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EXPERIMENTAL KNEE-RELATED PAIN ENHANCES ATTENTIONAL INTERFERENCE ON POSTURAL CONTROL

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Abstract

Purpose: To quantify how postural stability is modified during experimental pain while performing different cognitively demanding tasks.

Methods: Sixteen healthy young adults participated in the experiment. Pain was induced by intramuscular injection of hypertonic saline solution (1mL, 6%) in both vastus medialis and vastus lateralis muscles (0.9% isotonic saline was used as control). The participants stood barefoot in tandem position for one minute on a force plate. Center of pressure (CoP) was recorded before and immediately after injections, while performing two cognitive tasks: (i) counting forwards by adding one; (ii) counting backwards by subtracting three. CoP variables – total area of displacement, velocity in anterior-posterior (AP-velocity) and medial-lateral (ML-velocity) directions, and CoP sample entropy in anterior-posterior and medial-lateral directions were displayed as the difference between the values obtained after and before each injection and compared between tasks and injections.

Results: CoP total area (-84.5 ± 145.5 vs. 28.9 ± 78.5 cm^2) and ML-velocity (-1.71 ± 2.61 vs. 0.98 ± 1.93 cm/s) decreased after the painful injection vs. Control injection while counting forward ($P < 0.05$). CoP total area (12.8 ± 53.9 vs. -84.5 ± 145.5 cm^2), ML-velocity (-0.34 ± 1.92 vs. -1.71 ± 2.61 cm/s) and AP-velocity (1.07 ± 2.35 vs. -0.39 ± 1.82 cm/s) increased while counting backwards vs. forwards after the painful injection ($P < 0.05$).

Conclusion: Pain interfered with postural stability according to the type of cognitive task performed, suggesting that pain may occupy cognitive resources, potentially resulting in poorer balance performance.

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

List of abbreviations

ANOVA	Analysis of variance
au	Arbitrary units
CoP	Center of pressure
SaEn	Sample entropy
SD	Standard deviation
VAS	Visual analogue scale
VM	Vastus medialis
VL	Vastus lateralis

1. Introduction

Controlling of upright posture requires a significant amount of attention to ~~constantly~~ gather information from the body and the environment and to generate adapted and accurate muscle activation for postural control (Morasso and Sanguineti 2002). Although the majority of postural control is regulated via automatic neural processes (Bronstein and Buckwell 1997), higher cortical centers are significantly involved in processing sensory information to plan and execute the best motor strategy for postural control (Winter 1995). In daily life, postural control is challenging as several tasks simultaneously compete for the cognitive resources available (Woollacott and Shumway-Cook 2002), limited by the capacity of higher centers to process sensory information (Kahneman 1973). Therefore, sharing attentional resources may cause impairments in the performance of daily living activities (Brauer et al. 2004). ~~Evidence suggests that a~~For example, competition for cognitive resources during tasks involving postural stability results in body stability being prioritized over secondary tasks (Liston et al. 2014).

Dual tasks paradigms, where subjects perform an additional task during ~~quiet~~ standing, are employed to quantify the extent to which attention is associated with postural control. Decreases in postural sway while performing a secondary task compared with control conditions have been reported (Andersson et al. 2002; Pellecchia 2003) whereby focusing the attention on standing as still as possible increased postural sway compared with conditions without similar instructions (Vuillerme and Nafati 2007). Altogether, these results suggest that postural control demands attention (Woollacott and Shumway-Cook 2002) and that simultaneous cognitive loading plays an important role in balance stability (Swan et al. 2007).

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 control~~ subjects show controversial results (Huxhold et al. 2006; Fraizer and Mitra 2008). Young healthy subjects have probably more ability to allocate the attentional resources ~~during upright standing~~ without sacrificing postural stability, showing that a system without impairments prioritizes postural stability when dealing with dual-cognitive tasks (Siu and Woollacott 2007).

~~Evidence suggests that ~~S~~s~~ubjects with pain demonstrate increased postural sway compared with controls (Hirata et al. 2011). ~~Among several~~A ~~potential~~possible explanation~~s~~ for this finding~~,~~ ~~one hypothesis~~ is that the increased postural sway may relate to a disrupting effect of nociceptive stimuli on attention to other simultaneous non-nociceptive tasks (Eccleston et al. 1999), underlining that processing of nociceptive stimuli is cognitively demanding (Veldhuijzen et al. 2006). Thus, the execution of cognitive tasks during pain might interfere with postural control. Although previous studies have shown that patients with pain present impaired balance while performing a secondary cognitive task in comparison to health subjects (Van Daele et al. 2010; Larivière et al. 2013; Mazaheri et al. 2014; Sherafat et al. 2014; Etemadi et al. 2016; Levinger et al. 2016), it is not clear yet the isolate effect of pain ~~in these conditions and comparisons, ~~since ~~in clinical pain populations, besides pain, other factors like ~~reduced muscle strength, reduced flexibility and degenerative changes at the affected segment also cause both stiffness and instability in patients suffering from chronic pain (Knoop et al. 2012). Therefore, further investigation of the interaction between pain, cognition and postural stability is warranted. This investigation is of particular interest for clinical practice since there are evidences that attention can be directed away from pain using some specific strategies (Van Ryckeghem et al. 2018). If selective attention could be directed away from the painful stimulus and modify the deleterious effect of muscle pain on postural control, these results could have important implications for clinical settings. Likewise, if the execution of cognitive tasks impairs postural control in the presence of pain, this should also be taken into account in rehabilitation context.

Considering that posture can be defined as the dynamic stability of a continuous moving body (Harbourne and Stergiou 2003; Madeleine et al. 2011), nonlinear analysis of the dynamic structure of the center of pressure (CoP) time series would contribute to understand the physiological complexity of posture by accessing motor patterns that would be implicit in the CoP variability. Sample entropy (SaEn) measures variations in the system output along time~~, which is independent of the signal magnitude (Slifkin and Newell 1999; Richman and Moorman 2000). ~~. Therefore, measures of physiological complexity of the postural sway during quiet standing may relate to the system functionality as they are defined as the capacity of generating adaptive answers to an ever-changing environment such as controlling posture (Manor et al. 2010). SaEn provides a measure of “orderly structure” within the time series since it tests if there are any repeated patterns of various lengths, including the ones that are not repeated at regular intervals (Duarte and Sternad 2008). So, the lower the SaEn values are, the higher the similarity and lesser the complexity in the temporal series is (Richman and Moorman 2000). ~~SaEn has been used to measure the structure of the CoP variability (Roerdink et al. 2006; Donker et al. 2007; Duarte and Sternad 2008; Stins et al. 2009) and thus address the complexity of the signal.~~

~~Most definitions of complexity are driven by operational considerations on the number of system elements and their functional interactions. Therefore, c~~Complexity depends on the number of structural components of the system, the existing coupling among these components and how this interaction is influenced by the intrinsic dynamic properties of the system and the motor task demands (Vaillancourt and Newell 2002). Thus, if the presence of pain and the execution of a cognitive task are both concurring with the attentional resources used in postural control, then the coupling between the components of the system responsible for balance may be affected and, consequently, the complexity of the postural sway is affected. ~~The literature shows that the e~~Execution of a concurrent cognitive task during standing increases the complexity of the postural sway, and this increase has been attributed to a more automatized postural sway, when less attention is directed to the balance control (Donker et al. 2007; Stins et al. 2009; Kuczyński et al. 2011). On the other hand, there is some evidence that the complexity of postural control decreases with pain~~. Søndergaard et al. (2010) found a decrease SaEn of CoP displacement ~~during sitting with increased perceived discomfort in healthy young subjects (Søndergaard et al. 2010). ~~The same~~Similar finding was reported in young subjects with transient acute episode of low back pain during two continuous hours of standing, but without history of low back pain (Fewster et al. 2017), showing a relation between the occurrence of pain and the decrease in CoP complexity. Therefore, examining the complexity of postural sway in a dual task context and the effect of experimental pain in this condition may improve the understanding of the decrease in postural stability (Levinger et al. 2016) and complexity (Fewster et al. 2017) that may exist as a result of pain in an otherwise healthy system.

The aim of this study was to quantify how postural stability~~, i. e., CoP sway~~ [~~(~~CoP sway velocity and area of displacement~~)~~ and ~~CoP~~ complexity (CoP SaEn)], is modified during experimental pain while performing a cognitive task. It was hypothesized that (i) the kind of cognitive task (more or less demanding) in a non-painful condition will not interfere with CoP sway or CoP complexity, since the system would have enough cognitive resources to overcome it; (ii) experimental pain will increase CoP sway and decrease CoP complexity, regardless the type of cognitive task performed; (iii) the presence of experimental pain while performing a difficult cognitive task will overload the cognitive resources and impair postural stability, increasing CoP sway and decreasing CoP complexity.

