HIGH-INTENSITY EXERCISE AND MOTOR IMAGERY TRAINING PROGRAM: A THERAPEUTIC APPROACH IN NON-SPECIFIC CHRONIC LOWER BACK PAIN

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À minha mulher Cláudia e
aos meus filhos Gustavo e Maria
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Resumo

A dor lombar crónica não específica (DLC) tem, nos últimos anos, sido um dos flagelos da humanidade, apresentando elevadas taxas de prevalência e incidência, com reflexo nas altas taxas de absentismo, nos grandes custos sociais e sobrecarga de utilização dos cuidados de saúde. Esta doença não encontrou ainda a resposta terapêutica eficaz, seja na vertente farmacológica, seja na não farmacológica. Trata-se de uma doença de carácter global, e não apenas local, resultado das múltiplas disfunções que promove no indivíduo. Uma destas reflete-se a nível do sistema nervoso central e do sistema nervoso periférico, influenciando negativamente as conexões neuronais, a espessura cortical e o volume da substância cinzenta em determinadas áreas do encéfalo. A presença crónica da dor tem, por isso, repercussões na organização cerebral e no desempenho desta sobre a capacidade de modular e inibir a dor. Como reflexo, estão descritas alterações de sensibilidade discriminativa localizadas à região lombar dolorosa, no entanto, não se sabe ainda se a restante região do dorso é, ou não, também afetada. Dada a importância clínica desta informação para a correção postural e reforço muscular, o objetivo do primeiro trabalho foi o de averiguar a capacidade de discriminação sensorial táctil superficial e dolorosa em todo o dorso e compará-la com indivíduos saudáveis. Os resultados permitiram concluir que os doentes DLC apresentam menor capacidade de discriminação sensorial em todo o dorso, com diferenças acentuadas entre várias regiões. É sabido que programas de exercício físico têm sido os instrumentos de maior sucesso para diminuir os sintomas da DLC, pelo aumento do limiar de percepção da dor e da capacidade física destes doentes. Como exercício físico, particularmente o de alta intensidade, parece ter repercussões orgânicas favoráveis, periféricas e centrais, colocou-se a hipótese que o treino físico de alta intensidade melhora a capacidade discriminativa da sensibilidade táctil superficial e dolorosa destes doentes e diminui a intensidade da sua dor, hipótese essa que foi testada no segundo trabalho desta tese. Os resultados obtidos confirmaram a hipótese de estudo, concluindo-se que o treino físico de alta intensidade melhora a discriminação sensorial no dorso e reduz a intensidade da dor referida assim como a extensão da área dolorosa. Sabe-se que, dependendo da intensidade do exercício físico, há produção de um vasto conjunto de neurotrofinas, fundamentais para a criação de uma nova rede de conexões cerebrais com a ativação do sistema de modulação de inibição descendente e com a proliferação de novas conexões cerebrais. A criação de novas conexões cerebrais está também associada ao treino da imagética motora, cuja eficácia terapêutica tem sido testada, de forma isolada, na DLC. Considerando este facto, assim como os resultados do segundo estudo desta tese, colocou-se a hipótese que o treino de imagética motora conjugado com o treino físico de alta intensidade possui melhores resultados comparativamente aos do treino físico quando aplicado de forma isolada. Esta hipótese foi testada no terceiro e quarto trabalhos desta tese, tendo os resultados confirmado a hipótese de trabalho, com melhoria na intensidade e na área da dor dos doentes. Os resultados dos quatro estudos realizados permitem concluir que a DCL tem um componente de afeção central, com repercussões periféricas na intensidade e extensão da área da dor, na discriminação da sensibilidade do dorso e na capacidade funcional. O treino físico de alta intensidade, especialmente quando associado com o treino de imagética motora, minimiza estas consequências.

Abstract

The non-specific chronic lower back pain (CLBP) has been for the last few years one of the mankind "scourges", with high prevalence and incidence rates, reflected in high rates of absenteeism, high social costs and overburden of the healthcare systems. This disease is yet to find an effective therapeutic response, either in the pharmacological or non-pharmacological treatments. It is a systemic condition, not just a local one, considering all the multiple dysfunctions it entails. One of these is reflected on the central nervous system and the peripheral nervous system, negatively influencing the neuronal connections, the cortical thickness and the volume of the gray matter in certain areas of the brain. The chronic pain has therefore repercussions on brain organization and its performance on the ability to modulate and inhibit pain. As a result, changes in discriminatory sensitivity located in the painful lumbar region are described, however, it is not yet known whether the remaining region of the *dorsum* is also affected. Given the clinical importance of this information for postural correction and muscle strengthening, the purpose of the first work of this thesis was to investigate the ability for superficial and painful tactile sensory discrimination throughout the *dorsum* of CLBP patients and compare it with healthy individuals. The results led to the conclusion that CLBP patients have less capacity for sensitive discrimination throughout the *dorsum*, with marked differences between various regions. It is known that physical exercise programs have been the most successful instruments to decrease CLBP symptoms by raising the threshold of pain perception and physical capacity of these patients. Given that physical exercise, specially of high-intensity seems to have favourable physiological responses, either peripheral and central, the second work of this thesis tested the raised hypothesis that high-intensity physical training improves the discriminative ability of these patients' superficial and painful tactile sensitivity and decreases the intensity of their pain. The results supported the hypothesis, leading to the conclusion that high-intensity physical training improves sensitive discrimination in the *dorsum*, reduces the intensity of referred pain as well as the extent of the painful area. It is known that, depending on the intensity of physical exercise, there is production of a vast set of neurotrophins, crucial for the creation of a new network of brain connections with the activation of the modulation system of descending inhibition and with the growth of new brain connections. The creation of new brain connections is also associated with the training of motor imaging, whose therapeutic efficacy has been tested, in isolation, in CLBP. Considering this, as well as the results of the second study, it was hypothesized that motor imaging training combined with high-intensity physical training would have better results compared to physical training when applied on its one. This hypothesis was tested in the third and fourth works of this thesis, and the results confirmed the working hypothesis, with improvement in the intensity and pain area of the patients. The results of the four studies carried out allow us to conclude that CLBP has a central affection component, with peripheral repercussions on the intensity and extent of the pain area, on the discrimination of the sensitivity of the *dorsum* and on the functional ability. High-intensity physical training, especially when associated with motor imaging training, minimizes these consequences.

List of Abbreviations

ACC: Anterior Cingulate Cortex

BDNF: Brain-Derived Neurotrophic Factor

BMI: Body Mass Index

CES: Ethics Committee of S. João Hospital Center

CLBP: Non-specific Chronic Lower Back Pain

CNS: Central Nervous System

CPM: Conditional Pain Modulation

DLC: Dor Lombar crónica não especifica

DLPFC: Dorsolateral Prefrontal Cortex

HI: High-Intensity Exercise Training

IBM: International Business Machines Corporation

IPAC: International Physical Activity Questionnaire

LBP: Low Back Pain

M1: Primary Motor Cortex

M2: Pre Motor and Supplementary Motor Cortex

Md: Median

MI: Motor Imagery Training

OMS: Oxford Modified Scale

PAG: Periaqueductal Gray Area

PPT: Pain Pressure Threshold

PTP: Point-to-point Test

QST: Quantitative Sensory Test

RMDQ: Rolland Morris Disability Questionnaire

TDP: Two-point Discrimination Test

TENS: Transcutaneous Electrical Nerve Stimulation

TPE: Two Points Estimation Test

VAS: Visual Analogue Scale

1. GENERAL INTRODUCTION

Lower back pain has been defined as “pain and discomfort, located below the costal margin and above the inferior gluteal folds, with or without leg pain” [105]. Lower back pain has a spontaneous resolution in approximately 90% of the cases, however in 2 to 7% of cases it becomes a chronic condition [71]. It was shown that at age 45, over 65% of the population with acute lower back pain did not reveal any degenerative variations at the lower back, however 25% of adults reported at least an episode of vertebral pain and about 75% of these reported to have had an experience that led them to seek medical orientation [103]. The prevalence of active chronic lower back pain in the Portuguese adult population in 2016 was of 10.4% for the general population, with a mean age of 58.9 years, from which 71.4% were females [36]. If the pain persists for more than 3 months, it becomes a chronic disorder [24, 88]. The concept of chronic lower back pain dysfunction integrates three important features, which are pain [60], functional disability [47], and reduced levels of physical activity [26]. This disorder is usually classified as specific or non-specific, according to the possibility to identify a specific cause for symptoms [72, 103]. Approximately 90% of chronic lower back pain are termed as non-specific chronic low back pain (CLBP) [101]. In a Japanese population study, the prevalence of non-specific chronic lower back pain and specific chronic low back pain was 15.4% and 9.3%, respectively [50]. As results of this prevalence, the non-specific chronic lower back pain will be the main target of this thesis. The CLBP has a multifactorial nature, with repercussions on pain intensity as well as on the levels of physical performance and daily-life activities [24, 9]. Indeed, in addition to pain, it is also usual an increase of muscle tension [72], a general muscle weakness and a loss of mobility [38]. These common conditions, induced by chronic pain, reflect in sensorimotor, proprioceptive, and tactile deficits affecting postural stability and motion control [44, 33], which all combined lead to the persistent pain in a vicious cycle [42]. There are numerous central nervous system changes due to pain, which reduce physical activity levels. These changes are identifiable in gray matter volumes, in cerebral activity, in the descending pain modulation system, and in sensorimotor network. The cortical reorganization is correlated with pain intensity [78, 28] and was associated with lower gray matter volumes in the medial/dorsolateral and ventrolateral prefrontal cortices as well as in the anterior insular cortex, anterior cingulate cortex, and thalamus [31]. Many cortical areas can be activated during pain, although some are more involved than others and with a wide variability between individuals, these neuroanatomical structures are known as the "pain matrix" and have

an individual-specific pain neuromatrix [79]. The pain stimulates alterations in the somatosensorial cortical area of the lumbar spine in patients with CLBP [48], which can explain why these patients constitute a sensibility heterogeneous population [93]. The cortical thickness also decreases in sensory differentiation associated with disruption of the tactile process [69, 78]. The somatosensory pain memories manifest alterations in the somatotopic map present in somatosensory cortex which contributes to allodynia [28], a component in back painful area that could result from a mechanic stimulus [51], understood as pain by the conscientious somatosenrorial cortex. Pain sensitization involves an increased responsiveness of central and/or peripheral nervous system circuits, resulting in pain hypersensitivity as allodynia [75], a state where the presence of pain is concurrent with the absence of peripheral nociceptive stimulation [28] with a deficit of sensory information to the cortical representation [48]. A deficit in the location of sensory information on the back is a contributing factor to introduce errors in the motor command that will affect the final result, predisposing to injury and pain continuity [10]. Unfortunately, these sensorial deficits are not routinely assessed in clinical practice mainly due to the absence of practical and patronized tests. Although described in the referred pain zone [80, 10, 86], it is possible that these sensorial changes may also affect a larger dorsolumbar surrounded area. Understanding the extent of these sensorial limitations will be an important aid to define different therapeutic approaches for pain reduction and for an effective motor control. Indeed, it is essential to acknowledge skeletal muscles as important promoters of sensorial information to movement and posture by anticipatory mechanisms from premotor cortex [49].

A wide variety of pharmacological treatments and traditional physiotherapy interventions are used to CLBP, however without great success [81], being widely accepted exercise therapy as the most effective treatment for CLBP [66]. High-intensity aerobic exercise promotes pain relief in subjects with CLBP [16] and also increases the production of brain-derived neurotrophic factor (BDNF), which plays a crucial role in the maintenance and regeneration of neurons [53], favouring the formation of new synapses [57], promoting neural conduction [6] and generating alternative circuits of movement with recruitment of new muscle fibres, allowing movements without pain [78]. Indeed, it is known that physical exercise training has the potential to increase neurotrophins expression and induce neuroplasticity, neurogenesis and neuroprotection, helping to reconstruct motor function in patients with central nervous system disorders [70]. If low-intensity exercise training might be advantageous to CLBP patients [43],

when performed with higher intensities its benefits might be even better [16, 82, 39], probably due to its neurotrophic properties [16]. There are confirmed evidence for the higher efficacy of high-intensity aerobic exercise training, comparatively to the low-intensity, in treating CLBP's pain, disability, and psychological strain [16, 82, 17, 39]. However, there is no data in literature associating high-intensity exercise with the sensitivity and acuity neuropathic changes connected with CLBP. This is an important issue because the minor back sensitivity reported in these patients is a continued process that tends to perpetuate CLBP, which in turn, inhibits pain modulation mechanisms, increases the sensitivity to pain, creating a vicious cycle between pain and loss of sensibility and acuity discriminations [83].

The mapping of body surfaces in the primary sensory cortex is relatively simple, however the body scheme is more complex because it requires the combination of several body maps, such as visual field maps, body surface maps, maps from vestibular perception or maps of the cortex primary motor [10]. As consequence of the above-referred neural alterations, CLBP patients perform worse in the implicit task of motor imagery related to the torso [10] once it depends from an intact body scheme [98]. These patients have greater difficulty in generating both visual and kinesthetic motor images compared with asymptomatic subjects and also required more time to perform these mental tasks [58]. Motor imagery is defined as a cognitive operation of an imagined task that depends from the dynamic relationship between the individual characteristics, the movement, and the environment [25]. The subject try to copy the movement or attitude in our conscience without actually having the movement in reality [14]. It was observed a significant influence of the prefrontal cortex, motor supplementary area, premotor cortex, anterior cingulate cortex, and posterior parietal cortex in the process of imagining a motor task [58]. In CLBP, a decrease in the thickness of the cortex in the area for sensory differentiation [69] associated with the reduction of the tactile perceptions [78] was described, however it must be noted that the cortex is mutable and its decreased thickness is reversible, with a non-painful sensorimotor stimulation approach leading to a normal activation of cortex [48]. Undoubtedly, the central nervous system requires constant feedback from the sensorimotor system for postural stability and movement control [34]. Motor imagery training reduces pain, improves function and minimizes behaviours that trigger injury in CLBP [82], probably explained by its potential *i*) to promote new connectivity to a central nervous system operate, using these new links to acquire movements without

pain on the prefrontal cortex and the amygdala involvement, *ii*) to learn the first step of movement construction (pre-motor area and basal ganglia) and *iii*) to promote an inhibitory descending system effect on pain modulation in the periaqueductal area. The use of motor imagery programs in CLBP patients has been less explored and although the few existing studies reported favourable results [23, 59], it has never been tested with exercise training for pain control. Considering the great potential of isolated high intensity exercise and motor imagery training programs to solve the CNS dysfunctions associated with CLBP, their combination might be seen as a powerful therapeutic weapon to fight the vicious cycle that maintains the chronic disorder [100].
Considering the above raised problems/questions, the main aims of this work were:

1. To characterize the superficial tactile and painful discrimination accuracy in *dorsum* of patients with CLBP, comparing this data with healthy subjects;
2. To verify if high intensity exercise program promotes changes of *dorsum*'s superficial tactile and painful discrimination accuracy in CLBP patients;
3. To verify if high intensity exercise training combined with motor imagery training added advantages in pain and functionality of CLBP patients comparatively to exercise training applied on its one.

These three goals were achieved with four original studies composing chapter 4, being the present work organized in 6 chapters: Chapter 1 is a broad general introduction on the theoretical aspects of chronic lower back pain, in its personal and social repercussions and how the evidence supports this work and in what way theoretical background support the rationality and evidence of this work; Chapter 2 is a state of the art about the therapeutic interventions in CLBP, exploring disorder's cortex reorganization and the regenerative capacities of the nervous system through physical exercise and motor imagery for an innovative intervention; Chapter 3 consists of four original studies, where the first one fulfil the first objective, the second one achieves the second objective, and the third and fourth studies accomplished the third objective; Chapter 4 consists on the overall discussion; Chapter 5 presents the main conclusion of this work and perspectives for future research, and finally, the Chapter 6 is composed by the bibliographic references.

2. STATE OF THE ART

High Intensity Exercise Training and Motor Imagery as Therapeutic Options in Non-specific Chronic Lower Back Pain. A Narrative Review

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High intensity exercise training and motor imagery as therapeutic options in non-specific chronic lower back pain: a narrative review

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Abstract:	Non-specific chronic lower back pain (CLBP) integrates pain, disability and reduced mobility, making individuals gradually more sedentary. This condition with non-specific causes has a multifactorial nature without any anatomical reasons. Population in general is affected by this condition, especially those between 50-69 years old and in the female gender. This disorder has repercussions on different levels of the central nervous system (CNS), which makes it a self-conditioning disease with physical and emotional symptoms, changes in sensitivity and in the discrimination ability, being allodynia an important false perception. The current therapeutic measures to CLBP are insufficient, either the traditional physiotherapy or the pharmacological approach, whose results are very poor in comparison with the specific patients' needs. Nevertheless, it is known that high intensity exercise training promotes neuroplasticity and enhances the excitability of the descending inhibitory pain modulation system, supporting its potential use as a therapeutic tool in CLBP. Moreover, motor imagery may also be applied to solve the CNS problems associated with CLBP as this mental representation of the preconized movement without moving any part of the body activates the premotor, the preparatory and the anticipatory motor system. Consequently, the stimulation of new brain connections and new pathways of movement without pain may arise from combining training of high intensity exercise with motor imagery. The aim of this study is to review the literature about the CNS changes described in CLBP its potential application and the efficacy of high intensity exercise training and motor imagery training on these patients.

Title

High intensity exercise training and motor imagery as therapeutic options in non-specific chronic lower back pain: a narrative review

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Abstract

Non-specific chronic lower back pain (CLBP) integrates pain, disability and reduced mobility, making individuals gradually more sedentary. This condition with non-specific causes has a multifactorial nature without any anatomical reasons. Population in general is affected by this condition, especially those between 50-69 years old and in the female gender. This disorder has repercussions on different levels of the central nervous system (CNS), which makes it a self-conditioning disease with physical and emotional symptoms, changes in sensitivity and in the discrimination ability, being allodynia an important false perception. The current therapeutic measures to CLBP are insufficient, either the traditional physiotherapy or the pharmacological approach, whose results are very poor in comparison with the specific patients' needs. Nevertheless, it is known that high intensity exercise training promotes neuroplasticity and enhances the excitability of the descending inhibitory pain modulation system, supporting its potential use as a therapeutic tool in CLBP. Moreover, motor imagery may also be applied to solve the CNS problems associated with CLBP as this mental representation of the preconized movement without moving any part of the body activates the premotor, the preparatory and the anticipatory motor system. Consequently, the stimulation of new brain connections and new pathways of movement without pain may arise from combining training of high intensity exercise with motor imagery. The aim of this study is to review the literature about the CNS changes described in CLBP its potential application and the efficacy of high intensity exercise training and motor imagery training on these patients.

Keywords

exercise therapy, pain modulation, somatosensorial, cortical thickness, allodynia, recognition

Introduction

Lower back pain has been defined as “pain and discomfort, located below the costal margin and above the inferior gluteal folds, with or without leg pain” [1]. The concept of lower back pain integrates three important aspects, which are pain [2], functional disability [3], and reduced mobility in physical activity [4]. This condition is usually classified as specific or as non-specific, depending on the identification of its cause [5, 6], and if the pain persists for more than 3 months, it is considered a chronic disorder [7, 8]. The current state of scientific evidence for chronic lower back pain reveals its multifactorial nature, increasing the need to stratify the disease impact in patients, as a combination of pain intensity, with daily activities interference and physical function, besides any presumed pathoanatomic repercussions [7, 9]. Some cases of chronic lower back pain are associated with a specific cause (e.g. radiculopathy, spinal stenosis, fracture, tumor or infection); however, in the majority of these cases, the origin of patients’ symptoms cannot be identified and the condition is labelled as a non-specific chronic lower back pain (CLBP) [10]. CLBP is a highly prevalent disorder without apparent identifiable patho-anatomic [11] or imagiological [2, 12-14] causes. Considering the high cost of personal, social, and economic impact of the disease, CLBP is considered as a multifactorial biopsychosocial syndrome [15]. It has a strong impact on patients’ daily activities such as walking, doing housework and maintaining an independent lifestyle. These limitations can be exacerbated by the increased associated fatigue, which can lead to loneliness, an important risk factor for depression in CLBP [16]. Conservative physical therapy has very small benefits on CLBP as it is widely assumed that the current therapeutic measures to treat CLBP are

insufficient, either the traditional physiotherapy or the pharmacological approach, being the results very poor in comparison with the specific patients' needs [16, 17].

Contrasting with the relative inefficiency of the pharmacological and traditional physiotherapy approaches, the high intensity exercise training has been recently applied to CLBP with great advantages [18, 19]. This can be mainly explained by the promotion of neuroplasticity and by the enhancing of the excitability of the descending inhibitory pain modulation system. Additionally, in order to solve their associated neural problems, the motor imagery has also been successfully applied in these patients [20, 21], through the stimulation of new brain connections and new pathways of movement. These great advantages of high intensity exercise programs and imagery training are related with their power to solve the CSN dysfunctions associated with CLBP, which in a vicious cycle tends to maintain the chronic disorder [22]. Considering that CLBP is not just a peripheral disease, but a sum of symptoms with source in CNS with peripheral sensorial repercussion and impact, the aim of this study is to review the literature about the main CNS dysfunction associated with CLBP, trying to understand the potential application and efficacy of high intensity exercise training and motor imagery training in disease control.

Non-specific chronic lower back pain

Lower back pain is recognized as a major public health problem, affecting about 80% of the population at least once in their lives [23]. An optimized analysis of the low back pain showed that by age 45, over 65% of the population tested did not reveal any degenerative variations at the lower back; however, 25% of

adults reported having had a vertebral pain at least once and about 75% of these had an experience that led them to seek for medical care [6]. In approximately 90% of the cases the lower back pain has a spontaneously resolution; nevertheless, in between 2% and 7% of these cases, it becomes a chronic condition [24]. The prevalence of CLBP appears to be increasing worldwide [6, 25], affecting a great number of individuals over 55 years-old [6]. This professional active age associated to a chronic condition provides a high social-economic burden to CLBP [26]. The prevalence of degenerative changes increases with age and it is high in patients over 55 years-old [6]. In fact, chronicity and functional disability are resulting problems [27], making CLBP patients more dependent on government-sponsored insurance plans with more often visits to health care providers [22]. It is a chronic social condition characterized by a lower education, poor annual household income, receiving income from disability, depression, sleep disturbances, and other medical comorbidities [22]. In Portugal, the prevalence of CLBP in the adult population is 10.4%, with an average age of 58.9 years, from which 71.4% are female [26]. The most part of Portuguese population with active CLBP did not practise any regular physical activity and only 22.3% practised some physical exercise [26]. In 2003 the Dutch Physiotherapy Guidelines for CLBP gave recommendations for all kind of exercise therapy and behavioural treatment, which may be useful [28]; Physiotherapy promotes physical activity in CLBP which is more relevant for patients due to the high prevalence of comorbidities. However, there was a small response to physical therapy intervention guided by self-reported guidelines for chronic low back pain [29]. Physiotherapy treatments, including lumbar mobility exercises, can be beneficial in the short term [30]; however,

many authors have not found evidence about which specific type of exercise therapy is clearly more effective than others [31].

There is a multiple options treatment with restrict success for patients with chronic low back pain; nevertheless, patients could select a nonpharmacologic treatment with a multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction, tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, low-level laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation [32]; however, there is no consensus about the best practice as they only have low to moderate-quality level of evidence [33]. There is also no significant evidence about yoga when compared to conservative physiotherapy even when it is performed using some type of therapeutic exercise [34]. The clinical efficacy of acupuncture and TENS is difficult to prove [35] and acupuncture effects were observed immediately after treatment, with no evidence of long-term effects [36]. The efficacy of vertebral manipulation method in treating CLBP has also been demonstrated [37]; nevertheless, the real spinal manipulation was less effective than a simulated manipulation for CLBP [36].

In summary, the current therapeutic measures to CLBP seem to be insufficient, either the traditional physiotherapy or the pharmacological approach, once their results are very poor in comparison with the specific patients' needs.

Changes in central nervous system with CLBP

Cortical degeneration and brain reorganization have been described in CLBP [38]. The cortical reorganization is correlated with pain intensity [39, 40] and was associated with lower gray matter volumes in the medial/ dorsolateral and

ventrolateral prefrontal cortices as well as in the anterior insular cortex [41]. This regional atrophy dictates the brain activity, which displaces the brain activity from the anterior cingulate cortex to the orbitofrontal cortex by a great number of connections from thalamus [42]. This is the reason why CLBP patients showed an attenuated activity at the right dorsolateral prefrontal cortex (DLPFC) due to the pain, where premotor area is including, as well as in the left anterior cingulate cortex (ACC), and at the bilateral superior parietal cortex [43]. This cortical reorganization of the prefrontal cortex and of the thalamus was quantified by a decreased neocortical brain volume [42]. The prefrontal cortex has numerous connections with the periaqueductal gray area (PAG), which is part of the descending pain modulatory system capable for endogenous pain modulation [41, 44]. In fact, prefrontal cortex presents a decrease in thickness in the number of connections in the brain and from the prefrontal cortex to the brainstem, probably explained by an impairment of activity in descending pain inhibitory mechanism favoring the maintenance and exacerbation of pain [45]. This compromised mechanism might be associated with the dysfunction of the endogenous modulatory process [46]. The cortical thickness also decreases in sensory differentiation associated with disruption of the tactile process [39, 47]. Pain sensitization involves an increased responsiveness of central and/ or peripheral nervous system circuits, resulting in pain hypersensitivity as allodynia [48], a state where the presence of pain is concurrent with the absence of peripheral nociceptive stimulation [40] with a deficit of sensory information to the cortical representation [49]. The somatosensory pain memories manifest alterations in the somatotopic map and in the somatosensory cortex which contribute to allodynia [40], a component in back painful area that could result

from a mechanic stimulus [50], which is caused by the recruitment of low-threshold Aβ mechanoreceptive fibers that leads to central sensitization [51]. The Aβ mechanoreceptive fibers do synapses with the C fibers in gelatinous substance nucleus and the stimuli transmitted by spinothalamic tract to the nucleus ventroposterolateral of the thalamus sending as well collateral branches to the periaqueductal gray area, to hypothalamus, and to amygdala [52, 53], which are fundamental structures for pain modulation [46]. The lose effect on gray matter near the amygdala may reflect alterations of circuits to and from the periaqueductal gray area and to the spinal cord, where the amygdala plays a fundamental role in descending inhibitory pain control as well as in the enhancement of pain responses following a stressor [54]. The hypothalamus also has a strong relation with amygdala, being responsible for controlling the autonomic system that commands the heart rate, blood pressure, sweating, shortness of breath and physiologic changes of intensity exercise [55], closely associated with the descending pain modulation system [44]. Central nervous system requires constant feedback from the sensorimotor system for postural stability and motion control [56]. In chronic pain condition, the peripheral, cortical and subcortical inputs are abnormal, therefore the cortico-basal ganglia-thalamus presents a dysfunctional loop, which generates an altered integration of the sensory-motor responses [57]. This is why CLBP patients show a motor deficit in paraspinal muscle [58, 59]. The pain promotes changes in the sensory information and in the cortical representation of the lumbar spine in patients with CLBP [49], explaining why these patients constitute a sensibility heterogeneous population [60]. Many cortical areas can be activated during pain, however some of them are involved more than others and a wide great

variability existing within and between individuals, these neuroanatomical structures are known as the "pain matrix" and have an individual-specific pain neuromatrix [61].

Subjects with a neuropathic pain presented greater disinhibition of pain modulation comparatively to those with a persistent peripheric nociceptive input [62]. In CLBP patients, the somatotopic representation of the lumbar spine in somatosensorial cortex S2 has a reduced neuronal activity, a maladaptive change and a reorganization in higher-order processing of sensory information, which might have repercussion in a decreased to sensory acuity, to body perception, and subsequently to the lumbar spine functionality [49]. Sensory representation of body image is constructed and modified from the proprioceptive stimuli of the body; however, the painful stimuli clearly distorts the image of the injured segment [63]. The same occurred with movement-related pain which provokes inconsistency between predicted and actual sensory feedback due to a disturbed body scheme and irregular sensory function [64]. CLBP is associated with disruption of body schema perception [65] because of a wrong perceptual sensitization of human brain caused by changes in sensitivity at various CNS levels, such as the spinal cord, brainstem and cerebral cortex [66]. It should be noted that this maladaptive reorganization of cortex may be reversible, with a special approach to non-painful sensorimotor stimulation treatments applied to restore normal somatosensory through the activation of the lower back [49].

