**Universidade de São Paulo
Instituto de Psicologia**

Rafael Krasic Alaiti

**MOVEMENT-RELATED PAIN AS A LEARNED RESPONSE: AN
INVESTIGATION OF THE POSSIBLE MECHANISMS UNDERLYING
MOVEMENT-RELATED PAIN PERSISTENCE AND RECOVERY IN
SUBJECTS WITH CHRONIC MUSCULOSKELETAL PAIN**

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**A DOR RELACIONADA AO MOVIMENTO COMO UMA RESPOSTA
APRENDIDA: UMA INVESTIGAÇÃO DOS POSSÍVEIS MECANISMOS
SUBJACENTES À PERSISTÊNCIA E MELHORA DA DOR
RELACIONADA AO MOVIMENTO EM INDIVÍDUOS COM QUADROS
DE DOR MUSCULOESQUELÉTICA CRÔNICA**

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Orientador: Prof. Livre-Docente Dr. Marcelo Fernandes da Costa
Co-orientadores: Prof. João Paulo Caneiro

**São Paulo
2021**

AUTORIZO A REPRODUÇÃO E DIVULGAÇÃO TOTAL OU PARCIAL DESTES
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DEDICATÓRIA

Há cerca de 4 anos, me matriculei no doutorado acreditando que estava apenas galgando mais um degrau em minha formação de base. Demorei muito para perceber que, na verdade, eu havia me matriculado em um processo que iria me transformar ao longo do trajeto de formas que eu não poderia ter imaginado.

O processo de doutoramento é uma continuação do mestrado e envolve fazer disciplinas, estudar, planejar e executar experimentos, adquirir novas habilidades constantemente e elaborar uma dissertação, ou pelo menos era isso que eu imaginava. Na verdade, ao longo do caminho percebi que os pontos mais importantes do doutoramento tem pouco a ver com isso. O processo de doutoramento envolve um treinamento intenso no método e raciocínio científico e te ensina a questionar e levantar boas perguntas, para as quais na maior parte das vezes ainda não existem boas respostas. Enquanto temos um acesso cada vez maior a informações simples e superficiais para problemas complexos na internet e mídias sociais, aprendi a ser cético, questionador e a planejar e executar processos para poder chegar a conclusões baseadas em dados, minimizando o efeito dos meus viéses e limitações humanas.

O processo de doutoramento não foi apenas mais um degrau em minha formação de base, mas sim um processo de capacitação em uma nova profissão: a de pesquisador. O interessante é que não existem disciplinas que te ensinam a ser um pesquisador ao longo do doutorado. Você aprende isso literalmente ao longo do caminho.

A primeira grande lição que aprendi foi a de que boas ideias não significam nada se você não tiver os meios para executá-las. Para cada pergunta que me propus a responder, fui desafiado ao meu limite em adquirir novos conhecimentos e habilidades. Apesar de ter compreendido que é possível aprender qualquer coisa com tempo e disciplina, muitos dos desafios com que me deparei exigiram habilidades para as quais eu não dispunha de tempo ou energia para adquirir no momento. Foi aí que aprendi sobre a importância da cooperação no processo da pesquisa. Sem a ajuda de colegas de laboratório, do campus e de fora da instituição, que compartilhavam de outras formações e habilidades, eu não teria conseguido seguir em frente em muitas das barreiras que encontrei ao longo do processo. Deixo aqui o

meu muito obrigado a todos que me ajudaram construindo hardwares, programando ou me auxiliando no planejamento e análise de experimentos. Sem vocês, eu não teria conseguido fazer todas as coisas que fiz.

Outro ponto importante que aprendi é que concluir o experimento não quer dizer muito. É preciso traduzir o que foi feito em artigos científicos e submetê-los ao processo de revisão por pares. Afinal, a ciência não é uma entidade. Ela é feita por pessoas, por outros pesquisadores. Aprender a colocar as ideias no papel de forma coesa e em uma língua estrangeira exige um processo árduo e constante de lapidação da escrita por parte de pesquisadores mais experientes. Deixo aqui o meu muito obrigado a todos os co-autores que participaram dos trabalhos e, em especial, ao meu co-orientador JP Caneiro por toda a dedicação, atenção e carinho durante as dezenas de revisões realizadas nos trabalhos que compuseram esta tese. Me sinto apto e confiante em comunicar minhas ideias e opiniões ao mundo por causa de vocês.

Talvez um dos principais aprendizados que tive ao longo do processo de doutoramento tenha sido sobre oportunidades. Ao longo destes 4 anos, conheci e tive a oportunidade de trabalhar com grandes pesquisadores nacionais e internacionais das áreas em que atuo. Tais pesquisadores simplesmente me deram a oportunidade de falar minhas ideias, me escutaram e acreditaram em minha capacidade de executá-las, mesmo sem nunca ter me conhecido. A pessoa a quem mais devo agradecer neste quesito é meu orientador Marcelo Costa, por acreditar em mim, me oferecer a oportunidade de viver este processo e por deixar que eu encontrasse meus próprios caminhos no meu próprio ritmo. Esta liberdade foi essencial para que eu me tornasse o que sou hoje. Deixo aqui o meu muito obrigado a todos que me deram oportunidades ao longo desta trajetória, mesmo quando nem eu acreditava que era capaz.

Por fim, o processo de doutoramento não foi uma corrida de 100 metros. Ele foi mais parecido com uma maratona, talvez até com uma montanha russa dependendo do momento. Na verdade, ao longo dos últimos 7 anos de pós-graduação stricto sensu (mestrado e doutorado), foram muitos os buracos, tombos, curvas e mudanças de direção.

Me dediquei de corpo e alma ao processo, fazendo o maior número de disciplinas que pude sobre todos os assuntos que julguei serem relevantes para a minha formação como pesquisador (foram cerca de 2130 horas de disciplinas), me

atualizei diariamente lendo artigos científicos, me dediquei a adquirir e aprimorar habilidades que eu não tinha facilidade, mas que julguei como importantes para a minha formação (e.g. estatística, programação e ciência de dados), e fiz tudo isso enquanto trabalhava como clínico e empreendia na área da fisioterapia musculoesquelética. Apesar de compreender como esta dedicação dividida foi fundamental para que eu conseguisse desenvolver uma noção pragmática da interface entre clínica, mercado e pesquisa, este processo não foi inócuo e deixou consequência tanto em mim quanto e em pessoas que ficaram pelo caminho.

Apesar dos momentos de alegria e celebração, todo o processo de pós-graduação envolveu ficar continuamente fora de minha zona de conforto. Em muitos momentos, não encontrei a motivação necessária para continuar seguindo em frente e fiquei tão imerso nas dificuldades que eu estava enfrentando que não consegui enxergar além dos problemas. Não fosse o apoio de minha mãe e de minha esposa, eu não teria conseguido chegar ao fim deste processo transformador. Vocês sempre acreditaram nas minhas capacidades, me apoiaram e me incentivaram a seguir em frente em todos os momentos em que tive vontade de desistir ou parei de ver sentido nas coisas que fazia. A vocês, deixo aqui o meu muito obrigado e minha eterna gratidão.

Concluir o doutorado sempre foi um dos meus maiores sonhos. Passei toda a minha formação profissional imaginando o momento em que eu seria PhD. Agora, vislumbrando o título, percebo que estas 3 letras não tem significado em si. Foi o processo e as pessoas que conheci ao longo do caminho que me transformaram, e não o título. Apesar de compreender o significado e a importância de ostentar o título de PhD, especialmente no Brasil onde o investimento em ciência é irrisório e a proporção de doutores é baixíssima com relação a muitos outros países, entendo mais do que nunca que títulos não são um sinônimo de autoridade ou um sinal de que a pessoa está atualizada, mas uma responsabilidade.

Nosso país carece de pessoas conhecedoras do método científico, que consigam desenvolver processos para responder perguntas e resolver problemas que afligem o povo brasileiro. Nosso país carece, mais do que nunca, de pesquisadores que consigam implementar soluções no mundo real. Espero conseguir retribuir para a sociedade a oportunidade que me foi dada de me tornar um pesquisador.

EPÍGRAFE

“The best way to predict the future is to create it” (Drucker, 2009)

RESUMO

Alaiti RK, Caneiro JP e Costa MF. Movement-related pain as a learned response: An investigation of the possible mechanisms underlying movement-related pain persistence and recovery in subjects with chronic musculoskeletal pain [Tese de Doutorado]. São Paulo: Universidade de São Paulo, Instituto de Psicologia; 2021.

Apesar do entendimento sobre a neurobiologia da dor ter aumentado exponencialmente ao longo das últimas décadas, ainda existem lacunas de conhecimento importantes relacionadas aos mecanismos associados à persistência da dor e aos mecanismos de ação de abordagens voltadas para o tratamento da dor musculoesquelética crônica. O objetivo desta tese foi contribuir para o preenchimento desta lacuna de conhecimento através da condução de quatro estudos. Os primeiros três estudos investigaram premissas de hipóteses atuais sobre a persistência da dor por uma perspectiva de teorias de aprendizagem, investigando (1) se a dor pode ser condicionada ao movimento através de aprendizado associativo; (2) os fatores associados com a sua manifestação clínica através de movimentos e atividades de vida diária comumente relatadas como dolorosas em pacientes com quadros de dor persistente; e (3) a associada da dor musculoesquelética crônica com distorções perceptuais em outros contínuos perceptuais relacionados ao movimento que podem estar associados com a manutenção de comportamentos de evitação. O último estudo desta tese foi (4) uma revisão sistemática da literatura científica sobre estudos de mediação, conduzidos a partir de ensaios clínicos randomizados, que avaliaram os mediadores de efeito de intervenções baseadas em exercício e cognitivo-comportamentais para a dor e função em pacientes com quadros de dor musculoesquelética crônica. As bases para a condução destes estudos e os seus principais achados foram discutidos ao longo da dissertação.