2. Methods

2.1. Subjects

Sixteen young adults, all university students, (to control for the effect of education level on 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 ± 4.0 years; body mass = 68.8 ± 5.2 kg; height = 1.68 ± 0.06 m). The exclusion criteria were body mass index above 25 kg/m², pregnancy, drug addiction, previous neurologic, musculoskeletal or mental illness, lack of ability to cooperate, current use of medications (e.g. analgesics, anti-inflammatory medicine), consumption of alcohol, caffeine, nicotine or painkillers 8 hours prior to the data collection, recent history of acute pain affecting the ~~upper~~ lower limb and/or trunk, past history of chronic pain conditions, participation in other pain trials throughout the study period. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the local Ethics Committee (N-20120077). This sample size was calculated to detect a minimum difference of 40% in the CoP area assuming type error 1 as 5% and power of 80% between the conditions before and after the induction of experimental pain. All participants gave signed informed consents prior to inclusion in the study.

2.2. *Experimental protocol*

Since in healthy individuals approximately 70% of the information used for controlling posture originates from proprioceptive systems (Peterka 2003), we controlled the effect of different footwear on postural control by asking the subjects to stand barefoot during the experiment. -The participants stood on a triangular force plate that measures vertical forces (Good Balance System, Metitur, Jyväsklä, Finland; dimensions: equilateral triangle – 800-mm; sampling frequency: 50-Hz as suggested by the International Society for Posture and Gait Research Standardization Committee (Scoppa et al. 2013)). This is a valid and reliable system for postural sway measurements (Era et al. 2006; Ha et al. 2014) with accuracy better than 1-mm for the CoP position measurement (Good Balance System User Manual). The CoP position was calculated via the Good Balance Software (Metitur, Jyväsklä, Finland) which uses the weighted arithmetic mean between the vertical force measured by four sensors and their corresponding position: one in each corner of the force-plate and the last one in the centroid of the force-plate (Fig. 1). The rational for using the tandem position for the feet was based in previous studies showing that greater pain effects are presented when posture is challenged (Hirata et al. 2013). This was important to ensure that postural stability adaptations due to pain could be observed.- Therefore, subjects were asked to stand in tandem position, to increase postural challenge during the tasks, with the right leg behind (Fig. 1), arms hanging relaxed alongside the body, and were instructed to maintain balance while looking forward. Tape markers were placed on the force plate to ensure that the same foot position was maintained through all conditions. During the assessment of postural control, subjects were instructed to look forward at a target positioned at eye-level approximately 45-cm from the subjects to minimize the influence of the target distance on postural sway (Kapoula and Lê 2006). CoP records were made under eight experimental conditions, depending on the type of injection (control or painful), the dual-task (counting forward or counting backward as the less and more challenging tasks, respectively), before (pre-injection) and immediately after the injection. The counting forward task consisted of adding one and the counting backward was performed by subtracting 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, 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 performing the first randomly assigned task (cognitive task 1 or 2) over 60-s (pre-injection 1); (ii) 1-min rest; (iii) CoP measurement over 60-s while performing the second randomly assigned task (cognitive task 1 or 2) over 60-s (pre-injection 2); (iv) injections of the first saline solution (painful or control) into vastus medialis (VM) and vastus lateralis (VL) muscles; (v) assessment of pain intensity by visual analogue scale (VAS); (vi) CoP measurement over 60-s while performing task A; (vii) collecting VAS scores of the pain intensity and 1-min rest; (viii) CoP measurement over 60-s while performing task B; (ix) collecting VAS scores of the pain intensity. After the final step, the pain VAS scores were taken each minute until the pain had subsided which was followed by a 5-min break. Following the break, all steps of the experiment were performed again with the injection of the other saline solution, including new pre-injection CoP recordings. Before each CoP measurement, all subjects confirmed that no tiredness or other problems were presented. The duration of the CoP measurements were performed according to guidelines proposed by the International Society for Posture and Gait Research (Scoppa et al. 2013). Fig. 2 summarizes the study procedures along time.

2.3. *Experimental muscle pain*

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 they would not know which kind of injection they would be receiving. Pain was induced through intramuscular injection of 1-mL of 6% sterile hypertonic saline solution or as a control condition 1-mL of isotonic (0.9%) saline solution (Graven-Nielsen et al. 1997; Farina 2003; Schulte et al. 2004; Falla et al. 2006). The injections were performed with a 2-mL syringe with a disposable needle (27G, 40-mm) into right VM muscle and right VL muscle. Both injections locations were marked to ensure that they were applied 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 at two thirds of the distance from the anterior spina iliaca to the lateral side of the patella (Fig. 3). The depth of the injection was determined by an ultrasound scanner (LOGIQ™ S7, General Electric, USA). This pain model has been successfully used previously to mimic knee-related pain during quiet standing tasks providing moderate pain intensities for approximately five minutes (Hirata et al. 2011). Hypertonic saline injections have been shown to activate nociceptors around the injected site (Mense 1993) whereas the 0.9% isotonic saline injections have induced little or no pain during postural control tasks similar to the one used in the present study (Hirata et al. 2010, 2011, 2013).

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2.4. Assessment of pain intensity

The subjects were asked to rate the pain intensity using a 10-cm VAS from 0-cm to 10-cm (0-cm means “no pain” and 10-cm means “maximum pain”) immediately after the injections and after each balance measurement. Therefore, three VAS scores were obtained for each set of experiments (balance measurements after isotonic injection and balance measurements after hypertonic injection, respectively; Fig. 2), and the mean values of the three VAS scores were considered as the pain intensity after each injection paradigm. Additionally, following each set of experiments subjects were asked to indicate the overall pain areas during the trials on a body chart and to respond the McGill Pain Questionnaire (Melzack 1975). The area of pain was extracted from the body charts with VistaMetrix 1.38 software. The pain rating index based on the rank values of the words chosen within each category (sensory, affective, evaluative and miscellaneous) from McGill Pain Questionnaire were obtained and the score for each category, as well as the total pain rating index were determined as the sum of the ranked values of the words (Melzack 1975).

2.5. Data analysis

All variables for postural sway were calculated based on 50-s of the standing tasks, with the first and last 5-s from the original 60-s time series being excluded. The analyses were performed with Matlab R2016a software *(*Mathworks, Massachusetts, USA). The area fitted to 95% confidence interval of the CoP displacement was calculated as representative of the total CoP area displacement (95% confidence interval ellipse), along with the CoP velocity in both directions (anterior-posterior and medial-lateral). The structural variability of the CoP was calculated by means of SaEn with the embedding dimension (*m*) and the tolerance distance (*r*) set to *m*=2 and *r*=0.2xSD (Vaillancourt and Newell 2000). All CoP variables are displayed as the difference between the values obtained immediately after the injection and the correspondent pre-injection condition. Negative values show that the CoP variable decreased after the injection of the saline solution compared to its respective pre-injection condition. Likewise, positive values show that the CoP variable increased after the injection compared to its respective pre-injection condition.

2.6. Statistical analysis

Pain outcomes were compared between injection types (isotonic or hypertonic injections) with paired T-tests when normal distribution was present (VAS scores and pain area data) and with the Wilcoxon Signed Rank Test when the data distribution was non-normal (McGill scores). The task measures (number of answers, number of correct answers) were evaluated with a 3-way RM-ANOVA with *injection* (isotonic vs hypertonic), *time* (pre-injection vs after injection) and *task* (counting forward vs backwards) as main factors. The CoP parameters were compared with a 2-Way RM-ANOVA with *task* and *injection* as main factors, and the p-values are shown in the table 3. Bonferroni post-hoc correction for multiple comparisons was applied and p-values are shown in the results texts. The alfa-value (α) for statistical significance was set to 0.05.

3. Results

~~*3.1. Experimental muscle pain and cognitive task performance*~~

3.1 Area and amplitude of perceived pain'

Fig. 4 shows the reported pain areas following both isotonic and hypertonic injections. Pain was present in the anterior and lateral portions of the thigh after both isotonic and hypertonic injections, being more concentrated in the lower half of the thigh after the isotonic injections. The hypertonic saline injections induced higher pain area (mean area ± SD: isotonic = 518.6 ± 690.6 au; hypertonic = 1659.3 ± 1574.0 au; *P*=0.003) and higher VAS scores (mean score ± SD: isotonic = 0.9 ± 1.1 cm; hypertonic = 4.7 ± 1.7 cm; *P*<0.001) than isotonic saline injections. Table 1 shows the scores for each class of words from McGill Pain Questionnaire and the pain rating index. Subjects presented a higher total pain rating index and scored higher in all the categories, with the exception of the affective class, after the hypertonic injections (*P*<0.05).

3.2 Cognitive task performance

~~*3.2.*~~ Only for the analysis of the cognitive task performance, one subject was not included due to problems in the answers recording. The total number of answers and the number of correct answers decreased during backwards counting conditions compared with forwards counting despite the injection effect (significant main effect for *task factor*; Table 2).

~~*3.3.*~~ *3.3 Center of pressure*

Effect of experimental pain in CoP variables

There were no statistical differences between the different conditions for the factor *injection* on any of the CoP variables (Table 3).

Effect of cognitive task in CoP variables

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A main effect of *task* was found for the CoP AP-velocity (F=5.82; *P*=0.028), showing that there was an increased AP-velocity during the counting backwards task compared to the counting forwards task, regardless the type of injection (Table 3).

