plays an important role in balance stability (Swan et al. 2007).

₈₃ 43 Although detrimental effects of cognitive loading on postural sway during unperturbed standing are more commonly reported for older adults and patients, studies using dual-task approaches in young and 4 Zontrol-subjects show controversial results (Huxhold et al. 2006; Fraizer and Mitra 2008). Young healthy 4 gubjects have probably more ability to allocate the attentional resources during upright standing without

gacrificing postural stability, showing that a system without impairments prioritizes postural stability when 9 1 dealing with dual-cognitive tasks (Siu and Woollacott 2007). 12 Evidence suggests that Seubjects with pain demonstrate increased postural sway compared with ¹ $\frac{1}{2}$ controls (Hirata et al. 2011). <u>Among several</u> <u>A potential possible</u> explanations for this finding, one hypothesis $1\frac{1}{5}$ that the increased postural sway may relate to a disrupting effect of nociceptive stimuli on attention to 92 17 ther simultaneous non-nociceptive tasks (Eccleston et al. 1999), underlining that processing of nociceptive 93 1 9timuli is cognitively demanding (Veldhuijzen et al. 2006). Thus, the execution of cognitive tasks during pain 2.0 94 2 might interfere with postural control. Although previous studies have shown that patients with pain present $\frac{22}{2}$ graphiced balance while performing a secondary cognitive task in comparison to health subjects (Van Daele $^{24}_{_{2}$ et al. 2010; Larivière et al. 2013; Mazaheri et al. 2014; Sherafat et al. 2014; Etemadi et al. 2016; Levinger et $^{26}_{27}$ al. 2016), it is not clear yet the isolate effect of pain in these conditions and comparisons, since in clinical $^{27}_{27}$ pain populations, besides pain, other factors like reduced muscle strength, reduced flexibility and 3 degenerative changes at the affected segment also cause both stiffness and instability in patients suffering 3 2rom chronic pain (Knoop et al. 2012). Therefore, further investigation of the interaction between pain, 34 ognition and postural stability is warranted. This investigation is of particular interest for clinical practice 102 3 gince there are evidences that attention can be directed away from pain using some specific strategies (Van 103 38 syckeghem et al. 2018). If selective attention could be directed away from the painful stimulus and modify $\begin{array}{c} 39\\ 4 \end{array}$ the deleterious effect of muscle pain on postural control, these results could have important implications $\begin{array}{c} 41 \\ 105 \\ 42 \end{array}$ or clinical settings. Likewise, if the execution of cognitive tasks impairs postural control in the presence of $\begin{array}{c} 42 \\ 42 \end{array}$ $4\frac{3}{2}$ ain, this should also be taken into account in rehabilitation context. 107 45 Considering that posture can be defined as the dynamic stability of a continuous moving body 108 4 PHarbourne and Stergiou 2003; Madeleine et al. 2011), nonlinear analysis of the dynamic structure of the 4 genter of pressure (CoP) time series would contribute to understand the physiological complexity of posture $5\dot{b}$ y accessing motor patterns that would be implicit in the CoP variability. Sample entropy (SaEn) measures

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111	gariations in the system output along time , which is independent of the signal magnitude (Slifkin and Newell
112	$1^{\frac{9}{1999}}$; Richman and Moorman 2000) Therefore, measures of physiological complexity of the postural sway
113	11 during quiet standing may relate to the system functionality as they are defined as the capacity of generating 12
114	$^{13}_{\ 14}$ adaptive answers to an ever-changing environment such as controlling posture (Manor et al. 2010). SaEn $^{14}_{\ 14}$
115	1 provides a measure of "orderly structure" within the time series since it tests if there are any repeated 16
116	1 patterns of various lengths, including the ones that are not repeated at regular intervals (Duarte and Sternad 18
117	1 Q 008). So, the lower the SaEn values are, the higher the similarity and lesser the complexity in the temporal
118	20 2 peries is (Richman and Moorman 2000). SaEn has been used to measure the structure of the CoP variability
119	22 2 $\frac{3}{3}$ Roerdink et al. 2006; Donker et al. 2007; Duarte and Sternad 2008; Stins et al. 2009) and thus address the
120	24 25 complexity of the signal.
121	26 27 Most definitions of complexity are driven by operational considerations on the number of system
122	$2\frac{8}{8}$ elements and their functional interactions. Therefore, c <u>C</u> omplexity depends on the number of structural 29
123	3Q omponents of the system, the existing coupling among these components and how this interaction is 31
124	3 2n fluenced by the intrinsic dynamic properties of the system and the motor task demands (Vaillancourt and 33
125	3 Alewell 2002). Thus, if the presence of pain and the execution of a cognitive task are both concurring with
126	$_{3}^{35}$ the attentional resources used in postural control, then the coupling between the components of the system
127	$\frac{37}{36}$ sesponsible for balance may be affected and, consequently, the complexity of the postural sway is affected.
128	39 The literature shows that the eExecution of a concurrent cognitive task during standing increases the 40
129	4 Complexity of the postural sway, and this increase has been attributed to a more automatized postural sway, 42
130	4 3/hen less attention is directed to the balance control (Donker et al. 2007; Stins et al. 2009; Kuczyński et al. 44
131	4 2 011). On the other hand, there is some evidence that the complexity of postural control decreases with 46
132	4 pain . Søndergaard et al. (2010) found a decrease SaEn of CoP displacement during sitting with increased 48
133	4 perceived discomfort in healthy young subjects (Søndergaard et al. 2010). The sameSimilar finding was
134	50 5 feported in young subjects with transient acute episode of low back pain during two continuous hours of
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5	gtanding, but without history of low back pain (Fewster et al. 2017), showing a relation between the
	9
6	10 ccurrence of pain and the decrease in CoP complexity. Therefore, examining the complexity of postural
	$\overset{11}{\overset{5}{\overset{5}{\overset{5}{\overset{5}{\overset{5}{\overset{5}{\overset{5}$
8	13 understanding of the decrease in postural stability (Levinger et al. 2016) -and complexity (Fewster et al. 2017) 14
	1 That may exist as a result of pain in an otherwise healthy system. 16

The aim of this study was to quantify how postural stability, i. e., CoP sway [{CoP sway velocity and 18
19 rea of displacement) and CoP complexity (CoP SaEn)], is modified during experimental pain while 20
2 performing a cognitive task. It was hypothesized that (i) the kind of cognitive task (more or less demanding) 22
2 an a non-painful condition will not interfere with CoP sway or CoP complexity, since the system would have 24
2 fonough cognitive resources to overcome it; (ii) experimental pain will increase CoP sway and decrease CoP 145
2 complexity, regardless the type of cognitive task performed; (iii) the presence of experimental pain while 27
2 shoreasing CoP sway and decreasing CoP complexity.

148 3**2. Methods**

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149 3 **4**.1. Subjects

Sixteen young adults, all university students, (to control for the effect of education level on Sixteen young adults, all university students, (to control for the effect of education level on Sixteen young adults, all university students, (to control for the effect of education level on Sixteen young adults, all university students, (to control for the effect of education level on Sixteen young adults, all university students, (to control for the effect of education level on Sixteen young adults, all university students, (to control for the experiment – 8 males (mean ± SD: age = Sixteen young adults, all 2015)), participated in the experiment – 8 males (mean ± SD: age = 27.1 ± Advection for the study period. All procedures performed in studies involving human participants Sixteen young adults, all university students, (to control for the effect of education level on Sixteen young adults, all university students, (to control for the study period. All procedures performed in studies involving human participants Sixteen young adults, all university students, (to control for the study period. All procedures performed in studies involving human participants Sixteen young adults, all university students, (to control for the study period. All procedures performed in studies involving human participants Sixteen young adults, all procedures performed in studies involving human participants Sixteen young adults, all procedures performed in studies involving human participants Sixteen young adults, all procedures performed in studies involving human participants Sixteen young adults, all procedures performed in studies involving human participants Sixteen young adults, all procedures performed in studies involving human participants Sixteen young adults, all procedures performed in studies involving human participants Sixteen young adults, all procedures performed in studies involving human participants Sixteen young adults, all procedures performed in studies involving human participants Sixteen youn

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 $\begin{array}{c} 19\\ 20\end{array}$. Experimental protocol

166 21 22 Since in healthy individuals approximately 70% of the information used for controlling posture 23 originates from proprioceptive systems (Peterka 2003), we controlled the effect of different footwear on 24168 ² Postural control by asking the subjects to stand barefoot during the experiment. -The participants stood on 26 169 27 triangular force plate that measures vertical forces (Good Balance System, Metitur, Jyväsklä, Finland; 170 2 glimensions: equilateral triangle – 800-mm; sampling frequency: 50-Hz as suggested by the International 171 3 pociety for Posture and Gait Research Standardization Committee (Scoppa et al. 2013)). This is a valid and 172 33 geliable system for postural sway measurements (Era et al. 2006; Ha et al. 2014) with accuracy better than $^{34}_{35}$ -mm for the CoP position measurement (Good Balance System User Manual). The CoP position was 174 ³ calculated via the Good Balance Software (Metitur, Jyväsklä, Finland) which uses the weighted arithmetic 175 ³ mean between the vertical force measured by four sensors and their corresponding position: one in each 4Q orner of the force-plate and the last one in the centroid of the force-plate (Fig. 1). The rational for using the 177 4 22andem position for the feet was based in previous studies showing that greater pain effects are presented 178 4 4 when posture is challenged (Hirata et al. 2013). This was important to ensure that postural stability 4 adaptations due to pain could be observed.- Therefore, subjects were asked to stand in tandem position, to $\frac{47}{48}$ postural challenge during the tasks, with the right leg behind (Fig. 1), arms hanging relaxed $\begin{array}{c} 49\\ 50 \end{array}$ ⁵ blaced on the force plate to ensure that the same foot position was maintained through all conditions. During 52

she assessment of postural control, subjects were instructed to look forward at a target positioned at eye- $\frac{9}{1 \text{ evel}}$ approximately 45-cm from the subjects to minimize the influence of the target distance on postural $1\frac{1}{12}$ way (Kapoula and Lê 2006). CoP records were made under eight experimental conditions, depending on the 13_{14} type of injection (control or painful), the dual-task (counting forward or counting backward as the less and 14 $\frac{1}{2}$ hore challenging tasks, respectively), before (pre-injection) and immediately after the injection. The 1 Zounting forward task consisted of adding one and the counting backward was performed by subtracting 189 1 Shree, beginning from a random number. The total number of answers and the number of correct answers 190 2 during each trial were recorded. The order of the injections and the order of the tasks were randomized, 191 2 with the same number of subjects receiving the hypertonic or isotonic injections first.