Influence of high intensity exercise training

In CLBP patients, physical exercise training activates a powerful top-down pain inhibitory action, typically referred as exercise-induced endogenous analgesia by influencing neurotrophic factors while exerting in central sensitization opposite effect [45]. The intensity of exercise seems to play an important role in the neuroplasticity of the brain and in its inhibitory effects on pain modulation [67]. Moreover, the influence of exercise training has also resulted in improvements of cognitive tasks on the prefrontal cortex, which improve learning and retention of motor skills dependent on the striatum and motor cortices [68]. In an animal model of complex regional pain syndrome Type I, where a neuropathic pain was presented, repeated sessions of high-intensity exercise caused a pronounced and long-lasting anti-allodynia reaction [69]. The activation of proprioceptive and muscle afferents may be one the mechanisms that inhibit the central pain circuit and it may involve the modulation of the descending inhibitory pathways [55]. High-intensity aerobic exercise promotes pain relief, reducing disability and psychological strain better than low intensity strengthening programs [37, 70, 71]. Comparatively to this low intensity, the high intensity exercise program promotes better results in pain and disability in CLBP [37]. Exercise intensity and duration are conditioning factors to trigger exercise-induced analgesia and 30-minute of exercise at 75% VO2max seems to be appropriate for this induction [55].

One of the most important questions is related with the kind of transformations operating in CNS after the high intensity exercise. Running exercise has effect on chronic pain symptoms which can be attributed to the modulation induced by the release of central or peripheral neurotrophins in nerve regeneration [72]. Endogenous Brain-derived neurotrophic factor (BDNF) deprivation prevents

axonal growth and myelination, and its endogenous exacerbation promotes nerve regeneration and neural conduction [73]. It is recognized that the serum BDNF levels are involved in the processes that mediate the disinhibition of motor cortex excitability and in the function of descending inhibitory pain modulation system, regardless of the physiopathology mechanism [62]. In humans, the serum BDNF levels increase with high intensity exercise [74, 75] and there is evidence that the serum concentration of BDNF reflects its expression in the brain and vice-versa [76]. BDNF serum concentrations increase in response to acute and chronic high intensity exercises protocols in healthy adult and in clinical populations [77]. Some reports showed that the BDNF release is exercise intensity-dependent, with higher-intensity workouts producing larger increases in neurotrophin levels [68].

BDNF is a protein encoded by the BDNF gene, and therefore, a member of the neurotrophin class of growth factors produced by a variety of neural cells [45]. BDNF is one of the main regulators of neurogenesis and it is also involved in the enhancing neuronal differentiation and survival as well as in synaptic transmission [68]. Apart from these BDNF-dependent mechanisms, several others must also be considered, such as the one involving lactate produced during high-intensity exercises, which is able to cross the blood-brain barrier and be used by the brain as an alternative source of energy for neuronal plasticity [68]. In the brain, lactate serves as a precursor to glutamate, which is the main excitatory neurotransmitter with increased peripheral lactate levels [68]. High intensity exercise training has the potential to improve the performance of neuroplasticity because it triggers the expression of neurotrophins with increased neural repair processes [78]. High intensity

exercise provides benefits and has effects in neurotransmitters and hormonal productions [79] particularly in the way cerebral cortex starts to interpret the signals from the periphery, identifying them as non-painful sensations but as the true and real sensations [80].

Influence of motor imagery training

Motor imagery is a mental representation of the movement without moving any part of the body, being a complex cognitive operation that is self-produced using the sensory and perception processes capable of reactivating a specific motor attitude [20]. It depends on the dynamic relationship between the individual's movement and task, the environment, and individual characteristics [20]. Motor imagery has been used to improve the performance of athletes for many years and it is based on the activity of mirror neurons [20]. The subject tries to copy the movement or attitude in our conscience without actually doing the movement in reality [81].

Mirror neurons are known to activate the pre-motor cortex and motor cortex; therefore, it is suggested that they have the capacity to activate the preparatory and anticipatory motor systems [20]. As pain theories emphasize a close relationship between pain and the stimulus of movement production, the strategy involves an initial activation of the premotor cortex and subsequent activation of the primary motor cortex. Moreover, no pain response to imagined movement was revealed [82]. It was observed a significant influence of the prefrontal cortex, the motor supplementary area, the premotor cortex, the anterior cingulate cortex and the posterior parietal cortex in the process of imagining a motor task [83]. Recognition of right and left body images also

activates areas of the brain involved in the upper order of the premotor cortex, while imagined movement activates the primary motor cortex [82], which involves initial decision making and confirms this choice by mental movement of one's own laterality to match it with of the image [84]. Recognition of limb laterality promotes activation of the pre-motor cortex, but not of the motor cortex [63], giving rise to the conception of movement, the first stage of a path for pain-free movement [82]. This activation is based not only on the visual system (e.g. chewing sound), but also on the motor response to improve function [63]. If body scheme had changes that contribute to a perturbed laterality, it would be a necessary competence and ability to imagine movement for restoring a normal motor function [85]. Motor imagery has been used in many kinds of disorders, but the principle is always the same: it is crucial to train the brain [63].

The purpose of motor imagery training placed in CLBP is to reduce pain, improve function and minimize behaviors that trigger injury [37]. Patients with bilateral CLBP performed worse in the implicit motor imaging task related to trunk laterality [65]. These patients have greater difficulty in generating both visual and kinesthetic motor images compared with asymptomatic subjects and also required more time to perform these mental tasks [83]. CLBP produces motor imagery deficits that could manifest altered accuracy, difficulty in defining if the image is from the right or the left side of the body and the time reaction to choose the correct answer [21]. People with CLBP also show spatial neglect-like responses to tactile stimuli, but results show no deficit reaction time in left/ right trunk judgments [21].

Conclusion

The concomitant development of neural changes tends to perpetuate CLBP, which in turn, inhibits pain modulation mechanisms and increases the sensitivity to pain, creating a vicious cycle in pain matrix. CLBP must not be seen as a peripheral disorder but instead, as a sum of symptoms with central source in the cortex cerebral, with peripheral sensorial repercussion and impact leading to allodynia. The proposal for a multimodal therapeutic intervention by the guidelines reflects the little that has been achieved with all the interventions available. The use of pharmacology in CLBP is very reserved and its adverse effects are many. Considering the reversible character of these neural alterations as well as their potential to counteract them, the high intensity exercise training and the motor imagery programs constitute new and promising approaches to control the disease. Moreover, taking into account the complementary advantages of each one, a combined program of motor imagery with high intensity exercise might bring more advantages than each one them by itself.

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3. ORIGINAL STUDIES

Study 1

Non-specific chronic lower back pain patients show impairments of sensorial and pain perception/discrimination in the back area

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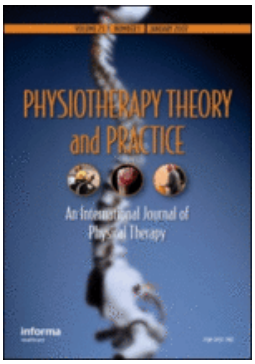

Non-specific chronic lower back pain patients show impairments of sensorial and pain perception/ discrimination in the back area

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Non-specific chronic lower back pain patients show impairments of sensorial and pain perception/ discrimination in the back area

Abstract

Background: The chronic lower back pain (CLBP) disorder is characterized by the existence of sensorial limitations in the referred painful zone, however it is possible that a larger dorsolumbar surrounded area might also be compromised. If so, this kind of information will be important to define effective therapeutic approaches. **Objective:** To characterize the perception of patients with CLBP, not only in the painful zone but also in the surrounding areas of the back, comparing this data with healthy subjects. **Methods:** A cross-sectional study, with a convenience sample of 22 CLBP and 22 pair-matching healthy subjects (for age, sex, and body mass index). Fourteen areas were drawn on the back region, being tactile and pain interspaced stimuli applied twice in each area, assessing the accuracy to identify the specific stimulated area. For data analysis, the 14 areas were grouped and classified into 3 different zones: the painful zone includes the area(s) of referred pain, the adjacent zone comprises the surrounding areas, and the peripheral zone includes the remaining marginal areas. **Results:** Comparatively to healthy subjects, a lower accuracy to identify superficial and pain stimulated areas was observed in the back of CLBP, without significant differences between zones. **Conclusion:** Although the occurrence of slight deficits in healthy subjects, CLBP present higher deficits of tactile and superficial pain areas discrimination distributed for all back zones. For these reasons, a sensory evaluation of the back is recommended in clinical practice.

Keywords

low back pain, clinical evaluation, sensorial discrimination protocol, superficial stimulation, pain stimulation

INTRODUCTION

Lower back pain, defined as pain and discomfort located below the costal margin and above the lower gluteal folds (van Tulder and Koes, 2006), with or without irradiation to the lower limbs, is recognized as an important health public problem affecting about 80% of the population at least one time in all life (Haas et al., 2005; Heiskanen, Roine, and Kalso, 2012; Waddell, 2005). The increased prevalence of osteoarticular degenerative changes with age may explain the higher occurrence of lower back pain above 55 years old (van den Bosch, Hollingworth, Kinmonth, and Dixon, 2004). However, the specific causes for lower back pain are not well established (Laslett et al., 2005; Waddell, 2005), being its chronicity dependent from the localization and duration (Waddell, 2005). The chronic condition is characterized by a persistent lower back pain for a period not less than 12 weeks (Airaksinen et al., 2006) presenting, in addition to pain, increased muscle tension (Manek and MacGregor, 2005), weakness and loss of mobility (Haas et al., 2005). With a multifactorial nature (Heiskanen, Roine, and Kalso, 2012), it is reported that chronic lower back pain (CLBP) also promotes changes in patients' sensorial and laterality perception and discrimination (Huge et al., 2008). These sensorimotor, proprioceptive and tactile deficits described in CLBP patients are paralleled with a decreased cortical thickness of the sensorial differentiation area compromising perception (Moseley and Flor, 2012). This lack of sensitivity of the body schema in the localization of sensory information from the back is a contributing factor to introduce errors in motor control, predisposing to the lesion and the continuity of the pain (Bray and Moseley, 2011).

Unfortunately, these sensorial deficits are not routinely assessed in clinical practice mainly due to the absence of practical and patronized tests. The evaluation of tactile sensitivity in the back has been approached with several methodologies but so far

there is no consensus on which one is the best to characterize these sensitivity changes. The two-point discrimination test (TDP) (Lotze and Moseley, 2007; Wand et al., 2014; Wand, Di Pietro, George, and O'Connell, 2010) is one of the most used but it has several limitations (Ehrenbrusthoff, Ryan, Gruneberg, and Martin, 2018), namely the pressure and the synchronization of the touches produced by the caliper (W Adamczyk, Slugocka, Saulicz, and Saulicz, 2016; Catley, Tabor, Wand, and Moseley, 2013). The point-to-point test (PTP), comparing to TDP technique, improves intra and inter-reliability (W Adamczyk, Slugocka, Saulicz, and Saulicz, 2016), and the evaluation was defined by a horizontal line near the spinous process of third lumbar vertebrae and only had three points of identification. Two point estimation task (TPE) (WM Adamczyk et al., 2019) was a variation of PTP, however it was not yet applied to healthy persons in order to verify normal behavior and moreover, it necessitates the existence of patient's spatial skills to identify and imagine the rear measurement. In TDP and PTP, differences side to side in horizontal discrimination are negligible in healthy persons (Wand et al., 2014) but not in CLBP patients (Wand et al., 2016), where these differences are also greater when comparing vertical to horizontal discrimination (Luomajoki and Moseley, 2011; Wand et al., 2014). In the quantitative sensory test (QST), pain thresholds were found to be significantly increased in the back in patients with CLBP (Puta et al., 2013), however its results are influenced by the inter-individual variability of anticipatory answer and by the reacting velocity of each patient (Neziri et al., 2011).

All these tests used for research purposes are not useful enough to be regularly applied in clinical practice, which necessitates an easy and intuitive test to detect the sensorial deficits. Moreover, although these sensorial limitations have been described in the referred pain zone (Bray and Moseley, 2011; Moseley, Gallagher, and Gallace,

2012; Nishigami et al., 2015), it is possible that a larger dorsolumbar surrounded zone may also be affected. Consequently, the required clinical assessing test must give sensorial information not only from the referred pain zone but also from the surrounding regions, which might be likewise compromised. Understanding the sensorial limitations is an important aid to define different therapeutic approaches for pain reduction and for an effective motor control. Indeed, it is essential to see skeletal muscles as important promoters of sensorial information to movement and posture by anticipatory mechanisms from premotor cortex (Hwang, Bae, Do Kim, and Kim, 2013). If the patients have lost back sensation, it is fundamental to reinforce good perception of the back to win control of movement and posture, losing the perception of pain (Hwang, Bae, Do Kim, and Kim, 2013; McCaskey, Schuster-Amft, Wirth, and de Bruin, 2015).

In this sense, using the assessment methodology used by Wand et al. (Wand et al., 2013), the aim of this study was to characterize the back perception of patients with CLBP, not only in the referenced pain zone but also in the adjacent and peripheral zones, comparing this data with healthy subjects.

MATERIALS AND METHODS

This research was approved by the Ethics Committee of the S. João Hospital Center (CES 89-14) and carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and all intervenient signed an informed consent.

In this transversal nature study, a convenience sample was divided into two pairs groups: the CLBP group (n = 22) and the healthy group (n = 22). For the CLBP group the inclusion criteria were age over eighteen years and fluently speaking Portuguese, with major diagnosis of non-specific chronic lower back pain for more than 6 months

and followed by the Pain's Unit at the S. João Hospital Center. The exclusion criteria in this group were pregnancy, postpartum up to one year, patients with severe cardiac, neurological or metabolic diseases and with motor dysfunction, patients with difficulty in performing a quick and visually impaired appointment task, patients with radicular pain or evidence of specific vertebral pathology like neoplasms, infection, fractures, inflammatory diseases, lumbar surgery in the last twelve months, and patients with a legal litigation because of their lower back pain. The healthy group was built by pair-matching with the CLBP group regarding age, gender, and body mass index, without lower back pain but respecting the same exclusion criteria.

Socio-demographic and functional disability characterization

Subjects were asked about their gender, date of birth, height, weight, dominant laterality, and current professional status. In the CLBP group, it was also enquired how much time chronic pain was present and request designing in an image (Figure 1) their zone of pain self-perception in posterior, anterior and lateral view. The intensity of pain and the functional disability were assessed in all CLBP patients using, respectively, the Visual Analogue Scale (Katz and Melzack, 1999) and the Roland Morris Disability Questionnaire (RMDQ) (Monteiro, Faisca, Nunes, and Hipolito, 2010) adapted and validated for the Portuguese language, which provides reliable and valid measures of patient incapacity with lower back pain.

Superficial tactile and pain sensitivity in the back

Both groups were submitted to a protocol for evaluating the individual's ability to identify sensorial information provided from their back evaluated through the Wand et al. methodology (Wand et al., 2013). This protocol was performed in a silent room, with

minimum levels of noise and distraction, with ambience temperature of 25-26º Celsius. All volunteers were instructed to strip themselves and remained wearing their pants and bra if the case.

In a prone position, on a treatment table and with a small table nearby on the right or left side according to hand dominance prepared for this purpose, subjects were allowed to adjust to the environment for 5 minutes while observing a schematic diagram of the dorsal surface of the body presented on a sheet of size A3 with 14 different areas defined by anatomical references following the Wand et al. (2013) protocol (Figure 2A). These areas were drawn on the back of the subjects, using a dermal pencil, where tactile and pain stimuli were applied. All areas were numbered, being the areas 1 through 7 located on the left hemibody and the areas 8 through 14 located on the right hemibody (Figure 2A).

In the defined back areas, the superficial tactile test was the first applied, using a standardized cotton pad (Figure 2B), followed by the superficial pain test performed with the standardized monofilament device (Medipin, Ltd., Bushey Hertfordshire, United Kingdom) (Figure 2B).

In the superficial tactile test, the sequence of stimulation of each area was random defined by software and using two touches for each area providing a total of 28 stimulations. The superficial pain was similarly assessed using a different random area sequence. The trained researcher who applied the test was not aware of which group the participants were part of. In order to ensure the sensorial consistency of the superficial and pain stimuli, attempts were made by the researcher to standardize the applied pressure of the cotton pad as well as the depth of the depression caused by the monofilament through a flat ring, thus limiting the depth of the impression.

Each stimulus was interspaced by at least 5 seconds and during the pauses the participant indicated in the schematic diagram which area of the body the stimulus was felt. If the body area indicated by the patient was different from the area of the stimulated body, it was recorded as a location error.

In the CLBP group three distinct zones were considered: the painful zone, composed by one or more areas of pain signed by the patient in Figure 1, the adjacent zone composed by the areas that closely surround the painful zone, and the peripheral zone composed by the areas that border the adjacent zone. The absolute and relative frequencies of correct and incorrect touches identified by the volunteers were evaluated in the painful, adjacent and peripheral zones, being further compared with the accuracy of the same areas assessed in the healthy group.

Statistical analysis

IBM's Statistical Package for the Social Science® software version 20.0 (IBM Corporation, Armonk NY, United States of America) was used for descriptive and inferential data analysis, with significance set at 0.05. The absolute/ relative frequencies were used to describe the distribution of gender and professional/ occupation variables. The Shapiro-Wilk test was used to test the normality of the quantitative data. Median, with percentiles 25 and 75, were used as central tendency measures for the time of CLBP disease. Considering the normal data distribution of the remained variables, the Mean ± Standard Deviation were used as central tendency measures. Chi-square was used to compare gender and professional occupation between groups. Independent samples T-test was used to compare between groups the anthropometric data and the correct identification to the superficial and pain stimuli. The ANOVA repeated

measures test was used to compare within CLBP group the correct identification in each defined zone (painful, adjacent and peripheric).

RESULTS

Sample characterization

Sociodemographic and anthropometric data were similar between CLBP and healthy groups (Table 1). However, the professional occupation was significantly different between groups ($p<0.001$) and it was possible to observe that the frequency distribution of active participants was minor in the chronic lower back pain group (n=5; 22.7%), when compared to the healthy group (n=19; 86.4%).

In the CLBP group, 100% of participants had complained in at least one area of the lower back region (lumbar and gluteal areas) (Figure 2A). The location of pain in the patients' posterior areas was distributed as follow: 86.4% in the right lower lumbar area, 77.3% in the left lower lumbar area, 50.0% in the right upper lumbar area, 40.9% in the right gluteal, 45.5% in the left upper lumbar area, 45.5% in the left gluteal area, 36.4% in the left lower thorax area, 27.3% in the thoracic right lower area and left upper area, 22.7% in the right upper thorax area and left upper thigh area, 18.2% in the left lower thigh area, 13.6% in the right lower thigh area, and 4.5% in the right upper thigh area.

The CLBP group reported pain as a chronic state in the past 78 months as median, with 47.5 and 138.0 months corresponding to percentiles 25 and 75, respectively; the current pain mean intensity was 62.5±16.89 mm (in VAS), with a mean physical disability score of 15.8±3.47.

Pair-matched comparison: CLBP group vs. Healthy group

There were significant differences between groups in the mean distributions of the correct identification to the superficial and pain stimuli (p<0.001). In fact, it was possible to observe that the mean and standard deviation of the correct identification of the superficial and pain stimuli was lower in the CLBP group, when compared to the healthy group (Table 2).

CLBP group: accuracy in the painful, adjacent, and peripheral zones

In the CLBP group, there were no significant differences between each defined zone (painful, adjacent, and peripheric) in the mean distributions of the correct identification to the superficial and painful stimuli (Table 3).

DISCUSSION

Our results revealed differences in the superficial and pain sensibilities between the healthy group and the CLBP patients affecting the back region, without variations in superficial and painful tactile stimulation in painful, adjacent, and peripheric zones of the CLBP patients. In fact, as expected, the occurrence of mistakes/ incorrect identification was not restricted in CLBP to the painful zone.

The observed loss of discriminative ability might have its origin in three vital segments for the gathering of information: i) at dermatome levels, ii) in the afferent stimulus conduction pathways, and iii) in the gain of awareness of the cortical somatosensorial region (Flor, Braun, Elbert, and Birbaumer, 1997). Considering the similar patterns presented by CLBP patients, presenting identical behaviors for superficial and pain sensibilities, it might be assumed that the greater impairment is located at cortical level once these stimuli are conducted by different afferent pathways, namely the dorsal columns and spinothalamic pathways. In agreement with this

assumption is the poor discriminative answer in the painful zone described in the literature for chronic low back pain patients, which reinforces the existence of a cortical impairment location (Catley et al., 2014; Wand, O'Connell, Di Pietro, and Bulsara, 2011).

It must be noted that chronic pain is referred as presenting a preferential pathway to pain awareness, with the inability to be modulated throughout the nervous system (Correa et al., 2015). This incapacity to modulate pain at the dorsal horn may explain in the CLBP group the higher inaccuracy in identification of the pain stimulus in all back zones. This inability increased neuronal activity of the spinal cord dorsal horn, increasing pain and hyperalgesia and hindering the stimulus assertiveness (Correa et al., 2015).

In the literature, several sensorial tests have been used to study this subject in chronic pain, especially in the CLBP patients (Ehrenbrusthoff, Ryan, Gruneberg, and Martin, 2018; Lotze and Moseley, 2007), namely TDP, PTP, QTS and PTE. It must be noted that all these tests only analyze the sensitivity of touch discrimination, not referring to other types of sensitivities such as superficial touch and superficial pain. Moreover, all these tests are only applied in the painful lumbar zone, without giving additional information about the sensibility disturbances that might occur in the adjacent and peripheric zones. All these limitations clearly contrast with the characteristics of the test used in our study, which is standardized, gives information from different back zones, is comfortable to patients, and easily applied in clinical practice, where the patients' perceptions are transmitted in a quick and well-defined way. Indeed, many times, the patients had difficulty to define and communicate their incapacity and loss of sensation to the clinician.

If the ability to identify the stimulus is significantly different between the CLBP group and the healthy group and there are no significant differences between the painful zone and the remained zones in the superficial tactile and painful sensibilities, so the entire back region should be a clinical approach target through the cortical re-education of sensorial dysfunctional areas. Indeed, maladaptive changes in sensory information processed in the cortical representation of the lower back in CLBP patients appears to be reversible with non-painful manual input activation of the mechanosensory cortices, contributing to alleviate pain levels and disability in CLBP patients (Hotz-Boendermaker et al., 2016). Due to this loss of discriminatory capacity at central level in the dorsal region, it is suggested that training with re-education programs should be provided throughout the back region in order to enhance proper identification to all kinds of stimulus. Additionally, the conditioned pain modulation shows evidence for endogenous changes in chronic lower back pain during short periods, indicating its therapeutic effectiveness (Mlekusch et al., 2016). Consequently, the patients' initial assessment must include collection of data regarding the responsiveness to the discriminatory stimulus that will define the patients' training goals. The tactile acuity training (Wand, O'Connell, Di Pietro, and Bulsara, 2011), graphesthesia (Kalin, Rausch-Osthoff, and Bauer, 2016), and sensorial retraining (Walti, Kool, and Luomajoki, 2015), requiring an active participation from patients (Moseley, Zalucki, and Wiech, 2008), have already been used with favorable results (Walti, Kool, and Luomajoki, 2015). This type of training in CLBP patients grows in recent years, suggesting a different approach in the management of pain therapeutic interventions (Wand, Di Pietro, George, and O'Connell, 2010). However, our results clearly show the necessity to apply the training in the complete back torso and not only in the painful lumbar region as it is usually

done (Walti, Kool, and Luomajoki, 2015; Wand, Di Pietro, George, and O'Connell, 2010).

Regarding the limitations of our study, the used sample size may appear small at a first glance. Nevertheless, based on the results of Wand, Di Pietro, George, and O'Connell (2010), which differentiates among groups regarding the two points discrimination reveals an effect size of 0.98, for a statistical power of 95% with an α=0.05, the a priori sample size calculation discloses a sample size of 22 persons per group. Moreover, the imbalance in the relationship between men and women observed in our study cannot be considered a limitation since it is in agreement with the populational prevalence of this disease (Gouveia et al., 2016). Since we used a different methodology from those usually utilized in literature, the quantitative data comparison to other studies is not possible because we did not assess the levels of sensorial discrimination in a specific lumbar area.

CONCLUSION

Although the occurrence of slight deficits in the perception of superficial and painful tactile stimulation at the back region of healthy subjects, chronic lower back pain patients present higher deficits of tactile and superficial pain discrimination distributed for all back zones. For these reasons, it is recommended integrating into clinical practice the sensory evaluation of these patients.

CONFLICT OF INTEREST/ DISCLOSURE SUMMARY

All authors report no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The manuscript was developed and written equally by all authors.

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Table 1 Sample characterization: sociodemographic, anthropometric, and professional occupation data in chronic lower back pain (CLBP) and healthy groups. Data are presented as absolute frequency (relative frequency) for qualitative variables, and mean (±standard deviation) for quantitative variables *p* values reflect the between-groups comparison.

Variable		CLBP group n=22	Healthy group n=22	Between-groups comparison *p* value
Sociodemographic data				
Gender (n)	Female	13 (59.1%)	13 (59.1%)	1.000
	Male	9 (40.9%)	9 (40.9%)	
Age (years)		51.36±8.72	52.91±9.33	0.573
Anthropometric data				
Body mass (kg)		70.8±11.55	73.9±14.76	0.447
Height (m)		1.7±0.08	1.7±0.08	0.399
BMI (kg/m^2)		25.7±3.85	26.1±4.55	0.778
Professional occupation data	Retired	4 (18.2%)	2 (9.1%)	<0.001
	Unemployed	7 (31.8%)	0 (0.0%)	
	Sick leave	6 (27.3%)	1 (4.5%)	

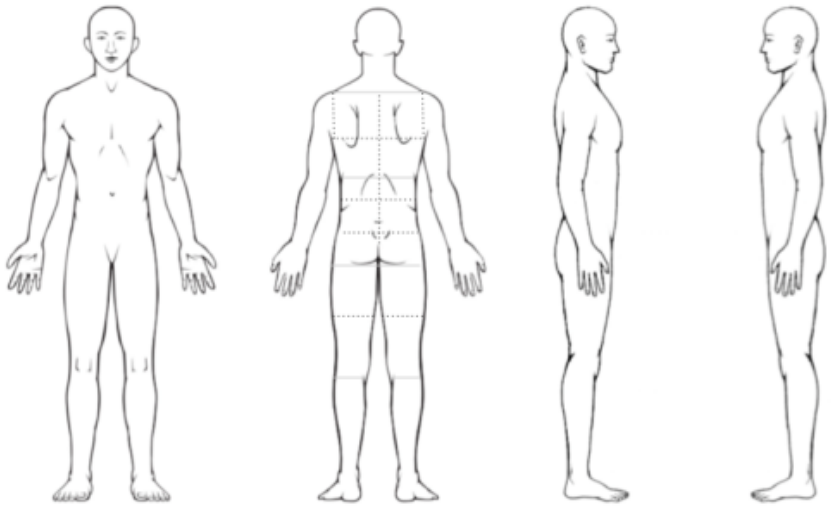
Active	5 (22.7%)	19 (86.4%)

Table 2 Mean values (±Standard Deviation) of the relative frequency (%) of correct identification to the superficial and pain stimuli in all areas, in the chronic lower back pain (CLBP) and healthy groups. *p* values reflect differences in percentage of correct identification among groups.