Palavras-chave: Dor, Dor Crônica, Comportamento, Aprendizagem, Mecanismos de Ação.

ABSTRACT

Alaiti RK, Caneiro JP e Costa MF. Movement-related pain as a learned response: An investigation of the possible mechanisms underlying movement-related pain persistence and recovery in subjects with chronic musculoskeletal pain [Tese de Doutorado]. São Paulo: Universidade de São Paulo, Instituto de Psicologia; 2021.

Although our understanding about pain neurobiology have increased over the last decades, there is still a gap of knowledge regarding the understanding of the mechanisms associated with pain persistence and the mechanisms of action of interventions for subjects with chronic musculoskeletal pain. The main focus of this thesis was to discuss in depth the possible underlying mechanisms associated with pain persistence and recovery in an effort to contribute to the bridging of this gap of knowledge through four researchs. The first three studies investigated assumptions of current hypothesis about pain persistence through the lens of learning theories, by verifying if (1) pain can be conditioned to movements through associative learning; (2) investigating which factors were associated with pain distribution through movements and daily activities commonly reported as painful by subjects with chronic pain; and by (3) investigating if chronic musculoskeletal pain is associated with perceptual distortions in other perceptual continuums associated with movements that could foster avoidance behaviors. The last study of this thesis was (4) a systematic review that aimed to systematically identify and synthesise studies that conducted mediation analyses of randomized controlled trials that test or estimate indirect effects of cognitive-behavioral and exercise-based interventions for pain and disability in people with chronic musculoskeletal pain. The basis for the conduction of these studies, as well as its main findings were discussed throughout this thesis.

Key-words: Pain, Chronic Pain, Behavior, Learning, Mechanisms of Action.

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Chapter 1: Introduction of Thesis

Throughout the last century, a dramatic change in the major health conditions afflicting developing and developed societies was observed. Since the beginning of the Global Burden of Disease study in 1990 by the Institute for Health Metrics and Evaluation (i.e. the most comprehensive global study analyzing 286 causes of death, 369 diseases and injuries and 87 risk factors in 204 countries and territories), a new picture of global health has been depicted: the rise of non-communicable diseases as the leading causes of health burden in modern societies ([1](#), [2](#)).

Among all health indicators associated with non-communicable diseases assessed by the Global Burden of Disease studies, the years lived with disability is one of the most relevant, since it is a proxy measure for human suffering and quality of life, and is strongly associated with the economic burden of a disease in a country or territory ([3](#)). Since 1990, there has been a 69.4% increase in years lived with disability in the world and its leading cause is low back pain as depicted in Figure 1, followed by headache and other chronic musculoskeletal painful conditions ([1](#), [2](#), [4](#)). The paradox here is that although most people will experience episodes of acute musculoskeletal pain during their lifetime, symptoms most often resolve quickly within a few days or weeks ([5](#)). Therefore, despite the relatively small percentage of people that develop chronic musculoskeletal pain from acute episodes of musculoskeletal pain, the former condition is among the most prevalent, disabling and costly sources of human suffering world-wide ([1](#), [2](#), [4](#)).

The Global Burden of Disease studies also suggest a more alarming situation. Despite of the great technological breakthrough and the scientific advances in health sciences over the last two decades, we are definitely losing the battle against chronic musculoskeletal pain ([2](#), [6-10](#)). Its prevalence, incidence and years lived with disability are increasing over the years ([1](#)). Chronic musculoskeletal pain is certainly a complex phenomenon. Therefore, simple explanations for the global burden of chronic musculoskeletal pain are at great risk of reproducing H.L. Mencken's quote: "For every complex problem there is an answer that is clear, simple, and probably wrong".

Nevertheless, the scientific literature offers some plausible and evidence based explanations for this situation.

Figure 1. Low back pain was the leading cause of years lived with disability in the world in 2017 according to the Global Burden of Disease study. Figure reproduced from James, Abate and Abate et al. (2018) with permission of the authors and the journal.

One possible explanation for this situation relies on the economic incentives embedded in the healthcare systems of most countries. Most countries use a fee-for-service model of remuneration for healthcare services (i.e. paying for action). However, although extremely lucrative, paying for action is not the same as paying for results. While the global healthcare industry market value in 2018 reached \$8.452 billion, representing from 10% to 15% of the gross domestic product in North America, Western Europe and Latin America ([11](#)), the management of chronic musculoskeletal pain was associated with substantial healthcare costs ([3](#), [12](#)) with a propensity for delivery of low-value care in many health systems (eg, for back pain ([13](#), [14](#)) and other persistent pain conditions ([15-17](#))). Peculiarly, while we are currently living a pandemic of overdiagnosis and overtreatment among those who can access the health system, one that does not seem to improve the population overall quality of live ([6](#), [10](#), [17](#)), significant disparities exist in awareness, priorities and access to pain care around the world, specially in low/middle-income countries ([17](#)).

Other possible explanation for the uncontrolled burden of chronic musculoskeletal pain lies on the evolutionary mismatch driven by lifestyle changes that

occurred over the past decades ([18](#), [19](#)). Lifestyle factors such as the increase of sedentary behaviors, sleep disturbance and low quality diets seems to be associated with chronic musculoskeletal pain and may be causally related with its development and maintenance ([20-22](#)).

Another possible and equally relevant explanation is associated with the lack of understanding, by researchers, clinicians and the general population, of what is pain, what are the factors that influence a person's pain experience, and how to address them, especially in cases of chronic musculoskeletal pain ([7](#), [23](#)). This gap of knowledge may be associated with unhelpful coping skills and health-related behaviors among subjects with chronic pain ([24-26](#)), and it may lead to the increase of overdiagnosis, misleading advices and the prescription of unnecessary treatments from clinicians ([10](#), [27](#)). Thus, understanding the mechanisms that drive pain and disability is paramount to better manage it.

The main focus of this thesis will be to discuss in depth the possible underlying mechanisms associated with musculoskeletal pain persistence and recovery in an effort to contribute to the bridging of this gap of knowledge. This thesis will specially focus on how musculoskeletal pain may be associated with movements through the lens of current knowledge of pain science and learning theories.

Pain Models and Current Theories

The early pain models and theories to understand pain reflected the philosophical ideas of time about life, existence and perception of the world based on empirical reflections. Up to Descartes dualistic philosophical proposal about body and mind in the XVII century, most pain models were based on religious beliefs or on current medical theories of health and disease, such as the Humoral Theory from Hippocrates and Galen ([28](#)). From Descartes to the XIX century, pain has slowly been characterized by the co-existence of four concepts:

(1) Pain is an emotion – this idea persisted from Plato's and Aristotle's writings of pain as an emotion. It was inferred that pain was also a characteristic of the mind and not a percept of the body ([29](#));

(2) Pain is a sensation, with specific sense organs and own transmissions - this is the

fundamental tenet of the Specificity Theory ([30](#)), which postulates that there is a dedicated fiber that leads to a dedicated pain pathway to the sensory modality's region of the brain ([31](#));

(3) Pain may be the product of the transmission of nerve impulse patterns coded at the periphery by nonspecific receptors - The Pattern Theory ([32](#)) stated that any somaesthetic sensation occurred by a specific and particular pattern of neural firing and that the spatial and temporal profile of firing of the peripheral nerves encoded the stimulus type and intensity ([31](#));

(4) Pain may occur in any sensory system when sufficient intensity was reached rather than being a stimulus modality in its own right - This is the fundamental tenet of the Intensity Theory, proposed by Erasmus Darwin and Wilhelm Erb ([33](#)). Arthur Goldscheider further advanced the initial Intensity Theory proposal by suggesting that there must be some form of summation that occurs for the subthreshold stimuli to become unbearably painful ([33](#)). Goldscheider suggested a neurophysiological model to describe this summation effect: repeated subthreshold stimulation or suprathreshold hyperintensive stimulation could cause pain ([33](#));

The Theories of Intensity and Specificity competed as the most accepted pain theories by the scientific community at that time. However, the Intensity Theory lost support with Charles Sherrington's evolutionary framework for the Specificity Theory in the XX century, which postulated the existence of sensory receptors that are specialized to respond to noxious stimuli, for which he coined the term "nociceptor" ([34-36](#)).

The essence of the Specificity Theory lies in the fact that each somatosensorial modality is dedicated to a specific way of transmission, with specific receptors that are sensitive to a particular stimulus connected to a primary sensory fiber. Thus, pain equals sensory activity in specific pain-related receptors and pathways.