The experiment always followed the same order for all participants: (i) CoP measurement while $\frac{26}{27}$ performing the first randomly assigned task (cognitive task 1 or 2) over 60-s (pre-injection 1); (ii) 1-min rest; $\frac{28}{2}$ (iii) CoP measurement over 60-s while performing the second randomly assigned task (cognitive task 1 or 2) 195 ³ Øver 60-s (pre-injection 2); (iv) injections of the first saline solution (painful or control) into vastus medialis 196 3 2VM) and vastus lateralis (VL) muscles; (v) assessment of pain intensity by visual analogue scale (VAS); (vi) 197 3 CoP measurement over 60-s while performing task A; (vii) collecting VAS scores of the pain intensity and 1-198 3 min rest; (viii) CoP measurement over 60-s while performing task B; (ix) collecting VAS scores of the pain $\frac{37}{38}$ 199 $\frac{37}{38}$ 195 $\frac{37}{38}$ 195 $\frac{37}{38}$ 195 $\frac{37}{38}$ 196 $\frac{37}{38}$ 100 $\frac{37}{38}$ 1 $\frac{39}{40}$ was followed by a 5-min break. Following the break, all steps of the experiment were performed again with 4^{1}_{the} injection of the other saline solution, including new pre-injection CoP recordings. Before each CoP 42 202 ⁴ <u>Aneasurement, all subjects confirmed that no tiredness or other problems were presented.</u> The duration of 203 4 She CoP measurements were performed according to guidelines proposed by the International Society for 204 4 Posture and Gait Research (Scoppa et al. 2013). Fig. 2 summarizes the study procedures along time.

205 4*3*.3. Experimental muscle pain

²⁰⁶ 51 Before the experiment all subjects were instructed about the nature and effects of the injections,

and that one type of injection would be painful while the other would be a non-painful stimulus, although $\frac{9}{1}$ they would not know which kind of injection they would be receiving. Pain was induced through 1 intramuscular injection of 1-mL of 6% sterile hypertonic saline solution or as a control condition 1-mL of 12 210 1 3 14 14 15 he injections were performed with a 2-mL syringe with a disposable needle (27G, 40-mm) into right VM $\,1$ muscle and right VL muscle. Both injections locations were marked to ensure that they were applied 213 1 approximately in the same location. The VM muscle injection was performed 5-cm proximal and 5-cm medial 214 2 to the medial corner of the patella (Shiozawa et al. 2013), and in the VL muscle, injections were performed 215 23 at two thirds of the distance from the anterior spina iliaca to the lateral side of the patella (Fig. 3). The depth $^{24}_{20}$ gf the injection was determined by an ultrasound scanner (LOGIQ^M S7, General Electric, USA). This pain $217 \frac{26}{27}$ model has been successfully used previously to mimic knee-related pain during quiet standing tasks 28 providing moderate pain intensities for approximately five minutes (Hirata et al. 2011). Hypertonic saline 219 3 hjections have been shown to activate nociceptors around the injected site (Mense 1993) whereas the 0.9% 220 3 Botonic saline injections have induced little or no pain during postural control tasks similar to the one used 221 3 4 the present study (Hirata et al. 2010, 2011, 2013).

222 3 g.4. Assessment of pain intensity

223 38 The subjects were asked to rate the pain intensity using a 10-cm VAS from 0-cm to 10-cm (0-cm $\begin{array}{c} 39\\ 40\\ \end{array}$ 4 measurement. Therefore, three VAS scores were obtained for each set of experiments (balance 42226 ⁴ measurements after isotonic injection and balance measurements after hypertonic injection, respectively; 227 4 \$ jg. 2), and the mean values of the three VAS scores were considered as the pain intensity after each injection 228 4 paradigm. Additionally, following each set of experiments subjects were asked to indicate the overall pain 229 4 greas during the trials on a body chart and to respond the McGill Pain Questionnaire (Melzack 1975). The 230 5 area of pain was extracted from the body charts with VistaMetrix 1.38 software. The pain rating index based

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231	$^{\circ}_{ m O}$ n the rank values of the words chosen within each category (sensory, affective, evaluative	and
232	$\frac{9}{10}$ miscellaneous) from McGill Pain Questionnaire were obtained and the score for each category, as we	l as
233	11 the total pain rating index were determined as the sum of the ranked values of the words (Melzack 1975)	5).
234	13.5. Data analysis 14	

as

₂₃₅ 15 All variables for postural sway were calculated based on 50-s of the standing tasks, with the first and $\,1$ Tast 5-s from the original 60-s time series being excluded. The analyses were performed with Matlab R2016a 237 19oftware (Mathworks, Massachusetts, USA). The area fitted to 95% confidence interval of the CoP 2.0 238 2 displacement was calculated as representative of the total CoP area displacement (95% confidence interval 239 $2\frac{9}{2}$ glipse), along with the CoP velocity in both directions (anterior-posterior and medial-lateral). The structural 24 2 yariability of the CoP was calculated by means of SaEn with the embedding dimension (*m*) and the tolerance 26_{distance} (r) set to m=2 and r=0.2xSD (Vaillancourt and Newell 2000). All CoP variables are displayed as the 242 ² ⁸ difference between the values obtained immediately after the injection and the correspondent pre-injection 243 3 Qondition. Negative values show that the CoP variable decreased after the injection of the saline solution 244 32ompared to its respective pre-injection condition. Likewise, positive values show that the CoP variable 245 3 Ancreased after the injection compared to its respective pre-injection condition.

246 3 g.6. Statistical analysis

Pain outcomes were compared between injection types (isotonic or hypertonic injections) with $\begin{array}{c} 39\\ 40\\ \end{array}$ baired T-tests when normal distribution was present (VAS scores and pain area data) and with the Wilcoxon $\frac{41}{42}$ Signed Rank Test when the data distribution was non-normal (McGill scores). The task measures (number of $\frac{42}{42}$ 43 answers, number of correct answers) were evaluated with a 3-way RM-ANOVA with *injection* (isotonic vs 251 4 Sypertonic), time (pre-injection vs after injection) and task (counting forward vs backwards) as main factors. 252 4 The CoP parameters were compared with a 2-Way RM-ANOVA with task and injection as main factors, and 253 4 ghe p-values are shown in the table 3. Bonferroni post-hoc correction for multiple comparisons was applied $5 \frac{1}{2}$ and p-values are shown in the results texts. The alfa-value (α) for statistical significance was set to 0.05.