Effect of the interaction between experimental pain and cognitive task in CoP variables

An interaction effect was found between *injection* and *task* factors for CoP total area and CoP ML-velocity (CoP total F=7.78, *P*=0.049; CoP ML F=4.69, *P*=0.021) (Table 3). Post-hoc comparisons showed that both variables decreased after the hypertonic injection in comparison to the condition with isotonic injection when subjects where counting forward (Bonferroni: *P* = 0.010 for total area; *P* = 0.015 for ML-velocity). After the hypertonic injection, CoP total area increased when subjects were counting backwards in comparison to when they were counting forwards (Bonferroni: *P* = 0.019). ML-velocity showed differences between the different cognitive tasks also after the injection of hypertonic solution, with a smaller decrease of ML-velocity while counting backwards (Bonferroni: *P* = 0.049).

4. Discussion

The present study aimed at quantifying how postural stability, represented by CoP sway (velocity and area of displacement) and CoP complexity (CoP SaEn), is modified during experimental pain while performing a cognitive task. The main results showed that the kind of cognitive task did not interfere with postural stability in the absence of pain. Experimental pain around the knee joint reduced CoP sway but did not affect CoP complexity during the performance of an easier cognitive task. During experimentally induced pain, the performance of a difficult cognitive task increased CoP sway but did not change CoP complexity.

Pain intensity and counting performance

The subjects showed higher pain intensity for the hypertonic saline injection and a larger pain area compared with the isotonic saline injection, as expected, indicating that experimental pain occurred (Hirata et al. 2011). The McGill pain questionnaire indicated that hypertonic saline was perceived more impairing than the isotonic injection in all subscales except for the affective one. It is important to note that during isotonic injections subjects rated pain around 1/10, which cannot be classified as a totally pain free condition.

Counting performance requires the use of cognitive process which relies on the working memory of the subject (Lemaire 1996), impairing motor output performance when executed simultaneously with a motor task (Vuillerme and Nafati 2007). Seminowicz and Davis (2007) showed that subjects are able to maintain performance of difficult cognitive task while experiencing different levels of pain. In this study, the painful condition did not affect the counting performance while performing a motor task (standing still) indicating that healthy subjects are able to engage multiple tasks (motor and cognitive) during pain without compromising performance. This suggests that sufficient cognitive resources were available to manage the cognitive process of counting forwards or backwards despite the interpretation of painful stimuli and the postural control task (Eccleston et al. 1999). Finally, education level is associate with both motor and perceptual performance, where higher education level is associated with better performance (Voos et al. 2015). Since our subjects were all university students, we believe that bias due to education level did not affect the present results.

Effect of cognitive tasks on postural stability

Our first initial hypothesis, that (i) the kind of cognitive task (more or less demanding) in a non-painful condition would not interfere with CoP sway or CoP complexity, was confirmed. The factor task affected the CoP anterior-posterior velocity, indicating an increased velocity during the execution of the more difficult task (counting backwards) in comparison to the easier task (counting ~~backwards~~forward). Nevertheless, the CoP SaEn was not affected by the kind of the performed cognitive task. These results indicate that enough cognitive resources were available to overcome the demands of both cognitive and postural tasks, which was expected since they were young individuals without any sensory-motor alterations.

Effect of experimental knee-related pain on postural stability

Our second initial hypothesis, that (ii) experimental pain would increase CoP sway and decrease CoP complexity was not confirmed since the type of saline solution injected did not affect the CoP variables. However, even though the factor *injection* did not show statistical differences between the different conditions for any of the studied CoP variables, there was a difference between total area and ML-velocity between the control and the painful condition when the subjects were counting forwards, i.e., in conditions where the kind of cognitive task performed was the same. Interestingly, during the counting forward, the type of injection resulted significant changes in postural sway (total area and ML-velocity) in opposite directions: positive values of the difference between pre-injection and after injection of the isotonic solution, whereas after the injection of the hypertonic solution both variables showed negative values. Additionally, no significant changes were observed in the structural variability of the CoP signal. This is contrary to the initial hypothesis, where an increase in postural sway and a decrease in structural variability during painful conditions were expected. It is also in contrast with previous findings (Mazaheri et al. 2013) but may relate to the different position of the feet used in this study, which affects the postural sway (Day et al. 1993). The tandem feet position adopted allows less displacement of the CoP due to the limited base of support compared to side-by-side feet position, since if the subjects increase the CoP amplitude they may fall (Day et al. 1993). This also may reflect a voluntary strategy, requiring a greater amount of cognitive resources and attention (Morasso and Sanguineti 2002), attempting to avoid large excursions of the body and consequent loss of balance. For the current study, this might indicate that the subjects prioritized the balance task over the other tasks, also known as *posture first strategy* (Vuillerme and Nafati 2007). The subjects were able to reduce the postural sway without compromising the counting performance during the easy cognitive task, suggesting that the available cognitive resource was sufficient to perform the less challenging cognitive task without compromising postural stability. Therefore, these results indicate that healthy subjects have the capacity to perform easy cognitive tasks while ensuring postural stability (Siu and Woollacott 2007). Reducing postural sway might reflect a motor strategy available for healthy subjects to avoid excessive translation of the body, which could lead to balance loss (Winter 1995). This strategy was also observed during the control injection while counting backwards, probably indicating that a high cognitive load seems to be interpreted as a treat to postural stability. An alternative explanation for the contrast between the present study and the previous studies with pain patients showing larger postural sway (Schulte et al. 2004; Levinger et al. 2016) might be the pain model used that is not a complete proxy to the impaired pain patients' sensory-motor system.

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 decrease CoP complexity only when performing a difficult cognitive task was partially confirmed since CoP sway increased during pain under a difficult cognitive task, but the CoP complexity did not change. ANOVA results showed an interaction between the task and injection factors for total area and ML-velocity. After the hypertonic injection CoP total area increased and CoP ML-velocity decreased less while counting backwards in comparison to counting forwards condition, corroborating our hypothesis. ANOVA results also showed an effect of the task factor on AP-velocity with post-hoc comparisons showing a difference only during the hypertonic injection condition: while counting backwards AP-velocity also increased. Altogether these results show that CoP sway increases when performing a more demanding cognitive task in the presence of experimental pain. This might reflect an interference with the information-processing capacity and an attention disruption from both postural control and cognitive task (Eccleston et al. 1999). Previous studies suggest that disruptions of sensory information lead to worsening of proprioception in the affected area (Matre et al. 2002), further impairing postural sway (Hirata et al. 2010, 2011). The results indicate that the posture first strategy (Vuillerme and Nafati 2007) found during the easy cognitive task during pain is no longer feasible when a difficult cognitive task is performed during painful conditions. The increased cognitive load in painful conditions seems to impair the motor performance maybe due to insufficient cognitive resource to simultaneously maintain postural stability (which requires significant amount of attention

(Morasso and Sanguineti 2002)) and execute a difficult cognitive task. These results might have important new implications in understanding the mechanisms related to fall accidents. Postural stability in daily life activities is usually performed in combination with additional tasks, for example, walking in a busy slippery sidewalk. These daily life activities involves simultaneously competition for the cognitive resources available (Woollacott and Shumway-Cook 2002) to evaluate the environment constrains in order to promote the best motor strategy (Winter 1995). Our present results indicate that, if the subject performs a challenging postural task in pain, his/her capacity for maintain balance while exposed to a difficult cognitive task is suboptimal, which could increase the likelihood of losing balance.

The complexity of postural sway did not show any differences between the experimental conditions. This result is contrary to the literature finding that young healthy subjects present a more regular and less automatic postural sway (decreased CoP SaEn) when the motor task is more difficult (e. g. standing with eyes closed) and more irregular postural sway and more automatic postural sway (increased CoP SaEn) when a cognitive task is added (Donker et al. 2007; Stins et al. 2009). The fact that the cognitive task did not interfere with CoP complexity may be due to the nature of both motor (standing in tandem position) and cognitive (subtraction calculus) tasks used in the experimental setup that did not interfere with the automaticity of postural control. Besides that, pain also did not affect CoP complexity, showing that experimental knee-related pain did not compromise the coupling between the components of the system responsible for balance in the current experimental setup. Future studies should investigate the interaction between pain, cognition and on CoP complexity with different motor and cognitive demands, in addition to different populations.

Despite interesting results regarding the effects of cognitive tasks in postural control during pain, the relevance of the findings for clinical populations should be interpreted with care. The experimental pain model used here is convenient to assess the effect of pain without the interference of potential structural or pathologies. However, extrapolating the current findings to an older population can only be done to some degree. Additionally, chronic pain patients may also suffer from depressive symptoms (Bair et al. 2003) or anxiety (McWilliams et al. 2003), which might increase cognitive load (Nebes et al. 2001). Furthermore, cognitive impairments are often found in chronic pain patients, decreasing the possibility to maintain performance of two or more concurrent tasks (Brauer et al. 2004), as opposed to what was observed in this study where young healthy subjects were recruited. Also, there was no recording of postural sway without any cognitive task. This would have allowed comparisons with a condition where neither pain nor cognitive tasks were influencing postural sway, and could have reduced type 2 errors given that multiple CoP variables were analyzed in the study. Thus, it can be considered a limitation to our interpretations.