The discovery of specific cutaneous touch receptors, such as Pacinian corpuscles [Pacini 1835], Meissner's corpuscles [Meissner 1853], Merkel's discs [Merkel 1875] and Ruffini's end-organs [Ruffini 1893], in the latter one-half of the 19th century, provided further evidence that specific sensory qualia were encoded by dedicated nerve fibers. With the later discovery of nociceptors and nociceptive

neurons in the XX century, Specificity Theory began to be recognized as the main explanatory model for pain ([28](#), [37](#)). However, such theory did not account for the influence of other sensory informations and top-down processes on pain processing and modulation. Besides that, Specificity Theory was, by itself, insufficient to account for the phenomena of clinical pain. In an attempt to bridge this gap, Melzack and Wall proposed the Gate Control Theory of pain in 1965 ([38](#)).

The clarity of the Gate Control Theory and its description gave this article immediate visibility, with numerous attempts made to test its various predictions and assumptions. It incorporated recently discovered mechanisms of presynaptic control of synaptic transmission from large and small sensory afferents, which was suggested to “gate” incoming information depending on the balance between these inputs. It also incorporated the possible role of central nervous system on pain modulation by influencing the “gate”. Although subsequent experiments and clinical findings have made clear that the model is not correct in detail, the general ideas put forth in the main article and the experiments they prompted in both animals and people with pain have transformed our understanding of pain mechanisms ([39](#)).

The advances in neuroscience about brain function and structure in the decade of the brain (from 1990 to 1999) sowed the ground for the Neuromatrix Theory of pain ([28](#), [40](#), [41](#)). The Neuromatrix Theory proposes that a genetically built-in matrix of neurons across the brain would be ontogenetically sculpted to process perceptions and other outputs, including pain. The cyclical processing and synthesis of nerve impulses in the neuromatrix imposes a characteristic output pattern or “neurosignature”, that would ultimately lead to an output (e.g. an emotion, thought or behavior). Therefore, the Neuromatrix Theory was the first conceptual model to propose that pain would be an output of the nervous system, and not the product of a specific pain-related sensory information as proposed by the Specificity Theory.

Recently, further evidence about the human connectome (i.e. the mapping of all neural connections within an organism nervous system ([42](#))), together with recent advances in understanding systems-level dynamic processes that suggest the existence of a “dynamic pain connectome” as a spatiotemporal physiological signature of pain at the brain gave rise to the Connectome Theory of Pain ([43](#), [44](#)).

All theories mentioned above contributed to our current understanding of pain since, in an attempt to refute or to strengthen the assumptions of these theories, scientists conducted experiments and advanced the available knowledge. In the pursuit of corroborating the tenets of Specificity Theory, for example, scientists discovered the nociceptive system. Nevertheless, until the Neuromatrix Theory of pain, none of the previous pain theories succeeded in explaining the complexity and multidimensionality associated with pain perception. In this aspect, the basic assumptions of the Neuromatrix and Connectome Theories have been confirmed by the scientific literature so far and these are currently the most accepted pain theories by the scientific community ([41](#), [45](#)).

Although pain models and theories have dramatically changed over time due to new evidence, mainly over the last decades, most of the conceptual models used by clinical researchers and clinicians to understand pain, propose new interventions and evaluate its mechanisms of action for people with chronic pain, especially chronic musculoskeletal pain, did not follow this paradigm shift driven by pain science. Although some interventions were developed based on this new understanding (e.g. pain neuroscience education ([46](#), [47](#))), the traditional view of Specificity Theory remained as the main framework for the clinical understanding and management of pain.

Pain Models commonly used in Clinical Research and Practice

One of the most common and disseminated pain models in clinical research and practice is the biomedical model ([45](#)). The basic assumption of this model is that pain equals damage (i.e. Specificity Theory). Therefore, pain is commonly viewed as an accurate representation of tissue damage. Whereby, higher pain intensities are viewed as evidence of more severe damage, or that more structures might be damaged ([48-53](#)).

A conceptual model is good as far as it can be tested. Every model is a temporary consensus, raised by the scientific community, that offers one or several explanations for a phenomenon with assumptions that can be verified through the scientific process. Before assuming that a model is correct and use it as a base to

propose interventions, explain its mechanisms of action or to explain what might be happening with a specific population, the predictions and assumptions of such model should be tested and verified. Otherwise, we would be at great risk of spending valuable research resources and exposing patients to unnecessary treatments.

Good conceptual models raise more promising clinical hypothesis to be investigated, which increase the pre-test probability of finding relevant results in clinical trials ([54](#)). Although the cost-benefit of raising good conceptual models to aid clinical research is crystal clear, this was not what have happened so far in studies with subjects with musculoskeletal pain. The biomedical model and its assumptions to explain pain have been systematically tested over the past decades and have not been supported by evidence. Nevertheless, a great number of treatment proposals for subjects with acute and chronic musculoskeletal pain were developed and justified based on the biomedical model proposal.

Over time, several case-control and cross-sectional studies have identified that the prevalence of imaging findings in subjects with painful conditions (that were always viewed as a precise sign of tissue damage in subjects with musculoskeletal pain) is similar to asymptomatic subjects in several body regions and increase with age, like any other physiological ageing process ([55-59](#)). The same studies suggest that general measures of pain intensity are not associated with the severity of imaging findings ([55-58](#)). Further longitudinal prospective studies have demonstrated that there is no association between imaging findings and the development of chronic musculoskeletal pain ([60-62](#)). Although there is evidence showing that the prevalence of some imaging findings is higher in symptomatic populations ([63](#)), this does not imply causation. Furthermore, an increased presence of nociception in the system is not necessarily related to pain occurrence ([37](#), [45](#)).

In addition, clinical studies investigating the effect of surgeries targeting to repair or fix “damaged” structures in subjects with chronic musculoskeletal pain in comparison to sham surgeries did not identify significant differences for pain and disability ([64-66](#)). Despite the limited utility and the increase of evidence and guidelines advocating against the use of imaging exams for most cases of chronic musculoskeletal pain ([67](#)) and the absence of recommendation for most surgeries ([66](#), [68](#)), it is still common practice to use these procedures in chronic musculoskeletal pain

populations ([66](#), [68](#), [69](#)). Nevertheless, the biomedical model is still widely accepted in society and amongst researchers and clinicians ([48](#), [49](#), [52](#), [53](#)).

Within physiotherapy and movement sciences, kinesio pathological frameworks based on the biomedical model have also been developed over time in an attempt to explain how specific patterns of movement could be associated with tissue overload, injury, pain onset and persistence in people with musculoskeletal pain ([70-72](#)). Again, a focus on the structure as the sole source of pain. Some of the assumptions of these kinesio pathological frameworks were initially raised through cadaveric ([73](#), [74](#)) and mathematical modeling studies ([75](#), [76](#)). This initial researches were followed by several case-control and cross-sectional studies which, for the most part, have identified differences between how people with and without musculoskeletal pain move ([70](#), [77-83](#)). These findings were commonly interpreted through the lens of the biomedical model, instead of being interpreted as evidence that pain and movement may be correlated by unmeasured common causes, as evidence of a causal relationship between changes in movement behavior, mechanical overload and pain, which led to the development of several evaluation frameworks and treatment proposals whose main objective was to restore ideal patterns of movement for reducing tissue overload and, ultimately, pain ([84-87](#)). However, with the quality of evidence level improvement over time, most of the assumptions of kinesio pathological proposals were also falsified by the scientific literature ([88](#), [89](#)).

Several kinesio pathological frameworks claimed that body posture could be associated with pain ([90-94](#)). However, current evidence does not support an association between postural alignment and pain in subjects with acute and chronic musculoskeletal complaints ([95-99](#)). Another core assumption of kinesio pathological frameworks is that abnormal patterns of movement may be associated with pain onset and persistence ([70-72](#), [79](#), [82](#)). Similarly, several longitudinal cohort prospective studies have demonstrated that such “abnormal” patterns of movement are not associated with pain onset ([100-102](#)) and offers very little or none explanatory support for pain persistence in subjects with musculoskeletal pain ([103](#), [104](#)). Indeed, there is a growing body of researchers starting to consider that what was usually labeled as abnormal movement patterns (e.g. dynamic knee valgus or scapular dyskinesis) may be normal human motor variability ([101](#), [102](#), [105](#)).

Finally, kinesio pathological frameworks usually claim that, in order to be effective, interventions for people with chronic musculoskeletal pain should specifically aim at correcting abnormal movement patterns and body posture ([72](#)). However, this assumption is not supported by current scientific literature. Several randomized clinical trials demonstrated that interventions developed to modify abnormal movement

patterns and/or body posture are not superior to general exercises for several musculoskeletal pain conditions ([106-109](#)). In fact, modifying movement patterns or body posture does not seem to mediate the effect of movement-based interventions on pain and disability in subjects with chronic musculoskeletal pain ([100](#), [110-114](#)).

In summary, the body of evidence presented above questions the main assumptions of the biomedical model to explain non-traumatic pain onsets, pain persistence and the mechanisms associated with pain improvement with treatments in people with chronic musculoskeletal pain. Further, growing evidence supports that broader biopsychosocial factors (e.g. fear of movement-related pain, pain catastrophizing, altered endogenous analgesia and peripheral or central sensitization), and not mechanical and structural variables (e.g. MRI findings, movement pattern, body posture), are predictors of pain chronicity ([26](#), [115-123](#)), delayed return to work ([124](#), [125](#)) and postoperative chronic pain ([126-131](#)). In addition, biopsychosocial factors such as fear of movement related pain, expectations and pain beliefs have been identified as treatment moderators ([120](#), [121](#), [132](#)).