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255	8 .	Results		
256	9	3.1. Experimental muscle pain and cognitive task performance	4	Formatted: Justified, Indent: First line: 0.49"
	10 11			
257	1 <u>3.1</u>	Area and amplitude of perceived pain	\sim	Formatted: Font: Italic
258	13	Fig. 4 shows the reported pain areas following both isotonic and hypertonic injections. Pain was	;	Formatted: Indent: First line: 0" Formatted: Font: 12 pt, Italic
259	14 15preser	nt in the anterior and lateral portions of the thigh after both isotonic and hypertonic injections, being	5	
260	17 more of 18	concentrated in the lower half of the thigh after the isotonic injections. The hypertonic saline injections	;	
261		ed higher pain area (mean area \pm SD: isotonic = 518.6 \pm 690.6 au; hypertonic = 1659.3 \pm 1574.0 au	;	
262	2 ₽ =0.00)3) and higher VAS scores (mean score \pm SD: isotonic = 0.9 \pm 1.1 cm; hypertonic = 4.7 \pm 1.7 cm; P<0.001)	
263	22 23 ^{than i}	sotonic saline injections. Table 1 shows the scores for each class of words from McGill Pair	1	
	25	onnaire and the pain rating index. Subjects presented a higher total pain rating index and scored		
265	26 higher 27	in all the categories, with the exception of the affective class, after the hypertonic injections (P <0.05)		
266	28 <mark>3.2</mark> 29	<u>Cognitive task performance</u>	•	Formatted: Indent: First line: 0"
	29 30 <u>3.2</u>	-Only for the analysis of the cognitive task performance, one subject was not included due to problem		Formatted: Font: 12 pt, Italic
207	31		,	Formatted: Font: Italic
268	32h the	answers recording. The total number of answers and the number of correct answers decreased during	Ş	Formatted: Normal, Justified, No bullets or numbering
269	3⊴⊉ackw	ards counting conditions compared with forwards counting despite the injection effect (significan	t	
270	35 3 é ^{nain e}	effect for <i>task factor</i> ; Table 2).		
271	37 38			
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273 274	42	<i>Effect of experimental pain in CoP variables</i> There were no statistical differences between the different conditions for the factor <i>injection</i> on any		
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275	45ofthe 46	CoP variables (Table 3).		
276		Effect of cognitive task in CoP variables		
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277	8 A main effect of <i>task</i> was found for the CoP AP-velocity (F=5.82; <i>P</i> =0.028), showing that there was an
278	$\overset{9}{_{10}}$ increased AP-velocity during the counting backwards task compared to the counting forwards task,
279	11 regardless the type of injection (Table 3). 12
280	13 14 Effect of the interaction between experimental pain and cognitive task in CoP variables
281	15 An interaction effect was found between <i>injection</i> and <i>task</i> factors for CoP total area and CoP ML- 16
282	1 Velocity (CoP total F=7.78, P=0.049; CoP ML F=4.69, P=0.021) (Table 3). Post-hoc comparisons showed that 18
283	1 b oth variables decreased after the hypertonic injection in comparison to the condition with isotonic injection 2.0
284	$_{2}$ when subjects where counting forward (Bonferroni: <i>P</i> = 0.010 for total area; <i>P</i> = 0.015 for ML-velocity). After 22
	$2^{\frac{1}{3}}$ the hypertonic injection, CoP total area increased when subjects were counting backwards in comparison to
	24 25 when they were counting forwards (Bonferroni: <i>P</i> = 0.019). ML-velocity showed differences between the
	²⁶ different cognitive tasks also after the injection of hypertonic solution, with a smaller decrease of ML-velocity 27
	² While counting backwards (Bonferroni: <i>P</i> = 0.049). 29
289	3 Q . Discussion
290	32 The present study aimed at quantifying how postural stability, represented by CoP sway (velocity and 33
291	3 Area of displacement) and CoP complexity (CoP SaEn), is modified during experimental pain while performing 35
	$\frac{36}{36}$ cognitive task. The main results showed that the kind of cognitive task did not interfere with postural $\frac{37}{37}$
	$\frac{37}{38}$ tability in the absence of pain. Experimental pain around the knee joint reduced CoP sway but did not affect
	$^{39}_{40}$ 40 core complexity during the performance of an easier cognitive task. During experimentally induced pain, the
	 ⁴ berformance of a difficult cognitive task increased CoP sway but did not change CoP complexity. 42
296	⁴ <u>∌ain intensity and counting performance</u> 44
297	The subjects showed higher pain intensity for the hypertonic saline injection and a larger pain area46
298	4 compared with the isotonic saline injection, as expected, indicating that experimental pain occurred (Hirata 48
299	$4 \frac{1}{9}$ t al. 2011). The McGill pain questionnaire indicated that hypertonic saline was perceived more impairing
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300	7 ghan the isotonic injection in all subscales except for the affective one. It is important to note that during
301	$\frac{9}{1}$ isotonic injections subjects rated pain around 1/10, which cannot be classified as a totally pain free condition.
302	$\begin{array}{c} 11\\ 12 \end{array}$ Counting performance requires the use of cognitive process which relies on the working memory of
	13 the subject (Lemaire 1996), impairing motor output performance when executed simultaneously with a 14
	15 fnotor task (Vuillerme and Nafati 2007). Seminowicz and Davis (2007) showed that subjects are able to 16
305	1 maintain performance of difficult cognitive task while experiencing different levels of pain. In this study, the
306	19 ainful condition did not affect the counting performance while performing a motor task (standing still) 20
307	2 indicating that healthy subjects are able to engage multiple tasks (motor and cognitive) during pain without
308	$^{22}_{2\$}$ compromising performance. This suggests that sufficient cognitive resources were available to manage the
309	$\begin{array}{c} 24\\ 25 \end{array}$ for process of counting forwards or backwards despite the interpretation of painful stimuli and the
310	$^{26}_{27}$ postural control task (Eccleston et al. 1999). Finally, education level is associate with both motor and $^{27}_{27}$
311	$^{28}_{\ 29}$ berceptual performance, where higher education level is associated with better performance (Voos et al. $^{29}_{\ 29}$
312	3QO15). -Since our subjects were all university students, we believe that bias due to education level did not 31
313	3 affect the present results.
314	3 Effect of cognitive tasks on postural stability
315	 Our first initial hypothesis, that (i) the kind of cognitive task (more or less demanding) in a non-painful
316	37 3 sondition would not interfere with CoP sway or CoP complexity, was confirmed. The factor task affected the
317	$^{39}_{40}$ CoP anterior-posterior velocity, indicating an increased velocity during the execution of the more difficult $^{40}_{40}$
318	$\frac{4}{1}$ ask (counting backwards) in comparison to the easier task (counting <u>backwardsforward</u>). Nevertheless, the $\frac{42}{2}$
319	$\overset{4}{\epsilon}$ coP SaEn was not affected by the kind of the performed cognitive task. These results indicate that enough $\overset{4}{4}$
320	$4{\rm 5}{\rm cognitive}$ resources were available to overcome the demands of both cognitive and postural tasks, which 46
321	4 Was expected since they were young individuals without any sensory-motor alterations. 48
322	4 ffect of experimental knee-related pain on postural stability
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Our second initial hypothesis, that (ii) experimental pain would increase CoP sway and decrease CoP $\frac{9}{16}$ S24 $\frac{1}{16}$ complexity was not confirmed since the type of saline solution injected did not affect the CoP variables. 11_{12}^{11} However, even though the factor *injection* did not show statistical differences between the different $\frac{12}{14}$ 326 $\frac{12}{14}$ 326 $\frac{12}{14}$ 326 $\frac{12}{14}$ 327 $\frac{12}{14}$ 328 $\frac{12}{14}$ $\frac{12}{14$ 1 between the control and the painful condition when the subjects were counting forwards, i.e., in conditions $\,1\,$ Where the kind of cognitive task performed was the same. Interestingly, during the counting forward, the 329 1 \$pype of injection resulted significant changes in postural sway (total area and ML-velocity) in opposite $_{2}$ directions: positive values of the difference between pre-injection and after injection of the isotonic solution, 331 23^{whereas} after the injection of the hypertonic solution both variables showed negative values. Additionally, 322 250 significant changes were observed in the structural variability of the CoP signal. This is contrary to the $\frac{26}{27}$ Initial hypothesis, where an increase in postural sway and a decrease in structural variability during painful $\frac{28}{2}$ conditions were expected. It is also in contrast with previous findings (Mazaheri et al. 2013) but may relate $\Im \phi$ the different position of the feet used in this study, which affects the postural sway (Day et al. 1993). The 336 3 2 andem feet position adopted allows less displacement of the CoP due to the limited base of support 337 34 ompared to side-by-side feet position, since if the subjects increase the CoP amplitude they may fall (Day 338 36t al. 1993). This also may reflect a voluntary strategy, requiring a greater amount of cognitive resources and 339 38 attention (Morasso and Sanguineti 2002), attempting to avoid large excursions of the body and consequent $\frac{39}{40}$ a loss of balance. For the current study, this might indicate that the subjects prioritized the balance task over ⁴ the other tasks, also known as *posture first strategy* (Vuillerme and Nafati 2007). The subjects were able to 42 4_2 educe the postural sway without compromising the counting performance during the easy cognitive task, 343 4 Suggesting that the available cognitive resource was sufficient to perform the less challenging cognitive task 344 4 Without compromising postural stability. Therefore, these results indicate that healthy subjects have the 345 4 gapacity to perform easy cognitive tasks while ensuring postural stability (Siu and Woollacott 2007). $\frac{1}{5}$ Reducing postural sway might reflect a motor strategy available for healthy subjects to avoid excessive

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granslation of the body, which could lead to balance loss (Winter 1995). This strategy was also observed 1 during the control injection while counting backwards, probably indicating that a high cognitive load seems $1\frac{1}{2}$ <u>be interpreted as a treat to postural stability.</u> An alternative explanation for the contrast between the 1°_{12} present study and the previous studies with pain patients showing larger postural sway (Schulte et al. 2004; 1°_{14} 19 Evinger et al. 2016) might be the pain model used that is not a complete proxy to the impaired pain patients' 353 1 Interactions between pain and cognitive load on postural stability

Our initial third hypothesis, that (iii) the presence of experimental pain would increase CoP sway and 22355 2 secrease CoP complexity only when performing a difficult cognitive task was partially confirmed since CoP 24356 25 way increased during pain under a difficult cognitive task, but the CoP complexity did not change. ANOVA $\frac{26}{27}$ esults showed an interaction between the task and injection factors for total area and ML-velocity. After 358 ²⁸ the hypertonic injection CoP total area increased and CoP ML-velocity decreased less while counting 359 3 Backwards in comparison to counting forwards condition, corroborating our hypothesis. ANOVA results also 360 33 showed an effect of the task factor on AP-velocity with post-hoc comparisons showing a difference only 361 34 during the hypertonic injection condition: while counting backwards AP-velocity also increased. Altogether 362 3 these results show that CoP sway increases when performing a more demanding cognitive task in the 363 3 presence of experimental pain. This might reflect an interference with the information-processing capacity $\begin{array}{c} 39\\ 40\end{array}$ $\frac{41}{42}$ Studies suggest that disruptions of sensory information lead to worsening of proprioception in the affected 43 rea (Matre et al. 2002), further impairing postural sway (Hirata et al. 2010, 2011). The results indicate that 367 45he posture first strategy (Vuillerme and Nafati 2007) found during the easy cognitive task during pain is no 46 368 4 Vionger feasible when a difficult cognitive task is performed during painful conditions. The increased cognitive 48 4 boad in painful conditions seems to impair the motor performance maybe due to insufficient cognitive 369 50 370 5 resource to simultaneously maintain postural stability (which requires significant amount of attention 52

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- Morasso and Sanguineti 2002)) and execute a difficult cognitive task. These results might have important $\frac{9}{10}$ 872 $\frac{9}{10}$ mew implications in understanding the mechanisms related to fall accidents. Postural stability in daily life $\frac{11}{12}$ activities is usually performed in combination with additional tasks, for example, walking in a busy slippery idewalk. These daily life activities involves simultaneously competition for the cognitive resources available 1415Woollacott and Shumway-Cook 2002) to evaluate the environment constrains in order to promote the best 16 $\,1\,$ 7notor strategy (Winter 1995). Our present results indicate that, if the subject performs a challenging 377 19postural task in pain, his/her capacity for maintain balance while exposed to a difficult cognitive task is 378 2 Juboptimal, which could increase the likelihood of losing balance. ³⁷⁹ 23 The complexity of postural sway did not show any differences between the experimental conditions. 24_{25} his result is contrary to the literature finding that young healthy subjects present a more regular and less $\frac{26}{27}$ automatic postural sway (decreased CoP SaEn) when the motor task is more difficult (e. g. standing with eyes 28 (losed) and more irregular postural sway and more automatic postural sway (increased CoP SaEn) when a 383 ³Qognitive task is added (Donker et al. 2007; Stins et al. 2009). The fact that the cognitive task did not interfere 384 3 2with CoP complexity may be due to the nature of both motor (standing in tandem position) and cognitive 385 34 subtraction calculus) tasks used in the experimental setup that did not interfere with the automaticity of 386 3 postural control. Besides that, pain also did not affect CoP complexity, showing that experimental knee-387 3g elated pain did not compromise the coupling between the components of the system responsible for $\begin{array}{c} 39\\ 40 \end{array}$ 41 cognition and on CoP complexity with different motor and cognitive demands, in addition to different 42
- 390 ⁴ populations.