5. Conclusions

Pain and cognitive task interfered on postural stability, changing its patterns. During the performance of a simple cognitive task, pain~~,~~ reduced postural sway, while during the performance of a more demanding cognitive task, postural sway was increased in young healthy subjects. Since our subjects were young healthy subjects, the direct translation of the present results to patients suffering from pain should be done with caution. However, ~~T~~these results may suggest that rehabilitation approaches should take into account that pain not only affects directly the motor system, but may occupy cognitive resources, potentially resulting in poorer performance when performing rehabilitation exercises. Additionally, rehabilitation strategies using both motor and cognitive resources need further investigation to outline the effect of interaction between pain and cognition on the performance during activities of daily life in patients.

Compliance with ethical standards

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Figure captions

Fig 1 Schematic drawing representing the force platform size, sensor locations, and the tandem position of the subjects during the experiment

Fig 2 Study design overview: pain assessments were performed immediately after each injection and each balance measurement; the order of the saline injections was randomized in a balanced way

Fig 3 Injections sites for vastus lateralis muscle, performed at two thirds of the distance from the anterior spina iliaca (a) to the lateral side of the patella (b); and for the vastus medialis muscle, performed 5 cm proximal and 5 cm medial to the medial corner of the patella (c),

Fig 4 Representation of the experimental pain distribution reported areas after isotonic (top, blue in the online version) and hypertonic (bottom, red in the online version saline injections (A); the individual distributions are superimposed in the anatomical drawings

EXPERIMENTAL KNEE-RELATED PAIN ENHANCES ATTENTIONAL INTERFERENCE ON POSTURAL CONTROL

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Abstract

Purpose: To quantify how postural stability is modified during experimental pain while performing different cognitively demanding tasks.

Methods: Sixteen healthy young adults participated in the experiment. Pain was induced by intramuscular injection of hypertonic saline solution (1mL, 6%) in both vastus medialis and vastus lateralis muscles (0.9% isotonic saline was used as control). The participants stood barefoot in tandem position for one minute on a force plate. Center of pressure (CoP) was recorded before and immediately after injections, while performing two cognitive tasks: (i) counting forwards by adding one; (ii) counting backwards by subtracting three. CoP variables – total area of displacement, velocity in anterior-posterior (AP-velocity) and medial-lateral (ML-velocity) directions, and CoP sample entropy in anterior-posterior and medial-lateral directions were displayed as the difference between the values obtained after and before each injection and compared between tasks and injections.

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) decreased after the painful injection vs. Control injection while counting forward ($P < 0.05$). CoP total area (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 ± 2.35 vs. -0.39 ± 1.82 cm/s) increased while counting backwards vs. forwards after the painful injection ($P < 0.05$).

Conclusion: Pain interfered with postural stability according to the type of cognitive task performed, suggesting that pain may occupy cognitive resources, potentially resulting in poorer balance performance.

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

List of abbreviations

ANOVA	Analysis of variance
au	Arbitrary units
CoP	Center of pressure
SaEn	Sample entropy
SD	Standard deviation
VAS	Visual analogue scale
VM	Vastus medialis
VL	Vastus lateralis

1. Introduction

Controlling of upright posture requires a significant amount of attention to gather information from the body and the environment and to generate adapted and accurate muscle activation for postural control (Morasso and Sanguineti 2002). Although the majority of postural control is regulated via automatic neural processes (Bronstein and Buckwell 1997), higher cortical centers are significantly involved in processing sensory information to plan and execute the best motor strategy for postural control (Winter 1995). In daily life, postural control is challenging as several tasks simultaneously compete for the cognitive resources available (Woollacott and Shumway-Cook 2002), limited by the capacity of higher centers to process sensory information (Kahneman 1973). Therefore, sharing attentional resources may cause impairments in the performance of daily living activities (Brauer et al. 2004). For example, competition for cognitive resources during tasks involving postural stability results in body stability being prioritized over secondary tasks (Liston et al. 2014).

Dual tasks paradigms, where subjects perform an additional task during standing, are employed to quantify the extent to which attention is associated with postural control. Decreases in postural sway while performing a secondary task compared with control conditions have been reported (Andersson et al. 2002; Pellecchia 2003) whereby focusing the attention on standing as still as possible increased postural sway compared with conditions without similar instructions (Vuillerme and Nafati 2007). Altogether, these results suggest that postural control demands attention (Woollacott and Shumway-Cook 2002) and that simultaneous cognitive loading plays an important role in balance stability (Swan et al. 2007).

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 subjects show controversial results (Huxhold et al. 2006; Fraizer and Mitra 2008). Young healthy subjects have probably more ability to allocate the attentional resources without sacrificing postural stability, showing that a system without impairments prioritizes postural stability when dealing with dual-cognitive tasks (Siu and Woollacott 2007).

Subjects with pain demonstrate increased postural sway compared with controls (Hirata et al. 2011). A possible explanation for this finding is that the increased postural sway may relate to a disrupting effect of nociceptive stimuli on attention to other simultaneous non-nociceptive tasks (Eccleston et al. 1999), underlining that processing of nociceptive stimuli is cognitively demanding (Veldhuijzen et al. 2006). Thus, the execution of cognitive tasks during pain might interfere with postural control. Although previous studies have shown that patients with pain present impaired balance while performing a secondary cognitive task in comparison to health subjects (Van Daele et al. 2010; Larivière et al. 2013; Mazaheri et al. 2014; Sherafat et al. 2014; Etemadi et al. 2016; Levinger et al. 2016), it is not clear yet the isolate effect of pain since reduced muscle strength, reduced flexibility and degenerative changes at the affected segment also cause both stiffness and instability in patients suffering from chronic pain (Knoop et al. 2012). Therefore, further investigation of the interaction between pain, cognition and postural stability is warranted. This investigation is of particular interest for clinical practice since there are evidences that attention can be directed away from pain using some specific strategies (Van Ryckeghem et al. 2018). If selective attention could be directed away from the painful stimulus and modify the deleterious effect of muscle pain on postural control, these results could have important implications for clinical settings. Likewise, if the execution of cognitive tasks impairs postural control in the presence of pain, this should also be taken into account in rehabilitation context.

Considering that posture can be defined as the dynamic stability of a continuous moving body (Harbourne and Stergiou 2003; Madeleine et al. 2011), nonlinear analysis of the dynamic structure of the center of pressure (CoP) time series would contribute to understand the physiological complexity of posture by accessing motor patterns that would be implicit in the CoP variability. Sample entropy (SaEn) measures variations in the system output along time. Therefore, measures of physiological complexity of the postural sway during quiet standing may relate to the system functionality as they are defined as the capacity of generating adaptive answers to an ever-changing environment such as controlling posture (Manor et al. 2010). SaEn provides a measure of “orderly structure” within the time series since it tests if there are any repeated patterns of various lengths, including the ones that are not repeated at regular intervals (Duarte and Sternad 2008). So, the lower the SaEn values are, the higher the similarity and lesser the complexity in the temporal series is (Richman and Moorman 2000).

Complexity depends on the number of structural components of the system, the existing coupling among these components and how this interaction is influenced by the intrinsic dynamic properties of the system and the motor task demands (Vaillancourt and Newell 2002). Thus, if the presence of pain and the execution of a cognitive task are both concurring with the attentional resources used in postural control, then the coupling between the components of the system responsible for balance may be affected and, consequently, the complexity of the postural sway is affected. Execution of a concurrent cognitive task during standing increases the complexity of the postural sway, and this increase has been attributed to a more automatized postural sway, when less attention is directed to the balance control (Donker et al. 2007; Stins et al. 2009; Kuczyński et al. 2011). On the other hand, there is some evidence that the complexity of postural control decreases with pain during sitting with increased perceived discomfort in healthy young subjects (Søndergaard et al. 2010). Similar finding was reported in young subjects with transient acute episode of low back pain during two continuous hours of standing, but without history of low back pain (Fewster et al. 2017), showing a relation between the occurrence of pain and the decrease in CoP complexity. Therefore, examining the complexity of postural sway in a dual task context and the effect of experimental pain in this condition may improve the understanding of the decrease in postural stability (Levinger et al. 2016) and complexity (Fewster et al. 2017) that may exist as a result of pain in an otherwise healthy system.

The aim of this study was to quantify how postural stability [CoP sway velocity and area of displacement and complexity (CoP SaEn)], is modified during experimental pain while performing a cognitive task. It was hypothesized that (i) the kind of cognitive task (more or less demanding) in a non-painful condition will not interfere with CoP sway or CoP complexity, since the system would have enough cognitive resources to overcome it; (ii) experimental pain will increase CoP sway and decrease CoP complexity, regardless the type of cognitive task performed; (iii) the presence of experimental pain while performing a difficult cognitive task will overload the cognitive resources and impair postural stability, increasing CoP sway and decreasing CoP complexity.