This growing body of evidence requires a reconceptualization about what is pain and what factors influence a person's pain experience among researchers, clinicians and the general population as a complex multidimensional experience rather than a precise sign of tissue damage ([133](#)).

What is Pain According to Current Evidence?

In 2020, the International Association for the Study of Pain (IASP) published the result of a two-years process multi-national, multidisciplinary Task Force whose main goal was to update the definition of pain ([134](#)). The first IASP pain definition was proposed in 1979 and did not received any major revision since. According to the current definition, pain is:

“An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”

The current definition was also expanded upon the addition of six key notes for

further valuable context:

- Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors;
- Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons;
- Through their life experiences, individuals learn the concept of pain;
- A person's report of an experience as pain should be respected;
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being;
- Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain;

The updated definition of pain is a cornerstone. It represents the advances in several fields of research that led to our current scientific understanding of what is pain and what seems to be the mechanisms associated with how it may persist in some people.

Modern pain science considers pain perception as a complex hardwired motivational system that minimizes body harm ([25](#), [135](#), [136](#)) by triggering physiological and behavioral defensive responses, according to an implicit evaluation that the body may be in danger ([23](#), [136](#), [137](#)). This defensive responses triggered by pain are usually adaptive, since they most often protect the integrity of the body. However, pain is not equal to nociception and neither nociception is equal to tissue damage ([136](#)). Pain is an output of the brain that is not solely formed by nociceptive inputs, but by several multidimensional factors such as the motivational state, attention, emotions, expectancy, memory and beliefs ([138-140](#)). The ultimate goal of this perceptual mechanism is to act as part of a response system that alerts and prepares the organism to face threatening situations ([23](#), [136](#), [141](#)). In this perspective, pain can be viewed as a strong driver of learning ([25](#)).

People in pain learn to identify cues (in the environment or in the body) that are interpreted as harmful and, consequently, they learn to take protective actions (consciously or non-consciously) to minimize and or avoid the negative impact of pain. Another way that people with pain may learn to adapt their behavior is by the consequences of the later, such as experiencing pain reduction after motor adaptations or avoiding some activities ([25](#), [142](#)). Although the process described above is certainly adaptive, the persistence of pain may become maladaptive and promote disability and suffering ([26](#)). In other words, chronic pain may lose its ability to appropriately identify and signal situations that are actually threatening to the organism, making the system become protective when it is not needed ([25](#), [143-145](#)).

Despite the global burden of chronic pain, until 2020 chronic pain diagnoses were not represented systematically in the International Classification of Diseases ([146](#), [147](#)). Chronic pain was only defined as pain that persists or recurs for more than 3 months. In cooperation with the World Health Organization, an IASP Working Group has developed a classification system that is a wide range of contexts, including pain medicine, primary care and low-resources environment ([147](#)). In conditions such as fibromyalgia or nonspecific low-back pain, chronic pain may be conceived as a disease in its own right (i.e. “chronic primary pain”). In 6 other subgroups, chronic pain is secondary to an underlying disease, such as chronic cancer-related pain, chronic neuropathic pain, chronic secondary visceral pain, chronic posttraumatic and postsurgical pain, chronic secondary headache and orofacial pain and chronic secondary musculoskeletal pain. These conditions are summarized as “chronic secondary pain” where pain may at least initially be conceived as a symptom.

There are many known risk factors for chronic pain conditions. Available evidence suggests that biopsychosocial and lifestyle factors increase the odds of an acute episode of pain ([148-150](#)) and are predictors and mediators of the development of chronic disabling pain ([115](#), [117-120](#), [126](#), [151](#), [152](#)). However, the biological underpinnings that link these factors to abnormal processing of painful signals are only beginning to be explored ([153](#)). Despite evidences suggesting that some innate (e.g. sex), acquired (e.g. stressful life events during childhood) and epigenetic mechanisms (e.g. personality) may increase the odds of developing chronic pain ([123](#), [133](#), [153](#), [154](#)), there is one thing that seems to be common to both chronic primary and

secondary pain conditions: the changes in nervous system structure and function ([141](#), [155-158](#)).

Whether measurable alterations in brain and nervous system function and structure are associated with pain chronicity, as a vulnerability marker, or are a consequence of pain it is not known yet. Since these changes are rarely studied in longitudinal studies, it is not possible to establish causality. Nevertheless, they might lead to a vicious cycle in which vulnerability leads to non-resilience to additional factors arising from the chronic pain state ([153](#)). Thus, in order to better understand the possible underlying mechanisms associated with pain persistence, it is necessary to comprehend what happens to the brain and nervous system of subjects with pain throughout the process of pain chronification.

Brain and Nervous System Modifications in Subjects with Chronic Pain

Chronic musculoskeletal pain does not seem to be a simple temporal continuity of acute episodes of pain. Several studies of brain imaging and electrophysiology have shown that the process of pain persistence is associated with a structural, functional, metabolic and chemical reorganization of the brain and nervous system in several painful conditions ([41](#), [136](#), [141](#), [158-171](#)).

The seminal study of Hashmi et al. (2013) identified that the default mode network brain activity of individuals who evolved to persistent low back pain after 1 year gradually migrated from areas associated to the sensory-discriminative components of pain to affective-emotional circuits ([65](#)). Similar findings were found in subjects with chronic migraine ([172](#), [173](#)), neck and shoulder pain ([174](#), [175](#)) and other painful conditions ([176](#)).

The function of several brain areas also seem to be affected due to cortical reorganization. In subjects with low back pain, pain chronification is associated with a shift of brain representation from nociceptive to emotional circuits during painful episodes ([177](#)). Sensory and motor brain representation are also affected in subjects with chronic low back pain ([178](#), [179](#)), persistent patellofemoral pain ([180](#)), phantom limb pain ([181](#)) and chronic pain in general ([182-184](#)). Other studies using functional magnetic resonance imaging with specific techniques to analyze structural changes in the brain, have identified gray and white matter density modifications in several areas,

mainly affecting the dorsolateral prefrontal cortex ([164](#), [165](#), [169](#), [185](#)) and several other relevant brain hubs, such as the anterior cingulate cortex and insular cortex ([186](#)). These structural changes may affect the brain's capacity of contextualizing pain experience due to reduced cortical inhibition ([139](#), [155](#), [164](#), [169](#), [185](#), [187](#), [188](#)), which may open new pathways for triggering pain perception in some populations of individuals with chronic pain (e.g. thinking about or seeing pictures of painful movements may cause pain and fear ([144](#), [189-191](#))).

While several brain areas exhibit a decrease of grey mass density and connectivity, some emotional and mesolimbic areas such as the medial prefrontal cortex and nucleus accumbens seems to increase its grey mass density ([152](#), [156](#), [157](#)) and connectivity ([163](#)). Indeed, the connectivity increase between these areas predict transition to chronic pain ([157](#), [163](#)). The increased activity of the corticolimbic and mesolimbic systems in subjects with chronic pain are also related to maladaptive emotional learning, leading to the widespread of defensive responses and pain amplification due to expectancy and anticipation ([136](#), [155-157](#), [192-194](#)). Finally, brain modifications are not limited to neurons. Glial cells activation were identified in several brain areas during pain persistence ([168](#), [195](#)) and where also identified in the spinal cord in animal studies ([196](#)). While the role of glial cells activation in pain chronification is not totally clear yet, it seems to be associated with neuroinflammation and modifications in synaptic excitability in the brain ([159](#)) and with tactile allodynia in the periphery ([196](#)).

Functional and structural modifications of the nervous system in the periphery, spinal cord and trigeminal system have also been identified in several painful conditions, such as osteoarthritis, temporomandibular disorders, low back pain, patellofemoral pain, shoulder pain and several tendinopathies ([136](#), [197-207](#)). These modifications are commonly associated with processes of peripheral and central sensitization of the nociceptive pathway which, in turn, seem to be associated with clinical manifestations of allodynia and hyperalgesia in varying degrees ([200](#), [201](#)).

In summary, several functional and structural modifications of the brain and nervous system may happen during the process of pain chronification. As previously mentioned, whether these changes are causally associated with pain persistence or are a consequence of pain it is not known yet ([153](#)). Nevertheless, they might contribute

to the maintenance of the chronic pain state once acquired through gain modifications of the nociceptive system, malfunction of the endogenous analgesic system ([208](#), [209](#)) and through changes in cognitive, behavioral and emotional factors associated with pain control and modulation ([26](#), [142](#), [156](#), [210](#)).

What may be the drivers of these nervous system modifications? Despite there are some biological vulnerability markers that may be associated with its occurrence ([153](#)), more or less permanent changes in nervous system function and structure as a result of experiences are usually understood as a by-product of learning processes in neuroscience ([211](#)). Several conceptual models providing frameworks that attempted to explain how gain modifications of the nociceptive system, pain-related behaviors and beliefs may be acquired and contribute to pain persistence and the development of pain-related disability were proposed over the last decades. These models are usually based on the assumption that pain is a salient experience that triggers physiological and behavioral defensive responses and, therefore, pain is a strong driver of learning ([25](#), [142](#)).

Pain and Learning

During episodes of pain, individuals may learn (consciously or non-consciously) to predict and control potentially harmful situations ([25](#)). This process is extremely adaptive, since it may help individuals to initially protect the body region in pain and foster healing in cases when there is an associated injury. Therefore, individuals with pain may learn to increase pain sensitivity, predict, avoid and/or control symptoms through the combination of explicit and implicit processes of learning during episodes of pain ([142](#), [209](#)).