- 391 45 Despite interesting results regarding the effects of cognitive tasks in postural control during pain, the 46
 392 4 7elevance of the findings for clinical populations should be interpreted with care. The experimental pain 48
 393 4 gnodel used here is convenient to assess the effect of pain without the interference of potential structural 50
 394 pr pathologies. However, extrapolating the current findings to an older population can only be done to some 52

 3 4 5 6 7 gegree. Additionally, chronic pain patients may also suffer from depressive symptoms (Bair et al. 2003) 9 10 anxiety (McWilliams et al. 2003), which might increase cognitive load (Nebes et al. 2001). Furthermod 11 20 12 20 13 21 20 21 20 21 20 21 20 21 20 21 21 21 22 21 22 21 25 25 24 25 24 25 	
 ⁶ ⁷ ⁸/₉ degree. Additionally, chronic pain patients may also suffer from depressive symptoms (Bair et al. 2003) ⁹ ¹⁰/₉ nxiety (McWilliams et al. 2003), which might increase cognitive load (Nebes et al. 2001). Furthermol ¹¹/₁₂ ognitive impairments are often found in chronic pain patients, decreasing the possibility to maint ¹³/₁₄ Performance of two or more concurrent tasks (Brauer et al. 2004), as opposed to what was observed in ¹⁴/₁₄ ¹⁵/₁₄ study where young healthy subjects were recruited. Also, there was no recording of postural sway with ¹⁶/₁₆ ¹⁷/₁₈ asks were influencing postural sway, and could have reduced type 2 errors given that multiple CoP varial ²⁰/₂ were analyzed in the study. Thus, it can be considered a limitation to our interpretations. ²¹/₂ ³² ³¹ ³² ³⁵ ³⁴ ³⁵ ³⁵ ³⁶ ³⁷ ³⁹ ³¹ ³¹ ³¹ ³² ³¹ ³² ³¹ ³¹ ³² ³¹ ³¹ ³² ³¹ ³² ³¹ ³¹ ³¹ ³² ³¹ ³² ³² ³¹ ³² ³¹ ³¹ ³² ³¹ ³² ³¹ ³² ³¹ ³² ³¹ ³² ³¹ ³³ ³¹ ³¹ ³² ³¹ ³² ³² ³³ ³⁴ ³⁴ ³⁵ ³⁴ ³⁵ ³⁵ ³⁵ ³⁵ <l< td=""><td></td></l<>	
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 ¹¹Cognitive impairments are often found in chronic pain patients, decreasing the possibility to main 12 performance of two or more concurrent tasks (Brauer et al. 2004), as opposed to what was observed in 14 15 tudy where young healthy subjects were recruited. Also, there was no recording of postural sway with 16 13 any cognitive task. This would have allowed comparisons with a condition where neither pain nor cogni 18 19 asks were influencing postural sway, and could have reduced type 2 errors given that multiple CoP varial 20 2 were analyzed in the study. Thus, it can be considered a limitation to our interpretations. 23 2 3. Conclusions 	or
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 16 17 any cognitive task. This would have allowed comparisons with a condition where neither pain nor cogninal 19 asks were influencing postural sway, and could have reduced type 2 errors given that multiple CoP varial 20 20 gwere analyzed in the study. Thus, it can be considered a limitation to our interpretations. 23 Conclusions 	his:
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 ⁴⁰² 2 were analyzed in the study. Thus, it can be considered a limitation to our interpretations. ²² 2³ ²³ Conclusions 	les
24 404 25 Pain and cognitive task interfered on postural stability, changing its patterns. During the performa	
25	nce
40 26_{0}^{6} f a simple cognitive task, pain, reduced postural sway, while during the performance of a more demand	ing
406 ²⁸ Cognitive task, postural sway was increased in young healthy subjects. <u>Since our subjects were young heal</u> 29	<u>thy</u>
407 3 <u>Qubjects, the direct translation of the present results to patients suffering from pain should be done v</u> 3.1	<u>/ith</u>
408 3 <u>2aution. However, \mpthese results may suggest that rehabilitation approaches should take into account t</u>	hat
409 3 pain not only affects directly the motor system, but may occupy cognitive resources, potentially resultin	g in
$_{3\mathfrak{G}}^{3\mathfrak{G}}$ oorer performance when performing rehabilitation exercises. Additionally, rehabilitation strategies us	ing
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413 41 42	
414 4 Compliance with ethical standards	
415 45 Sunding: Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National Resea	rch
 416 417 Foundation (DNRF121). The authors thank the State of São Paulo Research Foundation (FAPESP) for the State of	ıda
417 4 9 cholarship (FAPESP 2013/06123-7, 2015/00214-6).	
50_{5} Conflict of Interest: The authors declare that they have no conflict of interest.	
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	11_{12} Fig 1 Schematic drawing representing the force platform size, sensor locations, and the tandem position of 12
	$\frac{1}{1}$ the subjects during the experiment 14
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	1 Fig 2 Study design overview: pain assessments were performed immediately after each injection and each 18
	1 \mathfrak{B} alance measurement; the order of the saline injections was randomized in a balanced way 20
	21 22 2 § ig 3 Injections sites for vastus lateralis muscle, performed at two thirds of the distance from the anterior
	$2\frac{5}{10}$ Injections sites for vastus lateralis muscle, performed at two thirds of the distance from the anterior 24 $2\frac{5}{25}$ pina iliaca (a) to the lateral side of the patella (b); and for the vastus medialis muscle, performed 5 cm
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	29 $3 \mathbf{\hat{e}_{ig}} 4$ Representation of the experimental pain distribution reported areas after isotonic (top, blue in the
582	31 32nline version) and hypertonic (bottom, red in the online version saline injections (A); the individual
583	33 3 ψistributions are superimposed in the anatomical drawings
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586	Eneida Yuri Suda ¹ , Rogerio Pessoto Hirata ² *, Thorvaldur Palsson ² , Nicolas Vuillerme ³ , Isabel C N Sacco ¹ ,
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504	23 24 University, Denmark
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615	51 FAPESP 2017/15449-4, 2015/00214-6). 52
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Abstract

617 _{1 Surpose}: To quantify how postural stability is modified during experimental pain while performing different $\begin{array}{c} 11\\ \text{cognitively demanding tasks.}\\ 12 \end{array}$ $\frac{13}{Methods}$: Sixteen healthy young adults participated in the experiment. Pain was induced by intramuscular 14 $1\frac{1}{2}$ hjection of hypertonic saline solution (1mL, 6%) in both vastus medialis and vastus lateralis muscles (0.9% 621 1 % sotonic saline was used as control). The participants stood barefoot in tandem position for one minute on a 622 1 Sorce plate. Center of pressure (CoP) was recorded before and immediately after injections, while performing 623 2 two cognitive tasks: (i) counting forwards by adding one; (ii) counting backwards by subtracting three. CoP 624 2 variables – total area of displacement, velocity in anterior-posterior (AP-velocity) and medial-lateral (ML- $^{24}_{25}$ (25) $^{24}_{25}$ (25) $^{25}_{25}$ 26 26 displayed as the difference between the values obtained after and before each injection and compared

627 ² Between tasks and injections.

628 ³ Results: CoP total area (-84.5 ± 145.5 vs. 28.9 ± 78.5 cm²) and ML-velocity (-1.71 ± 2.61 vs. 0.98 ± 1.93 cm/s) 629 3 2 ecreased after the painful injection vs. Control injection while counting forward (P < 0.05). CoP total area 3412.8 ± 53.9 vs. -84.5 ± 145.5 cm²), ML-velocity (-0.34 ± 1.92 vs. -1.71 ± 2.61 cm/s) and AP-velocity (1.07 ± 2.61 cm/s) 631 $_3$ \mathcal{E} .35 vs. -0.39 ± 1.82 cm/s) increased while counting backwards vs. forwards after the painful injection (*P* < ³⁷ 632 38^{.05}). $^{39}_{40}$ conclusion: Pain interfered with postural stability according to the type of cognitive task performed, $\begin{array}{c} {}^{634} & {}^{41} \\ {}^{500} \\ {}^{42} \end{array}$ ₆₃₅ 43

636 4 Keywords: postural stability, center of pressure, attention, distraction, pain

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637	kist of	abbreviations	
638	9 10		
639	11	ANOVA	Analysis of variance
640	12 13	au	Arbitrary units
641		СоР	Center of pressure
642	16 17	SaEn	Sample entropy
643	18	SD	Standard deviation
544	19 20	VAS	Visual analogue scale
645	21 22	VM	Vastus medialis
646	23 24	VL	Vastus lateralis
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Introduction

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Controlling of upright posture requires a significant amount of attention to gather information from 1 the body and the environment and to generate adapted and accurate muscle activation for postural control 1 Morasso and Sanguineti 2002). Although the majority of postural control is regulated via automatic neural 15 Processes (Bronstein and Buckwell 1997), higher cortical centers are significantly involved in processing 17 Jensory information to plan and execute the best motor strategy for postural control (Winter 1995). In daily 19 fe, postural control is challenging as several tasks simultaneously compete for the cognitive resources 21 provide (Woollacott and Shumway-Cook 2002), limited by the capacity of higher centers to process sensory 23 formation (Kahneman 1973). Therefore, sharing attentional resources may cause impairments in the 25 erformance of daily living activities (Brauer et al. 2004). For example, competition for cognitive resources 28 tal. 2014).

Although detrimental effects of cognitive loading on postural sway during unperturbed standing are 44
Although detrimental effects of cognitive loading on postural sway during unperturbed standing are 44
45 nore commonly reported for older adults and patients, studies using dual-task approaches in young subjects 46
47 how controversial results (Huxhold et al. 2006; Fraizer and Mitra 2008). Young healthy subjects have 48
49 robably more ability to allocate the attentional resources without sacrificing postural stability, showing that

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- 2 3 4 5 6 7 a system without impairments prioritizes postural stability when dealing with dual-cognitive tasks (Siu and 671 9 672 1 Woollacott 2007). 673 11 12 Subjects with pain demonstrate increased postural sway compared with controls (Hirata et al. 2011). 674 13 A possible explanation for this finding is that the increased postural sway may relate to a disrupting effect of 14
- 675 1 ħociceptive stimuli on attention to other simultaneous non-nociceptive tasks (Eccleston et al. 1999), $\,$ 1 $\overline{
 m l}$ inderlining that processing of nociceptive stimuli is cognitively demanding (Veldhuijzen et al. 2006). Thus, 18 677 19he execution of cognitive tasks during pain might interfere with postural control. Although previous studies 20 678 2 have shown that patients with pain present impaired balance while performing a secondary cognitive task 22679 $2 \frac{1}{2}$ or comparison to health subjects (Van Daele et al. 2010; Larivière et al. 2013; Mazaheri et al. 2014; Sherafat $^{24}_{2,\text{gt}}$ al. 2014; Etemadi et al. 2016; Levinger et al. 2016), it is not clear yet the isolate effect of pain since reduced 26 muscle strength, reduced flexibility and degenerative changes at the affected segment also cause both 27 28 tiffness and instability in patients suffering from chronic pain (Knoop et al. 2012). Therefore, further 683 ³ hvestigation of the interaction between pain, cognition and postural stability is warranted. This investigation 684 32 of particular interest for clinical practice since there are evidences that attention can be directed away 685 3 4 from pain using some specific strategies (Van Ryckeghem et al. 2018). If selective attention could be directed 686 ஆகுway from the painful stimulus and modify the deleterious effect of muscle pain on postural control, these 687 3 gesults could have important implications for clinical settings. Likewise, if the execution of cognitive tasks $\frac{39}{40}$ mpairs postural control in the presence of pain, this should also be taken into account in rehabilitation 689 41 ontext.
- ₆₉₀ 43 Considering that posture can be defined as the dynamic stability of a continuous moving body 44 691 4 \$Harbourne and Stergiou 2003; Madeleine et al. 2011), nonlinear analysis of the dynamic structure of the 46 692 4 Zenter of pressure (CoP) time series would contribute to understand the physiological complexity of posture 48 693 $_4$ $_{\phi}$ y accessing motor patterns that would be implicit in the CoP variability. Sample entropy (SaEn) measures 50 $594 \frac{1}{5}$ variations in the system output along time. Therefore, measures of physiological complexity of the postural 52
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⁷/₈way during quiet standing may relate to the system functionality as they are defined as the capacity of
⁹/₁generating adaptive answers to an ever-changing environment such as controlling posture (Manor et al.
¹¹/₁₂010). SaEn provides a measure of "orderly structure" within the time series since it tests if there are any
¹³/₁₂epeated patterns of various lengths, including the ones that are not repeated at regular intervals (Duarte
¹⁴/₁₄
¹⁵/₁₄ and Sternad 2008). So, the lower the SaEn values are, the higher the similarity and lesser the complexity in
¹⁶/₁₆
¹⁷/₁₆ the temporal series is (Richman and Moorman 2000).