Variable	CBLP group n=22	Healthy group n=22	Between-groups comparison *p* value
Superficial stimuli (% of correct identification)	73.38±14.06	86.50±9.52	0.001
Pain stimuli (% of correct identification)	70.94±12.09	85.86±12.10	<0.001

Table 3 Mean values (±Standard Deviation) of the relative frequency (%) of correct identification to the superficial and pain stimuli in painful, adjacent and peripheric zones of chronic lower back pain (CLBP) group. *p* values reflect differences in percentage of correct identification among defined zones.

Variable	Painful zone	Adjacent zone	Peripheric zone	Within-CLBP group comparison *p* value
Superficial stimuli (% of correct identification)	75.70±18.00	73.36±20.84	70.03±22.10	0.472
Pain stimuli (% of correct identification)	70.78±18.48	73.18±19.79	67.28±21.55	0.760



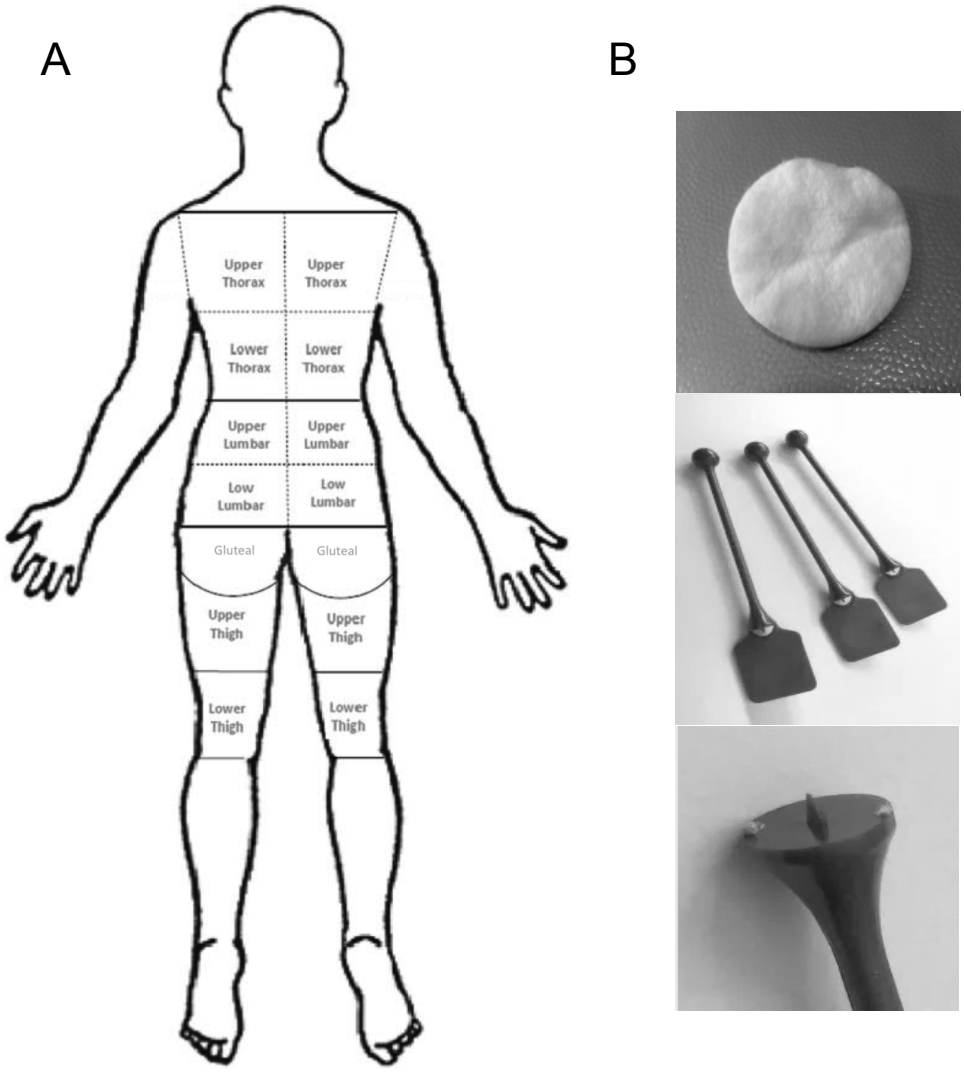

A
B
Upper Thorax
Upper Thorax
Lower Thorax
Lower Thorax
Upper Lumbar
Upper Lumbar
Low Lumbar
Low Lumbar
Gluteal
Gluteal
Upper Thigh
Upper Thigh
Lower Thigh
Lower Thigh

Figure 1 Image presented to patients where the painful zone is marked by themselves.

Figure 2 A. Defined areas through marked lines, based on the anatomical landmarks. Nine lines were defined, delimiting fourteen areas: 1st popliteal line marked on the popliteal face of the posterior region of the knee; 2nd midpoint of the thigh equidistant between the popliteal line and the gluteal fold line; 3rd line on the gluteal fold; 4th line joining the posterior superior iliac spines; 5th line marked by the spinous processes of L2; 6th line marked by the spinous processes of T10; 7th line marked by the spinous processes of T6; 8th line marked by the spinous processes of T2; 9th posterior medial line or middle vertebral line passing through the spinous processes of all vertebrae. B. Cotton pad and monofilament used to test, respectively, tactile and pain sensitivities in the defined areas.

Study 2

High–intensity exercise training improves *dorsum* superficial tactile and pain discrimination in non-specific chronic lower back pain patients.

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Title

High-intensity exercise training improves *dorsum* superficial tactile and pain discrimination in non-specific chronic lower back pain patients

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Running title

High-intensity exercise and descrimination in CLBP

Abstract

Background: Sensorimotor impairments in the *dorsum* of non-specific chronic lower back pain (CLBP) patients supports the existence of a pain vicious cycle perpetuating the disease, in which exercise-induced neural plasticity might have potential benefits. **Objective:** To verify the changes to superficial tactile and painful discriminations stimuli of the *dorsum* after a high-intensity exercise training (HIET). **Design:** Experimental longitudinal study. Subjects: 24 CLBP patients randomly distributed into two pairs groups: experimental (n = 12, with 10 females) and control (n = 12, with 6 females). **Methods:** 14 areas were drawn on the *dorsum* of each patient; tactile and painful stimuli were applied in each area to assess the individual's accuracy to identify the stimulated area. These areas were grouped into 3 different zones: the painful zone includes the area(s) of referred pain, the adjacent zone comprises the surrounding areas, and the peripheral zone includes the remaining marginal areas. The experimental group was submitted to a HIET during 12 weeks without intervention in control group. Location, extent, and intensity of lower back pain as well as the superficial tactile and painful discriminations tests were evaluated at the beginning and at the end of the protocol. **Results:** The experimental groups, comparatively to control group, showed an increased accuracy to identify superficial tactile and painful stimulated areas, paralleled by a decreased lower back pain intensity and extent area. **Conclusions:** Results support the concept that CLBP has a neural system influence with peripheral sensorial negative impact, which condition is minimized by HIET.

Keywords

low back pain, pain assessment, sensory testing, central sensitization, allodynia, conditioned pain modulation, neuroplasticity

Introduction

Non-specific chronic lower back pain (CLBP) is one of the most public health problems with high costs in national health plans, in addition to the absenteeism associated with it (1). Risk factors for CLBP include overweight, sedentary lifestyle, smoking, heavy physical work and repetitive movement or prolonged stay in an awkward posture (2). The existence of a chronic pain pathology, specially CLBP, reduces the individual's appetence to be physically active and to perform physical exercise (3), with negative repercussions on the range of motion, strength and endurance abilities, on the elementary or complex activities of daily living and, at last, the restrictions of work capacity, leisure activities, and private life (4). CLBP has a multifactorial nature, with the presence and influence of pathoanatomical, physical, neurophysiological, psychological, and social factors being different among individuals (5). These can be linked to the disturbance of the pathological process, to psychological and social factors and finally to impair the movement or the inability to control pain (5) related with emotional and cognitive disorders, including depression, anxiety, catastrophizing, sleep disorders, and decision-making abnormalities (6).

CLBP patients have sensorimotor impairments, enhance central sensitization to external painful stimuli, manifested by increased subjective pain sensitivity and increased brain activations in pain-related brain regions (7). On physical examination, it is possible to detect the severity of nerve root dysfunction and/ or assess the range of motion of the spine, elevation of the straight leg, knee strength and reflexes, dorsiflexion strength of the toes and feet, dorsiflexion strength of the big toe and toe, plantar flexion of the foot and ankle reflexes,

neurological deficit and paraesthesia or sensory loss (2), signs that might have serious repercussions in daily-life. Patients demonstrated a decrease in spatial acuity by somatosensory stimulus at the site of pain and also a greater hyperalgesia of deep tissue, as well as an increase in sensitivity to punctual mechanical pain (8, 9). It is essential to know that all these sensitivity abnormalities favour the maintenance of pain in CLBP (10). These changes in sensitivity are explained by a distortion of body representation at the level of the cortex, influenced by the intensity of pain, related to a convergence phenomenon between the motor cortex and the somatosensory cortex (11). Indeed, in CLBP it was reported a decrease of M1 excitability, changes of M1 area localization for the control of trunk muscles and a lack of intracortical motor inhibition within M1 circuits i.e., the loss of an inherent mechanism of motor preparation and planning (12), favouring a similar somatosensory cortex reduction thickness (13, 14), however these results are not consensual, once they lose some evidence when they are controlled for age and concurrent medications, reducing or eliminating some of the previously reported structural brain alterations (15, 16). It is also described an increased functional connectivity in S1 bilateral somatotopically-associated region (16), a significant cortical thickening in pain processing region at the level of the dorsal lateral prefrontal cortex (DLPFC), and a cortical thickening trend in S1 somatotopic region (15).

A wide variety of pharmacological treatments and traditional physiotherapy interventions are used to fight non-specific CLBP, however with some adverse events and without great success (2), being widely accepted exercise therapy as the most effective treatment for CLBP (17). Indeed, exercise training has the

potential to increase neurotrophins expression and induce neuroplasticity, neurogenesis and neuroprotection, helping to reconstruct motor function in patients with central nervous system disorders (18). If low-intensity exercise training might be advantageous to CLBP patients (19), when performed with higher intensities its benefits might be even better (20-22), probably due to its neurotrophic properties (20).

There are confirmed evidence for the higher efficacy of high-intensity aerobic exercise training, comparatively to the low-intensity one, in treating CLBP's pain, disability, and psychological strain (20-22). However, there is no data in literature associating high-intensity exercise training with the sensitivity and acuity neuropathic changes connected with CLBP. This is an important issue because the minor back sensitivity reported in these patients is a continued process that tends to perpetuate CLBP, which in turn, inhibits pain modulation mechanisms, increase the sensitivity to pain, creating a vicious cycle between pain and loss of sensibility and acuity discriminations (23).

So, the main objective of this work is to verify changes of the *dorsum* sensitivity and acuity discriminations in CLBP patients promoted by a high-intensity exercise program.

Materials and methods

This research was approved by the Ethics Committee of the S. João Hospital Center (CES 89-14) and carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and all intervenient signed an informed consent.

In this longitudinal study, a convenience sample of patients with non-specific chronic lower back pain followed for more than 6 months by the Pain's Unit at the S. João Hospital Center was used. Pregnancy, postpartum up to one year, patients with severe cardiac, neurological or metabolic diseases and with motor dysfunction, patients with difficulty in performing a quick and visually impaired appointment task, patients with radicular pain or evidence of specific vertebral pathology like neoplasms, infection, fractures, inflammatory diseases, lumbar surgery in the last twelve months, and patients with a legal litigation because of their lower back pain, were excluded. A selected sample of 24 patients was further distributed by stratified randomisation into two pairs groups: the experimental group, submitted to a high-intensity exercise training program of 12 weeks (experimental group, n=12, with 10 females), and the control group without intervention (n=12, with 6 females). Based on the results of Murtezani, Hundozi (21), analysing the influence of high-intensity exercise training on the intensity of chronic lower back pain, the calculated an effect size is 1.74, which for a statistical power of 95% and for an α=0.05, the a priori sample size calculation discloses a sample size of 6 persons per group. Age, body mass index (BMI), pain duration, and physical activity levels were used as stratifying criteria. During the experimental protocol, both groups maintained the pharmacological medication prescribed by the Pain's Unit of the hospital.

In both groups, subjects were characterized by their gender, date of birth, height, weight, current professional status, how much time chronic pain was present, and daily physical activity levels using the IPAQ short version. The superficial tactile and painful discriminations in the back were further evaluated in two different moments, at the beginning and at the end of the experimental

protocol, both interspaced by 12 weeks. It was also assessed in these two moments the lower back pain location, its intensity (assessed by the Visual Analogic Scale) (24, 25) and extent, expressed by the number of painful affected areas (Figure 1).

Superficial tactile and painful discriminations in the back

Both groups were submitted to a protocol for evaluating the individual's ability to identify sensorial information discrimination provided from their back evaluated through the Wand, Keeves (26) methodology. This protocol was performed in a silent room, with minimum levels of noise and distraction, with ambience temperature of 25-26º Celsius. All patients were instructed to strip themselves and remained wearing their pants and bra if the case.

In a prone position, on a treatment table and with a small table nearby on the right or left side according to hand dominance prepared for this purpose, subjects were allowed to adapt to the environment for 5-minutes while observing a schematic diagram of the dorsal surface of the body presented on a sheet of size A3 with 14 different areas defined by anatomical references following the Wand, Keeves (26) protocol (Figure 2A). These areas were drawn on the back of the subjects, using a dermal pencil, where tactile and pain stimuli were applied. All areas were numbered, being the areas 1 through 7 located on the left hemibody and the areas 8 through 14 located on the right hemibody (Figure 2A).

In the defined back areas, the superficial tactile discrimination test was the first applied, using a standardized cotton pad (Figure 2B), followed by the superficial

painful discrimination test performed with the standardized monofilament device (Medipin Ltd., Bushey Hertfordshire, United Kingdom) (Figure 2C).

In the superficial tactile discrimination test, the sequence of stimulation of each area was random defined by software and using two touches in the centre of each area providing a total of 28 stimulations. The superficial painful discrimination was similarly assessed using a different random area sequence. The trained researcher who applied the test was not aware of which group the participants belong. In order to ensure the sensorial consistency of the superficial tactile and pain stimuli, attempts were made by the researcher to standardize the applied pressure of the cotton pad as well as the depth of the depression caused by the monofilament through a flat ring, thus limiting the depth of the impression.

Each stimulus was interspaced by at least 5-seconds and during the pauses the participant indicated in the schematic diagram which area of the body the stimulus was felt (Figure 2A). If the body area indicated by the patient was different from the area of the stimulated body, it was recorded as a location error.

Three distinct zones were considered for data analysis: the painful zone, composed by one or more areas of pain signed by the patient in Figure 1, the adjacent zone composed by the areas that closely surround the painful zone, and the peripheric zone composed by the areas that border the adjacent zone, as depicted in Figure 3. The absolute and relative frequencies of correct and incorrect touches identified by the volunteers were evaluated in all *dorsum* and particularly in painful, adjacent and peripheric zones.

High-intensity exercise training protocol

This specific physiotherapy intervention consisted of a 12-week planning program of high-intensity therapeutic exercise training, performed three times a week. Each exercise session was performed during Tuesdays, Thursdays, and Saturdays morning (9.30 AM to 11.00 AM). The exercise program consisted of four distinct components: 5-minute warm-up, 20-minute high-intensity lumbar exercises, 35-minute cycle ergometer high-intensity exercise, and 5-minute calm-down exercises. The warm-up included stretching and exercise preparation involving hip and lumbar spine movements and neck movements. Afterwards, movements orientated for the trunk were performed with a stick in both hands in order to promote lumbar extension. The lateral flexion and rotation of the trunk to the right and left were performed with arms flexion on 90º. To complete this first phase, three stretching movements were performed for 30-seconds each, in the orthostatic position. The first movement stretched the back structures and posterior muscles with a trunk flexion, the second one stretched the anterior structures and anterior muscles with a lumbar force extension position, and the third one combined cross-anterior structures by the elongation of the one arm with the contralateral leg. The second phase of the therapeutic exercise program consisted of 20-minutes of high-intensity lumbar exercises controlled by individual answer, alternating 8-seconds of 6-10 movements with 12-seconds of rest (27), and was composed by three different groups of exercises performed in standing position, on a mattress, and using a chair. The first group involved exercises for lumbar strengthening performed in the standing position and were based on four alternating sequences of movements executed with the lower limbs. The exercise sequence was

designed with the lower limbs performing ten movements combining slight flexion, adduction, abduction and external rotation of the hip joint, flexion and extension knee alternating right and left leg with one-legged support. The second group of exercises involving legs, arms and trunk, was realized on a mattress, in all decubitus positions and in quadruped position. In the semi-kneeling position, the patient alternated the body load from the right knee to the left foot and vice versa. The third group of exercises was done in the standing position with the help of a chair where the patient performed repetitions of the lower limbs for each hip joint with flexion, abduction and extension always done with the knee extension. Another exercise was performed with the hands resting on the chair's seat and with the trunk flexion over the chair's top where the patient drew alternately with each lower leg a square in the space. A final exercise was done in upright position, simulating the movement of a run using both hands and legs, but without leaving the place for about 30-seconds, with a progressive increasing intensity. The third therapeutic exercise phase took place over 35-minutes in a cycle-ergometer (Monark E-824 – Monark Exercise Ab, Vansbro, Sweden), monitoring heart rate through a Polar FT7 Heart Rate Monitor (Polar Electro Oy, Kempele, Finland) in order to calculate exercise intensity using the Karvonen formula (21), considering an initial heart rate reserve of 60%, which progressively increased 5% weekly to reach 85% of heart rate reserve (20, 28) at the end of the program. The calm-down phase of 5-minutes, formed by small stretching exercises, allowed the patient to return to a restful condition. During the 12 weeks of training program, considering the number of expected exercise sessions, the median of patients' adherence was

82.0%, with percentiles 25 and 75 corresponding to 74.3% and 88.6%, respectively.

Statistical analysis

IBM's Statistical Package for the Social Science® software version 20.0 (IBM Corporation, Armonk NY, United States of America) was used for descriptive and inferential data analysis, with significance set at 0.05. The Shapiro-Wilk test was used to test the normality of the data. Mean (±standard deviation) or median (percentiles 25 and 75) were used to describe the distribution of quantitative variables; and absolute frequency and/ or relative frequency was used to describe the distribution of qualitative variables. Student t-test (for data with a normal distribution) or Mann-Whitney U test (for data with a non-normal distribution) were used to compare the quantitative data between groups at the beginning of the protocol. Chi-square was used to compare gender, professional occupation and physical activity between groups. This test was also used to compare the frequency distribution in general *dorsum* and per zone (painful, adjacent and peripheric) of the correct and wrong identification to the superficial tactile and painful discriminations stimuli, at the pre- and post-intervention assessment, between groups. Regarding the changes occurring in the experimental group from pre- to post-intervention, Pearson's correlation was used to correlate the intensity of pain/ number of referred pain areas and the stimuli discrimination. Pearson's correlation coefficient (r) values between 0 and 0.29 (0 and -0,29) indicate a weak linear relationship, between 0.30 and 0.69 indicate a moderate linear relationship, and between 0.70 and 1.00 indicate a strong linear relationship.

Results

Sample characterization

Sociodemographic, anthropometric, professional occupation, physical activity data and pain duration were similar between groups (Table 1).

Dorsum pain intensity and area characterization

In both groups, 100% of participants had a complain at the least in one of the defined areas of the lower back region (lumbar and/ or gluteal zones). At the pre-intervention assessment, the number of painful area and the pain intensity were similar between groups. However, at the post-intervention assessment, the number of painful area and the pain intensity were significantly lower in the experimental group, when compared to the control group (p=0.010 and p=0.002, respectively) (Table 2).

Superficial tactile and painful discriminations in general dorsum

As shown in Table 3, there were no significant differences among groups in the superficial tactile and painful discriminations at the pre-intervention assessment. At the post-intervention assessment, there were significant differences between groups regarding the frequency distribution of the overall correct and incorrect identification to the superficial and painful stimuli (p<0.001 and p=0.001, respectively). In fact, at the post-intervention assessment, it was possible to observe that the frequency distribution of the correct identification to the superficial tactile and painful discriminations stimuli in general *dorsum* was higher in experimental group, when compared to the control group (Table 3).

Superficial tactile and painful discriminations per dorsum zones

At the pre-intervention assessment, the frequency distributions of the correct and incorrect identification to the superficial tactile and painful discriminations stimuli in each defined zone were similar between groups (Table 4).

At the post-intervention assessment, there were significant differences between groups regarding the frequency distribution of the correct and incorrect identification to the superficial tactile discrimination stimuli in painful (p=0.003) and adjacent (p=0.009) zones, with a higher frequency of correct identification in experimental group. Moreover, comparatively to the control group, the experimental group had a higher frequency of correct identification to the painful discrimination stimuli in adjacent (p=0.038) and peripheric (p=0.027) zones (Table 4).

Regarding the changes occurring in the experimental group from pre- to post-intervention, the correlations among the intensity of pain/ number of referred pain areas and the stimuli discrimination, it was observed a moderate and negative correlation between the number of referred pain areas and the assertiveness of painful stimuli discrimination in the painful zone (r=-0.602; p=0.038), meaning that the decreased number of pain areas after intervention was paralleled by an increased assertiveness of painful discrimination. A similar correlation was also observed in the adjacent area for the same parameters, however without significance (r=-0.502; p=0.096).

Discussion

The present study examined the changes induced by a high-intensity exercise training on the accuracy of painful and superficial tactile stimuli discrimination in the *dorsum* as well as in the intensity and perceptive back area of pain in patients with CLBP. A decreased pain intensity as well as a reduction of pain area extent was manifested after exercise training, which were paralleled by an increased accuracy of superficial tactile and painful stimuli discriminations in general *dorsum*. Regarding the accuracy to discriminate stimuli per zone, the superficial tactile discrimination stimuli precision increased in the painful and adjacent zones while the painful stimuli discrimination improved in the adjacent and peripheric zones. No longitudinal changes of these parameters were observed in the control group.

These effects induced by high-intensity physical training are mainly explained by neural repercussions of physical exercise training, favouring the synaptogenesis and plasticity between different brain regions, with a favourable reorganization of neural network (29). In an animal model it was observed that acute exercise increased the densities cells in primary somatosensory cortex (30) which can be one mechanism to explain the increased superficial tactile and painful accuracy discrimination observed in our study. Moreover, the analgesic effect of high-intensity exercise was also described in literature, producing enough analgesia by endogenous β-endorphin to reduce the pain perception (3, 31) that may explain the decreased pain intensity and the reduction of pain area extent observed in our experimental group. This antalgic effect can be transiently observed in CLBP patients after a single bout of high-intensity exercise, with an increased pressure pain threshold (32). However, when the high-intensity exercise is repeated along the time, as in our study, this

increased pressure pain threshold tends to maintain as a chronic effect (33-35). Additionally, the reduction of pain area extent observed in the experimental group may also be justified by the minimization of allodynia in the spinal dorsal horn where the recruitment of low-threshold Aβ mechanoreceptive fibbers in CLBP leads to a central sensitization, however due to a descendent inhibitory pain modulation induced by the training program the touch stimuli are now perceived as tactile instead of painful stimuli (36). Beyond the hypothetical alterations in somatosensorial cortex, the decreased allodynia is probably another neural mechanism involved in the increased tactile and painful stimuli discrimination described in the experimental group. The recruitment of Aβ mechanoreceptive fibbers became more detailed in adjacent and peripheric zones with more accuracy and less confusion in somatosensorial cortical areas as described by others (9). Beyond the endogenous β-endorphin effects on painful sensitivity, other substances like brain-derived neurotrophic factors (BDNF) may also be involved in the improved accuracy discrimination in painful and adjacent zones for superficial tactile stimuli discrimination due to its hypothetical influence on the neural pathway linking cerebral nucleus with periaqueductal gray (PAG) area, promoting an improved inhibition of pain modulation system (37-39). An animal model study revealed that BDNF pathway is dependent from the intensity of exercise and only the highest intensity leads to this pathway activation in prefrontal cortex (40). In response to specific exercise training programs, it is described that PAG area promotes an antidepressant action through the contribution of descending inhibitory modulation, increasing the activity of serotonergic and noradrenergic projections from brainstem centres, explaining the decrease of neuropathic pain

(41) as well as the results showed by our experimental group. The observed correlation between the number of referred pain areas and the assertiveness of painful stimuli discrimination in the painful zone, reinforce the contribution of this mechanism meaning, with the decreased number of pain areas and increased assertiveness of painful discrimination.

The absence of longitudinal differences in our control group, although under medication, reinforces the concept that CLBP is a pathology with small intraindividual variations, where it is unusual to see alterations in pain, disability or physical activity levels along time (42). It is known that non-specific chronic lower back pain patients had lower pressure pain thresholds (43), which is usual in central sensitization that perpetuates the amplification of the central pain through pain chronicity, without peripheral causes (44, 45). Non-pharmacological and pharmacological therapies constitute first and second options for the treatment of CLBP respectively, however their efficacy to break this pain vicious cycle has a low scientific evidence (46, 47). Based on our results, the high-intensity exercise training, through its neural repercussion, increasing superficial tactile and painful discrimination stimuli in the *dorsum* and reducing the referred pain intensity and the pain extent area, revealed as a potential strategy to deal with the neural contributions of this disorder.

The imbalance in the relationship between men and women observed in our study cannot be considered a limitation since it is in agreement with the populational prevalence of CLBP (48).

Conclusions

High-intensity exercise training improved the sensorial discrimination in the *dorsum* and reduced the referred pain intensity and pain area extent, reinforcing the concept of a neural contribution to CLBP symptoms, which can be attenuated by specific physical exercise training.

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Conflict of interest/ Disclosure summary

All authors report no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The manuscript was developed and written equally by all authors.

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Table 1 Experimental and control groups' characterization: sociodemographic, anthropometric, professional occupation, physical activity data and pain duration. Data are presented as absolute frequency (relative frequency) for qualitative variables, and mean (±standard deviation) or median (percentile 25; percentile 75) for quantitative variables. *p* values reflect the between-groups comparison.

Variable		Experimental group n=12	Control group n=12	Between-groups comparison *p* value
Sociodemographic data				
Gender (n female)	Female	11 (91.7%)	6 (50,0%)	0.069
	Male	1 (8.3%)	6 (50,0%)	
Age (years)		54.50±7.94	54.25±9.19	0.944
Anthropometric data				
Body weight (kg)		69.57±10.66	73.50±14.80	0.463
Height (m)		1.62±0.07	1.65±0.09	0.347
BMI (kg/m^2)		26.62±4.54	26.84±3.66	0.896
Professional occupation and physical activity data				
Professional occupation	Retired	2 (16.7%)	2 (16.7%)	0.156
	Unemployed	6 (50.0%)	1 (8.3%)	

	Sick leave	2 (16.7%)	4 (33.3%)	
	Active	2 (16.7%)	5 (41.7%)	
Physical activity	Low	4 (33.3%)	5 (41.7%)	1.000
	Moderate	8 (66.7%)	7 (58.3%)	
Pain duration (months)		105.00 (64.25; 177.25)	77.50 (37.00; 129.00)	0.400

Table 2 Number of painful areas referred by the patients and respective pain intensity assessed by visual analogic scale (VAS, mm), at the pre- and post-intervention assessment, in experimental and control groups. Data are presented as median (percentile 25; percentile 75). *p* values reflect the between-groups comparison.

Variable	Pre-intervention			Post-intervention		
	Experimental group n=12	Control group n=12	Between-groups comparison *p* value	Experimental group n=12	Control group n=12	Between-groups comparison *p* value
Number of painful areas	4.50 (3.25; 5.75)	5.00 (3.50; 7.00)	0.563	2.00 (1.25; 3.75)	5.00 (4.00; 6.75)	0.010
Pain intensity (VAS, mm)	53.00 (47.25; 79.75)	66.00 (52.25; 79.75)	0.640	30.00 (20.25; 55.25)	67.50 (54.25; 81.25)	0.002

Table 3 Relative frequency (%) of the overall correct identification to the superficial tactile and painful discriminations stimuli, at the pre- and post-intervention assessment, in experimental and control groups. *p* values reflect differences in frequency distributions of the test result among each group.