2. Methods

2.1. Subjects

Sixteen young adults, all university students, (to control for the effect of education level on 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 ± 4.0 years; body mass = 68.8 ± 5.2 kg; height = 1.68 ± 0.06 m). The exclusion criteria were body mass index above 25 kg/m^2, pregnancy, drug addiction, previous neurologic, musculoskeletal or mental illness, lack of ability to cooperate, current use of medications (e.g. analgesics, anti-inflammatory medicine), consumption of alcohol, caffeine, nicotine or painkillers 8 hours prior to the data collection, recent history of acute pain affecting the lower limb and/or trunk, past history of chronic pain conditions, participation in other pain trials throughout the study period. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the local Ethics Committee (N-20120077). This sample size was calculated to detect a minimum difference of 40% in the CoP area assuming type error 1 as 5% and power of 80% between the conditions before and after the induction of experimental pain. All participants gave signed informed consents prior to inclusion in the study.

2.2. Experimental protocol

Since in healthy individuals approximately 70% of the information used for controlling posture originates from proprioceptive systems (Peterka 2003), we controlled the effect of different footwear on postural control by asking the subjects to stand barefoot during the experiment. The participants stood on a triangular force plate that measures vertical forces (Good Balance System, Metitur, Jyväsklä, Finland; dimensions: equilateral triangle – 800-mm; sampling frequency: 50-Hz as suggested by the International Society for Posture and Gait Research Standardization Committee (Scoppa et al. 2013)). This is a valid and reliable system for postural sway measurements (Era et al. 2006; Ha et al. 2014) with accuracy better than 1-mm for the CoP position measurement (Good Balance System User Manual). The CoP position was calculated via the Good Balance Software (Metitur, Jyväsklä, Finland) which uses the weighted arithmetic mean between the vertical force measured by four sensors and their corresponding position: one in each corner of the force-plate and the last one in the centroid of the force-plate (Fig. 1). The rational for using the tandem position for the feet was based in previous studies showing that greater pain effects are presented when posture is challenged (Hirata et al. 2013). This was important to ensure that postural stability adaptations due to pain could be observed. Therefore, subjects were asked to stand in tandem position, to increase postural challenge during the tasks, with the right leg behind (Fig. 1), arms hanging relaxed alongside the body, and were instructed to maintain balance while looking forward. Tape markers were placed on the force plate to ensure that the same foot position was maintained through all conditions. During the assessment of postural control, subjects were instructed to look forward at a target positioned at eye-level approximately 45-cm from the subjects to minimize the influence of the target distance on postural sway (Kapoula and Lê 2006). CoP records were made under eight experimental conditions, depending on the type of injection (control or painful), the dual-task (counting forward or counting backward as the less and more challenging tasks, respectively), before (pre-injection) and immediately after the injection. The counting forward task consisted of adding one and the counting backward was performed by subtracting 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, 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 performing the first randomly assigned task (cognitive task 1 or 2) over 60-s (pre-injection 1); (ii) 1-min rest; (iii) CoP measurement over 60-s while performing the second randomly assigned task (cognitive task 1 or 2) over 60-s (pre-injection 2); (iv) injections of the first saline solution (painful or control) into vastus medialis (VM) and vastus lateralis (VL) muscles; (v) assessment of pain intensity by visual analogue scale (VAS); (vi) CoP measurement over 60-s while performing task A; (vii) collecting VAS scores of the pain intensity and 1-min rest; (viii) CoP measurement over 60-s while performing task B; (ix) collecting VAS scores of the pain intensity. After the final step, the pain VAS scores were taken each minute until the pain had subsided which was followed by a 5-min break. Following the break, all steps of the experiment were performed again with the injection of the other saline solution, including new pre-injection CoP recordings. Before each CoP measurement, all subjects confirmed that no tiredness or other problems were presented. The duration of the CoP measurements were performed according to guidelines proposed by the International Society for Posture and Gait Research (Scoppa et al. 2013). Fig. 2 summarizes the study procedures along time.

2.3. *Experimental muscle pain*

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 they would not know which kind of injection they would be receiving. Pain was induced through intramuscular injection of 1-mL of 6% sterile hypertonic saline solution or as a control condition 1-mL of isotonic (0.9%) saline solution (Graven-Nielsen et al. 1997; Farina 2003; Schulte et al. 2004; Falla et al. 2006). The injections were performed with a 2-mL syringe with a disposable needle (27G, 40-mm) into right VM muscle and right VL muscle. Both injections locations were marked to ensure that they were applied 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 at two thirds of the distance from the anterior spina iliaca to the lateral side of the patella (Fig. 3). The depth of the injection was determined by an ultrasound scanner (LOGIQ™ S7, General Electric, USA). This pain model has been successfully used previously to mimic knee-related pain during quiet standing tasks providing moderate pain intensities for approximately five minutes (Hirata et al. 2011). Hypertonic saline injections have been shown to activate nociceptors around the injected site (Mense 1993) whereas the 0.9% isotonic saline injections have induced little or no pain during postural control tasks similar to the one used in the present study (Hirata et al. 2010, 2011, 2013).

2.4. *Assessment of pain intensity*

The subjects were asked to rate the pain intensity using a 10-cm VAS from 0-cm to 10-cm (0-cm means “no pain” and 10-cm means “maximum pain”) immediately after the injections and after each balance measurement. Therefore, three VAS scores were obtained for each set of experiments (balance measurements after isotonic injection and balance measurements after hypertonic injection, respectively; Fig. 2), and the mean values of the three VAS scores were considered as the pain intensity after each injection paradigm. Additionally, following each set of experiments subjects were asked to indicate the overall pain areas during the trials on a body chart and to respond the McGill Pain Questionnaire (Melzack 1975). The area of pain was extracted from the body charts with VistaMetrix 1.38 software. The pain rating index based on the rank values of the words chosen within each category (sensory, affective, evaluative and miscellaneous) from McGill Pain Questionnaire were obtained and the score for each category, as well as the total pain rating index were determined as the sum of the ranked values of the words (Melzack 1975).

2.5. *Data analysis*

All variables for postural sway were calculated based on 50-s of the standing tasks, with the first and last 5-s from the original 60-s time series being excluded. The analyses were performed with Matlab R2016a software *(*Mathworks, Massachusetts, USA). The area fitted to 95% confidence interval of the CoP displacement was calculated as representative of the total CoP area displacement (95% confidence interval ellipse), along with the CoP velocity in both directions (anterior-posterior and medial-lateral). The structural variability of the CoP was calculated by means of SaEn with the embedding dimension (m) and the tolerance distance (r) set to m=2 and r=0.2xSD (Vaillancourt and Newell 2000). All CoP variables are displayed as the difference between the values obtained immediately after the injection and the correspondent pre-injection condition. Negative values show that the CoP variable decreased after the injection of the saline solution compared to its respective pre-injection condition. Likewise, positive values show that the CoP variable increased after the injection compared to its respective pre-injection condition.

2.6. Statistical analysis

Pain outcomes were compared between injection types (isotonic or hypertonic injections) with paired T-tests when normal distribution was present (VAS scores and pain area data) and with the Wilcoxon Signed Rank Test when the data distribution was non-normal (McGill scores). The task measures (number of answers, number of correct answers) were evaluated with a 3-way RM-ANOVA with *injection* (isotonic vs hypertonic), *time* (pre-injection vs after injection) and *task* (counting forward vs backwards) as main factors. The CoP parameters were compared with a 2-Way RM-ANOVA with *task* and *injection* as main factors, and the p-values are shown in the table 3. Bonferroni post-hoc correction for multiple comparisons was applied and p-values are shown in the results texts. The alfa-value (α) for statistical significance was set to 0.05.

3. Results

3.1 Area and amplitude of perceived pain'

Fig. 4 shows the reported pain areas following both isotonic and hypertonic injections. Pain was present in the anterior and lateral portions of the thigh after both isotonic and hypertonic injections, being more concentrated in the lower half of the thigh after the isotonic injections. The hypertonic saline injections induced higher pain area (mean area ± SD: isotonic = 518.6 ± 690.6 au; hypertonic = 1659.3 ± 1574.0 au; P=0.003) and higher VAS scores (mean score ± SD: isotonic = 0.9 ± 1.1 cm; hypertonic = 4.7 ± 1.7 cm; P<0.001) than isotonic saline injections. Table 1 shows the scores for each class of words from McGill Pain Questionnaire and the pain rating index. Subjects presented a higher total pain rating index and scored higher in all the categories, with the exception of the affective class, after the hypertonic injections (*P*<0.05).

3.2 Cognitive task performance

Only for the analysis of the cognitive task performance, one subject was not included due to problems in the answers recording. The total number of answers and the number of correct answers decreased during backwards counting conditions compared with forwards counting despite the injection effect (significant main effect for *task factor*; Table 2).

3.3 Center of pressure

Effect of experimental pain in CoP variables

There were no statistical differences between the different conditions for the factor *injection* on any of the CoP variables (Table 3).

Effect of cognitive task in CoP variables

A main effect of *task* was found for the CoP AP-velocity (F=5.82; *P*=0.028), showing that there was an increased AP-velocity during the counting backwards task compared to the counting forwards task, regardless the type of injection (Table 3).