701 19 Complexity depends on the number of structural components of the system, the existing coupling 2.0 702 2 pmong these components and how this interaction is influenced by the intrinsic dynamic properties of the $^{22}_{2\frac{5}{2}}$ gystem and the motor task demands (Vaillancourt and Newell 2002). Thus, if the presence of pain and the 24_{26} 24 704 $_{26}$ execution of a cognitive task are both concurring with the attentional resources used in postural control, $\frac{26}{27}$ Then the coupling between the components of the system responsible for balance may be affected and, $\frac{28}{20}$ consequently, the complexity of the postural sway is affected. Execution of a concurrent cognitive task uring standing increases the complexity of the postural sway, and this increase has been attributed to a 708 3 2 nore automatized postural sway, when less attention is directed to the balance control (Donker et al. 2007; 709 3 \$tins et al. 2009; Kuczyński et al. 2011). On the other hand, there is some evidence that the complexity of 710 3 postural control decreases with pain during sitting with increased perceived discomfort in healthy young 711 $_{38}^{37}$ bubjects (Søndergaard et al. 2010). Similar finding was reported in young subjects with transient acute $\begin{array}{c} 39\\ 40\\ \end{array}$ pisode of low back pain during two continuous hours of standing, but without history of low back pain ⁷¹³ 4^{1} Fewster et al. 2017), showing a relation between the occurrence of pain and the decrease in CoP complexity. 43 herefore, examining the complexity of postural sway in a dual task context and the effect of experimental 4 $rac{1}{2}$ ain in this condition may improve the understanding of the decrease in postural stability (Levinger et al. 716 4 2016) and complexity (Fewster et al. 2017) that may exist as a result of pain in an otherwise healthy system. 717 49 The aim of this study was to quantify how postural stability [CoP sway velocity and area of $5\dot{f}$ displacement and complexity (CoP SaEn)], is modified during experimental pain while performing a cognitive

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⁷/₈ask. It was hypothesized that (i) the kind of cognitive task (more or less demanding) in a non-painful
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725 1**2. Methods**

726 22.1. Subjects

727 23 Sixteen young adults, all university students, (to control for the effect of education level on $^{24}_{25}$ multitasking performance (Voos et al. 2015)), participated in the experiment – 8 males (mean ± SD: age = 26.9 ± 2.8 years; body mass = 74.9 ± 13.8 kg; height = 1.76 ± 0.08 m) and 8 females (mean ± SD: age = 27.1 ± 2.1 \pm 0.08 m) $28_{-0.0}$ years; body mass = 68.8 ± 5.2 kg; height = 1.68 ± 0.06 m). The exclusion criteria were body mass index 731 3 bove 25 kg/m², pregnancy, drug addiction, previous neurologic, musculoskeletal or mental illness, lack of 732 32 bility to cooperate, current use of medications (e.g. analgesics, anti-inflammatory medicine), consumption 733 3 of alcohol, caffeine, nicotine or painkillers 8 hours prior to the data collection, recent history of acute pain 734 جaffecting the lower limb and/or trunk, past history of chronic pain conditions, participation in other pain 735 33 grials throughout the study period. All procedures performed in studies involving human participants were $\begin{array}{c} 39\\ 40\\ \end{array}$ accordance with the ethical standards of the institutional and/or national research committee and with 737 $^{41}_{42}$ he 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was $^{42}_{42}$ 4 $\frac{3}{4}$ pproved by the local Ethics Committee (N-20120077). This sample size was calculated to detect a minimum $4\,$ $\overline{
m g}$ ifference of 40% in the CoP area assuming type error 1 as 5% and power of 80% between the conditions 740 4 pefore and after the induction of experimental pain. All participants gave signed informed consents prior to 741 4 gnclusion in the study. 742 51.2. 52 Experimental protocol

Since in healthy individuals approximately 70% of the information used for controlling posture 9 744 $_{1}$ originates from proprioceptive systems (Peterka 2003), we controlled the effect of different footwear on $1 \frac{1}{12}$ postural control by asking the subjects to stand barefoot during the experiment. The participants stood on ¹³ triangular force plate that measures vertical forces (Good Balance System, Metitur, Jyväsklä, Finland; $1\frac{1}{2}$ imensions: equilateral triangle – 800-mm; sampling frequency: 50-Hz as suggested by the International 1 Society for Posture and Gait Research Standardization Committee (Scoppa et al. 2013)). This is a valid and 749 1 geliable system for postural sway measurements (Era et al. 2006; Ha et al. 2014) with accuracy better than 21-mm for the CoP position measurement (Good Balance System User Manual). The CoP position was $^{22}_{2,\$}$ 22 751 $_{2,\$}$ alculated via the Good Balance Software (Metitur, Jyväsklä, Finland) which uses the weighted arithmetic $^{24}_{25}$ mean between the vertical force measured by four sensors and their corresponding position: one in each $\frac{26}{27}$ corner of the force-plate and the last one in the centroid of the force-plate (Fig. 1). The rational for using the $2\frac{8}{2}$ and emposition for the feet was based in previous studies showing that greater pain effects are presented $\,^3 \mathbb{Q}$ when posture is challenged (Hirata et al. 2013). This was important to ensure that postural stability 756 32daptations due to pain could be observed. Therefore, subjects were asked to stand in tandem position, to 757 3 Ancrease postural challenge during the tasks, with the right leg behind (Fig. 1), arms hanging relaxed ج a alongside the body, and were instructed to maintain balance while looking forward. Tape markers were $\frac{1}{3}$ glaced on the force plate to ensure that the same foot position was maintained through all conditions. During $^{39}_{40}$ the assessment of postural control, subjects were instructed to look forward at a target positioned at eye-⁷⁶¹ $4\frac{1}{42}$ evel approximately 45-cm from the subjects to minimize the influence of the target distance on postural 42762 ⁴ 3way (Kapoula and Lê 2006). CoP records were made under eight experimental conditions, depending on the $4\,$ 5 ype of injection (control or painful), the dual-task (counting forward or counting backward as the less and 764 47 nore challenging tasks, respectively), before (pre-injection) and immediately after the injection. The 765 4 gounting forward task consisted of adding one and the counting backward was performed by subtracting $5\frac{1}{5}$ three, beginning from a random number. The total number of answers and the number of correct answers

during each trial were recorded. The order of the injections and the order of the tasks were randomized, $_1$ with the same number of subjects receiving the hypertonic or isotonic injections first. 769 11 12 The experiment always followed the same order for all participants: (i) CoP measurement while 1^{3}_{14} performing the first randomly assigned task (cognitive task 1 or 2) over 60-s (pre-injection 1); (ii) 1-min rest; 771 1 Şiii) CoP measurement over 60-s while performing the second randomly assigned task (cognitive task 1 or 2) 16 772 1 Øver 60-s (pre-injection 2); (iv) injections of the first saline solution (painful or control) into vastus medialis 773 1 gVM) and vastus lateralis (VL) muscles; (v) assessment of pain intensity by visual analogue scale (VAS); (vi) 774 2 CoP measurement over 60-s while performing task A; (vii) collecting VAS scores of the pain intensity and 1-775 2 \Re nin rest; (viii) CoP measurement over 60-s while performing task B; (ix) collecting VAS scores of the pain $^{24}_{25}$ Transity. After the final step, the pain VAS scores were taken each minute until the pain had subsided which $\frac{26}{27}$ was followed by a 5-min break. Following the break, all steps of the experiment were performed again with 28 he injection of the other saline solution, including new pre-injection CoP recordings. Before each CoP 779 3 measurement, all subjects confirmed that no tiredness or other problems were presented. The duration of 780 3 2 the CoP measurements were performed according to guidelines proposed by the International Society for 781 3 Posture and Gait Research (Scoppa et al. 2013). Fig. 2 summarizes the study procedures along time. 782 3 g.3. Experimental muscle pain Before the experiment all subjects were instructed about the nature and effects of the injections, ⁷⁸³ 38 $\begin{array}{c} 39\\ 40\end{array}$ and that one type of injection would be painful while the other would be a non-painful stimulus, although 4^{1}_{1} they would not know which kind of injection they would be receiving. Pain was induced through 42 4 $^+$ htramuscular injection of 1-mL of 6% sterile hypertonic saline solution or as a control condition 1-mL of 787 4 🕏 sotonic (0.9%) saline solution (Graven-Nielsen et al. 1997; Farina 2003; Schulte et al. 2004; Falla et al. 2006). 788 4 The injections were performed with a 2-mL syringe with a disposable needle (27G, 40-mm) into right VM 4 gnuscle and right VL muscle. Both injections locations were marked to ensure that they were applied