Test and its result	Pre-intervention			Post-intervention		
	Experimental group	Control group	*p* value	Experimental group	Control group	*p* value
Superficial tactile stimuli	73.5	69.4	0.250	79.5	68.4	<0.001
Painful stimuli	75.3	68.9	0.058	78.9	67.9	0.001

Table 4 Relative frequency (%) of the correct identification of superficial tactile and painful discriminations stimuli per dorso zone (painful, adjacent and peripheric), at the pre- and post-intervention assessment, in experimental and control groups. *p* values reflect differences in frequency distributions of the test result among each group.

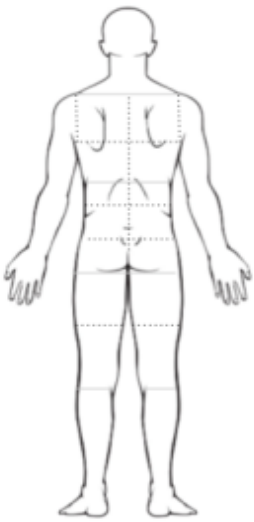
Test and its result	Pre-intervention			Post-intervention		
	Experimental group	Control group	*p* value	Experimental group	Control group	*p* value
Painful zone						
Superficial tactile stimuli	68.4	63.2	0.429	79.8	62.5	0.003
Painful stimuli	76.3	70.8	0.396	78.1	70.1	0.158
Adjacent zone						
Superficial tactile stimuli	74.5	65.1	0.174	80.4	63.2	0.009
Painful stimuli	72.5	62.3	0.139	74.5	60.4	0.038

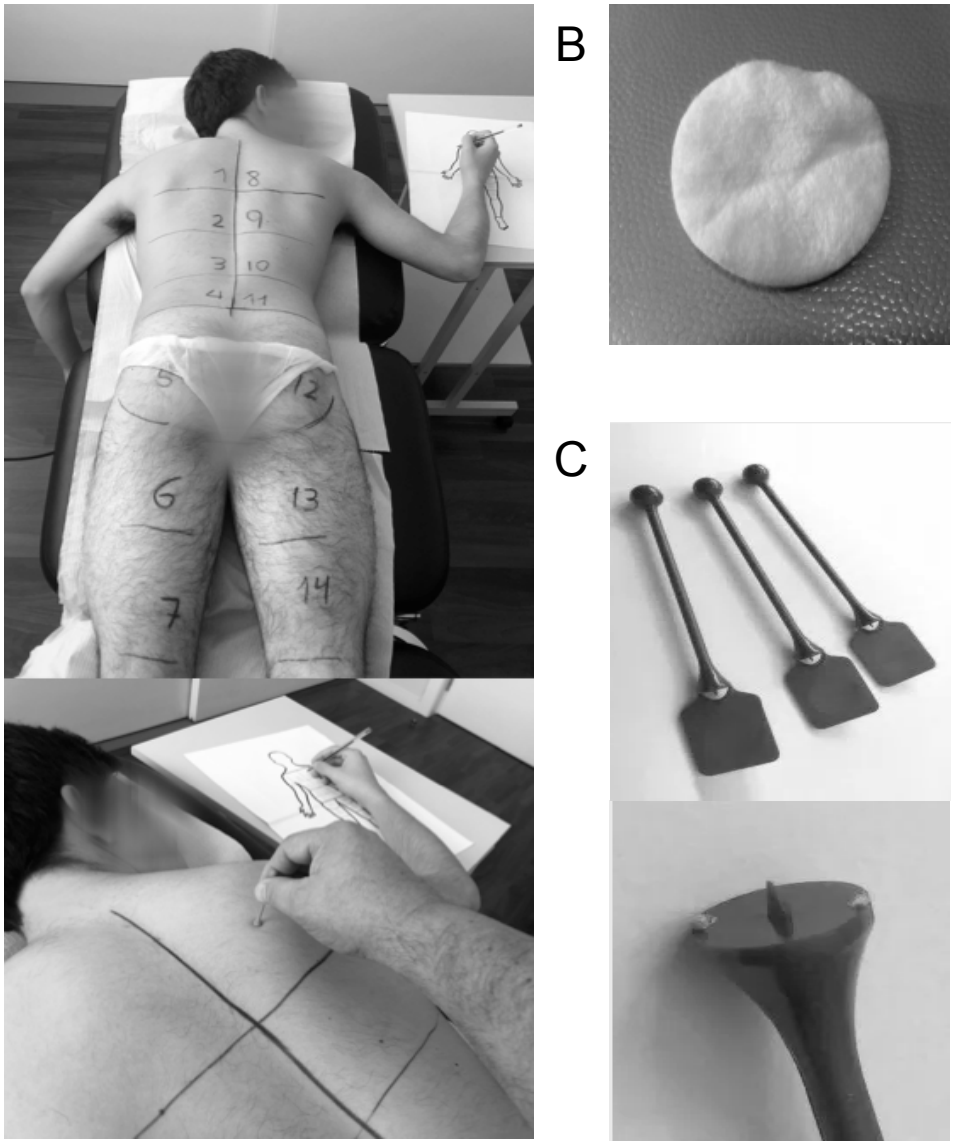
Peripheric zone						
Superficial tactile stimuli	77.5	78.9	0.881	78.3	78.2	1.000
Painful stimuli	76.7	71.8	0.399	83.3	71.1	0.027

Figure 1 Image presented to patients for painful areas self-identify.

Figure 2 Defined areas through marked lines, based on the anatomical landmarks (A). Nine lines were defined, delimiting fourteen areas: 1st popliteal line marked on the popliteal face of the posterior region of the knee; 2nd midpoint of the thigh equidistant between the popliteal line and the gluteal fold line; 3rd line on the gluteal fold; 4th line joining the posterior superior iliac spines; 5th line marked by the spinous processes of L2; 6th line marked by the spinous processes of T10; 7th line marked by the spinous processes of T6; 8th line marked by the spinous processes of T2; 9th posterior medial line or middle vertebral line passing through the spinous processes of all vertebrae. A Cotton pad (B) and the monofilament (C) used to test, respectively, tactile and pain sensitivities in the defined areas.

Figure 3 Example of the 3 defined zones in a patient with bilateral non-specific chronic lower back pain referred at areas 4, 5, and 11, which are stated as painful zone. Areas 3, 6, 10, and 12 composed the adjacent zone. Areas 1, 2, 7, 8, 9, 13, and 14 constituted the peripheric zone, as depicted in the figure.

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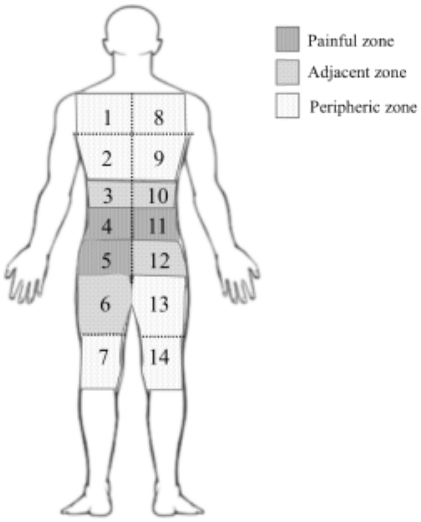
Painful zone
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Study 3

Does motor imagery program add a therapeutic advantage to high intensity exercise training in patients with chronic lower back pain?

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Abstract

Background: High-intensity exercise training (HI) and motor imagery training (MI) applied in isolation have already demonstrated therapeutic benefits in patients with chronic lower back pain (CLBP), however they have never been tested together as a combined program. Objective: To verify the therapeutic efficiency of adding MI to HI in the intensity of pain, extension of the pain area, and disability of CLBP patients. Design: Experimental longitudinal study. Subjects: Using the age, gender, body mass index, and pain duration as stratifying criteria, 31 CLBP patients were randomly distributed into three pairs groups: HI+MI (n=10, with 8 females), HI (n=11, with 10 females), and a control group without intervention (Cont; n=10, with 7 females). Methods: The high intensity exercise training consisted of 12-week exercise sessions, performed three times a week. The motor imagery training was daily performed through the recognized laterality approach using a specific software. In all groups, pain extent area, pain intensity and disability were evaluated at the beginning and at the end of the experimental protocol. Results: The findings showed a favourable post intervention clinical evolution in both HI+MI and HI when compared to Cont, with reduction of pain intensity and painful extent area as well as an increased functionality, however without significant differences among the intervention groups. Conclusion: High intensity exercise training is effective in CLBP patients to acquire benefits in pain intensity, extent area of pain, and functionality; however, the addition of a motor imagery training program did not bring any therapeutic value.

Keywords	cortical reorganization, pain extent area, allodynia, brain connectivity, recognition

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Highlights

- High intensity exercise training reduced pain intensity and pain extent area in CLBP patients.
- High intensity exercise training increased functionality in CLBP patients.
- The addition of a motor imagery training to high intensity exercise training does not bring additional therapeutic benefits to CLBP patients.

Abstract

Background: High-intensity exercise training (HI) and motor imagery training (MI) applied in isolation have already demonstrated therapeutic benefits in patients with chronic lower back pain (CLBP), however they have never been tested together as a combined program. Objective: To verify the therapeutic efficiency of adding MI to HI in the intensity of pain, extension of the pain area, and disability of CLBP patients. Design: Experimental longitudinal study. Subjects: Using the age, gender, body mass index, and pain duration as stratifying criteria, 31 CLBP patients were randomly distributed into three pairs groups: HI+MI (n=10, with 8 females), HI (n=11, with 10 females), and a control group without intervention (Cont; n=10, with 7 females). Methods: The high intensity exercise training consisted of 12-week exercise sessions, performed three times a week. The motor imagery training was daily performed through the recognized laterality approach using a specific software. In all groups, pain extent area, pain intensity and disability were evaluated at the beginning and at the end of the experimental protocol. Results: The findings showed a favourable post intervention clinical evolution in both HI+MI and HI when compared to Cont, with reduction of pain intensity and painful extent area as well as an increased functionality, however without significant differences among the intervention groups. Conclusion: High intensity exercise training is effective in CLBP patients to acquire benefits in pain intensity, extent area of pain, and functionality; however, the addition of a motor imagery training program did not bring any therapeutic value.

Keywords

cortical reorganization; pain extent area; allodynia; brain connectivity; recognition

Title

Does motor imagery program add therapeutic advantage to high intensity exercise training in patients with chronic lower back pain?

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Abstract

Acknowledging that high intensity exercise training and motor imagery training have never been tested as a combined program in the treatment of CLBP patients, the aim of this study was to test the therapeutic efficiency on pain intensity, extent area of pain, and disability when combining these two types of training. The sample was randomly distributed into three pairs groups: the high intensity exercise training with motor imagery training group (HI+MI; n = 10, with 8 females), the high intensity exercise training group (HI; n = 11, with 10 females), and the control group (Cont; n = 10, with 7 females) without intervention. In all groups, subjects were evaluated at the beginning and at the end of the experimental protocol. The high intensity exercise training performed by HI+MI and HI consisted of 12-week exercise sessions, performed three times a week. The motor imagery training done by HI+MI was daily performed through the recognized laterality approach using a specific software. The findings showed a favourable post intervention clinical evolution in both intervention groups (HI+MI and HI) when compared to the control group, with reduction of pain intensity and painful extent area as well as an increased functionality, however without significant differences among interventions groups. The results allowed the conclusion that high intensity exercise training is effective in CLBP patients to acquire clinical benefits in pain intensity, extent area and increased functionality; however, in this study, the addition of a motor imagery training program did not bring any therapeutic clinical value.

Keywords

cortical reorganization; pain extent area; allodynia; brain connectivity; recognition

1. Introduction

The non-specific chronic lower back pain (CLBP) patients present muscle tension or stiffness, pain discomfort, weakness and loss of mobility (Haas, et al., 2005), with or without pain radiated to the leg, for a period higher than 12 weeks (Manek & MacGregor, 2005). Chronic pain resulted from a multifactorial mechanism of pain persistence (Heiskanen, Roine, & Kalso, 2012), with a continuous cycle that maintain pain perception, which is associated with neural changes leading to a compromised connectivity (Vrana, et al., 2015). For instance, chronic pain is responsible for a decreased capacity of sensory differentiation due to a reduced cortex thickness (MacIver, Lloyd, Kelly, Roberts, & Nurmikko, 2008), with tactile process disturbance (Moseley & Flor, 2012). Moreover, motor deficits appear soon after the onset of pain (Hodges, 2003). The primary motor cortex (M1) of the back muscles representation in CLBP is more complex and with a different location than individuals without a history of pain (Elgueta-Cancino, Schabrun, & Hodges, 2018). The degree of cortical reorganization is correlated with pain intensity (Flor, 2002; Moseley & Flor, 2012) and was associated with lower gray matter volumes in the medial/ dorsolateral and ventrolateral prefrontal cortex as well as in thalamus, anterior insular cortex, and anterior cingulate cortex (Fritz, et al., 2016). This cortical reorganization was quantified by a decreased of neocortical brain volume (Apkarian, et al., 2004). The described decrease of amygdala gray matter may reflect afferent and efferent circuits alterations between the periaqueductal gray area (PAG) and the spinal cord, where amygdala plays a fundamental role in the descending inhibitory pain control, enhancing or decreasing pain responses (Ng, et al., 2018; Ung, et al., 2014). The periaqueductal gray area, hypothalamus and amygdala (Morgan, Corrigan, &

Baune, 2015; Purves, 2018), are fundamental structures for pain modulation (Lewis, Rice, & McNair, 2012). The amygdala also have a strong relationship with hypothalamus, being responsible to control the autonomic system that command the heart rate and blood pressure, the sweating, the shortness of breath, in order to re-establish the disturbed homeostasis induced by high intensity physical exercise (Hoffman, et al., 2004), hence promoting the activation of neural pathways closely associated with the descending pain modulation system (Tracey & Mantyh, 2007).

Contrasting with the low efficiency of conservative therapy and pharmacological strategies for the CLBP management (Nijs, et al., 2017), physical exercise training has evidence of a long-term effectiveness, with favorable effects in patients' pain and function (van Middelkoop, et al., 2011). Beyond its influence on the interaction between amygdala/ stressor and hypothalamus/ adaptation, the high-intensity aerobic exercise also increases brain-derived neurotrophic factors (BDNF) production and promotes pain relief in CLBP subjects (Chatzitheodorou, Kabitsis, Malliou, & Mougios, 2007). This BDNF released during exercise plays a crucial role in the maintenance and regeneration of neurons (Johnson, Charchanti, & Soucacos, 2008), in the creation of new synapses (Kraychete, Gozzani, & Kraychete, 2008) that come for an endogenous exacerbation (Allodi, Udina, & Navarro, 2012), and generation of alternative neural circuits of movement without pain (Moseley & Flor, 2012). High-intensity exercise training is recognized as being capable of interfering with the disease and its chronicity, with a great potential to restore the central nervous system alterations and the altered neural connectivity associated with CLBP

(Chatzitheodorou, et al., 2007; Murtezani, Hundozi, Orovcanec, Sllamniku, & Osmani, 2011; Verbrugghe, et al., 2018; Verbrugghe, et al., 2019).

Motor imagery is defined as a cognitive operation of an imagined task that depends from the dynamic relationship between the individual characteristics, the movement, and the environment (Dickstein & Deutsch, 2007). It is known that patients with bilateral CLBP perform worse motor imagery related to the trunk (Bray & Moseley, 2011) by a damaged body scheme (Schwoebel, Buxbaum, & Coslett, 2004). The body image of sensory representation is built and modified from the body's proprioceptive stimuli, so a painful stimulus distorts the image of the injured segment (Moseley, 2006). Motor imagery improves with the training of the recognition of the body scheme associated with laterality, defined by the ability to recognize images associated with laterality, about what is the right side and the left side (Yap & Lim, 2019). In chronic pain conditions, the motor imagery training improves the notion of body scheme, reducing pain, improving function and minimizing injury behaviors (Ravat, Olivier, Gillion, & Lewis, 2018). The use of motor imagery programs has been successful explored in the cortical reorganization of CLBP patients, with notorious benefits in pain and motor control (Christakou, Vasileiadis, & Kapreli, 2019; Christakou & Zervas, 2007; La Touche, Grande-Alonso, et al., 2019).

Although the potential for a helpful neuromodulation of high intensity exercise training and motor imagery training when applied solely, these approaches have never been tested as a combined program in CLBP patients. For this reason, the main aim of this study was to analyze in CLBP patients the effect of high intensity exercise training, applied alone or in combination with a motor imagery program,

on pain intensity, extent area of pain, and disability. Our working hypothesis is that the combined training produces better clinical outcomes then exercise alone.

2. Materials and methods

This research was approved by the Ethics Committee of the S. João Hospital Center (CES 89-14) and carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and all intervenient signed an informed consent.

In this longitudinal study, a convenience sample of 31 patients (25 females, 6 males) with non-specific chronic lower back pain followed for more than 6 months by the Pain's Unit at the S. João Hospital Center was used. Pregnancy, postpartum up to one year, patients with severe cardiac, neurological or metabolic diseases and with motor dysfunction, patients with difficulty in performing a quick and visually impaired appointment task, patients with radicular pain or evidence of specific vertebral pathology like neoplasms, infection, fractures, inflammatory diseases, lumbar surgery in the last twelve months, and patients with a legal litigation because of their lower back pain, were excluded. The sample was further distributed by stratified randomization into three pairs groups: the High Intensity Exercise training with Motor Imagery training (HI+MI Group; n = 10, with 8 females), the High Intensity Exercise training (HI Group; n = 11, with 10 females), and the control group (Cont Group; n = 10, with 7 females) without intervention.

Age, gender, body mass index (BMI), and pain duration were used as stratifying criteria. During the experimental protocol, all groups maintained the pharmacological medication prescribed by the Pain's Unit of the hospital.

In all groups, subjects were evaluated at the beginning and at the end of the experimental protocol, which last 12 weeks. Patients were characterized by their gender, date of birth, height, weight, current professional status, and how long chronic pain was present. It was also assessed in the two evaluation moments the lower back pain location, its extents, expressed by the number of painful affected areas, and its intensity (assessed by the Visual Analogic Scale) (Katz & Melzack, 1999; McMahon, 2013) as well as disability level, assessed by the Roland Morris Disability Questionnaire (RMDQ) adapted and validated for the Portuguese language, which provides reliable and valid measures of patient incapacity with lower back pain (Monteiro, Faisca, Nunes, & Hipolito, 2010). The RMDQ is a self-administered questionnaire of 24 items, which total score ranges from 0 to 24 according to the level of disability, being considered a clinically important change of two to five points baseline (Grande-Alonso, et al., 2019).

To assess the pain extent areas, expressed by the number of painful affected areas, a body chart from the *dorsum*, with 14 areas delimited by 9 lines outlined by anatomical references (Wand, et al., 2013), was presented to patients (Figure 1).

The high intensity exercise program performed by HI+MI and HI groups consisted of a 12-week of planning program, performed three times a week. Each exercise session was 75 minutes performed in a physiotherapy practice private during Tuesday, Thursday and Saturday mornings. The program consisted of four distinct components: 5 minutes warm-up, 20 minutes high intensity lumbar exercises, 35 minutes cycle ergometer high intensity exercise, and 5 minutes of calm-down exercises. The warm-up included stretching and exercise preparation involving hip and lumbar spine movements and neck movements. Afterwards,

movements orientated for the trunk were performed with a stick in both hands in order to promote lumbar extension. The lateral flexion and rotation of the trunk to the right and left were performed with arms flexion on 90º. To complete this first phase, three stretching movements were performed for 30 seconds each, in the orthostatic position. The first one stretched the back structures and posterior muscles with a trunk flexion, the second stretched the anterior structures and anterior muscles with a lumbar force extension position, and the third one combined cross-anterior structures by the elongation of the one arm with the contralateral leg. The second phase of the therapeutic exercise program consisted of 20 minutes of high intensity lumbar exercises controlled by individual answer, alternating 8 seconds of 6-10 movements with 12 seconds of rest (Heydari, Boutcher, & Boutcher, 2013), and was composed by three different sets of exercises performed in standing position, in a mattress, and using a chair. The first set involved exercises for lumbar strengthening performed in the standing position and were based on four alternating sequences of movements executed with the lower limbs. The exercise sequence was designed with the lower limbs performing ten movements combining slight flexion, adduction, abduction and external rotation of the hip joint, flexion and extension knee alternating right and left leg with one-legged support. The second set of exercises involving legs, arms and trunk, was realized on a mattress, in all decubitus position and in quadruped position. In the semi-kneeling position, the patient alternated the body load from the right knee to the left foot and vice versa. The third set of exercises was done in the standing position with the help of a chair where the patient performed repetitions of the lower limbs for each hip joint with flexion, abduction and extension always done with the knee extension. Another exercise was performed

with the hands resting on the chair's seat and with the trunk flexion over the chair's top where the patient drew alternately with each lower leg a square in the space. A final exercise was done in upright position, simulating the movement of a run using both hands and legs, but without leaving the place for about 30 seconds, with a progressive increasing intensity. The third therapeutic exercise phase took place over 35 minutes in a Monark E-824 cycle-ergometer, monitoring heart rate through a Polar FT7 Heart Rate Monitor in order to calculate exercise intensity using the Karvonen formula (Murtezani, et al., 2011), considering an initial heart rate reserve of 60%, which progressively increased 5% weekly to reach 85% of heart rate reserve (Chan, Mok, & Yeung, 2011; Chatzitheodorou, et al., 2007) at the end of the program. The calm-down phase of 5 minutes, formed by small stretching exercises, allowed the patient to return to a restful condition. The total program comprised 36 sessions and to be considered for final data analysis the patients should performed more then 80% of those. The concomitant motor imagery training performed by HI+MI group is part of the "Graded Motor Imagery" program, using the software (App Recognise Back commercialized by Neuro Orthopaedic Institute, Australia PTY LTD., version 1.2.) to daily training the motor imagery through the recognized laterality approach. The laterality recognition training performed by participants that could judge the task of an image where a person was oriented to the right or to the left, using the protocol already validated by Moseley (2004). The intervention in laterality and motor imagery using App Recognise Back consisted of restoring laterality, which is the ability to distinguish a part of the body presented various degrees of rotation/ inclination, identifying which is the left or right side. The protocol application of the laterality recognition program consisted in the installation the

application on the participant's smartphone so they can use many times as possible. The software installed on the patient’s mobile phone instated the patients to quickly identify if one randomized presented image from the back corresponds to the right or to the left side of the trunk. Images of a person with the torso rotated to the right or to the left in various postures and functions were randomly displayed on the smartphone showed in the commercially available software. The images exhibiting trunk orientation to left and right, appeared in different positions and in different situations and were presented every day, according to 4 levels of difficulty respectively named Basic, Vanilla, Context, and Abstract. The participants responded by choosing the right or left button according to their interpretation of the back-lateral right rotation or the back lateral left rotation. The number of correct answers is expressed as a percentage of the total number of photos displayed and is called accuracy and the average response time for the correct answers is called the reaction time, so the reaction time and accuracy are dependent variables, as well as the degree of difficulty of the image being ordered from the lowest to the highest respectively. The emphasis training was placed on the answer speed and accuracy, reason why all participants were instructed to give an accurate answer as quickly as they could. It was possible to manipulate the number of images during training and the period of the image exposure. All volunteers had an indication of the daily use of the training. The rotation of the trunk judgments to the left and to the right was made by large number of images in a wide variety of positions. In each position, the trunk was rotated and the images mirror varying degrees of rotation of the trunk to the left and to the right. It was presented to each participant a minimum of twenty and a maximum of fifty images indistinctly during the day. The number of

correct responses and the average reaction time were used as feedback for the patient's changed the difficulty degree and it is the patient's decision to define the difficulty level changed. The total motor imagery program was advised to comprised 84 days of practice and in order to be considered for final data analysis the patients should performed more then 80% of those.

2.1. Statistical analysis

IBM's Statistical Package for the Social Science® software version 20.0 (IBM Corporation, Armonk NY, United States of America) was used for descriptive and inferential data analysis, with significance set at 0.05. The Shapiro-Wilk test was used to test the normality of the data. Mean (±standard deviation) or median (percentiles 25 and 75) were used to describe the distribution of quantitative variables; and absolute frequency and/ or relative frequency was used to describe the distribution of qualitative variables. Two-way ANOVA (for data with a normal distribution, followed by the Tukey post-hoc test) or Kruskal-Wallis test (for data with a non-normal distribution, followed by the Dunn-Bonferroni post-hoc test) were used, to compare the quantitative data between groups (HI+MI vs. HI vs. control). Chi-square was used to compare gender and professional occupation between groups.

3. Results

3.1. Sample characterization

One male from HI+MI group was excluded from the final data analysis once he did not accomplish the home sessions of the motor imagery program, having

280 performed only 42% of all planed sessions. All the remained patients from both
281 groups accomplished the minimal sessions required.
282 Age, gender, anthropometric, professional occupation, and pain duration were
283 similar between groups (Table 1).
284
285 3.2. *Dorsum* pain intensity, pain extent, and physical disability
286 At the pre-intervention assessment, the pain intensity, pain extent areas, and
287 physical disability score were similar between groups. However, at the post-
288 intervention assessment, the painful extent areas, pain intensity and physical
289 disability score were significantly lower in HI+MI (painful extent areas: p=0.019;
290 pain intensity and physical disability score: p<0.001) and HI (painful extent areas:
291 p=0.035; pain intensity: p=0.002 and physical disability score: p<0.001) groups,
292 when compared to the control group and to the intragroup pre-intervention
293 values. At the post intervention assessment, no statistical differences in clinical
294 outcomes were found between HI+MI and HI groups (Table 2).
295
296 4. Discussion
297 The findings showed in both intervention groups (HI+MI and HI) a favorable post
298 intervention clinical evolution when compared to the control group, with reduction
299 of pain intensity and painful extent areas as well as increased functionality;
300 however without significant differences between intervention groups, suggesting
301 that motor imagery program does not had value to high intensity exercise training
302 in the CLBP patients.
303 It is known that general chronic pain leads to a connectivity decrease between
304 nuclear and cortical brain structures, expressed by a decreased cortical thickness

(Fritz, et al., 2016) and changes of gray matter density in cerebral nucleus and ganglion (Zhang, et al., 2019). These neural changes induce by pain enhance the volume of gray matter of amygdala (Kregel, et al., 2015; Seno, et al., 2018) and decrease the connectivity between structures such as the prefrontal cortex, motor areas M1/M2, somatosensory areas S1/S2, and periaqueductal gray (PAG) area (Flor, 2002; Kong, et al., 2013; Kregel, et al., 2015), which are related with movement and/ or pain modulation. In our study, the high intensity exercise training showed important favorable results, mainly explained by the counteraction of these neural mechanisms affecting pain modulation and functionality. In fact, the exercise practice is by itself responsible for the endogenous endorphins or serotonin productions as well as neuroplasticity induction, increasing the number of connections (Kami, Tajima, & Senba, 2017; Sexton, et al., 2016), minimizing the pain afferents at the spinal cord and brainstem levels. Additionally, the decrease of pain intensity and extent areas seen in our intervention groups can also be explained by the decrease of allodynia (Adamczyk, Buglewicz, Szikszay, Luedtke, & Babel, 2019; Brito, Rasmussen, & Sluka, 2017). Certainly, one of the causes that most disperses the pain area and intensity is allodynia, where afferents peripheral stimuli from vibration, discrimination or light touch, are interpreted as pain due to the spinal cord segmentary integration of the afferent Aβ with the C-fibers, enhancing the pain stimulus and pain extent area (Colloca, et al., 2017; Konopka, et al., 2012; Loken, Duff, & Tracey, 2017). Due to pain, CLBP patients have usually little mobility (Wand & O'Connell, 2008) and reduced levels of daily physical activity (O'Sullivan, 2005; Tagliaferri, et al., 2020), which provides at long-term a lower functional capacity, as observed at the pre intervention assessment in all groups.