Non-associative learning is an implicit form of learning, observed in most sensory modalities, that systematically attenuates or augments a sensory percept or behavioral response to a sensory stimulus upon repeated or continual presentation of the stimuli ([212](#)). Through non-associative learning, individuals may modify the gain of their nociceptive system, presenting processes of allodynia and hyperalgesia in varying degrees ([142](#), [199-202](#), [209](#), [213-215](#)). While some painful conditions (e.g. acute nociceptive pain, secondary chronic musculoskeletal pain associated with osteoarthritis or secondary chronic peripheral neuropathic pain) may be mainly

associated with processes of peripheral sensitization ([197](#), [216](#), [217](#)), leading to the local or neuroanatomical spreading of allodynia and hyperalgesia, several painful conditions may be associated with processes of central sensitization ([198-203](#), [205](#), [206](#), [209](#), [214](#), [218](#)), leading to a more or less precise widespread of allodynia and hyperalgesia through the body.

These findings led to the popularization of the concept of central sensitization as an causal explanation for chronic pain, which stimulated the development of screening instruments ([219](#), [220](#)) and diagnostic criteria for the clinical classification of central sensitization which, due to questionable criteria and the lack of a gold standard reference, should be used with caution ([221](#), [222](#)). However, one important fact about sensitization processes is that they might be present in both acute and chronic pain conditions. Moreover, while peripheral sensitization is usually associated with conditions of nociceptive pain (i.e. ankle sprain) or peripheral neuropathy (i.e. diabetic polyneuropathy), central sensitization is a neurophysiological phenomenon that may accompany any mechanism of pain ([209](#)).

In accordance with current evidence that central sensitization is not a universal causal explanation for chronic pain ([223](#), [224](#)) and that sensitization processes are common to both acute and chronic conditions, a third mechanism of pain was described in 2016 by an IASP Task Force to contain the growing use of central sensitization as a third mechanism of pain to explain conditions that did not fit well with nociceptive and neuropathic mechanisms ([225](#)). The nociplastic mechanism of pain is defined as:

“Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain ([225](#))”

Although this term clearly gives us more resources to explain several clinical manifestations of pain that were not well explained by the other mechanisms of pain (i.e. nociceptive and neuropathic), it lacks precision ([226](#), [227](#)). It does not explain well clinical manifestations of pain driven by central mechanisms (e.g. expectancy) that are clearly present in several populations of chronic pain.

In addition to pro-nociception (i.e. sensitization), individuals with chronic pain may also present a dysfunction of endogenous pain modulatory mechanisms ([169](#), [208](#), [209](#)). This may be related with disrupted pain habituation during the execution of repetitive movements ([142](#), [228-232](#)) which, in turn, may be associated with movement-related pain episodes. Despite the increasing interest in studying the association between non-associative learning and the development of chronic pain by the scientific literature, this process of learning is not able to explain how individuals in pain learn to predict harmful situations and modify their behavior to avoid and/or control symptoms ([144](#), [233-238](#)), which seems to be important aspects for pain persistence ([24](#)).

Fear and Avoidance Behaviors

The identification of cues that predict harmful or threatening situations can be a driver for the development of pain-related defensive behaviors ([239](#)), such as avoidance behaviors, pain-related fear and fear of movement-related pain. Although fear is commonly used to name the whole package of physiological responses and behaviors that occurs in the face of a threat, it can be considered the conscious interpretation of a threat ([240](#), [241](#)).

Nonconscious responses and behaviors in the anticipation or in the face of a threat are not synonymous of the conscious feeling of fear or anxiety. These responses may represent different facets of how an individual may respond to a threat that are influenced by different phenomena and share different, but overlapping, neural networks ([240](#)). While fear is an evolutionarily conserved survival response triggered by imminent threats that evokes rapid defensive responses, anxiety is a long-lasting response that is triggered in anticipation of imagined or unpredictable threats ([242](#)).

Putting it simply, fear seems to be what happens when the sentient brain is aware that its personal well-being (physical, mental, social, cultural, existential) is challenged, while anxiety seems to be what happens when it may be challenged at some point ([241](#)). Similarly to pain and nociception, these nonconscious mechanisms initiate responses in the brain and body that indirectly contribute to conscious fear and anxiety ([240](#)). However, once subjectively experienced, fear and anxiety serves as a basis for deliberative explicit decision-making and behavioral control so as to guide

avoidance of or escape from an existing or anticipated threatening situation ([240](#)).

One way that individuals may learn to predict harmful and threatening situations is by associative learning, or pavlovian conditioning ([243](#)). Individuals can rapidly learn to predict painful situations by the detection of cues that precede or coincide with the occurrence of pain (e.g. the visual stimuli of a box before bending to lift it during low back pain episodes). In such cases, environmental or contextual cues and sensory stimuli (known as a conditioned stimuli – CS) that co-occur or preempt the occurrence of pain (i.e. the unconditioned stimuli - US) may start to elicit the responses that previously only occurred in the presence of the US (known as a conditioned response – CR). Through associative learning, individuals with pain may learn to fear and present other neurophysiological defensive responses (e.g. increased arousal, vocalizations, flight or freezing, muscle startles) to contexts and sensory cues that preempt painful situations ([25](#), [142](#), [240](#), [241](#), [244](#), [245](#)). However, as musculoskeletal pain is usually perceived during the execution of voluntary movements, individual with musculoskeletal pain may learn to fear and avoid movements perceived as harmful ([144](#), [239](#), [246-254](#)).

In addition, associative learning mechanisms may be involved in fear and other defensive responses distribution through contexts and movements by *stimulus generalization* ([255](#), [256](#)). Stimulus generalization ([239](#), [255](#), [257](#)) is an adaptive learning process because it enables individuals to extrapolate the predictive value of one stimulus (e.g. pain during lifting) to novel stimuli based on perceptual resemblances without the necessity to learn a new (e.g. carry weights). These findings endorse the idea that pain-related fear can be acquired without direct experience and may help explain why patients are fearful of novel movements that were never experienced as painful ([239](#), [247](#)).

Another mechanism of learning is the operant conditioning, that has been deeply studied by Skinner ([258](#), [259](#)) and initially adapted to explain pain behaviors by Fordyce ([260](#)). Fordyce ([260](#)) considered the effects of behavior as causes of future action and identified at least three pathways through which operant conditioning could maintain disabling pain behaviors: direct positive reinforcement (e.g. social attention), negative reinforcement (e.g. escape/avoidance from pain), and insufficient positive reinforcement for “well behavior” (e.g. lack of praise for leisure activity, working) ([142](#)). Therefore, although avoidance behaviors can sometimes be driven by fear, a powerful

pathway of learning to avoid occurs through the consequences of behaviors, such as the reduction of pain that may follow avoiding a class of movements (e.g. lifting) or motor adaptations (e.g. lifting without bending the spine).

The operant conditioning paradigm was also used as background by one of the most studied frameworks in the pain field, that has been proposed to explain the role of cognitive and behavioral factors in the development of chronic disability associated with pain: the Fear and Avoidance Model of Chronic Pain (FAM). The FAM was originally formulated in the context of chronic back pain patients ([261](#)), depicted in Figure 2, and has been adapted and updated since ([24](#), [25](#), [103](#), [262](#), [263](#)). The model takes as its starting point the experience of a pain episode and describes a set of cognitive, emotional and behavioral responses that may or may not exacerbate disability ([263](#)).

According to Crombez et al. (2012), the core of the FAM is how subjects interpret pain. If pain is perceived as non-threatening, they will test and correct pain expectations as symptoms gradually improve. On the other hand, if pain is misinterpreted as a sign of serious injury or tissue pathology one has little or no control, excessive fear of physical movements and the increase of avoidance behaviors may occur. Because avoidance limits one's opportunity to update expectations to actual experiences, subjects will tend to overestimate their future pain and its possible negative consequences, creating a vicious cycle of avoidance and disability. Therefore, although avoidance may lead the individual to protect the body from further injury and promote healing in the short term, it can become maladaptive in long term by fostering disability.

There is now ample evidence to support the validity of the FAM in chronic pain populations, and several reviews have summarized the current state of evidence ([104](#), [264](#), [265](#)). There are also longitudinal prospective studies suggesting that fear-avoidance beliefs may influence the transition from acute to chronic pain and associated outcomes, such as disability ([119](#)) and sick leave ([124](#)). However, the initial FAM assumptions to explain the mechanisms by which pain would persist were not supported by the literature.

Figure 2. The Fear and Avoidance Model of Chronic Pain according to the paper of Vlaeyen and Linton (2016). Figure reproduced with permission of the authors and the journal.

The first iteration of the FAM hypothesized that the pain persistence was related to tissue disuse by avoidance, that would lower the pain threshold at which pain is experienced (266). Nevertheless, there was no direct support for this assumption. Although not described in the original model, the automatic selection of pain or pain-related information at the expense of other information in the environment may also occur (267). It was later introduced in the model as “hypervigilance” and it has been proposed that it could foster pain due to expectancy and threat anticipation

mechanisms. Indeed, attention to pain or pain-related information may be associated with increased sensitivity and hyperalgesia due to expectancy and threat anticipation ([235](#), [236](#), [267-272](#)).