 $\frac{1}{5}$ approximately in the same location. The VM muscle injection was performed 5-cm proximal and 5-cm medial

to the medial corner of the patella (Shiozawa et al. 2013), and in the VL muscle, injections were performed 9 792 $_{1}$ 9 two thirds of the distance from the anterior spina iliaca to the lateral side of the patella (Fig. 3). The depth 1_{10}^{10} f the injection was determined by an ultrasound scanner (LOGIQ[™] S7, General Electric, USA). This pain 13 model has been successfully used previously to mimic knee-related pain during quiet standing tasks 14 $1\frac{5}{16}$ providing moderate pain intensities for approximately five minutes (Hirata et al. 2011). Hypertonic saline 16 $\,1$ Thjections have been shown to activate nociceptors around the injected site (Mense 1993) whereas the 0.9% 797 1 sotonic saline injections have induced little or no pain during postural control tasks similar to the one used 798 2 in the present study (Hirata et al. 2010, 2011, 2013). 799 2**3**.4. Assessment of pain intensity 800 24 25 The subjects were asked to rate the pain intensity using a 10-cm VAS from 0-cm to 10-cm (0-cm $\frac{26}{27}$ means "no pain" and 10-cm means "maximum pain") immediately after the injections and after each balance 802 ² measurement. Therefore, three VAS scores were obtained for each set of experiments (balance 803 3 measurements after isotonic injection and balance measurements after hypertonic injection, respectively; 804 3 Žig. 2), and the mean values of the three VAS scores were considered as the pain intensity after each injection 34 garadigm. Additionally, following each set of experiments subjects were asked to indicate the overall pain 806 3 greas during the trials on a body chart and to respond the McGill Pain Questionnaire (Melzack 1975). The 807 38 rea of pain was extracted from the body charts with VistaMetrix 1.38 software. The pain rating index based $\begin{array}{c} 39\\ 40\end{array}$ the rank values of the words chosen within each category (sensory, affective, evaluative and 4^{1} miscellaneous) from McGill Pain Questionnaire were obtained and the score for each category, as well as 4^{2} $4\frac{2}{3}$ he total pain rating index were determined as the sum of the ranked values of the words (Melzack 1975). 811 452.5. Data analysis All variables for postural sway were calculated based on 50-s of the standing tasks, with the first and 812 47 813 4 bast 5-s from the original 60-s time series being excluded. The analyses were performed with Matlab R2016a 814 5 foftware (Mathworks, Massachusetts, USA). The area fitted to 95% confidence interval of the CoP

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815	displacement was calculated as representative of the total CoP area displacement (95% confidence interval م				
816	10^{9} lipse), along with the CoP velocity in both directions (anterior-posterior and medial-lateral). The structural				
817	11 12 variability of the CoP was calculated by means of SaEn with the embedding dimension (<i>m</i>) and the tolerance				
818	¹ distance (r) set to $m=2$ and $r=0.2xSD$ (Vaillancourt and Newell 2000). All CoP variables are displayed as the 14				
819	1 a ifference between the values obtained immediately after the injection and the correspondent pre-injection 16				
820	1 Condition. Negative values show that the CoP variable decreased after the injection of the saline solution 18				
821	1 gompared to its respective pre-injection condition. Likewise, positive values show that the CoP variable 20				
	2 increased after the injection compared to its respective pre-injection condition.				
	22 2 ³ .6. Statistical analysis				
824	Pain outcomes were compared between injection types (isotonic or hypertonic injections) with				
825	$^{26}_{27}$ paired T-tests when normal distribution was present (VAS scores and pain area data) and with the Wilcoxon $^{27}_{27}$				
826	2 Signed Rank Test when the data distribution was non-normal (McGill scores). The task measures (number of $_{29}$				
827	3 Q nswers, number of correct answers) were evaluated with a 3-way RM-ANOVA with <i>injection</i> (isotonic vs 31				
828	3 D ypertonic), <i>time</i> (pre-injection vs after injection) and <i>task</i> (counting forward vs backwards) as main factors. 33				
829	3 4 he CoP parameters were compared with a 2-Way RM-ANOVA with <i>task</i> and <i>injection</i> as main factors, and 35				
	$_{3}$ the p-values are shown in the table 3. Bonferroni post-hoc correction for multiple comparisons was applied				
	37 38 and p-values are shown in the results texts. The alfa-value (α) for statistical significance was set to 0.05.				
832	39 40 . Results				
833	42				
834	Fig. 4 shows the reported pain areas following both isotonic and hypertonic injections. Pain was				
835	4 present in the anterior and lateral portions of the thigh after both isotonic and hypertonic injections, being 46				
836	4 Thore concentrated in the lower half of the thigh after the isotonic injections. The hypertonic saline injections 48				
837	$4 \frac{1}{2}$ nduced higher pain area (mean area ± SD: isotonic = 518.6 ± 690.6 au; hypertonic = 1659.3 ± 1574.0 au; 50				
838	$5f^2$ =0.003) and higher VAS scores (mean score ± SD: isotonic = 0.9 ± 1.1 cm; hypertonic = 4.7 ± 1.7 cm; P<0.001) 52				
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839	7 ghan isotonic saline injections. Table 1 shows the scores for each class of words from McGill Pair	ı					
840	$\frac{9}{1}$ Questionnaire and the pain rating index. Subjects presented a higher total pain rating index and scored	b					
	10^{-10} does not include and the pain rating index. Subjects presented a higher total pain rating index and scored 11^{-11}_{-12} higher in all the categories, with the exception of the affective class, after the hypertonic injections (P<0.05).						
	13.2 Cognitive task performance						
843	 Only for the analysis of the cognitive task performance, one subject was not included due to problems 	s					
844	16 1 h the answers recording. The total number of answers and the number of correct answers decreased during						
845	18 19 ackwards counting conditions compared with forwards counting despite the injection effect (significant	t					
846	20 2 main effect for <i>task factor</i> ; Table 2).						
347	22 2 ³ 3. Center of pressure						
848	24 25 <i>Effect of experimental pain in CoP variables</i>						
849	There were no statistical differences between the different conditions for the factor <i>injection</i> on any There were no statistical differences between the different conditions for the factor <i>injection</i> on any test of the factor <i>injection</i> of the factor <i>inject</i>	У					
850	$\frac{28}{29}$ f the CoP variables (Table 3).						
851	30 Effect of cognitive task in CoP variables31						
852	A main effect of <i>task</i> was found for the CoP AP-velocity (F=5.82; <i>P</i> =0.028), showing that there was ar 33	ı					
853	34 ncreased AP-velocity during the counting backwards task compared to the counting forwards task 35	,					
854	3 degardless the type of injection (Table 3).						
855	 Effect of the interaction between experimental pain and cognitive task in CoP variables 						
856	An interaction effect was found between <i>injection</i> and <i>task</i> factors for CoP total area and CoP ML	-					
857	$\frac{41}{\text{Velocity}}$ (CoP total F=7.78, P=0.049; CoP ML F=4.69, P=0.021) (Table 3). Post-hoc comparisons showed tha 42	t					
858	4 Both variables decreased after the hypertonic injection in comparison to the condition with isotonic injection 44	ı					
859	45 when subjects where counting forward (Bonferroni: $P = 0.010$ for total area; $P = 0.015$ for ML-velocity). After 46	r					
860	 4 The hypertonic injection, CoP total area increased when subjects were counting backwards in comparison to 4 8 						
861	$_{40}^{10}$ gyhen they were counting forwards (Bonferroni: <i>P</i> = 0.019). ML-velocity showed differences between the 50 51	9					
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different cognitive tasks also after the injection of hypertonic solution, with a smaller decrease of ML-velocity 863 1 while counting backwards (Bonferroni: P = 0.049). 12 Discussion 865 13 14 The present study aimed at quantifying how postural stability, represented by CoP sway (velocity and 866 ¹ area of displacement) and CoP complexity (CoP SaEn), is modified during experimental pain while performing 867 17 cognitive task. The main results showed that the kind of cognitive task did not interfere with postural 868 19 tability in the absence of pain. Experimental pain around the knee joint reduced CoP sway but did not affect 869 2 CoP complexity during the performance of an easier cognitive task. During experimentally induced pain, the 22_{2} gerformance of a difficult cognitive task increased CoP sway but did not change CoP complexity. 24_{2} <u>Bain intensity and counting performance</u> The subjects showed higher pain intensity for the hypertonic saline injection and a larger pain area 28 compared with the isotonic saline injection, as expected, indicating that experimental pain occurred (Hirata 874 3 et al. 2011). The McGill pain questionnaire indicated that hypertonic saline was perceived more impairing 875 3 2 han the isotonic injection in all subscales except for the affective one. It is important to note that during 876 3 Asotonic injections subjects rated pain around 1/10, which cannot be classified as a totally pain free condition. ⁸⁷⁷ 36 Counting performance requires the use of cognitive process which relies on the working memory of 878 3 she subject (Lemaire 1996), impairing motor output performance when executed simultaneously with a $\begin{array}{c} 39\\ 40\\ \end{array}$ 4^{1} maintain performance of difficult cognitive task while experiencing different levels of pain. In this study, the 4^{2} 43 3 ainful condition did not affect the counting performance while performing a motor task (standing still) 882 4 Endicating that healthy subjects are able to engage multiple tasks (motor and cognitive) during pain without 883 4 Zompromising performance. This suggests that sufficient cognitive resources were available to manage the 884 4 gognitive process of counting forwards or backwards despite the interpretation of painful stimuli and the $_{5}$ postural control task (Eccleston et al. 1999). Finally, education level is associate with both motor and