The high-intensity exercise training, through the reduction of pain and improvement of physical fitness (Brito, et al., 2017), enhances the patients' ability to perform tasks with a decreased pain perception, explaining the increased levels of functionality observe after intervention in both HI+MI and HI groups. In the comparison with other studies, it is possible verify in high intensity training at the CLBP also improved pain and disability like our study (Murtezani, et al., 2011; Verbrugghe, et al., 2018; Verbrugghe, et al., 2019), however these fundamentally analyze the difference between of pre and post intervention and did not analyze pain extent area and the difference among interventions.

Based on the available literature (Anderson & Meyster, 2018; Cramer, Orr, Cohen, & Lacourse, 2007; Vrana, et al., 2015), it was expected that the motor imagery training would bring additional value to exercise training, improving the reduced connectivity between the neural structures described in CLBP patients. Although not being consensual, after motor imagery sessions several authors described an improvement of accuracy and reaction time, both explained by an increased neural connectivity that, similarly to high intensity exercise training, may have beneficial repercussions on the pain-modulation descending inhibitory system (Vrana, et al., 2015). Since both interventions in HI+MI group have action at the neural level, it was expected a reduced painful intensity and area extent in this group comparatively to HI group, which was not observed. However, the literature shows a beneficial influence of motor imagery training on cerebral connectivity of CLBP patients (Pijnenburg, et al., 2015; van der Meulen, Allali, Rieger, Assal, & Vuilleumier, 2014). Moreover, several studies reported that motor imagery training was the most effective mode for developing the motor control task in an accurate and controlled manner in CLBP patients (La Touche,

Sanchez-Vazquez, et al., 2019; Rubio-Oyarzún, et al., 2018). Nevertheless, and contrary to expectations, in our study the high intensity training and motor imagery training did not bring any added value compared to high intensity training applied alone. Although the favorable results reported in literature for motor imagery training, it must be noted other authors have studied different dependent variables, namely accuracy, reaction time, and nervous functionality, while in our study we have just evaluated clinical outcomes as pain intensity, painful area extent and patients' functionality. It is possible that motor imagery training has had neural advantages in our study, however their lightness compared to those induced by high intensity training, may have been diluted in the clinical outcomes. The motor imagery training used in our study followed the pattern and parameters used by other authors (Rubio-Oyarzún, et al., 2018; Wand, O'Connell, Di Pietro, & Bulsara, 2011; Yap & Lim, 2019) through a software application for laterality identification. Considering the frequency of training sessions and the number of images presented per session, this kind of training was not enough attractive for patients or sufficiently demanding, which may explain lightness of its neural repercussions comparatively to high intensity exercise training. For futures studies different strategies should be used with greater attractiveness for patients, generating challenge, in order to gain higher demanding and training adherence.

Regarding the limitations of our study, the apparently reduced sample size used in each group might be considered a limitation. However, based on the results of Murtezani, et al. (2011), analyzing the influence of high intensity exercise training on the intensity of chronic lower back pain, the calculated effect size was 1.76, which for a statistical power of 95% and for an $\alpha=0.05$, the a priori sample size

380 calculation discloses a sample size of 8 patients per group. Moreover, based on
381 the results of Rubio-Oyarzún, et al. (2018) that have analyzed the effect of a
382 motor imagery training on shoulder chronic pain, the calculated effect size was
383 2.75, which for a statistical power of 95% and for an $\alpha=0.05$, the a priori sample
384 size calculation discloses a sample size of 4 patients per group. Consequently,
385 the used sample size allowed sufficient statistical power to test our hypothesis.
386 Nevertheless, within the study limitations, it must be noted the inability of the
387 software program to inform the clinician about the patients' number of tasks
388 performed along the motor imagery program in order to have a constant control
389 of it. This control was only done during the presence of patients at the lab to
390 perform the high intensity exercise sessions.
391
392 5. Conclusion
393 High intensity exercise training in CLBP patients is effective to acquire benefits
394 in pain and increased functionality. The current motor imagery program addition
395 does not bring value to decrease pain intensity, pain extent area and disability.

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400 Conflict of interest/ Disclosure summary

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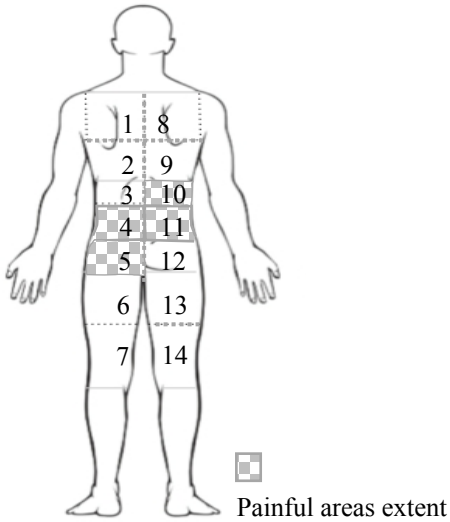
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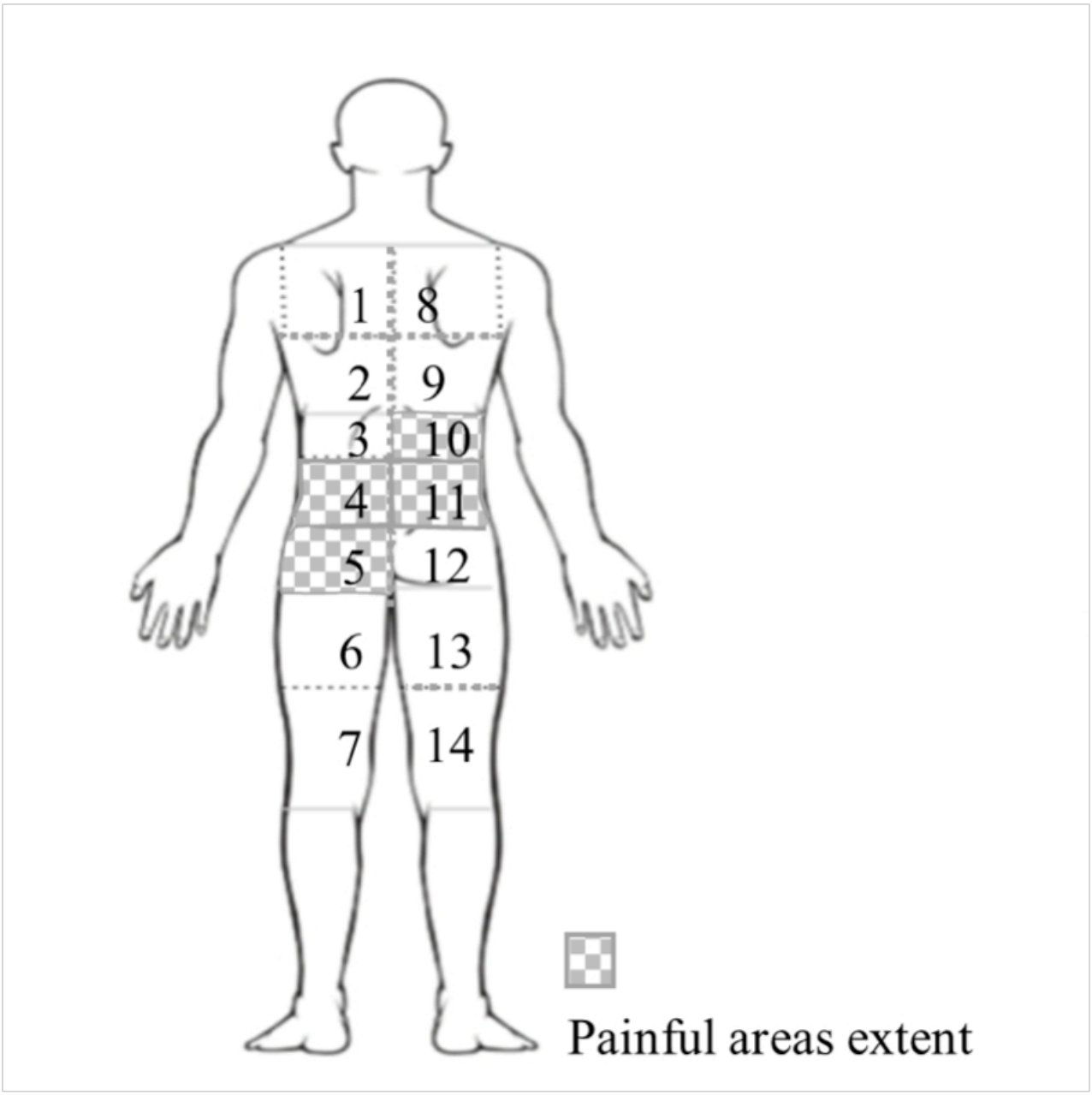
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Figure 1 – Example of the painful area extent in HI+MI patient at pre intervention, referring pain at areas 4, 5, 10, and 11 (n=4). The fourteen delimited areas were defined through nine lines, based on anatomical references: 1st line, marked on the popliteal face of the posterior region of the knee; 2nd line, defined by the midpoint of the thigh equidistant between the popliteal line and the gluteal line; 3rd line in the gluteal fold; 4th line, through the upper posterior iliac spines; 5th line, referenced by the L2 spinous process; 6th line, referenced by the T10 spinous process; 7th line, referenced by the T6 spinous process; 8th line, referenced by the T2 spinous process, and the 9th line was marked link al spinous process.

Table 1 – High Intensity Exercise with Motor Imagery Group (HI+MI, n=9), High Intensity Exercise Group (HI, n=11) and control (Cont, n=10) groups' characterization: sociodemographic, anthropometric, professional occupation, and pain duration. Data are presented as absolute frequency (relative frequency) for qualitative variables, and mean (±standard deviation) or median (percentile 25 – percentile 75) for quantitative variables. *p* values reflect the between-groups comparison.

Variable		**HI+I group**	**HI group**	**Cont group**	**Between-groups comparison (*p* value)**
<u>Sociodemographic data</u>					
Gender	Female (n)	8 (88.9%)	10 (90.9%)	7 (70.0%)	0.475
	Male (n)	1 (11.1%)	1 (0.1%)	3 (30.0%)	
Age (years)		47.0±7.68	53.9±8.04	54.5±8.72	0.105
<u>Anthropometric data</u>					
Body mass (kg)		68.8±11.68	70.9±10.17	71.4±9.98	0.853
Height (m)		1.6±0.08	1.6±0.06	1.6±0.07	0.955
BMI (kg/m^2)		26.1±4.05	26.8±4.72	26.8±2.94	0.911
<u>Professional occupation data</u>					
Retired (n)		1 (11.1%)	2 (18.2%)	2 (20.0%)	0.400
Unemployed (n)		4 (44.4%)	5 (45.5%)	1 (10.0%)	

Sick leave (n)	0 (0.0%)	2 (18.2%)	3 (30.0%)	
Active (n)	4 (44.4%)	2 (18.2%)	4 (40.0%)	
Pain duration (months)	53 (47.0 – 131.0)	90 (64.0 – 180.0)	78 (39.0 – 144.0)	0.557

BMI – Body mass index

Table 2 – Pain intensity (mm), pain extent (number of affected areas), and physical disability score, at the pre- and post-intervention assessment, in high intensity exercise training with motor imagery training (HI+MI, n=9), high intensity exercise training (HI, n=11), and control (Cont, n=10) groups. Data are presented as mean (±standard deviation) or median (percentile 25 – percentile 75). *p* values reflect the within-group comparison in each group (pre- vs. post-intervention assessment) or the between-groups comparison at the pre- and post-intervention assessment.

Variable	Group	Pre-intervention	Post-intervention
Painful extent (number of areas)	HI+MI	6.00 (3.50 – 7.00)	2.00 (2.00 – 4.00)*#
	HI	5.00 (3.00 – 6.00)	2.00 (2.00 – 4.00)*#
	Cont	5.00 (3.50 – 7.00)	5.50 (3.75 – 7.00)
Pain intensity (VAS, mm)	HI+MI	59.56±11.96	27.22±14.40**&
	HI	63.91±18.89	40.64±19.81**&
	Cont	69.50±20.48	70.10±18.00
Physical disability score	HI+MI	12.78±2.68	6.78±4.44*&
	HI	14.73±3.47	7.27±5.00**&
	Cont	15.70±4.86	16.10±3.78

* $p<0.05$ vs. Pre-intervention; ** $p<0.001$ vs. Pre-intervention; # $p<0.05$ vs. Cont; & $p<0.001$ vs. Cont

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Study 4

Resolving chronic lower back pain symptoms through high intensity therapeutic exercise and motor imagery program: a case-study

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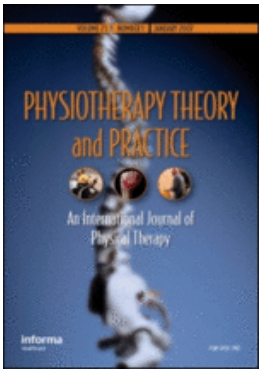

Resolving chronic lower back pain symptoms through high intensity therapeutic exercise and motor imagery program: a case-study

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Manuscript ID	UPTP-2019-0712
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Keywords:	low back pain, functionality, physiotherapy, laterality, physical exercise

Resolving chronic lower back pain symptoms through high intensity therapeutic exercise and motor imagery program: a case-study

ABSTRACT

Background and Purpose: Low back pain incorporates three important aspects in human activity such as pain, functional disability and reduced mobility in physical activity. In adolescents aged 14-18 years old, 26% of boys and 33% of girls reported recurrent and chronic low back pain. The manuscript reports a case study of a non-specific severe Chronic Lower Back Pain (CLBP). **Case Description:** A 13-year-old girl with common symptoms and with radicular pain to both lower limbs, unmanageable by traditional medical therapy was proposed to a specific physiotherapy intervention, with 36 sessions, 3 times/week during 12 weeks, composed by high intensity therapeutic exercise associated with motor imagery training. **Results:** It was presented a favorable clinical evolution, with pain relief, improved posture, and decreased disability at the end of the intervention, which clinical situation remains stable during the follow-up done approximately 3 years after. **Conclusion:** The results allow concluding that the combined program of high intensity therapeutic exercise associated with motor imagery training reveals advantageous for CLBP, with a favourable and clinical evolution of the disease, which results were sustained long-term after finished the intervention.

Keywords: low back pain; functionality; physiotherapy; laterality; physical exercise

INTRODUCTION

The Low Back Pain (LBP) is well recognized as a major public health problem affecting 80% of the population at least once in their all life (Wilder et al., 2011). LBP incorporates three important aspects in human activity such as pain (Laslett et al., 2005), functional disability (SL Hoffman, Johnson, Zou, and Van Dillen, 2011) and reduced mobility in physical activity (Dubois, Piche, Cantin, and Descarreaux, 2011). LBP is currently classified as specific, if it results from a previously identified pathology, or non-specific, if it is idiopathic (Manek and MacGregor, 2005; van den Bosch, Hollingworth, Kinmonth, and Dixon, 2004) – the non-specific conditions being the most prevalent with approximately 90% of cases (Manek and MacGregor, 2005). Approximately 90% of cases of LBP are resolved spontaneously or with therapeutic action within six weeks of its beginning, however 2-10% become a chronic problem (Manchikanti et al., 2009).

Among the different available definitions of chronic lower back pain (CLBP), i.e. the extension of LBP for more than 12 weeks (Mendonca, Monteiro-Soares, and Azevedo, 2018; Oliveira et al., 2018), with impact on patient's daily activity, are common characteristics of the pain, discomfort, weakness and loss of mobility experienced by patients (Haas et al., 2005). Beyond the pain, the functional status or the perceived recovery, the duration of these symptoms is the most important factor for CLBP diagnosis (van Middelkoop et al., 2011). Indeed, a multidisciplinary panel of experts has defined CLBP as the pain which persists over 3 months and is felt at least half the days in the past 6 months; and CLBP should be stratified by its daily impact resulting from the combination of pain intensity, pain interference in normal activities and functional status of patients (Deyo et al., 2015). The prevalence of active CLBP in the adult Portuguese population in 2016 was 10.4% for the general population and 1.9% for 18-25 years old (Gouveia et al., 2016). In adolescents aged 14-18 years old, 26% of boys and 33% of girls reported recurrent and chronic low back pain (Taimela, Kujala, Salminen, and Viljanen, 1997). As reported, CLBP happened in adolescents within specific conditions, which may represent a strong disability negatively

impacting the quality of life and the academic outcomes and of these groups.

In CLBP, the severity of pain is a personal experience involving multidimensional features (McMahon, Koltzenburg, Tracey, and Turk, 2013) where is included the sensory-discriminative dimension, because it combines discriminative aspects such as intensity, duration and the location of the pain (Butler, 2000; Pud and Sapir, 2006). Common conditions induced by chronic pain, like sensorimotor, proprioceptive, and tactile deficits may affect postural stability and motion control (Gibbons, 2011; Hodges, 2003). Furthermore they may represent maladaptive changes in sensorimotor network with a reduced cerebral activity in Supplemental Motor Area and in Superior Temporal Gyrus (Vrana et al., 2015). In young adults with CLBP the reorganization of primary motor cortex revealed a discrete loss of trunk representation in brain (Tsao, Danneels, and Hodges, 2011). Moreover, CLBP is also associated with an inability of laterality recognition and a reduced accuracy of left/right judgments (Bray and Moseley, 2011; Flor, Braun, Elbert, and Birbaumer, 1997; Stanton et al., 2013). The recognition of laterality is fundamental to the integrity of the body schema and involves an initial decision making and the mental movement (GL Moseley, Sim, Henry, and Souvlis, 2005).

Regarding the CLBP treatment, physical therapy procedures like ultrasound, transcutaneous electrical nerve stimulation, electrical muscle stimulation, percutaneous electrical stimulation, interferential therapy, short-wave diathermy, use of lumbar supports, and taping are inefficient. Only the low level laser therapy seems to be effective for pain relieve and functional improvement but with a small effect (Chou et al., 2016; Jauregui et al., 2016). The majority of guidelines recommended the use of nonsteroidal anti-inflammatory drugs, antidepressants and psychosocial intervention if necessary, complemented by physiotherapy intervention, which mainly includes manual therapy, massage, stretching, and physical exercise (L Moseley, 2002; Oliveira et al., 2018). Some specific types of exercise, such as Pilates, Yoga or Tai Chi seems to be totally ineffective in CLBP (Chou et al., 2016; Wells et al., 2014). However, it is known that general

physical exercise is indicated in a large spectrum of pathologies for the reduction of pain (Kujala, 2009). Moreover, in a healthy person, the aerobic exercise produces analgesia with a 30 minutes exercise session at 75% of VO2max, which is sufficient to induce a change in pain rating in healthy youngsters (MD Hoffman, Shepanski, Mackenzie, and Clifford, 2005). In CLBP patients, it is reported that a high-intensity aerobic exercise promotes pain relief (Chatzitheodorou, Kabitsis, Malliou, and Mougios, 2007). The same effect is found in running exercises, where the pain relief is attributed to the central or peripheral neurotrophins released during and after exercising (Udina, Cobianchi, Allodi, and Navarro, 2011). Moreover, considering the consequences of CLBP associated with sensorial and motor deficits, the motor imagery might also be a valid perceptual cognitive modality to apply in CLBP through the performance of mental physical exercises without physical movements; this is reported in literature as leading to a decrease of the impact of chronic pain (Paolucci et al., 2013), with significant reductions in pain intensity, pain interference, and disability (Wand, O'Connell, Di Pietro, and Bulsara, 2011), thus reinforcing the importance of integrating the sensibility and laterality training in the CLBP physiotherapist practice (Bowering, Butler, Fulton, and Moseley, 2014).

Consequently, a potentially successful physiotherapy approach in CLBP patients would be the association of high intensity therapeutic exercise with motor imagery. Studies with patients with different chronic pain locations, such as facial pain and shoulder pain, revealed a great efficacy of motor imagery combined with exercise (von Piekartz and Mohr, 2014). There are a few studies in CLBP patients combining motor imagery with physical exercise and, even with the reduced intensity of the exercise performed, results are promising (Bagg et al., 2017). Therefore, it is important to verify the effect of combining these two strategies in CLBP – high intensity exercises and motor imagery – evaluating its efficacy in pain and functionality. For that reason, we will present one case of a non-specific severe CLBP patient with common symptoms and with radicular pain to both lower limbs, unmanageable by traditional medical therapy.

CASE PRESENTATION

The patient was a 13-year-old girl, student, born in 4/05/2003 and right-handed, attending the 7th year of schooling with a good performance. No extracurricular or sport activities, and a history of 6 months of severe left side lower back pain with irradiation to both lower limbs.

Clinical History

The pain started on November 18th, 2015 after a small lumbar trauma during the sport class at school. Pain was initially localized in the bilateral periscapular region, more intense in the left scapula and neck, with anterior flexion of the trunk as antalgic posture. After a 15-day evolution, medicated by her pediatrician with paracetamol, tramadol (1 pill 12/12h SOS), diazepam 5 mg 8/8h, and conservative physiotherapy (e.g. hydrotherapy, hot wet, and relaxation), the clinical outcomes worsened. Beyond lumbar pain, the patient also reported paresthesias and intermittent muscle weakness in the right lower limb.

On 02/12/2015, the patient was observed at the hospital emergency services where an x-ray of the spine was done, showing no abnormal changes. Without any other complaint or clinical signal and presenting normal blood and urine tests, the patient was hospitalized for a deeper clinical study. Imageology exams were performed, namely spinal magnetic resonance, pelvic magnetic resonance, cerebral magnetic resonance, cerebral computed tomography without contrast, and lumbar computed tomography, which did not show any signs of pathology justifying the clinical situation. During the hospitalization period the patient was medicated with Omeoprazol 20 mg, Paracetamol 500 mg, Amitriptyline 10 mg (7days), Morphine 10 mg MI (3 days), Ibuprofen 400 mg, Prednisolone 20 mg (7 days), Diazepam 5 mg, Fentanil 0.2 mg, Diclofenac 50 mg, and was also submitted to conservative physiotherapy. The patient was observed by several medical specialties but no objective conclusion concerning a definitive diagnosis was accomplished. Although the lumbar pain persisted, the patient was discharged from the hospital on 01/01/2016 medicated with Diclofenac 50 mg 2/day, Fentanil 0.2 mg SOS until 2/day, Diazepam 5 mg,

Omeoprazol 20 mg, plus the continued supervision of the Hospital Pain Unit.

On 29/03/2016 the patient was observed in that Unit and maintained a defensive posture with trunk flexion both when sitting and standing, as well as an important claudication, with the level 10 on the Visual Analogue Scale (VAS) for the lumbar area. After infiltration with lidocaine in left erector of spine on the back, the patient was medicated with local Transact, Paracetamol, and acupuncture. On 11/05/2016 she was again observed at the Hospital Pain Unit, maintaining the clinical situation of chronic lower back pain with mechanic features. The magnetic resonance that was done to lower limbs did not report any objective change to justify the clinical complaints. The final diagnosis was nonspecific chronic lower back pain, and the patient was recommended to integrate a specific program of physiotherapy, composed by motor imagery and high intensity therapeutic exercise, which started on 13/05/2016.

Personal and Familiar Backgrounds

Regarding personal antecedents, there was a history of asthma and allergic rhinitis with sensitivity to mites and pollen, medicated with Symbicort 2 times/day and Desloratadine 1 pill/day, as well as a single hospitalization due to fever in the first year of life – no other hospitalizations or surgeries. In the family history, the patient reported a healthy father and mother, no siblings a maternal aunt with multiple sclerosis.

Clinical Objective Evaluation

Patient complained about continuous lumbar pain for more than 6 months, with irradiation to both lower limbs, assuming an antalgic fetal posture, with anterior trunk flexion and neck extension. She presented a bend trunk position induced by pain with hip flexion at approximately 90º and a slight inclination of the trunk to the left, with great difficulty in gait plus an inability to assume the orthostatic position; pain irradiation to the lower limbs with great intensity on the right limb and spasms in back muscles; gait disturbance with atypical claudication with predominance in external rotation of right limb and trunk flexion and lateral flexion. The muscle strength and the range of

motion in the trunk were seemingly symmetrical and limited by pain. The patient showed a symmetrical slight weakness in muscles of lower limbs with range of motion also limited by pain. Regarding the upper limbs, patient showed normal range of motion and muscle mass. The mobility of the cervical region was conservative with some limitation in flexion and extension due to the presence of pain, impacting with lesser degree the dorsal kyphosis. Likewise, the patient had a horizontal sacrum, as well as a postural instability at the lumbosacral level, and a discreet dextroscoliosis in the lumbar spine.

Abdominal masses or organomegalies were not detected by a painless palpation and there were normal signs of breath and cardiopulmonary auscultation.

The intensity of low back pain assessed with VAS was 80/100. The whole disability repercussion score assessed by the Roland Morris Disability Questionnaire (RMDQ) (Monteiro, Faisca, Nunes, and Hipolito, 2010) validated for Portuguese language was 12/24. These clinical specifications are described in table 1, first observation.

Specific Physiotherapy Intervention

This specific physiotherapy consisted of a 12-week planning program combining a high intensity therapeutic exercise training, performed three times a week, with a concomitant daily motor imagery training. Each exercise session was performed in a physiotherapy space during Tuesday, Thursday and Saturday mornings.

The therapeutic exercise program consisted of four distinct components: 5 minutes warm-up, 20 minutes high intensity lumbar exercises, 35 minutes cycle ergometer high intensity exercise, and 5 minutes calm-down exercises. The warm-up included stretching and exercise preparation involving hip and lumbar spine movements and neck movements. Afterwards, movements orientated for the trunk were performed with a stick in both hands in order to promote lumbar extension. The lateral flexion and rotation of the trunk to the right and left were performed with arms flexion on 90º. To complete this first phase, three stretching movements were performed for 30 seconds each, in the

orthostatic position. The first one stretched the back structures and posterior muscles with a trunk flexion, the second stretched the anterior structures and anterior muscles with a lumbar force extension position, and the third one combined cross anterior structures by the elongation of the one arm with the contralateral leg. The second phase of the therapeutic exercise program consisted of 20 minutes of high intensity lumbar exercises controlled by individual answer, alternating 8 seconds of 6-10 movements with 12 seconds of rest (Heydari, Boutcher, and Boutcher, 2013), and was composed by three different groups of exercises performed in standing position, in a mattress, and using a chair. The first group involved exercises for lumbar strengthening performed in the standing position and were based on four alternating sequences of movements executed with the lower limbs. The exercise sequence was designed with the lower limbs performing ten movements combining slight flexion, adduction, abduction and external rotation of the hip joint, flexion and extension knee alternating right and left leg with one-legged support. The second group of exercises involving legs, arms and trunk, was realized on a mattress, in all decubitus position and in quadruped position. In the semi-kneeling position, the patient alternated the body load from the right knee to the left foot and vice versa. The third group of exercises was done in the standing position with the help of a chair where the patient performed repetitions of the lower limbs for each hip joint with flexion, abduction and extension always done with the knee extension. Another exercise was performed with the hands resting on the chair's seat and with the trunk flexion over the chair's top where the patient drew alternately with each lower leg a square in the space. A final exercise was done in upright position, simulating the movement of a run using both hands and legs, but without leaving the place for about 30 seconds, with a progressive increasing intensity. The third therapeutic exercise phase took place over 35 minutes in a cycle-ergometer (Monark E-824), monitoring heart rate through a Polar FT7 Heart Rate Monitor in order to calculate exercise intensity using the Karvonen formula (Murtezani et al., 2011), considering an initial heart rate reserve of 60%, which progressively increased 5% weekly to reach 85% of heart rate reserve

(Chan, Mok, and Yeung, 2011; Chatzitheodorou et al., 2007) at the end of the program. The calm-down phase of 5 minutes, formed by small stretching exercises, allowed the patient to return to a restful condition.