Effect of the interaction between experimental pain and cognitive task in CoP variables

An interaction effect was found between *injection* and *task* factors for CoP total area and CoP ML-velocity (CoP total F=7.78, *P*=0.049; CoP ML F=4.69, *P*=0.021) (Table 3). Post-hoc comparisons showed that both variables decreased after the hypertonic injection in comparison to the condition with isotonic injection when subjects where counting forward (Bonferroni: *P* = 0.010 for total area; *P* = 0.015 for ML-velocity). After the hypertonic injection, CoP total area increased when subjects were counting backwards in comparison to when they were counting forwards (Bonferroni: *P* = 0.019). ML-velocity showed differences between the different cognitive tasks also after the injection of hypertonic solution, with a smaller decrease of ML-velocity while counting backwards (Bonferroni: *P* = 0.049).

4. Discussion

The present study aimed at quantifying how postural stability, represented by CoP sway (velocity and area of displacement) and CoP complexity (CoP SaEn), is modified during experimental pain while performing a cognitive task. The main results showed that the kind of cognitive task did not interfere with postural stability in the absence of pain. Experimental pain around the knee joint reduced CoP sway but did not affect CoP complexity during the performance of an easier cognitive task. During experimentally induced pain, the performance of a difficult cognitive task increased CoP sway but did not change CoP complexity.

Pain intensity and counting performance

The subjects showed higher pain intensity for the hypertonic saline injection and a larger pain area compared with the isotonic saline injection, as expected, indicating that experimental pain occurred (Hirata et al. 2011). The McGill pain questionnaire indicated that hypertonic saline was perceived more impairing than the isotonic injection in all subscales except for the affective one. It is important to note that during isotonic injections subjects rated pain around 1/10, which cannot be classified as a totally pain free condition.

Counting performance requires the use of cognitive process which relies on the working memory of the subject (Lemaire 1996), impairing motor output performance when executed simultaneously with a motor task (Vuillerme and Nafati 2007). Seminowicz and Davis (2007) showed that subjects are able to maintain performance of difficult cognitive task while experiencing different levels of pain. In this study, the painful condition did not affect the counting performance while performing a motor task (standing still) indicating that healthy subjects are able to engage multiple tasks (motor and cognitive) during pain without compromising performance. This suggests that sufficient cognitive resources were available to manage the cognitive process of counting forwards or backwards despite the interpretation of painful stimuli and the postural control task (Eccleston et al. 1999). Finally, education level is associate with both motor and perceptual performance, where higher education level is associated with better performance (Voos et al. 2015). Since our subjects were all university students, we believe that bias due to education level did not affect the present results.

Effect of cognitive tasks on postural stability

Our first initial hypothesis, that (i) the kind of cognitive task (more or less demanding) in a non-painful condition would not interfere with CoP sway or CoP complexity, was confirmed. The factor task affected the CoP anterior-posterior velocity, indicating an increased velocity during the execution of the more difficult task (counting backwards) in comparison to the easier task (counting forward). Nevertheless, the CoP SaEn was not affected by the kind of the performed cognitive task. These results indicate that enough cognitive resources were available to overcome the demands of both cognitive and postural tasks, which was expected since they were young individuals without any sensory-motor alterations.

Effect of experimental knee-related pain on postural stability

Our second initial hypothesis, that (ii) experimental pain would increase CoP sway and decrease CoP complexity was not confirmed since the type of saline solution injected did not affect the CoP variables. However, even though the factor *injection* did not show statistical differences between the different conditions for any of the studied CoP variables, there was a difference between total area and ML-velocity between the control and the painful condition when the subjects were counting forwards, i.e., in conditions where the kind of cognitive task performed was the same. Interestingly, during the counting forward, the type of injection resulted significant changes in postural sway (total area and ML-velocity) in opposite directions: positive values of the difference between pre-injection and after injection of the isotonic solution, whereas after the injection of the hypertonic solution both variables showed negative values. Additionally, no significant changes were observed in the structural variability of the CoP signal. This is contrary to the initial hypothesis, where an increase in postural sway and a decrease in structural variability during painful conditions were expected. It is also in contrast with previous findings (Mazaheri et al. 2013) but may relate to the different position of the feet used in this study, which affects the postural sway (Day et al. 1993). The tandem feet position adopted allows less displacement of the CoP due to the limited base of support compared to side-by-side feet position, since if the subjects increase the CoP amplitude they may fall (Day et al. 1993). This also may reflect a voluntary strategy, requiring a greater amount of cognitive resources and attention (Morasso and Sanguineti 2002), attempting to avoid large excursions of the body and consequent loss of balance. For the current study, this might indicate that the subjects prioritized the balance task over the other tasks, also known as *posture first strategy* (Vuillerme and Nafati 2007). The subjects were able to reduce the postural sway without compromising the counting performance during the easy cognitive task, suggesting that the available cognitive resource was sufficient to perform the less challenging cognitive task without compromising postural stability. Therefore, these results indicate that healthy subjects have the capacity to perform easy cognitive tasks while ensuring postural stability (Siu and Woollacott 2007). Reducing postural sway might reflect a motor strategy available for healthy subjects to avoid excessive translation of the body, which could lead to balance loss (Winter 1995). This strategy was also observed during the control injection while counting backwards, probably indicating that a high cognitive load seems to be interpreted as a treat to postural stability. An alternative explanation for the contrast between the present study and the previous studies with pain patients showing larger postural sway (Schulte et al. 2004; Levinger et al. 2016) might be the pain model used that is not a complete proxy to the impaired pain patients' sensory-motor system.

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 decrease CoP complexity only when performing a difficult cognitive task was partially confirmed since CoP sway increased during pain under a difficult cognitive task, but the CoP complexity did not change. ANOVA results showed an interaction between the task and injection factors for total area and ML-velocity. After the hypertonic injection CoP total area increased and CoP ML-velocity decreased less while counting backwards in comparison to counting forwards condition, corroborating our hypothesis. ANOVA results also showed an effect of the task factor on AP-velocity with post-hoc comparisons showing a difference only during the hypertonic injection condition: while counting backwards AP-velocity also increased. Altogether these results show that CoP sway increases when performing a more demanding cognitive task in the presence of experimental pain. This might reflect an interference with the information-processing capacity and an attention disruption from both postural control and cognitive task (Eccleston et al. 1999). Previous studies suggest that disruptions of sensory information lead to worsening of proprioception in the affected area (Matre et al. 2002), further impairing postural sway (Hirata et al. 2010, 2011). The results indicate that the posture first strategy (Vuillerme and Nafati 2007) found during the easy cognitive task during pain is no longer feasible when a difficult cognitive task is performed during painful conditions. The increased cognitive load in painful conditions seems to impair the motor performance maybe due to insufficient cognitive resource to simultaneously maintain postural stability (which requires significant amount of attention (Morasso and Sanguineti 2002)) and execute a difficult cognitive task. These results might have important new implications in understanding the mechanisms related to fall accidents. Postural stability in daily life activities is usually performed in combination with additional tasks, for example, walking in a busy slippery sidewalk. These daily life activities involves simultaneously competition for the cognitive resources available (Woollacott and Shumway-Cook 2002) to evaluate the environment constrains in order to promote the best motor strategy (Winter 1995). Our present results indicate that, if the subject performs a challenging postural task in pain, his/her capacity for maintain balance while exposed to a difficult cognitive task is suboptimal, which could increase the likelihood of losing balance.

The complexity of postural sway did not show any differences between the experimental conditions. This result is contrary to the literature finding that young healthy subjects present a more regular and less automatic postural sway (decreased CoP SaEn) when the motor task is more difficult (e. g. standing with eyes closed) and more irregular postural sway and more automatic postural sway (increased CoP SaEn) when a cognitive task is added (Donker et al. 2007; Stins et al. 2009). The fact that the cognitive task did not interfere with CoP complexity may be due to the nature of both motor (standing in tandem position) and cognitive (subtraction calculus) tasks used in the experimental setup that did not interfere with the automaticity of postural control. Besides that, pain also did not affect CoP complexity, showing that experimental knee-related pain did not compromise the coupling between the components of the system responsible for balance in the current experimental setup. Future studies should investigate the interaction between pain, cognition and on CoP complexity with different motor and cognitive demands, in addition to different populations.

Despite interesting results regarding the effects of cognitive tasks in postural control during pain, the relevance of the findings for clinical populations should be interpreted with care. The experimental pain model used here is convenient to assess the effect of pain without the interference of potential structural or pathologies. However, extrapolating the current findings to an older population can only be done to some degree. Additionally, chronic pain patients may also suffer from depressive symptoms (Bair et al. 2003) or anxiety (McWilliams et al. 2003), which might increase cognitive load (Nebes et al. 2001). Furthermore, cognitive impairments are often found in chronic pain patients, decreasing the possibility to maintain performance of two or more concurrent tasks (Brauer et al. 2004), as opposed to what was observed in this study where young healthy subjects were recruited. Also, there was no recording of postural sway without any cognitive task. This would have allowed comparisons with a condition where neither pain nor cognitive tasks were influencing postural sway, and could have reduced type 2 errors given that multiple CoP variables were analyzed in the study. Thus, it can be considered a limitation to our interpretations.