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886	gerceptual performance, where higher education level is associated with better performance (Voos et al.
887	10^{9} 2015). Since our subjects were all university students, we believe that bias due to education level did not
888	11 affect the present results.
889	1 <u>Effect of cognitive tasks on postural stability</u> 1 4
890	15 Our first initial hypothesis, that (i) the kind of cognitive task (more or less demanding) in a non-painful 16
891	1 Condition would not interfere with CoP sway or CoP complexity, was confirmed. The factor task affected the 18
892	1 CoP anterior-posterior velocity, indicating an increased velocity during the execution of the more difficult
893	20 $2 \pm ask$ (counting backwards) in comparison to the easier task (counting forward). Nevertheless, the CoP SaEn
894	22 23^{yas} not affected by the kind of the performed cognitive task. These results indicate that enough cognitive
895	$^{24}_{25}$ esources were available to overcome the demands of both cognitive and postural tasks, which was expected
896	26 since they were young individuals without any sensory-motor alterations. 27
897	² & <u>effect of experimental knee-related pain on postural stability</u> 29
898	30 Our second initial hypothesis, that (ii) experimental pain would increase CoP sway and decrease CoP 31
899	32 complexity was not confirmed since the type of saline solution injected did not affect the CoP variables.
900	34 owever, even though the factor <i>injection</i> did not show statistical differences between the different
	35 3 conditions for any of the studied CoP variables, there was a difference between total area and ML-velocity
902	$\frac{37}{38}$ between the control and the painful condition when the subjects were counting forwards, i.e., in conditions
903	$^{39}_{40}$ where the kind of cognitive task performed was the same. Interestingly, during the counting forward, the
904	$\overset{4}{}_{1}$ type of injection resulted significant changes in postural sway (total area and ML-velocity) in opposite $\overset{4}{}_{2}$
905	4 directions: positive values of the difference between pre-injection and after injection of the isotonic solution, 44
906	45 whereas after the injection of the hypertonic solution both variables showed negative values. Additionally, 46
907	4 no significant changes were observed in the structural variability of the CoP signal. This is contrary to the 48
908	$4\dot{g}$ nitial hypothesis, where an increase in postural sway and a decrease in structural variability during painful
909	50 5 conditions were expected. It is also in contrast with previous findings (Mazaheri et al. 2013) but may relate
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to the different position of the feet used in this study, which affects the postural sway (Day et al. 1993). The 9 911 $_{1}$ transformed and the set of the CoP due to the limited base of support 11_{15} compared to side-by-side feet position, since if the subjects increase the CoP amplitude they may fall (Day $1\frac{2}{2}$ et al. 1993). This also may reflect a voluntary strategy, requiring a greater amount of cognitive resources and 14 $\,^1$ $\overline{3}$ ttention (Morasso and Sanguineti 2002), attempting to avoid large excursions of the body and consequent $\,1$ Toss of balance. For the current study, this might indicate that the subjects prioritized the balance task over 916 19he other tasks, also known as posture first strategy (Vuillerme and Nafati 2007). The subjects were able to 917 21educe the postural sway without compromising the counting performance during the easy cognitive task, 918 $_2$ §uggesting that the available cognitive resource was sufficient to perform the less challenging cognitive task $^{24}_{25}$ Sithout compromising postural stability. Therefore, these results indicate that healthy subjects have the $\frac{26}{27}$ capacity to perform easy cognitive tasks while ensuring postural stability (Siu and Woollacott 2007). 921 ² Reducing postural sway might reflect a motor strategy available for healthy subjects to avoid excessive 922 ³ Pranslation of the body, which could lead to balance loss (Winter 1995). This strategy was also observed 923 3 2 uring the control injection while counting backwards, probably indicating that a high cognitive load seems 924 340 be interpreted as a treat to postural stability. An alternative explanation for the contrast between the 925 3 present study and the previous studies with pain patients showing larger postural sway (Schulte et al. 2004; 38 evinger et al. 2016) might be the pain model used that is not a complete proxy to the impaired pain patients' $\begin{array}{c} 39\\ \text{sensory-motor system.}\\ 40\end{array}$ 928 41 <u>Interactions between pain and cognitive load on postural stability</u> 42

929 43 44
930 45 Our initial third hypothesis, that (iii) the presence of experimental pain would increase CoP sway and 44
930 45 Decrease CoP complexity only when performing a difficult cognitive task was partially confirmed since CoP 46
931 47 way increased during pain under a difficult cognitive task, but the CoP complexity did not change. ANOVA 48
932 49 esults showed an interaction between the task and injection factors for total area and ML-velocity. After 5 the hypertonic injection CoP total area increased and CoP ML-velocity decreased less while counting

packwards in comparison to counting forwards condition, corroborating our hypothesis. ANOVA results also $_1\delta$ howed an effect of the task factor on AP-velocity with post-hoc comparisons showing a difference only 11_{12} 936 11_{12} auring the hypertonic injection condition: while counting backwards AP-velocity also increased. Altogether 1^{2}_{these} results show that CoP sway increases when performing a more demanding cognitive task in the 14 $1\frac{5}{2}$ bresence of experimental pain. This might reflect an interference with the information-processing capacity 16 $\,1$ and an attention disruption from both postural control and cognitive task (Eccleston et al. 1999). Previous 940 1 Studies suggest that disruptions of sensory information lead to worsening of proprioception in the affected 941 2 prea (Matre et al. 2002), further impairing postural sway (Hirata et al. 2010, 2011). The results indicate that $^{22}_{2,\frac{1}{2}}$ he posture first strategy (Vuillerme and Nafati 2007) found during the easy cognitive task during pain is no $^{24}_{25}$ Solution $^{24}_{25}$ Solution $^{24}_{25}$ Solution $^{24}_{25}$ Solution $^{24}_{25}$ Solution $^{24}_{25}$ Solution $^{22}_{25}$ Solution $\frac{26}{27}$ load in painful conditions seems to impair the motor performance maybe due to insufficient cognitive 28 esource to simultaneously maintain postural stability (which requires significant amount of attention 3 (Morasso and Sanguineti 2002)) and execute a difficult cognitive task. These results might have important 947 32ew implications in understanding the mechanisms related to fall accidents. Postural stability in daily life 948 3 Activities is usually performed in combination with additional tasks, for example, walking in a busy slippery 949 3 gidewalk. These daily life activities involves simultaneously competition for the cognitive resources available 950 36Woollacott and Shumway-Cook 2002) to evaluate the environment constrains in order to promote the best 40^{39} 951 40^{10} where 40^{10} (Winter 1995). Our present results indicate that, if the subject performs a challenging $\frac{4}{2}$ bostural task in pain, his/her capacity for maintain balance while exposed to a difficult cognitive task is 953 ⁴ Juboptimal, which could increase the likelihood of losing balance. 954 45 The complexity of postural sway did not show any differences between the experimental conditions.

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955 4 This result is contrary to the literature finding that young healthy subjects present a more regular and less 48
956 4 gutomatic postural sway (decreased CoP SaEn) when the motor task is more difficult (e. g. standing with eyes 50
957 5 flosed) and more irregular postural sway and more automatic postural sway (increased CoP SaEn) when a 52

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958	gognitive task is added (Donker et al. 2007; Stins et al. 2009). The fact that the cognitive task did not interfere
959	9_1 with CoP complexity may be due to the nature of both motor (standing in tandem position) and cognitive
960	11 (subtraction calculus) tasks used in the experimental setup that did not interfere with the automaticity of 12
961	$^{13}_{14}$ postural control. Besides that, pain also did not affect CoP complexity, showing that experimental knee- $^{14}_{14}$
962	1F elated pain did not compromise the coupling between the components of the system responsible for 16
963	1 <code>Balance</code> in the current experimental setup. Future studies should investigate the interaction between pain, 18
964	1 gognition and on CoP complexity with different motor and cognitive demands, in addition to different 20
965	2 populations.
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967	$\begin{array}{c} 24\\ 25 \end{array}$ relevance of the findings for clinical populations should be interpreted with care. The experimental pain
968	$^{26}_{27}$ model used here is convenient to assess the effect of pain without the interference of potential structural $^{27}_{27}$
969	28 r pathologies. However, extrapolating the current findings to an older population can only be done to some 29
970	³ degree. Additionally, chronic pain patients may also suffer from depressive symptoms (Bair et al. 2003) or 31
971	3 anxiety (McWilliams et al. 2003), which might increase cognitive load (Nebes et al. 2001). Furthermore,
972	34 ognitive impairments are often found in chronic pain patients, decreasing the possibility to maintain
	3 performance of two or more concurrent tasks (Brauer et al. 2004), as opposed to what was observed in this
974	$\frac{37}{38}$ tudy where young healthy subjects were recruited. Also, there was no recording of postural sway without
975	$^{39}_{40}$ any cognitive task. This would have allowed comparisons with a condition where neither pain nor cognitive $^{40}_{40}$
976	4 Lasks were influencing postural sway, and could have reduced type 2 errors given that multiple CoP variables 42
977	4 were analyzed in the study. Thus, it can be considered a limitation to our interpretations. 44
978	45. Conclusions

Pain and cognitive task interfered on postural stability, changing its patterns. During the performance 48
 4 p f a simple cognitive task, pain reduced postural sway, while during the performance of a more demanding 50
 5 f cognitive task, postural sway was increased in young healthy subjects. Since our subjects were young healthy 52