Despite pain expectancy and attentional focus to pain-related information can be driven through cognition ([273](#), [274](#)), it can also be learned by association without the need of conscious awareness ([267](#), [275](#)). The role of associative processes in operant-associative interactions was late recognized in the FAM as a possible mechanisms to explain pain persistence both in avoiders and goal-seeking subjects ([25](#), [276](#)). But how exactly associative processes may explain pain persistence?

Pain by Association: a learn-based mechanism that could explain pain persistence?

Much of the literature of aversive associative learning on pain consider it analogous to nociception, using pain as an US to study conditioned responses such as fear ([254](#)). However, a very large body of evidence suggests that nociception is not sufficient for pain ([37](#), [187](#)). The Imprecision Hypothesis of Chronic Pain (IH), a framework that was recently proposed in the literature ([137](#)), uses an extension of the associative learning framework of pain-related fear to an approach that has pain itself as the response, as depicted in Figure 3.

The first assumption of the IH is that pain can be conditioned through associative learning. It considers the nociceptive input as the US, for which there is no need of previous learning to evoke pain, the UR. Therefore, the multisensory events that are directly paired with the US or that preempt it can acquire a CS function and come to elicit pain, that would be the CR. This mechanism would be associated with the persistence of pain during movements.

Another main assumption of the IH is that the extent of pain generalization through movements, postures and contexts would be negatively related to the precision with which the original painful event was encoded by the brain ([277](#)). The precision of this encoding may be influenced by the predictability of the learning context (e.g. low back pain just during lifting vs low back pain for every movement with the back) and by the somatotopic precision of the body region in pain (e.g. the somatotopic representation

of the hand is much more precise than the representation of the lower back). As proposed by Moseley & Vlaeyen (2015), “Once the nociceptive and non-nociceptive inputs are associated, a process termed acquisition, not just the initial multisensory event will elicit the painful response but also events that share some features with that multisensory event. This process is called stimulus generalization”. This concept is depicted in Figure 4.

Figure 3. Associative learning of pain. (A) The nociceptive input is the US that will usually elicit pain, which is the UR. (B) The multisensory and meaningful events that routinely coincide with, or preempt, the nociceptive input can be considered the CS. (C) Through established processes of associative learning, the CS comes to elicit pain, which is therein considered the CR. US, unconditioned stimulus; UR, unconditioned response; CS, conditioned stimulus; CR, conditioned response (Figure and caption reproduced from Moseley and Vlaeyen 2015 with permission of the authors and the journal).

Thus, according to the IH, the learning produced by these pairings during acute episodes of musculoskeletal pain could be the behavioral base by which other cognitive, behavioural and neural modifications associated with pain persistence take

place, and the precision of the encoding of these pairings could explain the highly variable *spectrum* of clinical manifestations of pain during movements commonly observed in people chronic pain ([133](#), [224](#)).

Although the effects are moderate to small ([278](#)), associative learning can influence an individual's pain perception, producing effects such as pain threshold modulations ([279-281](#)), conditioned hyperalgesia ([250](#), [282](#), [283](#)) and pain generalization ([284](#)). These evidences strengthen the first assumption of the IH. However, one study demonstrated that classical conditioning failed to elicit allodynia ([285](#)), which appears to be mainly the result of non-associative learning.

Figure 4. Left panel: Precise encoding by the brain of the multisensory and meaningful event leads to no generalization such that the organism is protected only from the multisensory event that has been associated with nociceptive input. Right panel: Imprecise encoding of the multisensory event leads to generalization such that the CR, pain, is also triggered by events that share some features with the conditioning

multisensory event. Note that some degree of generalization is biologically advantageous, but overgeneralization will manifest in a wide array of triggering events, allodynia and hyperalgesia, such as is observed in the vast majority of chronic pain states. That is, overgeneralization leads to pain being evoked by events that are not in fact dangerous, and the organism becomes “overprotected.” CR, conditioned response (Figure and caption reproduced from Moseley and Vlaeyen 2015 with permission of the authors and the journal).

Recently, one study demonstrated that conditioned pain expectancy was greater when sensory information about location of the body part in pain was less precise ([286](#)). There is also experimental data demonstrating that the specificity of fear responses appears to be affected by the somatotopic precision of the body part ([287](#)) and that people with chronic pain may present a less precise US-expectancy and fear learning than control subjects ([239](#), [288](#), [289](#)), which partially strengthens the second assumption of the IH.

Other responses can also be conditioned through associative learning, such as movement-related fear ([144](#), [239](#), [251](#), [254](#)), attentional bias to the region of pain ([272](#), [275](#)), protective behavioral responses (e.g. bracing of shoulder and neck muscles ([290](#))) and sympathetic arousal ([291](#)). One study of Forkmann et al (2015) used functional magnetic resonance imaging to investigate the neural reinstatement of pain-related and tone-related activations during the recognition of neutral images that have been associated to painful stimulation, auditory stimulation of comparable unpleasantness, or no additional stimulation. The data of this study demonstrated a partial reinstatement of brain regions frequently associated with pain perception during the presentation of images previously paired with painful heat. This neural reinstatement may also be a CR that could leave the individual more primed to feel pain during future exposures to the CS, even with a less intense peripheral stimulation ([237](#)).

Although the assumptions of the IH were strengthened by the data presented above, whether proprioceptive stimuli (during voluntary movements) can become conditioned and influence painful responses is yet to be evaluated. One of the major points of the first assumption of the IH is that pain can be conditioned to movements,

which has not been properly investigated by the scientific literature so far. Because movements are complex behaviors that involve a chain of planning and anticipatory actions ([292-295](#)), it is not possible to fully understand how pain conditioning takes place during movements without observing how an individual change the responses to cues that predict painful movement executions. This research question will be addressed in Chapter 2.

Related research questions: *Can pain be conditioned to movement through associative learning? How does pain conditioning interact with motor behavior?*

If pain can be conditioned to movements (i.e. an increased chance of perceiving pain during movements in the presence of nociception), can it also be influenced by stimulus generalization? Despite there is experimental data supporting the idea of pain modulation generalization after associative learning ([284](#)), as movement-related pain reports are often still viewed as an accurate representation of tissue damage ([48](#), [49](#), [51-53](#), [190](#)), a greater number of painful movements or activities is commonly viewed as evidence that more structures might be damaged (e.g. more rotator cuff tendons are damaged in subjects with shoulder pain) or of more severe structural damage (e.g. labral tears in subjects with hip pain). Therefore, in order to strengthen the assumption that the precision of pain distribution through movements could be a by-product of stimulus generalization after pain conditioning, it is necessary to verify if the precision of pain distribution through movements and activities might be associated with the number or severity of tissue injuries in people with chronic pain. This research question will be addressed in Chapter 3.

Related research question: *The precision of pain distribution through movements and activities is associated with the number or severity of structures reported as damaged in people with chronic pain?*

Current evidence suggesting that pain can be conditioned to visual ([282](#), [283](#)), visceral ([296](#), [297](#)), vibrotactile ([250](#), [280](#), [281](#)) and proprioceptive stimuli ([298](#)) and that expectancy and threat anticipation play an important role in pain modulation by influencing pain threshold and producing hyperalgesia ([156](#), [235-237](#), [268-270](#), [282](#), [283](#),

[299](#), [300](#)) strengthen the idea that the pain threshold is a zone of uncertainty that signals the possibility that body may be under threat ([136](#), [137](#), [301](#)). Further evidences suggesting that learning to predict harmful situations may be an important aspect to understand how individual's may modulate pain and behavior ([25](#), [142](#)) and that pain anticipation through cognitive and associative mechanisms may bias pain perception by facilitating its occurrence ([135](#), [138-140](#), [296](#), [302](#), [303](#)), raises the need to understand perception as an contextual representation of the body and the world. Therefore, to further understand the mechanisms underlying pain persistence, we need to better understand what is perception according to modern neuroscience. The next section will briefly present some evidence about the current frameworks and theories that explain perception.

Perception as a Guide to Behavior

The discussion about the mechanisms of perception is not new, with its firsts insights in the XIX century by Helmholtz ([304](#)). For long, it was a common sense among scientists that perception would be a precise representation of reality based on imprecise, but redundant, information transduced from our peripheral sensory organs.

In the 1990s, perceptual psychologists began constructing detailed Bayesian models of perception ([305](#)). Since then, evidence from researches of vision ([306](#)), hearing ([307](#)), smell ([308](#)), somatosensation ([309](#)) and even pain ([310](#), [311](#)) have formed the foundations of the research field that is now called predictive coding ([312-315](#)). Our current knowledge about perception is that it is a non-conscious inference made by our brains on the basis of our previous experiences, the current sensory information and the predicted outcomes ([312](#)).

Despite the beauty and complexity of this Bayesian process, the construction of our perceptual reality evolved to optimize action, rather than to perfectly represent reality ([316](#), [317](#)). Pain perception itself is being considered a response of the brain tied to the probability that the body may be in danger, and not the perfect representation of a tissue injury ([45](#)). Because of its biological value, a person's pain experience elicits overt and covert behaviors that prioritize the processing of pain-related information in order to optimize its behavioral function in the future, a process

which can also facilitate its occurrence ([135](#), [237](#), [272](#), [310](#), [311](#)). The main goal of this “best guess” about what may be harmful to the body is to increase the predictive power of the brain under situations that are potentially dangerous for the individual, allowing the early selection of protective behaviors ([136](#)). Although this process makes sense during acute episodes of pain, it can become maladaptive during chronic stages and lead to differences in the way people in pain interact with the environment and their own body ([182](#), [318](#), [319](#)).