The used motor imagery training program is part of the "Graded Motor Imagery" program using a software (App Recognise Back commercialized by Neuro Orthopaedic Institute, Australia PTY LTD. Version 1.2.) to daily training the motor imagery through the recognized laterality approach. The intervention in laterality and motor imaging using App Recognise Back consisted of restoring laterality, which is the ability to distinguish a part of the body presented various degrees of rotation/inclination, identifying which is the left or right side. The software installed on the patient's mobile phone asked her to quickly identify if one randomised presented image from the back corresponds to the right or to the left side of the trunk; the images showing trunk orientation left and right appeared in different positions and different situations and were presented every day, according to 4 levels of difficulty respectively named Basic, Vanilla, Context, and Abstract. The number of correct responses and the average response time were used as feedback for the patient's change in the difficulty degree.

Treatment Application and Patient Progression

The specific physiotherapy program started on 14.05.2016 and finished at 6.08.2016, with 32 sessions of therapeutic exercise performed by the patient within the 36 sessions initially planned (Table 1, second observation). After 12 weeks of programmed combined training, and an evident favourable and progressive clinical evolution, the patient was evaluated and due to the absence of main symptoms and was discharged from the program. On 16.04.2019, 32 months after the discharge, the patient was re-evaluated to assess the long-term repercussions of the intervention program (Table 1, third observation).

DISCUSSION

The results clearly showed important clinical improvements deriving from the 12-week specific

physiotherapy intervention, with a significant decrease in the total area referenced with pain and its intensity, accompanied by an absence of paraesthesia and irradiated pain, an improvement of set disabilities, a drastic decrease in medication, as well as the absence of claudication, antalgic position, muscle spasms and functional joint limitations. This clinical situation persisted to the next stage, whereby without program intervention and in the follow up after proximally 30 months the clinical situation was stable with no need of any kind of medication or therapeutic intervention.

The absence of behavioural patterns with free pain in standing and sitting positions revealed a good postural adaptation and even an absence of pain in the patient. Improvement in muscle strength was a sign of improved ability to produce force in association with load and it was possible to understand a significant muscle spasm decreased in the lumbar region associated with better range of motion in the cervical and lumbar regions. Posture changes, the muscular strength and a gait without claudication acquired during program were the most important functional acquisitions. With some surprise, these remained through the follow up, even though the return to the previous clinical situation would be expected. These favorable and stable modifications strengthen the fact that high intensity therapeutic exercise associated with motor imagery training promotes the development of new brain pathways, which in turn decrease pain perception and improve the functional perception of movement.

It is well known that high-intensity physical exercise has natural advantages in pain reduction (Griffin et al., 2011; MD Hoffman et al., 2005; Kujala, 2009). Specifically for CLBP, several studies have reported its ability to promote pain relief and improve dysfunction (Chatzitheodorou et al., 2007; Lewis, Morris, and Walsh, 2008), and whose effects are attributed to pain modulation associated with the release of neurotrophins of central or peripheral origin (Udina et al., 2011). The intrinsic mechanisms of pain inhibition can be located at the level of the posterior horn of the spinal cord (Brito, Rasmussen, and Sluka, 2017; Kami, Tajima, and Senba, 2017) and in the segments of the brainstem or thalamic level (Yen and Lu, 2013), with a better back redefinition of

the corticosensorial brain area, possible resulting from the appearance of new pathways of sensorial information not associated with pain and movement information (Lee et al., 2015). These descending inhibitory mechanisms, which modulate pain processing, are the diffuse nociceptive inhibitory control referred to as conditional pain modulation (CPM) and result in an increase in pain threshold at the site of the lesion stimulus (Correa et al., 2015). CPM presents evidence for some changes in endogenous modulation in chronic lower back pain, resulting in a loss of CPM activity (Mlekusch et al., 2016). Activation of CPM reduces the neuronal activity of the dorsal horn of the spinal cord, decreasing pain and hyperalgesia (Correa et al., 2015). High intensity exercise also has the advantage of increasing the production of brain derived neurotrophic factor (BDNF) (Griffin et al., 2011; Knaepen, Goekint, Heyman, and Meeusen, 2010), promoting the development of new synapses in order to define new pathways for muscle recruitment, but also the construction of alternative ways of transporting sensory information to the cortex pain-free somatosensorial area (without feeling pain) (Wand, Parkitny, et al., 2011). The current CLBP guidelines (National Guideline Centre (UK), 2016; Oliveira et al., 2018; Wong et al., 2017) do not make any reference to the intensity or type of exercise to be prescribed to these patients and this should be publicised for future research. Regarding the contribution of motor imagery training and its underlying mechanisms, it is accepted that the repeated stimulation of sensory perception promotes the capacity for laterality differentiation at the cortical level, leading to a decrease in the perception of pain (MacIver et al., 2008). This strategy to drive adaptive cortical neuroplasticity was already successfully used in the management of CLBP (Wand et al., 2014; Wand, Parkitny, et al., 2011), which reinforces the importance to integrate the sensibility and laterality training in the CLBP physiotherapist practice (Bowering et al., 2014).

It should be noted that the association of demanding exercises with body image training was already successfully used in literature to treat shoulder and facial chronic pain (Anderson and Meyster, 2018; Paolucci et al., 2013; Wilder et al., 2011). However, to the best of our knowledge,

the strategy to associate both was never applied to CLBP. In our opinion, the success of the proposed program comes from the combined strategies oriented to the consequence of CLBP and not from the causal foci of the dysfunction. Indeed, due to the idiopathic CLBP being a multifactorial pathology, it must be noted that interventions directed to its cause are doomed to failure, as evidenced by the ineffectiveness of most common treatments for CLBP.

Although restricted to patients who are able to support high intensity exercises, the use of this specific physiotherapeutic approach in clinical practice makes perfect sense by way of its easy applicability, its low cost, and its innovative qualities. The combination of high intensity therapeutic exercise with the training of the motor imagery does not intend to completely resolves CLBP but, on the other hand, it has proved to be a powerful tool to minimize the impact of pain and thus to benefit patients' quality of life.

CONCLUSION

This kind of specific physiotherapeutic intervention successfully attenuated short-term chronic lower back pain and its dysfunction, and these advantages were sustained long-term after finishing the intervention. However, other studies with appropriated samples and designs are required to support this conclusion.

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Conflict of Interest

The authors report no conflict of interest.

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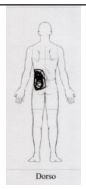
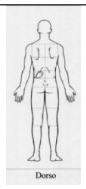
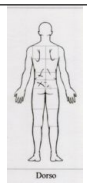
Table 1. Clinical data from the three observations done.

	1st observation 13.05.2016	2nd observation 03.08.2016	3rd observation 16.04.2019
Patient's complains			
Areas of perceived pain	3	1	2
Painful areas and pain intensity (VAS) marked by herself	 80	 39	 34
Pain irradiation and paresthesias	Sporadic posterior left thigh	Absent	Absent
Roland Morris	12	5	3
Clinical examination			
Height (cm)	160	160	163
Weight (Kg)	55	56	68
IMC (Kg/m^2)	21.4	21.8	25.6
Standing antalgic position	Present, severe	Absent	Absent
Sitting antalgic position	Present, severe	Absent	Absent
Claudication	Present, severe	Absent	Absent
Muscle spasms	Severe, bilateral	Light, unilateral	Light, unilateral
Clonus	Absent	Absent	Absent
Patellar and plantar flexor reflexes	Preserved	Preserved	Preserved
Right/left lower limb muscle strength (OMS)	4/5	5/5	5/5
Spinae erector muscles bilateral strength (OMS)	1	4	5
Cervical range of movement	Deficit in extension and flexion	Absent	Absent
Lumbar range of movement	Deficit in extension	Absent	Absent
Limbs range of movement	Deficit in upper limbs flexion	Absent	Absent
Medication	Diazepan 5mg 1/day Paracetamol 500mg 8h/8h Local Transact 12h/12h	Local Transact 12h/12h	Absent

OMS – Oxford modified scale

4. GENERAL DISCUSSION

This discussion section is organized in two sub-chapters: the first aiming to discuss the methodology used in the three experimental articles and in the case report, and the second focus on the general analysis of the main results obtained. This work seeks to draw attention to the issue of chronic non-specific lower back pain by looking at alternative therapeutic options for this important chronic disease, which affects a large number of people.

Discussion of methodology

This sub-chapter is dedicated to discuss the methodology used, analysing the reasons that underlie our methodological options. Fundamentally, it is a general reflection in order to represent what has been done, considering the limitations of the studies and how these may be reflected in future studies.

Regarding the alterations in the acuity sensations reported by different authors in the area of pain, it seems that they affect tactile and painful stimuli [109, 1, 3]. However, it is unknown whether this sensitivity problem is located only in the area of pain or if it extends to the whole *dorsum*, as the studies that focused on this topic were limited to the area of pain [7, 4, 40]. In addition, the tests used to assess different types of sensitivities in the painful area of these patients have several limitations, such as reproducibility problems or difficulties of application in clinical practice, among the main ones. For instance, the calliper is a device currently used by many authors to test sensitivity changes, but it has numerous limitations, such as the pressure applied and the synchronization of the touches produced [13, 2], as well as a moderate inter-examiner reliability [2] in the two-point discrimination test [110, 108, 65]. Moreover, the calliper application point-to-point test is just limited to three points in pain area using a horizontal line perpendicular to the spinous process of third lumbar vertebrae [2]. Regarding other reported tests, the pain threshold induced by pressure suffers from the same limitations, as it refers to the pain area [109]. On the other hand, using the quantitative sensory test, where the patient presses a button to signal the occurrence of pain stimuli [84], the inter-individual variability of the reaction time is pointed out as an additional limitation. The sensory feedback test is another technique to evaluate the limitations of sensitivity of patients with CLBP through the ability to identify letters or words (graphesthesia) on the *dorsum* [112], however in this test the cognitive capacity

of patients emerges as the greatest limitation. Despite the intrinsic limitations of each test, it seems clear that patients with chronic lower back pain present a decrease in sensory acuity in the lower back affected by pain compared to healthy subjects [12, 67, 2]. However, it should be noted that changes in sensitivity may not be restricted to the lower back pain area, as reported by Puta *et al.* that showed an increase not only in the back but also in remote areas not painful, such as the hands assessing pain thresholds by quantitative sensory testing [92]. On the other hand, an increase in sensitivity thresholds was reported [91], without differences in the lower back pain area and other distant non-painful regions when comparing patients with non-specific back pain to healthy individuals [30].

Considering that painful and superficial tactile sensitivity changes may not be limited to the pain area, but are likely to occur throughout the *dorsum*, as well as the limitations to apply and replicate the above referred tests in clinical practice, we felt it necessary, in the first and second studies, to choose a standardized test covering the entire dorsal area, easy for the physiotherapist to use and apply during his clinical evaluation. For that purpose, we opted for an adaptation of the Wand *et al.* protocol [111], where the *dorsum* is divided into fourteen different areas using anatomical references that can be easily reproduced in all subjects. This methodological approach allows us to verify whether the changes are limited to the pain area or whether they are dispersed throughout the *dorsum*. In the original protocol of Wand *et al.* [111], the fourteen defined areas contemplated the shoulder regions instead of the gluteal regions, which in our opinion makes no sense, since the gluteal region is an area adjacent to the lumbar region and often affected by pain. For this reason, in our adaptation of this protocol, the gluteal regions were considered instead of the shoulders, which are more distant from the location of the main pain area, reported by patients, and thus less affected by pain. In opposition to the tests usually described in the literature to assess sensory acuity, our main objective in the first and second studies was to assess the area of discrimination of patients after superficial and painful tactile stimulation, which, although not being a marker of sensory acuity, it somehow reveals the existence of neural alterations integrating information from the periphery [7].

In our approach we used two light touches and two pinprick stimuli applied randomly for each defined area, like others that used the same methodology [111]. However, there are many authors with other options such as using only one touch [110, 40], two touches [4, 67] or even more [21, 2, 40, 5, 75], but applying different tests. Although using two

touches per defined area for each kind of sensibility allowed us to reach our aims, we are now convinced that a higher number of touches per area would have increased the sensitivity and the specificity of the test. It was our option to use both, superficial tactile and painful stimuli, instead of just one, because having different pathways ascending tracks, it would be possible to assess whether the discrimination problem would be located, if in each pathway or in their higher integration brain areas. Consequently, although not assessing the accuracy of sensibility, our methodology allowed us to detect errors in the ability of patients to identify stimulated areas and thus, indirectly, the existence of neural alterations.

Regarding the size of the sample used in our first study, although it may appear small at a first glance, based on the results of Wand *et al.* [110] when evaluating the capacity to discriminate two points in the lumbar area of healthy subjects and CLBP patients, the calculated effect size was 0.98, which for a statistical power of 95% with an α=0.05, allowed an *a priori* sample size calculation of 22 persons per group. This is in accordance with the size of our sample, which had the statistical power to accept or exclude the null hypothesis, with the minimum of type 1 or type 2 errors associated. Moreover, the imbalance observed between men and women cannot be considered a limitation, since it is in convergence with the prevalence of the disease in the population [35].

Although the patients of our first study constituted a convenience sample, it must be noted the absence of any national database of CLBP patients in order to allow selecting them randomly. While classified as a quasi-experimental study, we had the concern to built the healthy group by pair-matching with the CLBP group regarding age, gender, and body mass index, in order to attenuated the errors associated with the lack of sample randomization. It must be highlighted that due to the different methodologies and variables accessed in our first and second studies, the results comparison with other published studies in literature is not possible since, as above referred, the literature reports to the differences in acuity sensibility among healthy subjects and CLBP patients in the lumbar area of pain, while our results in these groups only expressed the ability to discriminate areas in all *dorsum*.

For statistical treatment of the first and the second studies, we considered three zones according to the self-referenced pain areas, which were the painful zone, the adjacent zone, and the peripheral zone, encompassing all the 14 areas. This was the approach used to minimize the inter-individual variability regarding the different pain location.

Moreover, the distribution of the fourteen areas in three different zones, based on the pain location, also intended to analyse the allodynia influence to pain perception and, consequently, in the extent of chronic pain area.

For the second study, the same methodological options were used for tactile and painful discrimination, since this test showed to be sensitive enough to discriminate healthy individuals from patients with CLBP in the first study. We chose to use high-intensity exercise training instead of low or moderate intensity exercise training taking into account the great neuroplasticity resulting from the higher afferent and efferent stimulations, being expected at long term the construction of a larger number of inter-neuronal connections [62, 117]. Furthermore, it is also known that high-intensity exercise training, comparatively to moderate intensity training, induces greater increase in neurotrophins release, favouring the synaptogenesis [52].

The concept of high-intensity exercise used in our second, third, and fourth studies is based on the maximal exercise intensity that allows patients to perform a prolonged and exigent exercise, close to their anaerobic threshold, controlled by the heart rate using the Karoven formula [17]. Although it may not be considered a very demanding exercise for healthy subjects, it must be noted that CLBP patients usually show low physical aptitudes conditioned by the continued presence of pain, the intensity of the exercise for these patients is considered very demanding, justifying its designation in our second, third and fourth studies as high-intensity exercise, in order to differentiate it from those currently used in literature with significant lower intensity [106, 104, 55, 114]. Regarding the training exigency, we were careful to measure the blood pressure of the patients during the exercises, in order to avoid cardio-vascular intercurrences. Three exercise sessions per week were considered to ensure the occurrence of chronic adaptations in patients, both at central and peripheral levels [76, 68, 29], since performing one or only two exercise sessions per week would generate slight adaptations and the option for more than three times per week would compromise the adherence of patients to the program due to their personal and professional commitments. It is noteworthy that the physiological principles of physical training, namely the individuality and overload principles, were respected in our second, third, and fourth studies, once the intensity of exercise was defined for each subject and increased along the time according to the patient fitness improvement. The key elements of any kind of exercise training programme are the frequency, intensity and duration of exercise sessions that will be different from subject to subject [74]. Training is initially

characterized by neural adaptations, namely increased motor learning and coordination that dictates the pattern of adaptations, which are expected to be higher for high-intensity muscular effort, for explosive resistance exercise and for concentric muscle actions [94]. Therefore, our high-intensity exercise training was organized in order to be diverse, integrating strength and endurance combinations, joint mobility, and the returning to calm with a set of specific stretching for the muscle groups most requested. An important objective of high-intensity exercise training was to be associated with the appearance of new connections and new neural pathways expected to arise in central nervous system reorganization. The training was applied for 12 weeks, not only because it is the training period most often used for these patients in the literature [82, 17, 61, 115], but also because it is known that during endurance, strength and mobility training all the phenotype adaptations appear in different phases being required a prolonged stimulation period [22, 51, 97]. The same high-intensity exercise training was maintained in the third and fourth studies considering the benefits experienced in tactile and painful areas discrimination observed in CLBP patients submitted to this protocol in the second study.

Although considered a convenience sample obtained from S. João Hospital Center, the patients' distribution per groups was randomized according to age (studies 2 and 3), gender (just in study 3, due to the sample size limitation in study 2), body mass index (BMI, studies 2 and 3), pain duration (studies 2 and 3), and physical activity levels (just in study 2, based on the obtained results of this study) as stratifying criteria. For this reason, our second and third manuscripts are characterized as longitudinal experimental studies. Supported by the results of Murtezani *et al*. [82] analyzing the influence of high-intensity exercise training on the level of chronic lower back pain, the calculated effect size for studies 2 and 3 was 1.74, which for a statistical power of 95% and for an α=0.05, discloses an *a priori* sample size calculation of 6 persons per group that is about half of our used sample size in studies 2 and 3. Moreover for study 3, based on the results of Oyarzún *et al*. [96] that have analysed the effect of a motor imagery training program on shoulder chronic pain, the calculated effect size was 2.75, which for a statistical power of 95% and for an α=0.05, the *a priori* sample size calculation discloses a sample size of 4 patients per group. Consequently, the sample size used in studies 2 and 3 allowed the sufficient statistical power to test our working hypotheses. In order to avoid bias resulting from medical treatment, during the experimental

protocol of both studies all patients maintained the pharmacological medication prescribed by the Pain's Unit of the hospital.

Regarding the motor imagery training, several types could be chosen, such as mirror therapy, imagined movement and laterality training [54, 77]. We opted for the laterality training because it enhances the activation of the cortical pre-motor and supplementary areas as well as the activation of primary mechanisms associated with the basal ganglia in the motor planning [107, 116, 102], which are compromised pathways in patients with CLBP [113]. Additionally, the laterality training was the easiest to be applied and to control the patient's compliance, once the training was based on a computer application, which was supposed to control patients' evolution and adherence.

Taking into account the neuromodeling potential of high-intensity exercise and motor imagery trainings, it was therefore our aim to assess in third study the clinical outcomes in order to understand the training repercussions on the patients' well-being. Our initial experimental design was to evaluate four groups, instead of three as we reported, with a fourth group performing only motor imagery training. However, the number of patients who carried out the entire the program was very reduced (n = 6), attesting their little motivation to perform the motor imagery training, reason why we opted to exclude this group from the final data analysis.

Although the lack of statistical differences between HI+MI and HI groups observed in the third study, attesting the absence of motor imagery beneficial effects, it might be assumed the existence of underling beneficial effects masked by the magnitude of adaptations produced by physical training. So, in the 4th study, the motor imagery programme was also applied in a case of a young girl with CLBP of a poor prognosis and without high expectations from conservative pharmacological or traditional physiotherapeutic therapies, such as hydrotherapy, manual therapy, massage, or ultrasounds.

Being a case report it is important to highlight the impossibility to attribute to high-intensity exercise training or to motor imagery training the individual responsibility for the obtained results. Seeing this as clinical challenge, the patient well-being outcomes were our main focus without concern with the sensibility discrimination areas assessed in the first and second original studies. Considering that chronic adaptations induced by repetitive stimulation have a reversible character at long term after the stimulation ending, in this fourth study we opted to evaluated the patient not only at the ending of

the training protocol but also three years after, in order to evaluate the maintenance of the obtained training benefits along the time.

Discussion of results

This sub-chapter intent to make a general discussion of results, agglutinating the more significant data found in the four original studies.

From the first study it can be inferred that superficial tactile and painful sensitivity discrimination changes in CLBP patients are extended to all *dorsum*, probably explained by central mechanisms and not by peripheral ones like those located in skin, skeletal muscles, joints, fascia, dura-mater, and visceral organs, among others [89, 8, 15]. This assumption is supported by the extent of the *dorsum*-affected area, with changes of sensitivity discrimination area not just restricted to the patient referred pain area as supported by literature [90]. Moreover, the results of literature reinforce our assumption of a central nervous system commitment (central mechanism), since it is reported that the presence of continuous lower back pain for more than six months generates a deficit of sensitivities in the sensoriomotor, proprioceptive and tactile pathways paralleled by a central integrative dysfunction [45, 93]. This sensory information discrimination deficit from the *dorsum* is considered a factor that predisposes to the pain continuity [10], compromising the patients discrimination between tactile and nociceptive stimuli [69, 78]. Sensory hyposensitivity and mislocalization in the perception of tactile stimuli was reported in CLBP patients [111, 110], which have impaired sensory awareness of the back [37]. The reported neural changes in these patients reflect an adverse neuroplasticity, with adaptive modifications that occur as a result of altered afferent stimuli [56, 90], which includes the neuropathic transmission from spinal areas to subcortical areas and from these to other cortical zones, affecting the inhibitory modulation system [85, 95]. These adverse neuroplasticity changes affecting different areas of the CNS help to explain the maintenance of chronic pain condition, with the occurrence of allodynia that justifies the conservation of chronic pain without any identifiable cause [99].

Although these sensorial disturbances can be well-demonstrated through viable but complex methods to detect changes in central nervous system [41], it must be pointed out that other more simple tests, as the one we used in first and second studies, could

indirectly detect their existences. Consequently, our results support the evaluation of the tactile and painful stimulation discrimination areas of CLBP patients during routine clinical practice in order to assess these kinds of central nervous system dysfunctions. All physiotherapists during their clinical evaluation of chronic lower back pain patients should evaluate the tactile and painful discriminatory sensitivities in the different areas in order to establish a proper and effective treatment. Moreover, being a standardized test, comfortable to patients and easily applied in clinical practice, it gives information from different back zones, crucial to define a treatment approach. In fact, only by knowing the limitations of sensory discrimination of each patient it is possible to define an efficient therapeutic approach [101]. Consequently, traditional physiotherapy may not be enough to treat CLBP, being required to define a treatment plan that integrates this sensory insufficiency and limitation favoured by chronic pain. A recent example is the use of graphesthesia, sensorial stimulation and proprioceptive training as new physiotherapeutic options to skilfully treat CLBP patients [12, 27, 40, 23].

Our results showed that high-intensity exercise training improved the tactile and painful superficial discrimination sensitivities areas, probably explained by enhancing brain afferents pathways through the improvement of neural transmission, with better integration at the central nervous system. One of the involved mechanisms seems to be the inhibition of allodynia, which has apparently decreased with high-intensity exercise training, as suggested in our second study by the reduction of pain area extent paralleled with an increased tactile discrimination in all *dorsum* areas. Allodynia results from a neural dysfunction, where a normally non-nociceptive stimulus, such as cold or light touch, is misunderstood by central nervous system as being a pain stimulus. One of the underlining mechanisms is the decreased pain threshold that promotes hyperalgesia, interpreting as pain all stimuli induced by pinprick or heat, an alteration that can never be detected by nerve-conduction studies [7]. Moreover patients with CLBP showed a decrease in the cortical volume for descending pain inhibitory modulation which is another explanation to justify allodynia [83]. Additionally, the disturbances of limbic-cerebellar pain network reported in these patients may also contribute to allodynia [32, 63].

The beneficial results obtained with high-intensity exercise training may be explained, for example, by the activation of a top-down inhibitory pain modulation system, which inhibited allodynia, a mechanism typically referred in literature as exercise-induced endogenous analgesia by neurotrophic factors [11, 85]. For instance, in an animal model

with a neuropathic pain, repeated sessions of high-intensity exercise caused a pronounced and long-lasting anti-allodynia reaction [73], probably explained by the activation of proprioceptive afferents during exercise modulating the descending inhibitory pathways [46, 63] including the spinal cord [83]. From our results, it was observed in the pain area an increased tactile and painful discrimination, as well as better discrimination in the adjacent and peripheral zones, suggesting an allodynia inhibition either by BDNF or by the increased signalling pathways associated to movement control. Since there are common pathways for movement control and for pain modulation, as PAG is reinforced [11, 64, 87], it is understandable an allodynia and painful sensibility decreased with high-intensity exercise training. The production of BDNF maintains the neurons regeneration [53], the new synapses formation [57], the neural conduction [6] and the generation of alternative motion circuits that allow painless movements [78]. Furthermore, this favourable environment for neural modulation created by high-intensity exercise training explains the observed improvements in tactile and painful discrimination sensitivity, intensity of pain and the pain extent area, which all together are explained by a decreased allodynia. Functional improvements induced by high-intensity exercise training were also observed in our studies, which can be explained either by muscular and articular peripheral mechanisms [106, 66] or by central and peripheral neural mechanisms [20, 18]. In addition to the central changes already described, peripheral neural changes can also improve functionality through the ability of mobilizing nerve roots and the ability to conduct the stimulus [19].

Although not supported by our results, it might be hypothesized that motor imagery training may also had some beneficial effects at a neural level, which were masked by the magnitude of the results provided by high-intensity exercise training. Consequently, the value of motor imagery training as a potential therapeutic tool in CLBP patients must not be disregarded. However, as referred in methodology discussion section, this kind of training should be more stimulating and challenging to patients in order to promote their greater involvement.

Although motor imagery training was apparently ineffective in our third study, the hypothesis of its underlying beneficial effect was considered in our fourth study and consequently the two types of training were associated to treat a female patient who was beyond the usual medical and physiotherapeutic control.

As expected, the fourth study results showed extremely favourable clinical effects, although they cannot be attributed to high-intensity exercise training or motor imagery independently, being the final results assumed as the consequence of training combination. The results post-intervention and follow-up after three years support the concept that high-intensity exercise training in association with motor imagery training bring to chronic lower back pain an efficient approach minimizing the pain level and dysfunctional impact of disease, reason why this option should be considered in clinical practice. Remarkably, as opposed to what was expected, the benefits of the approach have been perpetuated over time, in conflict with the principle of training reversibility, suggesting that the disruption of vicious cycle between pain perception and brain pain maintenance, promoted by high-intensity exercise training and motor imagery training, seems enough to solve the disease main problem.

5. CONCLUSIONS AND FUTURE PERSPECTIVES

The final conclusion of this work gathers the idea that non-specific chronic lower back pain is associated with an alteration in the central nervous system, with repercussions on the perception of pain in the *dorsum* area, which can be attenuated by a high-intensity exercise training programme and possibly combined with a motor imagery programme.
Patients with chronic lower back pain present greater deficits in discrimination of tactile and superficial pain distributed throughout the *dorsum* when compared with healthy subject. These deficits improved with high-intensity physical training and, at the same time, reduced the intensity of referred pain and the extent of the painful area. The pain centralization mechanism reinforces the concept of the important neural contribution to the maintenance of non-specific chronic lower back pain symptoms, and high-intensity exercise training attenuated this mechanism, with benefits to the pain intensity and increased functionality.
The motor imagery program apparently did not add any value for the reduction of pain intensity, pain extent area and patients' disability, nevertheless due to the methodological problems experienced in our work, other additional studies are required to support this conclusion and so to identify the real value of motor imagery training as a therapeutic tool for chronic lower back pain. Indeed, in a specific clinical patient with CLBP without pharmacological results, the high-intensity exercise training combined with motor imagery training was efficient to diminish pain intensity, pain extent and functionality, advantages that have been maintained in the long term.

Regarding the perspectives for future studies, it is important to note that during the third study protocol, patients experienced difficulties to adhere and to be committed with the motor imagery-training program. Apparently they did not felt the challenge to maintain daily practice. To efficiently perform this kind of training, a different software application is required for future research studies and for clinical practice.
Game nature software with well-defined objectives to reach and overcoming should substitute the current one, introducing challenges to the motor imagery training programme similarly to other apps games where people are motivated for a constant daily practice.
Considering the described neural disturbances associated with non specific chronic lower back pain, for a responsible and effective professional practice it is important to assess for each patient the lack of discriminative sensitivity in *dorsum* region, in order

to define the best individual clinical approach for pain reduction and effective motor control. Since the required clinical assessing test must give sensorial information from all *dorsum* and not only from the pain zone, we recommend the protocol used in our first and second studies because it is standardized, easy to apply, and provides essential discriminative information from all *dorsum* patients.