5. Conclusions

Pain and cognitive task interfered on postural stability, changing its patterns. During the performance of a simple cognitive task, pain reduced postural sway, while during the performance of a more demanding cognitive task, postural sway was increased in young healthy subjects. Since our subjects were young healthy subjects, the direct translation of the present results to patients suffering from pain should be done with caution. However, these results may suggest that rehabilitation approaches should take into account that pain not only affects directly the motor system, but may occupy cognitive resources, potentially resulting in poorer performance when performing rehabilitation exercises. Additionally, rehabilitation strategies using both motor and cognitive resources need further investigation to outline the effect of interaction between pain and cognition on the performance during activities of daily life in patients.

Compliance with ethical standards

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Figure captions

Fig 1 Schematic drawing representing the force platform size, sensor locations, and the tandem position of the subjects during the experiment

Fig 2 Study design overview: pain assessments were performed immediately after each injection and each balance measurement; the order of the saline injections was randomized in a balanced way

Fig 3 Injections sites for vastus lateralis muscle, performed at two thirds of the distance from the anterior spina iliaca (a) to the lateral side of the patella (b); and for the vastus medialis muscle, performed 5 cm proximal and 5 cm medial to the medial corner of the patella (c),

Fig 4 Representation of the experimental pain distribution reported areas after isotonic (top, blue in the online version) and hypertonic (bottom, red in the online version saline injections (A); the individual distributions are superimposed in the anatomical drawings

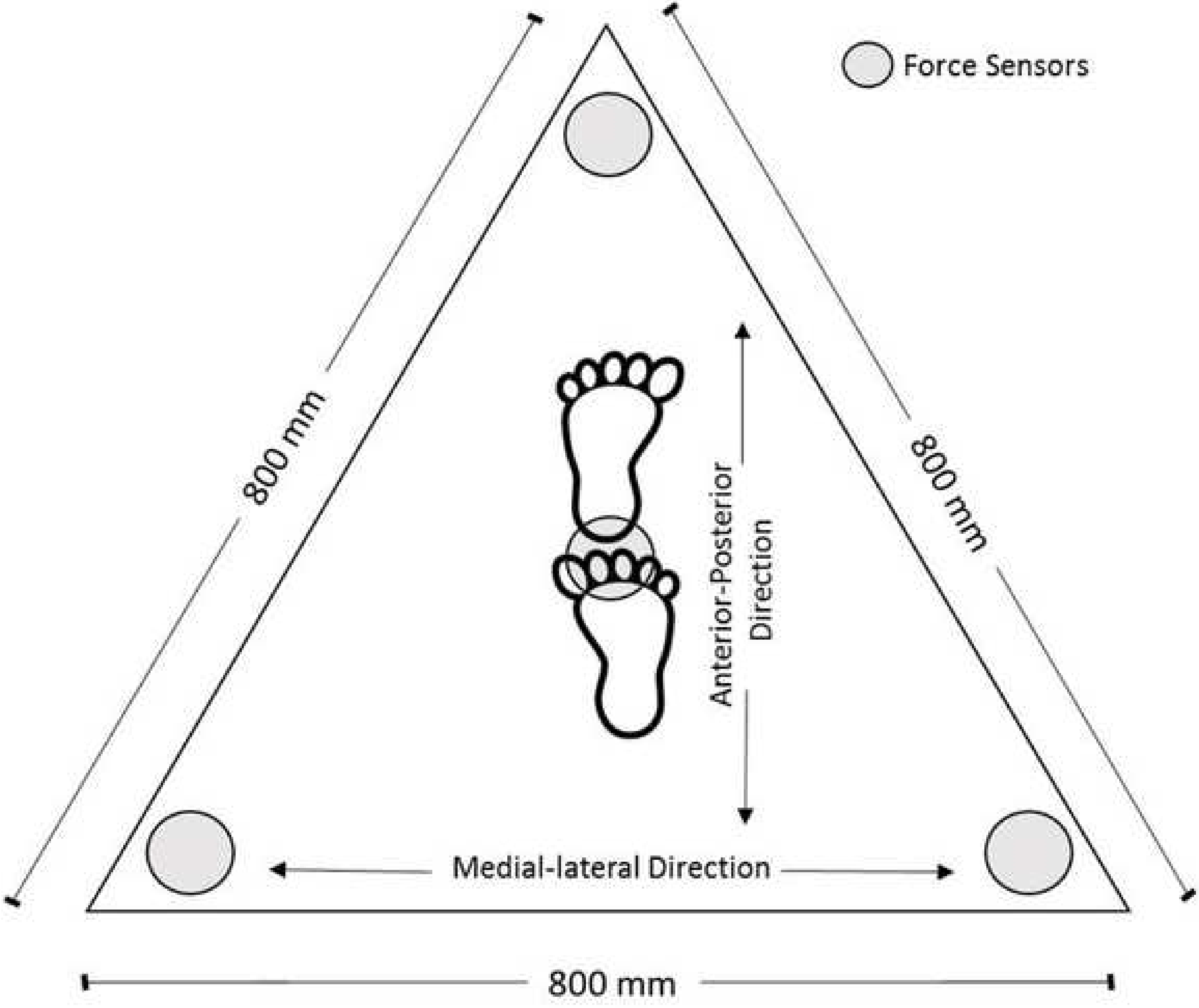

Force Sensors
800 mm
800 mm
Anterior-Posterior Direction
Medial-lateral Direction
800 mm

Figure 2

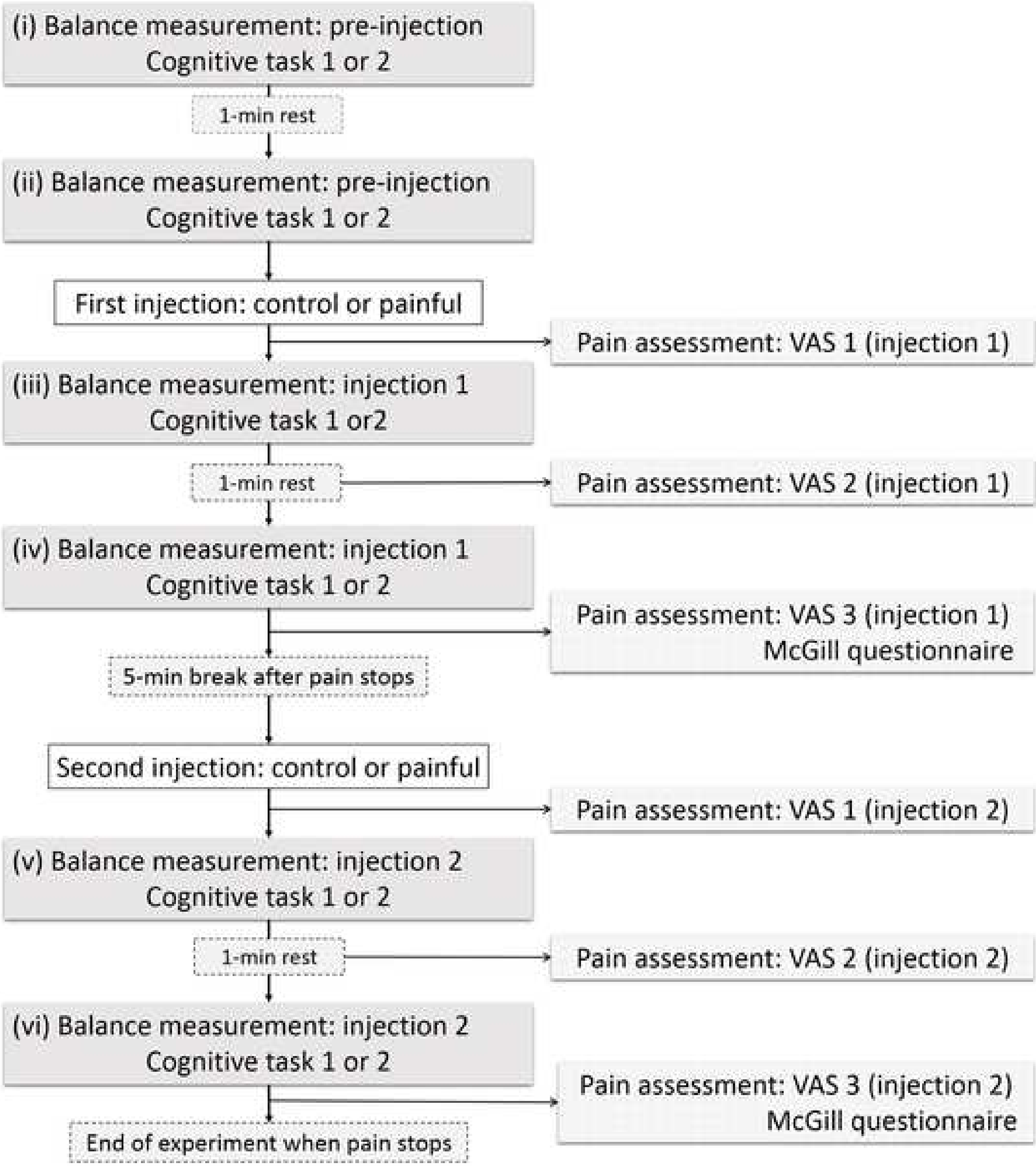

(i) Balance measurement: pre-injection
Cognitive task 1 or 2
1-min rest
(ii) Balance measurement: pre-injection
Cognitive task 1 or 2
First injection: control or painful
Pain assessment: VAS 1 (injection 1)
(iii) Balance measurement: injection 1
Cognitive task 1 or2
1-min rest
Pain assessment: VAS 2 (injection 1)
(iv) Balance measurement: injection 1
Cognitive task 1 or 2
Pain assessment: VAS 3 (injection 1)
McGill questionnaire
5-min break after pain stops
Second injection: control or painful
Pain assessment: VAS 1 (injection 2)
(v) Balance measurement: injection 2
Cognitive task 1 or 2
1-min rest
Pain assessment: VAS 2 (injection 2)
(vi) Balance measurement: injection 2
Cognitive task 1 or 2
Pain assessment: VAS 3 (injection 2)
McGill questionnaire
End of experiment when pain stops