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7 7 2 gubjects, the direct translation of the present results to patients suffering from pain should be done wit	
9 3 1 Gaution. However, these results may suggest that rehabilitation approaches should take into account tha	at
11 12 pain not only affects directly the motor system, but may occupy cognitive resources, potentially resulting i 12	in
13 boorer performance when performing rehabilitation exercises. Additionally, rehabilitation strategies usin 14	١g
15 both motor and cognitive resources need further investigation to outline the effect of interaction betwee 16	n
10 17 1 pain and cognition on the performance during activities of daily life in patients. 18	
38 19	
20 2^{2} fompliance with ethical standards	
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² §cholarship (FAPESP 2013/06123-7, 2015/00214-6). 27	
2 Conflict of Interest: The authors declare that they have no conflict of interest. 29	
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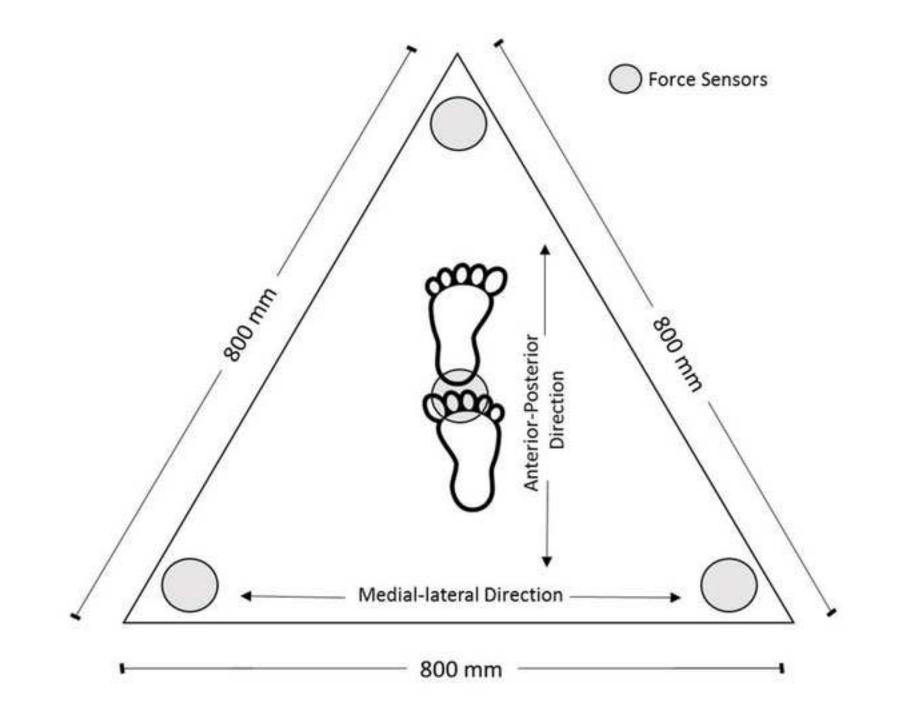
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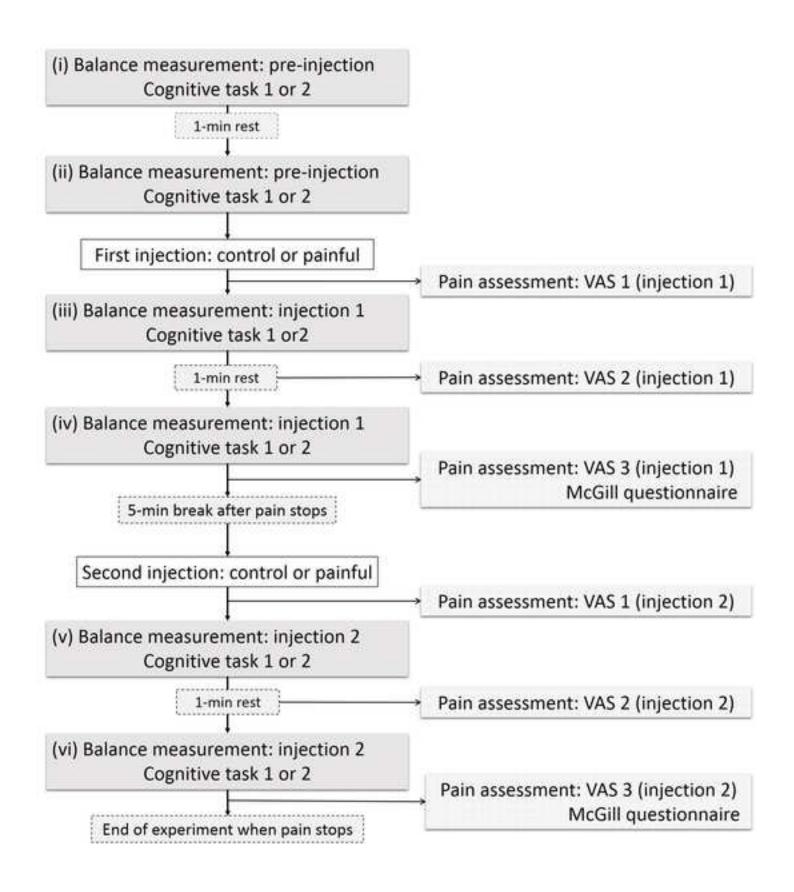
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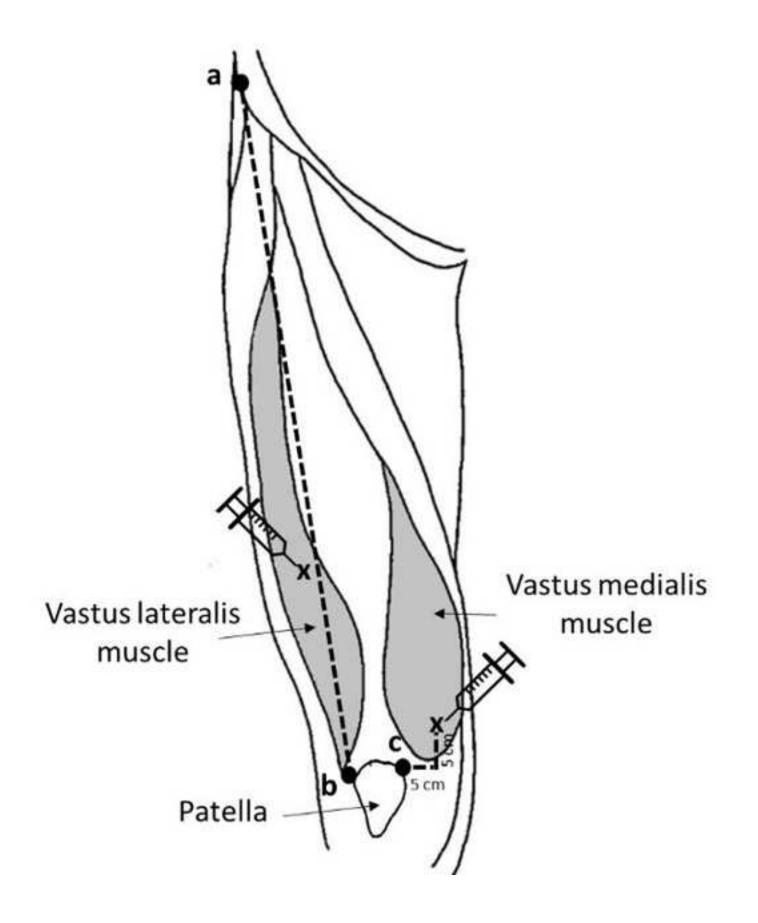
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.146	16 1 Fig 2 Study design overview: pain assessments were performed immediately after each injection and each	
.147	18 1 \mathfrak{B} alance measurement; the order of the saline injections was randomized in a balanced way	
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	22 $2\frac{5}{3}$ ig 3 Injections sites for vastus lateralis muscle, performed at two thirds of the distance from the anterior	
	24 25 pina iliaca (a) to the lateral side of the patella (b); and for the vastus medialis muscle, performed 5 cm	
	$^{26}_{27}$ proximal and 5 cm medial to the medial corner of the patella (c), 27	
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.154	32 nline version) and hypertonic (bottom, red in the online version saline injections (A); the individual 33	
.155	3 distributions are superimposed in the anatomical drawings	
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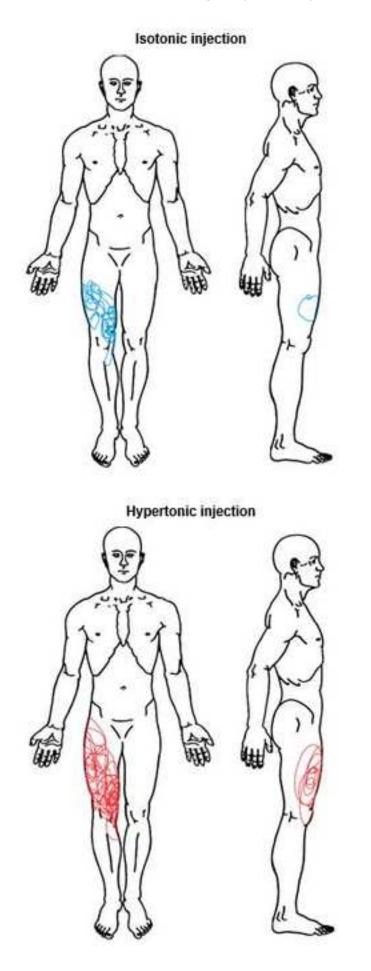


Table 1

Table 1 – McGill Pain Questionnaire scores (median [Range]) for each category and

total pain rating index for the pain experienced after isotonic and hypertonic

injections.

McGill scores	Inject	<i>P</i> -value		
	Isotonic	Hypertonic	P-value	
Sensory	1 [0-18]	8.5 [2-23]*	0.023	
Affective	0 [0-7]	0 [0-4]	0.174	
Evaluative	0 [0-1]	1.5 [0-4]*	0.001	
Miscellaneous	0 [0-7]	2.5 [0-10]*	0.004	
Total pain rating index	2.5 [0-33]	16 [5-30]*	0.001	

*Statistically significant (*P*<0.05) higher then isotonic condition (Wilcoxon Signed Rank Test with Bonferroni correction).

Table 2 – Mean (±SD) of the cognitive tasks performances before and during both

injections type (hypertonic and isotonic) and three-way repeated measures ANOVA

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results (F; P).

Task		Cognitive task		ANOVA (F; P value)				
performance	Condition	Counting forward	Counting backward	Time	Injection	Task	Time x Injection x Task	
	Before control injection	63.3±7.5	31.3±13.5	0.05; 0.833		68.0; <0.00 1 *	0.28; 0.608	
Total	After control injection	63.5±8.1	30.4±15.0		0.22: 0.644			
answers	Before painful injection	63.3±10.4	32.1±12.7		0.22; 0.644			
	After painful injection	63.3±9.1	32.3±12.7					
	Before control injection	63.3±7.5	30.9±13.9					
Total correct	After control injection	63.5±8.1	29.8±8.1	0.05; 0.819	0.00.0.015	64.00.001*	0.20.0540	
answers	Before painful injection	63.3±10.4	30.9±14.2		0.06; 0.815	64.8; <0.001*	0.39; 0.540	
	After painful injection	63.3±9.0	31.3±13.5					

* Statistically significant (P<0.05).

Table 3 – Mean (\pm SD) of center of pressure (CoP) variables represented as the difference between the measures after and before each injection (isotonic injection considered as control, hypertonic injection considered as painful) and two-way repeated measures ANOVA results (F; *P*).

CoP Variable	Control injection		Painful injection		ANOVA (F; <i>P</i> value)		
	Counting forward	Counting backward	Counting forward	Counting backward	Injection	Task	Injection x task
Total area (cm²)	28.9±78.5ª	-25.1±138.7	- 84.5±145.5 ^{а,} ^ь	12.8±53.9 ^b	1.84; 0.196	0.75; 0.400	7.78; 0.049*
AP Velocity (cm/s)	-0.36±2.24	-0.07±1.66	-0.39±1.82	1.07±2.35	0.61; 0.446	5.92; 0.028*	1.168; 0.614
ML Velocity (cm/s)	0.98±1.93 ^{c,} d	-0.73±2.23d	- 1.71±2.61 ^{c,} e	-0.34±1.92°	3.90; 0.067	6.68; 0.697	4.69; 0.021*
AP SaEn (a. u.)	0.007±0.067	- 0.003±0.089	0.041±0.081	0.001±0.048	0.73; 0.406	1.51; 0.238	1.01; 0.331
ML SaEn (a. u.)	- 0.019±0.050	- 0.003±0.038	- 0.004±0.045	- 0.104±0.052	0.12; 0.116	0.12; 0.738	0.10; 0.755

* Statistically significant (*P*<0.05). ^{a, b, c, d, e} Statistically significant difference between conditions detected in post-hoc tests (*P*<0.05).

Author Contribution Statement

RPH, TP, NV and TGN conceived and designed research. EYS and TP conducted experiments. EYS and RPH analyzed data. EYS, RPH, ICNS, TP, NV and TGN wrote the manuscript. All authors read and approved the manuscript.