How this “biased” predictive brain toward danger and the prioritization of pain-related information processing influence other perceptual *continuums* related to painful movements in people with chronic pain? This research question will be addressed in Chapter 4.

Related research question: *How does the previous history of movement-related pain influence the way people with chronic pain perceive other perceptual continuums associated with movements?*

As mentioned before, pain is a strong driver of learning. During episodes of pain, individuals may modify the gain of their nociceptive system through non-associative learning and may learn to predict, avoid and control symptoms through associative learning and operant conditioning ([25](#), [142](#), [320](#)). Furthermore, people in pain may learn to modulate their pain and behavior from others ([116](#), [321](#), [322](#)), from rules ([323](#)) and even generalize predictions and protective behaviors by higher-order forms of reasoning and cognition such as conceptual knowledge, semantic relatedness within verbal networks, and category membership ([53](#), [142](#), [239](#)). These learning processes may be present in varying degrees and interact in different ways between and within individuals. Nevertheless, learning is an adaptive process. Through learning, individuals in pain most often protect their body from potentially harmful situations and learn to behave differently in the future in order to avoid similar events.

During pain persistence, however, pain may become maladaptive since it may lose its ability to signal potentially harmful situations. As described in the **Pain and Learning** section, learning mechanisms seems to be associated with pain chronicity.

Once acquired, they may be associated with or may be potentialized by the brain and nervous system modifications described in **Brain and Nervous System Modifications in Subjects with Chronic Pain** section, and lead to a vicious cycle in which vulnerability leads to non-resilience to additional factors arising from the chronic pain state. The social isolation and lifestyle changes that commonly co-occur with pain chronicity are one example of it. They may be associated with the development of more disability and the maintenance of pain behaviors in subjects with chronic pain by fostering pain sensitivity and associated symptoms, such as chronic fatigue and cognitive deficit ([115](#), [117-120](#), [126](#), [151](#), [152](#), [156](#), [324](#)).

Chronic pain is certainly a complex phenomenon. However, the first steps to understand how to better deal with it are being made. Through a better understanding of what is pain and what are the mechanisms associated with its persistence, we may start identifying more promising clinical hypothesis to be investigated about what may be the best interventions to deal with it, as well as its mechanisms of action. A brief presentation about current evidence-based treatments for people with chronic musculoskeletal pain and its putative mechanisms of action will be further discussed in the next section.

Evidence-based Interventions for Subjects with Chronic Musculoskeletal Pain and its Putative Mechanisms of Action

The first step of evidence-based practice is to choose among the available evidence-based treatments for the targeted health condition ([325](#)). After all, according to the philosophy of science, we should embrace the null hypothesis that a treatment has no effect until we have compelling evidence suggesting the opposite ([326](#), [327](#)). This is the most ethical and correct way of acting in healthcare since, unless the concept of efficacy of an intervention for an outcome in a given population has been proven (with some flexibility due to the concepts of generalizability and extreme plausibility ([328](#), [329](#))), we can not distinguish between the interventions real effect from the effect of contextual factors or confounding ([330](#), [331](#)). Therefore, better treatment approaches for chronic pain come from the investigation of good clinical hypothesis based on current knowledge of pain science. This approach have a higher

pre-test probability of finding relevant results in clinical trials ([54](#)) and is a much more cost-effective way of spending research resources.

As mentioned in the **Pain Models commonly used in Clinical Research and Practice** section, most of the available treatments targeting pain and disability in people with chronic musculoskeletal pain were proposed based on the biomedical model of pain or on kinesiopathological frameworks. Several of these interventions have no clinical support to be recommended ([66](#), [332](#)) and, even among those interventions that seems to be effective for some populations of individuals with chronic musculoskeletal pain, it is very difficult to take the next step into improving the intervention or to discovery for whom they might be more effective without good explanatory models of pain.

Although active interventions such as exercise or cognitive-behavioral approaches are all effective on reducing pain and disability in people with chronic musculoskeletal pain, effect sizes are often small ([20](#), [333-336](#)). Besides that, these approaches are very different in terms of their proposed mechanisms of action. While the effect of exercise-based approaches is usually explained through structural, biomechanical or metabolic putative mechanisms of action, cognitive-behavior approaches are usually explained through psychosocial putative mechanisms. This raises the question if available approaches are targeting the right mediators of effect, or if there are common mechanisms that explain the small mean effects of all these treatment approaches ([337](#)). One way to answer this question is to better investigate how pain interventions work (or not). To our knowledge, currently there is no systematic evidence about mechanisms of action in the literature to answer this question. This research question will be addressed in Chapter 5.

Related research question: Which factors mediate the effect of cognitive-behavioral and exercise-based interventions on pain intensity and disability in people with chronic musculoskeletal pain?

Key Gaps of Knowledge that Will Be Addressed during the Thesis

There are still several gaps of knowledge in the literature regarding the possible underlying mechanisms associated with pain persistence and recovery. This thesis will contribute to the bridging of this gap of knowledge by:

- Investigating if pain can be conditioned to voluntary movements through associative learning;

Chapter 2 aims to address these questions, entitled ‘Pain can be conditioned to voluntary movements through associative learning: an experimental study in healthy participants’.

- Verifying the assumption that pain occurrence through movements and activities is associated with the number or severity of tissue damage in subjects with chronic musculoskeletal pain;

Chapter 3 aims to address this question, entitled ‘Shoulder pain across more movements is not related to more tissue damage in people with chronic shoulder pain diagnosed with subacromial pain syndrome’.

- Investigating if chronic musculoskeletal pain is associated with perceptual distortions in other perceptual continuums associated with movements that could foster avoidance behaviors;

Chapter 4 aims to address these questions, entitled ‘Distorted distance perception to reachable points in people with chronic shoulder pain’.

- Verify which factors mediate the effect of cognitive-behavioral and exercise-based interventions on pain intensity and disability in patients with chronic musculoskeletal pain;

Chapter 5 aims to address these questions, entitled ‘Mechanisms of Action of Cognitive-Behavioral and Exercise-Based Interventions for Pain and Disability in People with Chronic Musculoskeletal Pain: a systematic review and meta-analysis of mediation studies from randomized controlled trials’.

Chapter 2

Pain can be conditioned to voluntary movements through associative learning: an experimental study in healthy participants

For long, the isolated investigation of pain, nociception and motor behavior resulted in mostly separate bodies of evidence, with few lines of research investigating the interplay between pain and movement ([338](#)). Early researches of pain and motor control demonstrated that experimental induced pain leads to local and systemic motor adaptations in healthy subjects ([89](#)), which was in line with the findings of several case-control cross-sectional studies which found that people in pain actually move differently from healthy individuals ([89](#)). This first line of evidence raised further discussions about causality: whether altered movement patterns cause pain or pain leads to altered movement patterns ([70-72](#))?

However, current knowledge about the mechanisms underlying pain perception (for more details, see the **Perception as a Guide to Behavior** section in thesis introduction) and motor behavior ([292](#), [294](#), [339](#)) evolved and modified our understanding of the relationship between pain and movement from linear causation to a complex interaction where both pain and movement are outputs of the nervous system based on multidimensional factors ([136](#)). In other words, it changed our understanding from pain *and* movement to pain *with* movement ([338](#)). Nevertheless, how pain learning takes place during movements? Can pain be conditioned to voluntary movements through associative learning?

This chapter describes a study that aimed at investigating whether proprioceptive inputs associated with arm movements can increase the chance of a stimuli at-pain-threshold to be perceived as painful after successive painful associations in healthy participants (i.e. an increased chance of perceiving pain during movements in the presence of nociception). We hypothesized that a Pavlovian conditioning procedure would lead to a higher percentage of stimuli at-pain-threshold level being perceived as painful during movements that were previously associated

with an US-nociceptive stimulus (CS+ movements) in comparison with movements that were not previously associated with nociception (CS- movements). Furthermore, we hypothesized that pain conditioning would also lead to higher pain intensities during the CS+ in comparison with the CS- movements and higher defensive responses, including higher skin conductance responses (SCRs) (ie, measure of sympathetic arousal ([340](#))), and higher movement onset latency (MOL) (ie, measure of avoidance tendency), before the CS+ movement initiation in comparison with the CS- movements. This study adopted an ecological approach to better understand how pain conditioning could interact with real-world movements.

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Pain can be conditioned to voluntary movements through associative learning: an experimental study in healthy participants

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Abstract:

Experimental data suggest that associative learning can influence defensive avoidance behavior and pain perception in humans. However, whether voluntary movements can become conditioned stimuli (CSs) and influence pain responses is yet to be evaluated. Forty healthy volunteers participated in this study. Electrocutaneous stimuli applied to the shoulder at pain threshold level (US^{test}) and at pain tolerance level (US) were determined before a movement-conditioning paradigm. First, reaching movements to visual cues shown on one side of a computer screen were associated with the US (CS+ movements) on 80% of trials, whereas reaching movements to visual stimuli shown on the other side were never associated with the nociceptive-US (CS− movements). Next, participants underwent a test phase in which movements to visual cues on both sides were paired with the US^{test} on 50% of trials. During the test phase, participants were asked to evaluate whether the movement was painful (yes/no) and to rate pain intensity after each trial. Movement onset and duration as well as skin conductance responses were collected. The US^{test} stimuli were more likely to be perceived as painful and were also rated as more painful during CS+ movements. Movement onset latency and skin conductance responses were significantly higher in anticipation of the CS+ movement as compared to the CS− movement. These findings suggest that pain can be conditioned to voluntary movements.