Figure 3

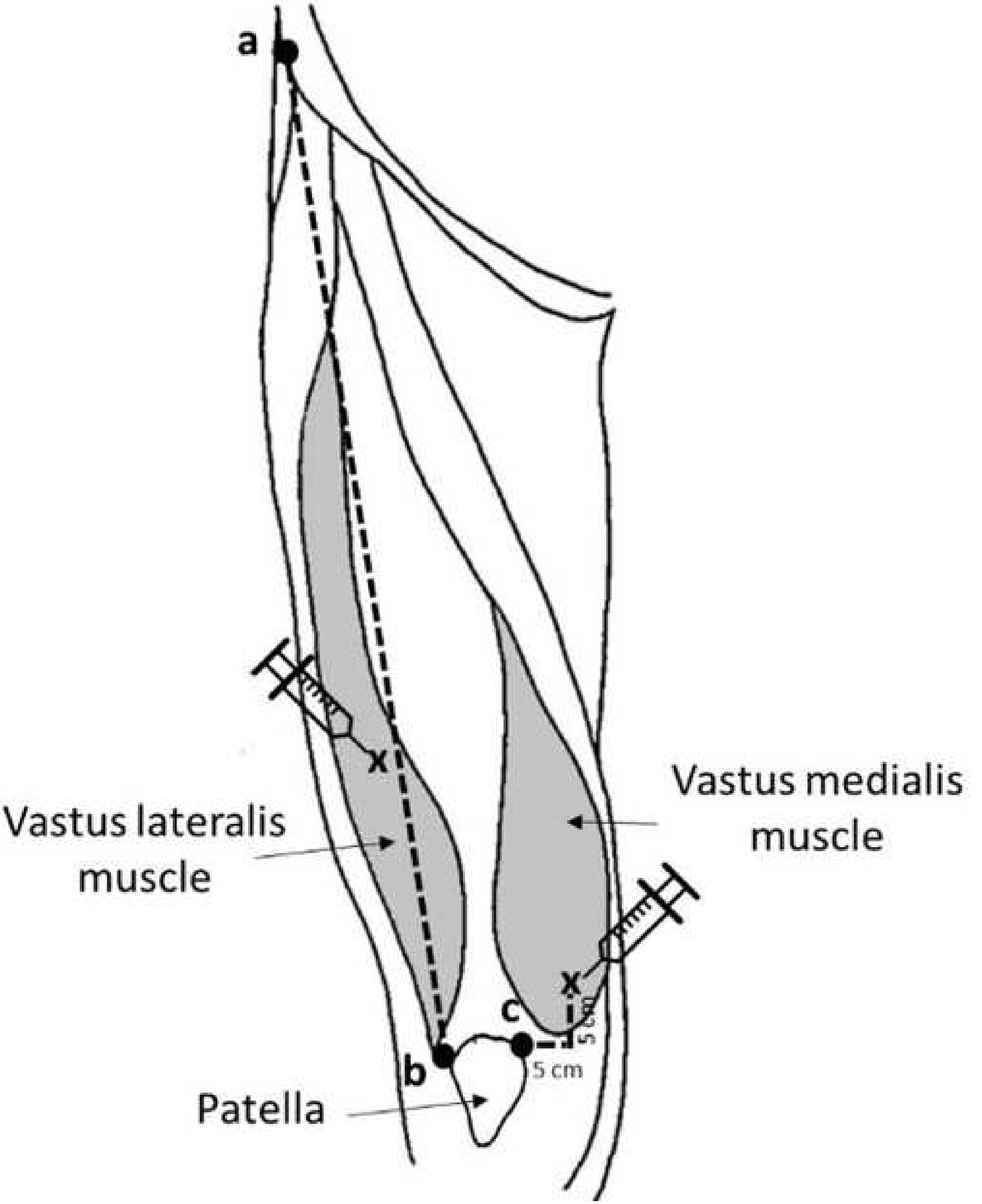
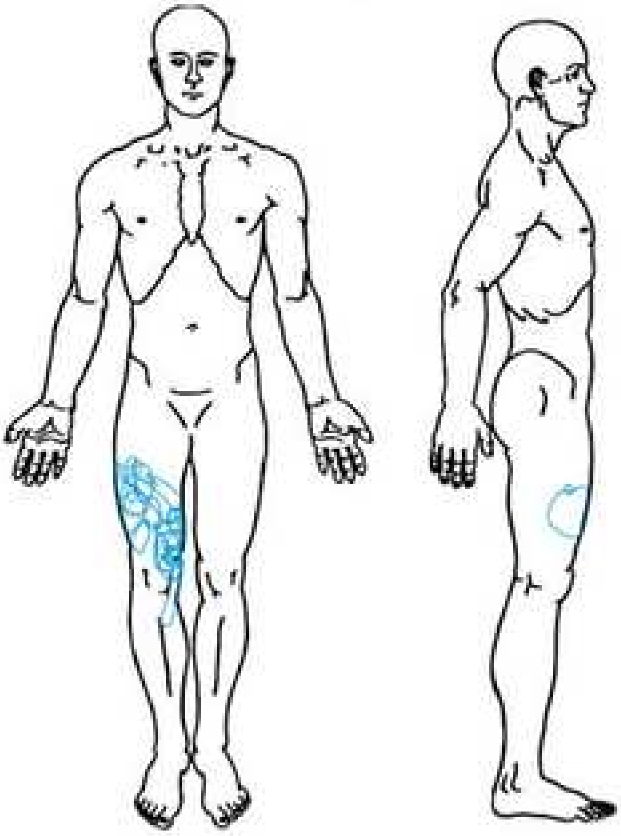

a
x
Vastus lateralis muscle
Vastus medialis muscle
x
c
5 cm
b
5 cm
Patella

Figure 4

Isotonic injection



Hypertonic injection

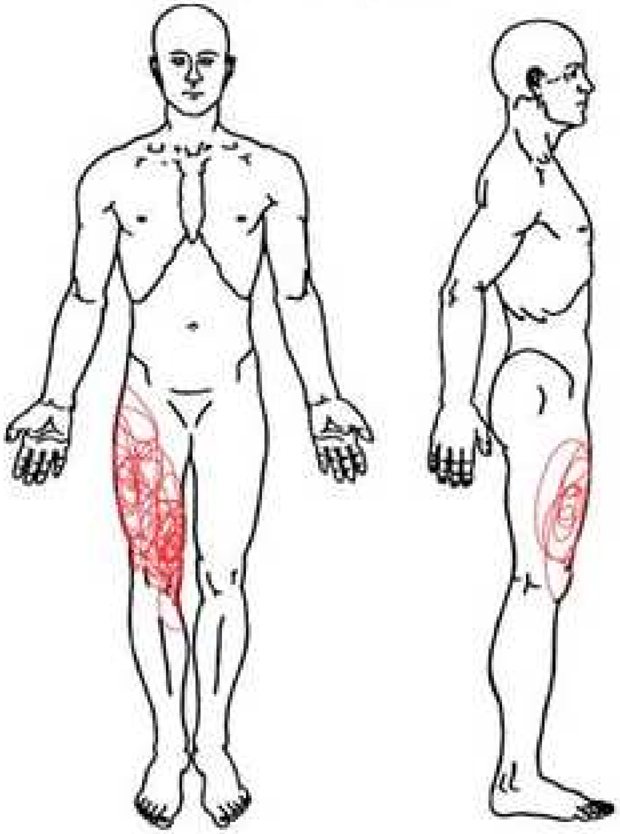


Table 1 – McGill Pain Questionnaire scores (median [Range]) for each category and total pain rating index for the pain experienced after isotonic and hypertonic injections.

McGill scores	Injection		*P*-value
	Isotonic	Hypertonic	
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

Table 2 – Mean (±SD) of the cognitive tasks performances before and during both injections type (hypertonic and isotonic) and three-way repeated measures ANOVA results (F; *P*).

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

* Statistically significant (*P*<0.05).

Table 3

Table 3 – Mean (±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; *P* value)		
	Counting forward	Counting backward	Counting forward	Counting backward	Injection	Task	Injection x task
Total area (cm^{2})	**28.9±78.5**[a]	-25.1±138.7	**-84.5±145.5**[a, b]	**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±2.23**[d]	**-1.71±2.61**[c, e]	**-0.34±1.92**[e]	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.