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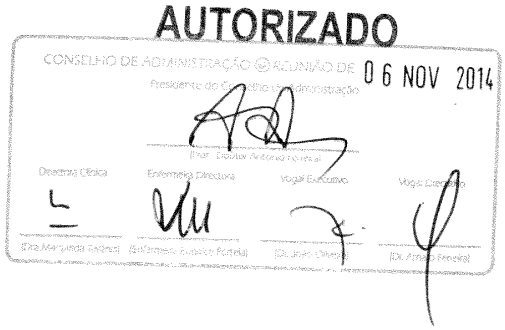
7. APPENDIXES

CES 89-14



Exmo. Senhor
Presidente do Conselho de Administração do
Centro Hospitalar de S. João – EPE

Assunto: Pedido de autorização para realização de estudo/projecto de investigação

Nome do Investigador Principal: Jorge Luís de Miranda Ribas

Título do projecto de investigação: A influência do uso combinado de alta intensidade de exercício terapêutico e do programa de imagética motora na dor em pacientes com lombalgia crónica

Pretendendo realizar no(s) Serviço(s) de Anestesiologia na Consulta da Dor do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.
Para o efeito, anexa toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de S. João respeitante a estudos/projectos de investigação, à qual endereçou pedido de apreciação e parecer.

Com os melhores cumprimentos.

Porto, __21/ _março / 2014

O INVESTIGADOR/PROMOTOR

Exmo. Senhor
Presidente da Comissão de Ética para a Saúde do
Centro Hospitalar de S. João – EPE

Assunto: Pedido de apreciação e parecer para estudo/projecto de investigação

Nome do Investigador Principal: Jorge Luís de Miranda Ribas

Título do projecto de investigação: A influência do uso combinado de alta intensidade de exercício terapêutico e do programa de imagética motora na dor em pacientes com lombalgia crónica.

Pretendendo realizar no(s) Serviço(s) de Anestesiologia na Consulta da dor_____ do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, a sua apreciação e a elaboração do respectivo parecer.
Para o efeito, anexo toda a documentação referida no dossier dessa Comissão respeitante a estudos/projectos de investigação.

Com os melhores cumprimentos.

Porto, __25/ outubro_ / 2013___

O INVESTIGADOR/PROMOTOR

_____

CES

COMISSÃO DE ÉTICA PARA A SAÚDE

Questionário para submissão de projecto de investigação à Comissão de Ética para a Saúde do Centro Hospitalar de São João EPE

SÃO JOÃO
HOSPITAL

A preencher pela CES

Projecto: ____ / _____

Relator: _____

Data de Recepção: ____ / ____ / _____

Data de Parecer da CES: ____ / ____ / _____

NOTA: A Comissão de Ética para a Saúde do Centro Hospitalar de S. João (CES) chama a atenção dos investigadores para a legislação actual, Lei 46/2004 de 19 de Agosto, que comete à CEIC a responsabilidade de elaborar pareceres sobre Ensaios Clínicos.

1. IDENTIFICAÇÃO DO ESTUDO / PROJECTO

a. *Nome do Investigador Principal:*

b. *Título do Estudo / Projecto de Investigação:*

c. *Nome da Entidade Promotora (se aplicável):*

d. *Serviço(s) hospitalar(es) onde será realizada a investigação:*

e. *Existem outros centros, nacionais ou não, onde a mesma investigação será efectuada?*

SIM ☐
NÃO ☐

f. *Descreva, sucintamente, os objectivos da investigação:*

g. *Data previsível de conclusão do Estudo / Projecto de Investigação:*

(Após a conclusão do estudo / projecto de investigação deve comunicar à CES o seu término, bem como enviar cópia dos resultados obtidos)

2. RISCOS / BENEFÍCIOS

a. *A investigação envolve doentes?*

SIM ☐
NÃO ☐

b. *A investigação envolve voluntários sãos?*

SIM ☐
NÃO ☐

c. *Que benefícios imediatos poderão advir para os participantes?*

d. *Que riscos ou incómodos lhes podem ser causados?*

e. *A investigação envolve indivíduos privados do exercício de autonomia (crianças, pessoas com incapacidade temporária ou permanente do exercício de autonomia)?*

SIM ☐ *Quais?*

Que razões justificam este envolvimento?

NÃO ☐

3. <u>CONFIDENCIALIDADE</u>

a. *Serão realizados questionários aos participantes?*

SIM ☐ (Se sim, junte, por favor, um exemplar do questionário que será utilizado)
NÃO ☐

b. *Indique como será garantida a confidencialidade dos dados obtidos?*

c. Está previsto o acesso aos dados do processo clínico do doente?

SIM ☐
NÃO ☐

c.1. *Se sim, por quem?*

c.2. *Se sim, está assegurada a utilização da Ficha Clínica Avaliável (FCA)?*

SIM ☐
NÃO ☐
NÃO APLICÁVEL ☐

4. <u>CONSENTIMENTO</u>

a. Está prevista a obtenção de Consentimento Informado, Livre e Esclarecido?

SIM ☐
NÃO ☐
NÃO APLICÁVEL ☐

b. Está contemplada uma informação escrita para o participante, clarificadora dos objectivos, dos riscos e dos benefícios decorrentes deste estudo/projecto de investigação, bem como da sua inteira liberdade para decidir da sua aceitação em participar?

SIM ☐
NÃO ☐
NÃO APLICÁVEL ☐

(se sim, junte uma cópia da informação a prestar ao doente, bem como do impresso a ser assinado para esse fim – pelo doente, por quem o represente, se incapaz, se analfabeto ou a rogo. O modelo disponibilizado pela Comissão de Ética para a Saúde para obtenção de consentimento após adequada informação é **optativo**)

5. PROPRIEDADE DOS DADOS

a. *Os dados obtidos constituirão propriedade exclusiva do Promotor/Investigador?*

SIM ☐
NÃO ☐

b. *Estão definidos critérios de publicação dos resultados da investigação?*

SIM ☐
NÃO ☐
NÃO APLICÁVEL ☐

6. RETRIBUIÇÃO FINANCEIRA

a. *A investigação proposta envolve exames complementares?*

SIM ☐ *Quem suportará os seus custos?*

(Deve apresentar declaração da entidade referida, bem como o protocolo financeiro com o Centro Hospitalar de São João EPE)

NÃO ☐

b. *Este projecto é financiado?*

SIM ☐ *Qual a entidade financiadora?*

NÃO ☐

c. *Estão clarificados no protocolo financeiro o âmbito e as condições do financiamento?*

SIM ☐

NÃO ☐

d. *Está contemplado qualquer ressarcimento ou remuneração aos doentes:*

	SIM	NÃO	NÃO APLICÁVEL
Pela participação no estudo	☐	☐	☐
Pelas deslocações	☐	☐	☐
Pelas faltas ao serviço	☐	☐	☐
Pelos danos resultantes da sua participação no estudo	☐	☐	☐

7. SEGURO

a. Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)

NÃO ☐

NÃO APLICÁVEL ☐

8. TERMO DE RESPONSABILIDADE

Eu,_____,

abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, ____ / _____ / 20____

_____

O Investigador Principal

	PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO
emitido na reunião plenária da CES de ___/___/___	

Parecer

Título do Projecto: A influência do uso combinado de alta intensidade de exercício terapêutico e do programa de imagética motora na dor em pacientes com lombalgia crónica
Nome do Investigador Principal: Jorge Luís Miranda de Ribas
Serviço onde decorrerá o Estudo: Serviço de Anestesiologia do Centro Hospitalar de S. João e Faculdade de Desporto da Universidade do Porto

Objectivo do Estudo:

O estudo tem como objectivo verificar se um programa de exercícios terapêuticos de alta intensidade combinado com um programa de imagética motora melhora a dor, a quantidade de movimento e a sua percepção em doentes adultos com dor lombar crónica não específica, com duração superior a 6 meses.

Em sua reunião plenária de 29 de Abril, a CES apreciou e aprovou o parecer do relator, que se anexa, e entendeu colocar algumas questões adicionais em reunião a solicitar ao investigador:

1. Na metodologia do estudo prevê-se a randomização de doentes em quatro grupos; no entanto, esta metodologia não está referida no documento informativo que visa obter consentimento dos participantes
2. Nesta randomização, há um grupo de controlo, cujas características e fundamentação não estão identificadas
3. Para o recrutamento dos doentes, estão definidos critérios de inclusão e de exclusão, adequados ao perfil a investigação, mas estes critérios incluem avaliação clínica dos doentes; ora, não está previsto na equipa de investigação nenhum médico que possibilite a aferição destes critérios e o investigador é Fisioterapeuta, não médico
4. Na avaliação dos doentes, ser-lhes-á solicitado que se desnudem e vistam uma "cueca descartável" para possibilitar a correcta avaliação: trata-se de uma manobra

que invade a intimidade das pessoas, pelo que, sendo uma metodologia necessária à boa prossecução do estudo, tal medida invasiva da intimidade deve estar prevista na informação a disponibilizar aos doentes

5. Está prevista a utilização de uma câmara de vídeo durante a avaliação dos doentes, mas nada é adiantado sobre a preservação da identidade para os doentes
6. Estão definidos três centros para a realização do estudo: o Centro Hospitalarr de S. João, a faculdade de Desporto da UP e uma Clínica Particular na cidade; não está definida a articulação entre estes três centros, nem dada qualquer informação sobre a idoneidade desta Clínica
7. Sendo realizadas colheitas sanguíneas, não é identificado qual o local nem quais os profissionais envolvidos
8. Não é coerente a informação do nº de colheitas sanguíneas indicado no Questionário da CES (1), na informação aos doentes (2)
9. A terminologia utilizada na informação para obtenção de CI é inadequada, por complexa, para a população geral, o que deve ser corrigido
10. Não estão cabalmente definidos os riscos inerentes à participação dos doentes, particularmente no grupo que se submeterá à realização do programa de exercícios terapêuticos de alta intensidade; esta informação é devida aos participantes e a esta CES para adequada avaliação
11. Importa ainda clarificar se os exercícios a propor a este grupo de doentes estão consignados como de utilidade assistencial para doentes com esta patologia
12. No questionário electrónico enviado à CES é indicado não haver exames complementares, o que está incorrecto, já que está prevista a realização de colheitas sanguíneas para doseamentos de BDNF
13. Não está indicado onde serão efectuados estes doseamentos
14. Está indicado que o projecto será financiado (embora no questionário electrónico tenha sido exarado não haver financiamento!), mas nenhuma declaração emitida pela entidade responsável, a Faculdade de Deporto, foi anexa
15. Os questionários previstos para aplicação aos participantes no estudo estão identificados e devem ser anonimizados, salvo se outras medidas de protecção estiverem previstas para salvaguarda da confidencialidade a respeitar
16. Estão previstas medidas compensatórias para as despesas eventuais com a deslocação dos doentes (embora, no questionário electrónico da CES esteja negada esta disponibilidade!); mas nada é adiantado quanto à disponibilidade para outro tipo de ressarcimentos que possam ser devidos aos doentes, nomeadamente com eventuais perdas salariais, já que a amostra admite população maior de 18 anos, portanto activa!

17. Deve ser clarificada/justificada a não realização de um Seguro para o Estudo, atendendo ao seu recorte de intervenção

Estas questões foram colocadas verbalmente ao Investigador, em reunião havida com o relator do parecer e do presidente da CES, hoje, 7 de Maio de 2014.
Aguardam-se os esclarecimentos que a estas questões o investigador entender disponibilizar.

Porto e C.H.S.João, 2014-04-23

O Relator

Doutor Manuel Pestana

O Presidente da CES

Doutor Filipe Almeida

Resposta aos pareceres emitidos pela Comissão de Ética do Centro Hospitalar de S. João

Titulo do projeto: A Influência do uso combinado de alta intensidade de exercício terapêutico e do programa de imagética motora na dor em pacientes com lombalgia crónica

Nome do Investigador Principal: Jorge Luís de Miranda Ribas

Ponto 1 - A distribuição do voluntários pelos grupos em estudo será casual e de forma aleatória, sendo os sujeitos distribuídos nos grupos de forma sequencial após serem referenciados para o estudo. Esta situação passou também a estar definida no documento informativo aos participantes.

Ponto 2 - O grupo de controlo passou a ter uma posição clarificada enquanto grupo sujeito aos procedimento de avaliação e não de intervenção dos programas de exercício terapêutico e de imagética motora. Esta situação passou também a estar definida no documento informativo aos participantes.

Ponto 3 - A sua inclusão no estudo estará dependente da avaliação clínica que estará a cargo da equipe clínica da consulta da dor do Centro Hospitalar de S. João. Respeitando que serão os critérios de inclusão e de exclusão.

Ponto 4 - Esta situação passou também a estar clarificada e definida no documento informativo aos participantes.

Ponto 5 - Foi retirada a existência da câmara de vídeo

Ponto 6 - Foi retirado a possibilidade de utilização de uma Clinica Privada de Fisioterapia registada na Entidade Reguladora de Saúde pelo que só serão utilizados a Faculdade de Desporto da Universidade do Porto e o Centro Hospitalar de S. João, estruturas protocoladas para a investigação.

Ponto 7 – Passou a estar identificado o local de recolha sanguínea e os profissionais que a irão efetuar no documento informativo aos participantes e no projeto.

Ponto 8 – O Questionário electrónico foi alterado

Ponto 9 - A linguagem utilizada no documento informativo foi simplificada e clarificada.

Ponto 10 – É referido claramente no documento informativo a existência de riscos ou incómodos, estes estão associados à prática do exercício físico, à fadiga muscular e à recolha sanguínea, no entanto estes riscos são claramente minimizados pela presença de pessoal qualificado e competente para as tarefas desenvolvidas. Estes riscos são atenuados pelo constante acompanhamento durante a prática do exercício, pela monitorização a que estes voluntários estão sujeitos durante essa prática. Está consignado que este tipo de abordagem

terapêutica, sediada em utentes a quem a terapêutica médica já não tem mais a oferecer, espera poder encontrar neste programa uma abordagem diferente centrada no movimento e no reconhecimento da imagem corporal, uma das estratégias da evidência em fisioterapia.

Ponto 11 – É clarificado e passo a citar o referido no documento de informativo:
"Os efeitos benéficos dos programas aplicados separadamente já estão comprovados, pelo que podemos concluir que o exercício terapêutico de alta intensidade e o treino da imagética motora em associação estão declarados como sendo opções terapêuticas válidas isoladas para os estados crónicos de lombalgia, por este motivo é válida a sua integração num programa único e espera-se por isso uma melhoria nas condições da dor e no nível de atividade física dos voluntários participantes no programa.
Estes programa tem um carácter assistencial, motivo pelo qual as mais valias a extrair para os voluntários serão positivas. É dada a possibilidade aos utentes de participarem num programa que vai procurar minimizar o seu desconforto e melhorar o seu nível de mobilidade, bem o diminuir a sua percepção de dor"

Ponto 12 – O questionário electrónico foi alterado no respeitante à realização de exames complementares, no entanto os encargos financeiros decorrentes da analise da recolha sanguínea será da responsabilidade da faculdade de Desporto. Os recursos humanos utilizados serão os do Centro hospitalar de S. João.

Ponto 13 - A análise bioquímica das amostras sanguíneas serão efetuadas no Laboratório de Bioquímica da Faculdade de Desporto da Universidade do Porto.

Ponto 14 - Não está previsto nenhum tipo de financiamento, os custo serão suportados pela Faculdade de Desporto da Universidade do Porto e pelo Investigador.

Ponto 15 – Os questionário foram alterados e anonimizados

Ponto 16 – Não esta previsto qualquer tipo de ressarcimento ao voluntários, entende-se que este programa apresenta uma alternativa terapêutica e por isso integra-se no regime assistencial que visa melhorar as condições de saúde e de funcionalidade dos utentes da Consulta da Dor do Centro Hospitalar de S. João, Os voluntários são livres de aceder ao programa que perspectiva uma melhoria da sua condição ou então de continuarem a manter a sua terapêutica médica, sem qualquer prejuízo da sua situação como utente na Consulta da Dor

Ponto 17 – O Centro Hospitalar de S. João integra o Hospital de S. João, instituição que aufere do estatuto de Hospital Universitário. A Universidade do Porto com profundas raízes na relação com o Hospital, tem sempre privilegiado, o Hospital como Parceiro Institucional. A Faculdade de Desporto é uma Instituição que procura no seu desempenho social, realizar tarefas que visam a melhoria do estado de condição física e de saúde das populações. Este estudo procura melhorar a condição de saúde de um população particular que padece de um estado crónico de dor. Deve ser entendido como uma opção terapêutica para doentes que tem uma condição crónica de dor lombar. A abordagem terapêutica

pelo exercício terapêutico de alta intensidade e a imag motora são evidencias da fisioterapia com resultados evidentes na dor crónica. O que se propõe é encontrar benefícios acrescidos na associação das duas terapêuticas. Não fará sentido a realização de um seguro quando se pretende facultar aos utentes da Consulta da Dor uma possibilidade de utilização de um programa terapêutico inovador e com resultados parcelarmente evidenciados pela comunidade científica.

Jorge Ribas

7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)
NÃO ☑
NÃO APLICÁVEL ☐

8. TERMO DE RESPONSABILIDADE

Eu, Jorge Luís de Miranda Ribas,
abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 15 / maio / 2014

O Investigador Principal

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO

emitido na reunião plenária da CES de ___/___/___

Considerados os esclarecimentos e as alterações efectuadas pelo investigador, de acordo com as normas aplicáveis da CES,

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética

29/4/07.17 (17)

VI

SÃO JOÃO

Comissão de Ética para a Saúde do HSJ

Parecer

Projeto intitulado "A influência do uso combinado de alta intensidade de exercício terapêutico e do programa de imagética motora na dor em pacientes com lombalgia crónica".

Projeto que pretende vir a ser desenvolvido no Serviço de Anestesiologia – Consulta da Dor - do Centro Hospitalar São João como tema de dissertação de doutoramento em Fisioterapia pela Faculdade do Desporto da Universidade do Porto pelo licenciado Jorge Luís Miranda de Ribas, sob orientação da Prof. José Alberto Ramos Duarte.

O projeto visa demonstrar que um programa de exercícios terapêuticos de alta intensidade (conjunto de exercícios com duração aproximada de 1 hora, com ciclo-ergómetro), combinado com um programa de imagética motora (treino de reconhecimento da lateralidade) durante 12 semanas, 3 vezes por semana melhora a dor, a quantidade de movimento e a sua percepção em doentes adultos com dor lombar crónica não específica, com duração superior a 6 meses. Serão realizados questionários validados para a população portuguesa, dos quais se anexam as respetivas cópias mas que *deverão ser anonimizados*. Os dados recolhidos serão tratados com confidencialidade. Está ainda prevista uma colheita de sangue para doseamento do factor neurotrófico derivado do cérebro (BDNF), factor de crescimento a quem são atribuídas funções na regeneração dos neurónios e cuja libertação se pressupõe que seja aumentada na circulação após o exercício.

Como benefícios previsíveis contam-se os que resultem do alivio da dor e da melhoria da atividade física dos doentes. Como riscos ou incómodos associados contam-se a realização dos exercícios físicos e outros previstos e a colheita de sangue igualmente prevista para doseamento do BDNF.

Não está previsto o acesso a dados clínicos de doentes. O acesso aos doentes será obtido através da Drª Armanda Gomes, que servirá de elo de ligação.

Está prevista a obtenção de consentimento informado que é acompanhado de uma informação escrita para os participantes que contempla as questões éticas relevantes, mas que *poderá ser melhorado na terminologia utilizada, para poder ser mais facilmente compreendido por qualquer leigo (p. ex., poderá ser descodificado o que se deseja que seja transmitido com termos como "imagética motora" ou "exercícios terapêuticos de alta intensidade").*

O investigador dispõe da competência científica para a realização do estudo, que está autorizado pela Drª Fátima Pina, diretora do Serviço de Anestesiologia. Está previsto o ressarcimento aos participantes pela sua intervenção no estudo, designadamente para as deslocações em transporte público.

Em face da análise do protocolo proponho que a sua aprovação pela CES do HSJ fique a aguardar pela resposta do investigador às questões em itálico.

Porto, 27 de abril de 2014

O relator

Prof. Manuel Pestana

SÃO JOÃO

Comissão de Ética para a Saúde do HSJ

Parecer

Projeto intitulado "A influência do uso combinado de alta intensidade de exercício terapêutico e do programa de imagética motora na dor em pacientes com lombalgia crónica".

Em face da análise da resposta do investigador às questões colocadas em 23 de Abril de 2014, a CES do CHSJ entende colocar as seguintes questões adicionais:

- Deverá ser incluída uma declaração de concordância dos Srs. Enfermeiros da Consulta da Dor do CHSJ em relação à colheita das amostras de sangue que fazem parte do protocolo do estudo;

- Deverá ser incluída uma declaração da Faculdade do Desporto de UP a confirmar o suporte finaceiro dos custos;

- Deverá ser corrigido o texto do documento informativo para os participantes nos seguintes pontos (ver sublinhado e rasurado):

Onde se lê:

"Do programa de exercícios terapêuticos.....constará:

a) Uma primeira fase de preparação.....5 minutos;
b) Em seguida, numa fase de condicionamento físico, ...em que o voluntário estará fixo ao_(incluir o texto que falta) para evitar .....durante as 12 semanas do treino;
c) Uma fase.....em que os exercícios serão realizados .... descanso".

- A seguir à frase "A existência de riscos e incómodos.....sanguínea", deverá acrescentar-se a informação que consta do ponto 10 da resposta do investigador aos pareceres emitidos pela CES.

- Deverá ser corrigida a frase "Estes programa tem um carácter assistencial, motivo pelo qual se espera que as mais valias a extrair .... mobilidade, bem como ~~e~~ diminuir a sua....dor".

- "Condições de financiamento: o estudo....." deverá ser corrigido acrescentando no texto a informação de que não haverá lugar a qualquer forma de ressarcimento de despesas aos participantes decorrentes da sua participação no estudo.

Nas condições em que se realizará o estudo, a CES do CHSJ considera aceitável a dispensa do seguro, ao abrigo do nº 3 do artº 6 da lei nº21/2014. A CES chama, no entanto, a atenção do investigador para as responsabilidades legais inerentes (nºs 1 e 2 do artº 15º da mesma lei nº 21/2014).

Porto, 1 de Julho de 2014

O relator

Prof. Manuel Pestana

Parecer

Título do Projecto: A influência do uso combinado de alta intensidade de exercício terapêutico e do programa de imagética motora na dor em pacientes com lombalgia crónica

Nome do Investigador Principal: Jorge Luís Miranda de Ribas

Serviço onde decorrerá o Estudo: Serviço de Anestesiologia do Centro Hospitalar de S. João e Faculdade de Desporto da Universidade do Porto

Objectivo do Estudo:

O estudo tem como objectivo verificar se um programa de exercícios terapêuticos de alta intensidade combinado com um programa de imagética motora melhora a dor, a quantidade de movimento e a sua percepção em doentes adultos com dor lombar crónica não específica, com duração superior a 6 meses.

Em sua reunião plenária de 29 de Abril, a CES apreciou e aprovou o parecer do relator, que se anexa, e entendeu colocar algumas questões adicionais em reunião a solicitar ao investigador:

1. Na metodologia do estudo prevê-se a randomização de doentes em quatro grupos; no entanto, esta metodologia não está referida no documento informativo que visa obter consentimento dos participantes
2. Nesta randomização, há um grupo de controlo, cujas características e fundamentação não estão identificadas
3. Para o recrutamento dos doentes, estão definidos critérios de inclusão e de exclusão, adequados ao perfil a investigação, mas estes critérios incluem avaliação clínica dos doentes; ora, não está previsto na equipa de investigação nenhum médico que possibilite a aferição destes critérios e o investigador é Fisioterapeuta, não médico
4. Na avaliação dos doentes, ser-lhes-á solicitado que se desnudem e vistam uma "cueca descartável" para possibilitar a correcta avaliação: trata-se de uma manobra

que invade a intimidade das pessoas, pelo que, sendo uma metodologia necessária à boa prossecução do estudo, tal medida invasiva da intimidade deve estar prevista na informação a disponibilizar aos doentes

5. Está prevista a utilização de uma câmara de vídeo durante a avaliação dos doentes, mas nada é adiantado sobre a preservação da identidade para os doentes
6. Estão definidos três centros para a realização do estudo: o Centro Hospitalarr de S. João, a faculdade de Desporto da UP e uma Clínica Particular na cidade; não está definida a articulação entre estes três centros, nem dada qualquer informação sobre a idoneidade desta Clínica
7. Sendo realizadas colheitas sanguíneas, não é identificado qual o local nem quais os profissionais envolvidos
8. Não é coerente a informação do nº de colheitas sanguíneas indicado no Questionário da CES (1), na informação aos doentes (2)
9. A terminologia utilizada na informação para obtenção de CI é inadequada, por complexa, para a população geral, o que deve ser corrigido
10. Não estão cabalmente definidos os riscos inerentes à participação dos doentes, particularmente no grupo que se submeterá à realização do programa de exercícios terapêuticos de alta intensidade; esta informação é devida aos participantes e a esta CES para adequada avaliação
11. Importa ainda clarificar se os exercícios a propor a este grupo de doentes estão consignados como de utilidade assistencial para doentes com esta patologia
12. No questionário electrónico enviado à CES é indicado não haver exames complementares, o que está incorrecto, já que está prevista a realização de colheitas sanguíneas para doseamentos de BDNF
13. Não está indicado onde serão efectuados estes doseamentos
14. Está indicado que o projecto será financiado (embora no questionário electrónico tenha sido exarado não haver financiamento!), mas nenhuma declaração emitida pela entidade responsável, a Faculdade de Deporto, foi anexa
15. Os questionários previstos para aplicação aos participantes no estudo estão identificados e devem ser anonimizados, salvo se outras medidas de protecção estiverem previstas para salvaguarda da confidencialidade a respeitar
16. Estão previstas medidas compensatórias para as despesas eventuais com a deslocação dos doentes (embora, no questionário electrónico da CES esteja negada esta disponibilidade!); mas nada é adiantado quanto à disponibilidade para outro tipo de ressarcimentos que possam ser devidos aos doentes, nomeadamente com eventuais perdas salariais, já que a amostra admite população maior de 18 anos, portanto activa!

17. Deve ser clarificada/justificada a não realização de um Seguro para o Estudo, atendendo ao seu recorte de intervenção

Estas questões foram colocadas verbalmente ao Investigador, em reunião havida com o relator do parecer e do presidente da CES, hoje, 7 de Maio de 2014.
Aguardam-se os esclarecimentos que a estas questões o investigador entender disponibilizar.

Porto e C.H.S.João, 2014-04-23

O Relator

Doutor Manuel Pestana

O Presidente da CES

Doutor Filipe Almeida

2014.07.16

Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética

Todas as questões foram adequadamente respondidas pelo investigador, com correção e documento anexo transcrito.
Nestas circunstâncias, e na esteira do parecer do relator de 2014/7/01, a CES nada tem a opor à realização deste E.I., na sua atual configuração metodológica

Folheto explicativo do Projeto

Nome da Pesquisa: A influência do uso combinado de alta intensidade de exercício terapêutico e do programa de imagética motora na dor em pacientes com lombalgia crónica

Objetivos: Esta pesquisa pretende demonstrar que o programa de exercícios terapêuticos de alta intensidade quando combinado com um programa de imagética motora melhora a dor na lombalgia crónica.

Haverá quatro grupos em estudo sendo um de controlo, a escolha dos elementos para os grupos será feita de forma aleatória. As tarefas práticas a efetivar com os voluntários e com o investigador serão realizadas na Faculdade de Desporto da UP.

As sessões práticas poderão ter aproximadamente 60 minutos de duração. Espera-se que haja uma melhoria nas condições da dor e na atividade física dos voluntários não se esperando nenhum risco associado. O estudo decorrerá durante 12 semanas, 3 vezes por semana para o programa físico.

A participação neste estudo é voluntária e poderão ter acesso a todos os resultados. O seu nome não será divulgado em nenhuma parte da pesquisa, os voluntários respondem a um conjunto de questionários composto por diversas partes.

A primeira etapa é projetada para investigar os dados demográficas, dados referentes à dor crónica lombar, à sua atividade física, à sua incapacidade funcional e a uma avaliação das sensibilidades, e da atividade autonómica simpática assim como uma avaliação do reconhecimento da lateralidade. É também feita uma recolha sanguínea para quantificação do factor neurotrófico derivado do cérebro.

A segunda etapa é desenhado para a realização de um exercício físico de alta intensidade e um programa de imagética motora através do treino da lateralidade. Em nenhum momento esta pesquisa deverá causar risco ou qualquer desconforto à saúde dos voluntários, salvaguardados que estão os critérios para a interrupção do exercício.

Os dados recolhidos serão para uso exclusivo para a presente investigação e serão alvo de tratamento confidencial, garantindo que a identificação dos voluntários nunca será tornada pública pelo que fica garantida a confidencialidade. Desde já agradeço toda a colaboração prestada, coloco-me ao dispor para qualquer esclarecimento adicional.

Jorge Luís de Miranda Ribas,
Aluno de doutoramento em fisioterapia na Faculdade de Desporto da Universidade do Porto. Telemóvel 917586885, jorgelmribas@gmail.com.

Critérios de inclusão

- Os sujeitos elegíveis devem ter lombalgia crónica;
- Os participantes eleitos devem ter um diagnóstico de dor lombar crónica não específica, com duração superior a 6 meses;
- Devem ter idade superior a 18 anos de idade;
- Serem capazes de fazer um teste num cicloergómetro;
- Saber ler e escrever o português;
- Apresentar a lombalgia como o seu maior sintoma.

Critérios de Exclusão

- Gravidez;
- Mulheres no pós-parto e pós-natal até um ano;
- Indivíduos com problemas cardíacos graves, neurológicos, metabólicos ou com contraindicação clínica;
- Pacientes que apresentam dislexia ou disfunção motora, bem como indivíduos com dificuldade na realização de uma tarefa de nomeação rápida e visualmente prejudicada;
- Não deverão apresentar evidências de patologia vertebral específica (neoplasias, infecção, fracturas, doença inflamatória, etc.);
- Pacientes com quadros de toxicodependência ou alcoolismo
- Pacientes que tenham sido sujeitos a um procedimento invasivo ou a cirurgia lombar nos últimos doze meses,
- Pacientes que não estejam em litígio judicial por causa da sua dor lombar.

Procedimentos

1º Verificar os critérios de inclusão e exclusão;

2º Atribuir um Id no formulário próprio;

3º Registar o Id na folha de distribuição dos grupos;

Ficha para atribuição do ID ao voluntário participante

Nome: _____

Morada: _____

Cod. Postal: _____-_____ Localidade: _____

Contacto Telefónico: _____ Telemóvel _____

Atribuido o ID _____

DECLARAÇÃO DE CONSENTIMENTO

Considerando a "Declaração de Helsínquia" da Associação Médica Mundial
(Helsínquia 1964; Tóquio 1975; Veneza 1983; Hong Kong 1989; Somerset West 1996 e Edimburgo 2000)

Designação do Estudo (em português):

A influência do uso combinado de alta intensidade de exercício terapêutico e do programa de imagética motora na dor em pacientes com lombalgia crónica----------

Eu, abaixo-assinado, ----------
----------, declaro não ter participado em nenhum outro projecto de investigação durante este período na consulta externa em ambulatório, tendo compreendido a explicação que me foi fornecida acerca do meu caso clínico e da investigação que se tenciona realizar. Foi-me ainda dada oportunidade de fazer as perguntas que julguei necessárias, e de todas obtive resposta satisfatória.

Tomei conhecimento de que, de acordo com as recomendações da Declaração de Helsínquia, a informação ou explicação que me foi prestada versou os objectivos, os métodos, os benefícios previstos, os riscos potenciais e o eventual desconforto. Além disso, foi-me afirmado que tenho o direito de recusar a todo o tempo a minha participação no estudo, sem que isso possa ter como efeito qualquer prejuízo na assistência que me é prestada, assim como me é garantida a confidencialidade dos meus registos.

Por isso, consinto que me seja aplicado o método, o tratamento ou o inquérito proposto pelo investigador.

Data: ____ / _____ / 201___

Assinatura do doente ou voluntário são: _____

O Investigador responsável:

Nome:

Assinatura:

Questionário sobre os dados demográficos dos participantes no estudo sobre "A influência do uso combinado de alta intensidade de exercício terapêutico e do programa de imagética motora na dor em pacientes com lombalgia crónica"

Id participante:_____ Intervenção nº_____

Data de nascimento: _____/_____/_____ Dominância: Destro □

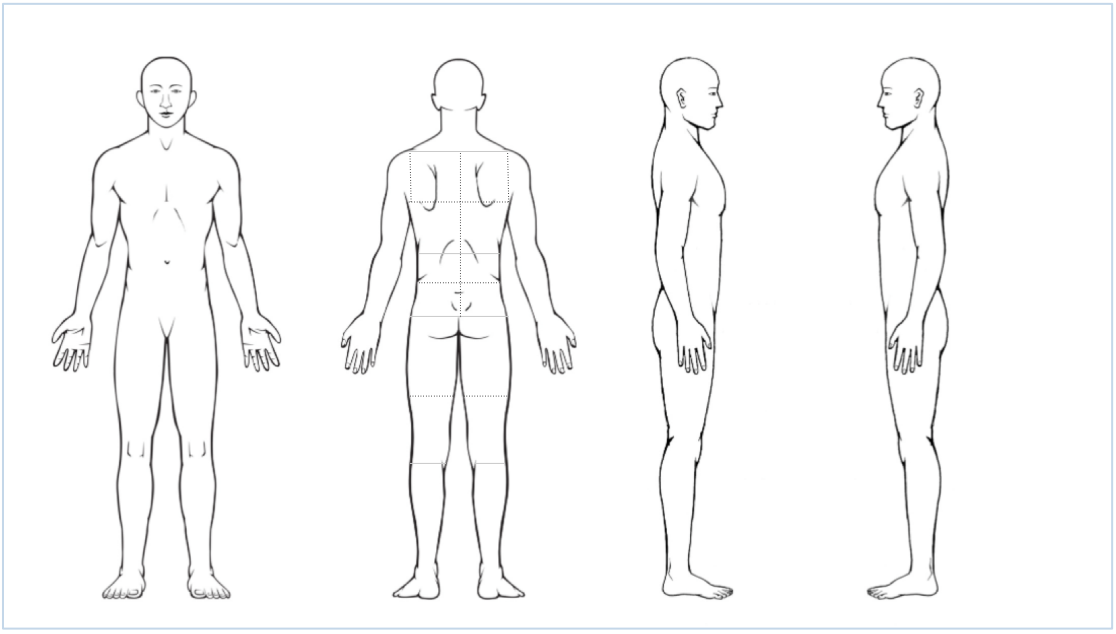
Altura: _____cm Esquerdo □

Peso: _____gr

Período (em semanas) em que o evento da dor crónica está presente :_____

Duração do episódio atual (dias ou semanas): _____

Distribuição da dor: Assinale no quadro as áreas onde a sua dor costuma estar mais presente



Frente Dorso Lateral direto Lateral esquerdo

Atual medicação para a dor: _____

_____

_____

Condições profissionais:

Ativo □
Desempregado □
Em situação de baixa médica □
Aposentado □

Frequência cardíaca em repouso (a registar pelo entrevistador após 5 minutos de repouso): _____

Data _____/_____/_________ ID:____________ Intervenção nº_______________

Por favor, assinale com um risco vertical na linha horizontal a intensidade média da sua dor durante os últimos 2 dias.

Sem dor | Pior dor que se pode imaginar

Data _____/_____/_________ ID:____________ Intervenção nº_______________

Por favor, assinale com um risco vertical na linha horizontal a intensidade média da sua dor durante os últimos 2 dias.

Sem dor | Pior dor que se pode imaginar

Data _____/_____/_________ ID:____________ Intervenção nº_______________

Por favor, assinale com um risco vertical na linha horizontal a intensidade média da sua dor durante os últimos 2 dias.

Sem dor | Pior dor que se pode imaginar

Data _____/_____/_________ ID:____________ Intervenção nº_______________

Por favor, assinale com um risco vertical na linha horizontal a intensidade média da sua dor durante os últimos 2 dias.

Sem dor | Pior dor que se pode imaginar

Data _____/_____/_________ ID:____________ Intervenção nº_______________

Por favor, assinale com um risco vertical na linha horizontal a intensidade média da sua dor durante os últimos 2 dias.

Sem dor | Pior dor que se pode imaginar

Questionário de Incapacidade de Roland Morris, Adaptado e Validado para os doentes de Língua Portuguesa com Lombalgia (RMDQ)

Data_____/_____/_____

ID_____

Intervenção_____

QUESTIONÁRIO DE INCAPACIDADE DE ROLAND MORRIS – RMDQ

Quando tem dores nas costas, pode sentir dificuldade em fazer algumas das coisas que normalmente faz. Esta lista contém frases que as pessoas costumam usar para se descreverem quando têm dores nas costas. Quando as ler, pode notar que algumas se destacam porque o descrevem hoje. Ao ler a lista, pense em si hoje. Quando ler uma frase que o descreve hoje, coloque-lhe uma cruz. Se a frase não o descrever, deixe o espaço em branco e avance para a frase seguinte. Lembre-se, apenas coloque a cruz na frase se estiver certo de que o descreve hoje.

1. Fico em casa a maior parte do tempo por causa das minhas costas.
2. Mudo de posição frequentemente para tentar que as minhas costas fiquem confortáveis.
3. Ando mais devagar do que o habitual por causa das minhas costas.
4. Por causa das minhas costas não estou a fazer nenhum dos trabalhos que habitualmente faço em casa.
5. Por causa das minhas costas, uso o corrimão para subir escadas.
6. Por causa das minhas costas, deito-me com mais frequência para descansar.
7. Por causa das minhas costas, tenho de me apoiar em alguma coisa para me levantar de uma poltrona.
8. Por causa das minhas costas, tento conseguir que outras pessoas façam as coisas por mim.
9. Visto-me mais lentamente do que o habitual por causa das minhas costas.
10. Eu só fico em pé por curtos períodos de tempo por causa das minhas costas.
11. Por causa das minhas costas, evito dobrar-me ou ajoelhar-me.
12. Acho difícil levantar-me de uma cadeira por causa das minhas costas.
13. As minhas costas estão quase sempre a doer.
14. Tenho dificuldade em virar-me na cama por causa das minhas costas.
15. Não tenho muito apetite por causa das dores das minhas costas.
16. Tenho dificuldade em calçar peúgas ou meias altas por causa das dores das minhas costas.
17. Só consigo andar distâncias curtas por causa das minhas costas.
18. Não durmo tão bem por causa das minhas costas.
19. Por causa da dor nas minhas costa, visto-me com a ajuda de outras pessoas.
20. Fico sentado a maior parte do dia por causa das minhas costas.
21. Evito trabalhos pesados em casa por causa das minhas costas.
22. Por causa das dores nas minhas costas, fico mais irritado e mal-humorado com as pessoas do que o habitual.
23. Por causa das minhas costas, subo as escadas mais devagar do que o habitual.
24. Fico na cama a maior parte do tempo por causa das minhas costas.

QA	ID							

QUESTIONÁRIO INTERNACIONAL DE ACTIVIDADE FÍSICA (IPAQ)

Estamos interessados em conhecer os diferentes tipos de actividade física, que as pessoas fazem no seu quotidiano. Este questionário faz parte de um estudo alargado realizado em vários países. As suas respostas vão-nos ajudar a conhecer o nosso nível de actividade física, quando comparado com o de pessoas de outros países.

As questões que lhe vou colocar, referem-se à semana imediatamente anterior, considerando o tempo em que esteve fisicamente activo/a. Por favor, responda a todas as questões, mesmo que não se considere uma pessoa fisicamente activa. Vou colocar-lhe questões sobre as actividades desenvolvidas na sua actividade profissional e nas suas deslocações, sobre as actividades referentes aos trabalhos domésticos e às actividades que efectuou no seu tempo livre para recreação ou prática de exercício físico / desporto.

Ao responder às seguintes questões considere o seguinte:

Actividades físicas vigorosas *referem-se a actividades que requerem um esforço físico intenso que fazem ficar com a respiração ofegante.*
Actividades físicas moderadas *referem-se a actividades que requerem esforço físico moderado e tornam a respiração um pouco mais forte que o normal.*

Ao responder às questões considere apenas as actividades físicas que realize durante pelo menos ***10 minutos seguidos****.*

Q.1 Diga-me por favor, nos últimos 7 dias, em quantos dias fez actividades físicas vigorosas, como por exemplo, levantar objectos pesados, cavar, ginástica aeróbica, nadar, jogar futebol, andar de bicicleta a um ritmo rápido?

☐ **Dias**

Q.2 Nos dias em que pratica actividades físicas vigorosas, quanto tempo em média dedica normalmente a essas actividades?

☐☐ **Horas** ☐☐ **Minutos**

Q.3 Diga-me por favor, nos últimos 7 dias, em quantos dias fez actividades físicas moderadas como por exemplo, carregar objectos leves, caçar, trabalhos de carpintaria, andar de bicicleta a um ritmo normal ou ténis de pares? Por favor não inclua o "andar ".

☐ **Dias**

Q.4 Nos dias em que faz actividades físicas moderadas, quanto tempo em média dedica normalmente a essas actividades?

☐☐ **Horas** ☐☐ **Minutos**

Q.5 Diga-me por favor, nos últimos 7 dias, em quantos dias andou pelo menos 10 minutos seguidos?

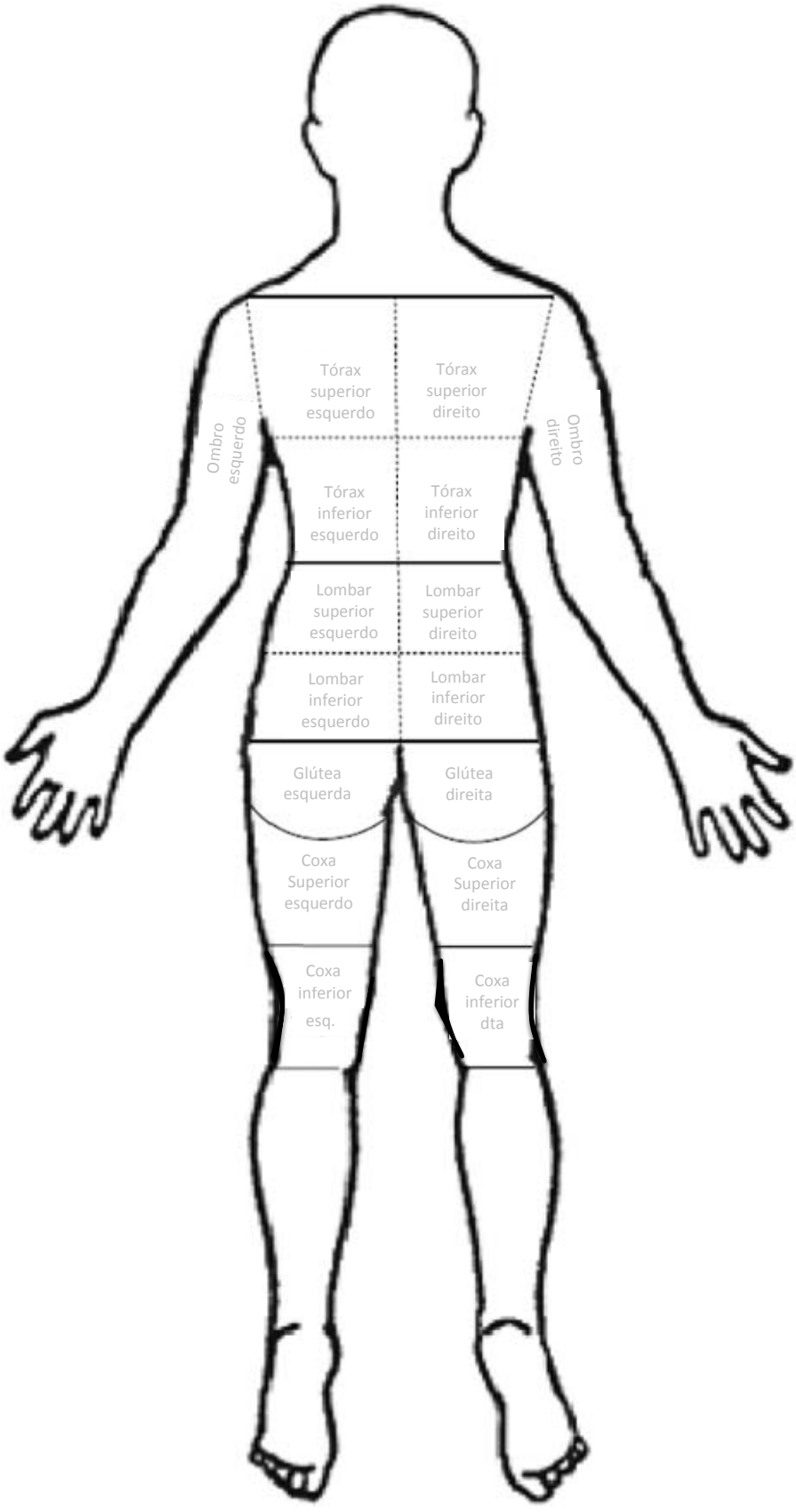
☐ **Dias**

Q.6 Quanto tempo no total, despendeu num desses dias, a andar/caminhar?

☐☐ **Horas** ☐☐ **Minutos**

Q.7 Diga-me por favor, num dia normal quanto tempo passa sentado? Isto pode incluir o tempo que passa a uma secretária, a visitar amigos, a ler, a estudar ou a ver televisão.

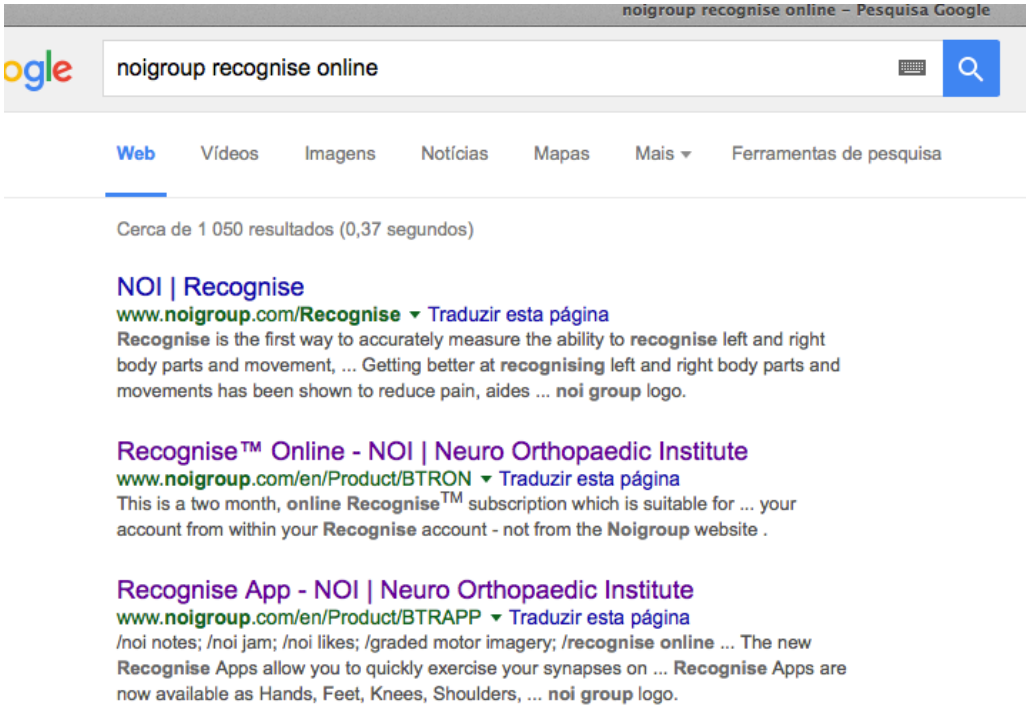
☐☐ **Horas** ☐☐ **Minutos**


Tórax superior esquerdo
Tórax superior direito
Ombro esquerdo
Ombro direito
Tórax inferior esquerdo
Tórax inferior direito
Lombar superior esquerdo
Lombar superior direito
Lombar inferior esquerdo
Lombar inferior direito
Glútea esquerda
Glútea direita
Coxa Superior esquerdo
Coxa Superior direita
Coxa inferior esq.
Coxa inferior dta

1º passo

https://www.google.pt/

procurar “noigroup recognise online”



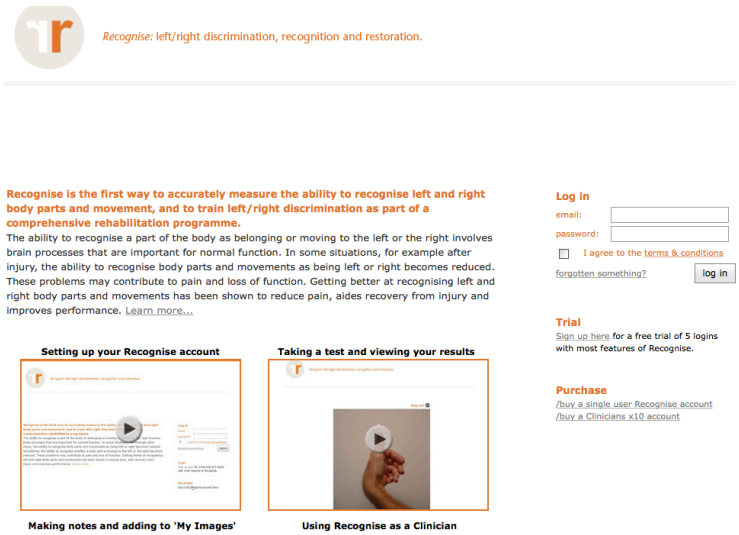
2º passo

abrir

http://www.noigroup.com/Recognise

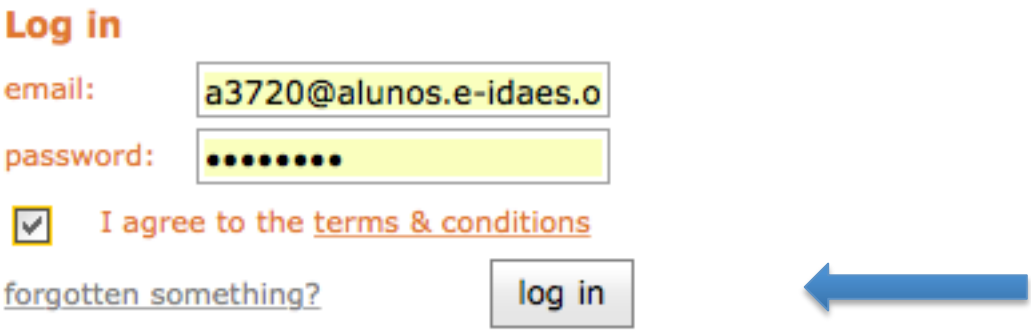
3º passo

inserir email e password



4º passo

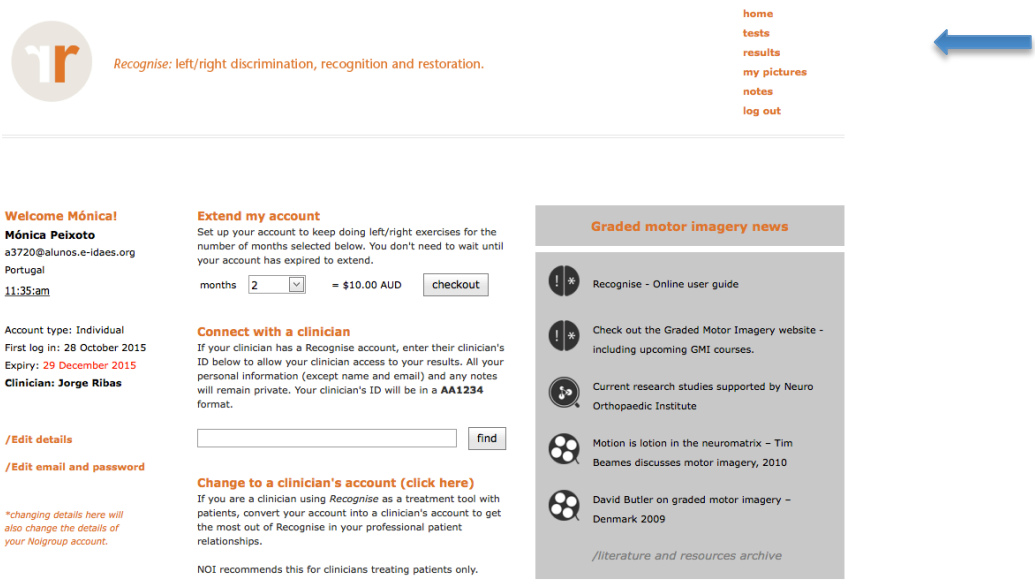
Clicar no quadrado para aceitar o “I agree to the terms & conditions”



Carregar no “Log in” onde está assinalada a seta.

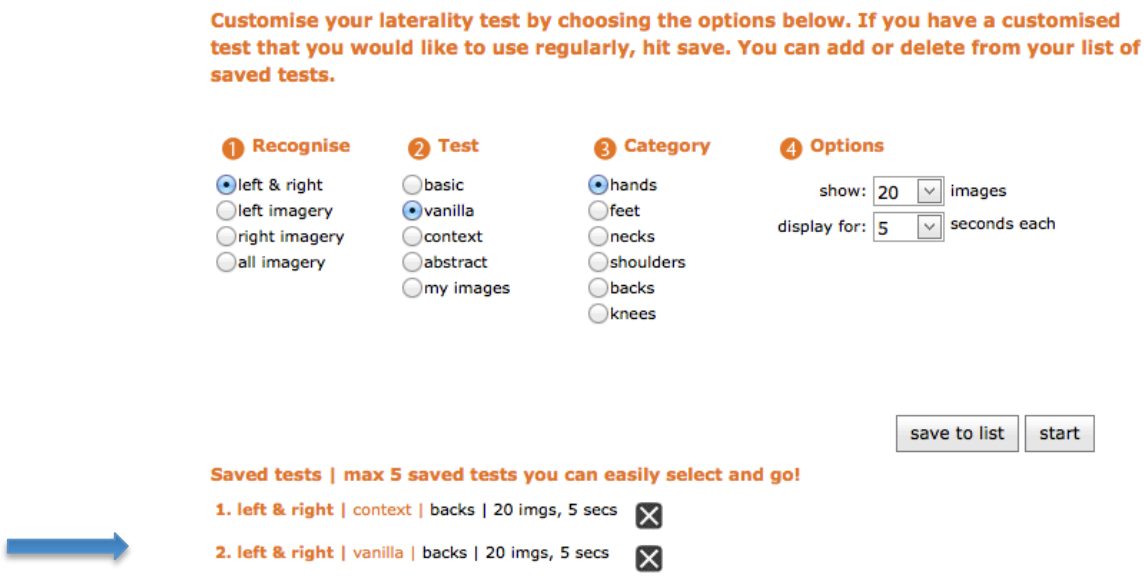
6º passo

já esta na sua página para poder fazer os exercicios e clica em test



7º passo

Escolher o teste



8º passo

fazer o teste como habitualmente escolhendo entre a direita e a esquerda

deverá fazer todos os dias.

ombalgia Crónica

Dor Incapacidade Mal estar

Mude a sua vida

Porque não a imagética motora e o exercício físico?