Keywords: Pain, Associative learning, Pain conditioning, Classic conditioning, Pavlovian conditioning

1. Introduction

Pain during voluntary movement is a common reason for seeking care in musculoskeletal clinical practice. Despite substantial scientific progress, it is still unclear why the spectrum of movement-related pain presentations is variable between individuals.^{29,31,32}

Contemporary studies have investigated possible sources of variability about the relation between pain and movement through the lens of learning models.^{24–26} The fear-avoidance model for chronic pain is one of the most known and studied learning models in the pain field, creating a theoretical framework for studies investigating the mechanisms that underpin pain persistence.^{39–42} Recent work conducted by Meulders et al. have evaluated the acquisition of fear of movement-related pain²⁵ and of operant pain-related avoidance²⁴ using a movement-based paradigm. The

results of these studies support the fear-avoidance model, indicating that fear of movement and avoidance can be acquired through learning during movement-related pain episodes.

It has been proposed that pain itself may be learned through Pavlovian conditioning.²⁷ Although the effects are moderate to small,²² associative learning can influence an individual's pain perception, producing effects such as pain threshold modulation^{9,21,37} and conditioned hyperalgesia.^{10,12} Through associative learning, a person may learn the association between different stimuli.³³ For instance, when a neutral proprioceptive stimulus such as a voluntary arm movement (conditioned stimulus [CS]) is paired with a noxious and potentially harmful stimuli signaling nociceptive input (unconditioned stimuli [USs]) to which the person responds without the need of previous learning, the CSs (visual, tactile and proprioceptive stimuli associated with or preceding the US) might come to elicit defense responses such as fear and avoidance behavior in anticipation of a threat (conditioned responses [CRs]).^{19,27}

Current evidence evaluating multisensory stimuli as CSs have used vibrotactile,^{10,21,37} visceral,^{11,48} or visual stimuli.^{12,13} However, whether proprioceptive stimuli (during voluntary movements) can become conditioned and influence painful responses is yet to be evaluated. Because movements are complex behaviors that involve a chain of planning and anticipatory actions,⁸ it is not possible to fully understand how pain conditioning takes place without observing how an individual changes the response to cues that predict painful movement execution.

This study aimed at examining whether proprioceptive inputs associated with arm movements can increase the chance of

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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a stimuli at-pain-threshold to be perceived as painful after successive painful associations in healthy participants. We hypothesized that a Pavlovian conditioning procedure would lead to a higher percentage of stimuli at-pain-threshold level being perceived as painful during movements that were previously associated with an US-nociceptive stimulus (CS+ movements) in comparison with movements that were not previously associated with nociception (CS– movements). Furthermore, we hypothesized that pain conditioning would also lead to higher pain intensities during the CS+ in comparison with the CS– movements and higher defensive response including higher skin conductance responses (SCRs) (ie, measure of sympathetic arousal),⁴ and higher movement onset latency (MOL) (ie, measure of avoidance tendency), before the CS+ movement initiation in comparison with the CS– movements.

2. Methods

2.1. Participants

Participants were recruited through flyers, social media, and word-of-mouth (on and off campus). This study included healthy participants aged 18 to 60 years old. The participants were excluded if they reported: (1) acute pain at the week of testing, (2) use of analgesic medication on the day of testing, (3) use of medications that could alter skin sensitivity, (4) a history of chronic pain (defined as pain every day for 3 months or longer), (5) use of an electronic implant (eg, a pacemaker), or (6) any serious reported psychological and neurological diagnosis.

Participants were informed that the purpose of the study was to investigate the relation between pain and movement, but were not informed about the experimental contingencies or the hypotheses. We conducted an a priori sample size calculation using G*POWER with the effect size obtained by Traxler et al. (2019), according to which 32 participants would need to be included for a power of 0.80% and 95% of statistical significance ($\alpha = 0.05$) to detect a 0.15 difference in primary outcome measure using Student *t* test.³⁷

This study was conducted at the University of São Paulo. Once participants agreed with the study conditions, they were informed of the broad nature of the study and signed an informed consent. All procedures were approved by the Ethics Committee on Human Research of the Psychology Institute of the University of São Paulo (approval number 78039817.1.0000.5561) and followed the statements of the Declaration of Helsinki.

2.2. Stimulus material

Two white squares, measuring 5 cm × 5 cm, were presented on the right and the left upper corners of a 21.5" computer screen (with gray background). Participants' reaching movements to these 2 visual stimuli were used as CSs. We considered the proprioceptive stimuli associated with reaching movement in addition to the appearance of the visual stimuli as CSs. CS+ movements were those towards the visual cue on one side of the screen, which were paired with the US, whereas CS– movements were those towards the visual cue on the other side of the screen, and which were never paired with the US. The assignment of which movement orientation served as CS+ or CS– was counterbalanced across participants. Moreover, movements were always performed with the dominant arm. Handedness was assessed using the Edinburgh Handedness Inventory,³⁰ and all participants were right-handed. The right arm was always used to perform the movements.

USs were electrocutaneous stimuli generated by an S48 stimulator (Grass Medical Instruments, West Warwick, RI). Specifically, we used a train of 100 electrocutaneous stimuli of 2-ms duration delivered through a rectangular bipolar surface electrode, placed on the shoulder region of the moving arm 1 cm above the acromion, with a delay of 10 ms. The anatomical location of the USs as well as its parameters was chosen because during 2 pilot studies with 15 participants each, other electrode placements and US characteristics were associated with strong muscle contractions that impaired the conditioning process. The final US parameters were perceived as a precise pinprick painful sensation during a qualitative pilot study. Using pulse trains also allowed for the production of more stable stimulus intensities.²⁸ Two different USs were calibrated before the experiment: US and US^{test}.

The USs intensities were individually calibrated to find the US and the pain threshold (US^{test}). The US^{test} was always calibrated before the calibration of the US. For the calibration of the US^{test}, a single ascending run of electrocutaneous stimuli was administered while the participant performed shoulder flexion movements to 90° in the scapular plane, until pain was perceived. The intensity that was considered painful was used as the central point of 5 different electrocutaneous stimulus intensities with a 0.4-mA difference between them, which were randomly varied 5 times each during arm flexion movements. The intensity of the central point was changed if all the 5 intensities were painful more than 3 times each. The US^{test} was determined using the method of constant stimuli as the intensity that produced a 50% probability of perceiving the stimulus as painful.³⁵ This method was adopted because response-dependent methods may be better suited to calibrate stimuli at-pain-threshold level that will be repeatedly delivered.²³

The calibration of the US was also performed while the participant performed shoulder flexion movements to 90° in the scapular plane using a staircase method with a single ascending run. The stimulus intensity (mA) corresponding to the pain tolerance was used as the US. Participants were instructed to signal the highest electrocutaneous stimulation intensity they were able to tolerate, knowing that there could be a next higher intensity electrical stimulus. This stimulus intensity was chosen because, during a third pilot study with 10 participants, subjects experienced strong hypoalgesia induced by movement with lower or moderate stimulus intensities during the acquisition phase, which compromised the conditioning process.

Skin conductance responses were registered by means of 2 Ag-AgCl electrodes placed on the index and middle finger of participants' left hand connected to a GSR100C skin conductance module. Data were processed and analyzed offline using AcqKnowledge 4.2 software (BIOPAC Systems Inc, Goleta, CA).

The presentation of the visual cues and the delivery of the USs were controlled by a script developed with Matlab. The interface with which the subjects interacted was delivered using Psychtoolbox for Matlab (MATLAB 9.2 and Psychtoolbox 3.0.12., The MathWorks, Inc, Natick, MA).

2.3. Experimental design

The experiment consisted of 4 phases (calibration, baseline, acquisition, and test) conducted on a single day. During all phases of the experiment, participants remained seated on a chair with their arms resting on a table in front of them. The beginning of each phase was signaled by the experimenter, who gave participants the corresponding instructions (see below).

During the calibration phase, the US stimulation and SCR assessment electrodes were attached and US calibration

procedure was conducted (see Stimulus material). During the baseline phase, a general instruction was presented in the computer screen and participants received the opportunity to ask questions. They were instructed to keep the space key in the keyboard, spatially located in the midline, pressed with their right index finger and pay attention to the computer screen. A small cross, which was used as fixation stimulus, appeared in the middle of the screen. Visual cues were presented either on the right or left superior corners of the screen in a pseudorandom order with an interval between trials from 2.5 seconds to 3.5 (3 seconds in average). Participants were instructed to release the space key as soon as they saw the visual cue, reach to touch the visual cue with their index finger, and press the space key again. After the visual cue was touched, the subjects were instructed to quickly press the space key with the same hand, which turned the screen black and started the countdown to the next trial. This procedure was repeated 10 times for each side and the subjects were instructed to perform the movement in a comfortable speed. The trials were programmed to run in a (semi)randomized order with the restriction of no more than 2 consecutive trials of the same CS type. Subjects were also reassured that no pain would be delivered during this phase. The basic temporal sequence of events during a trial is illustrated in **Figure 1**. During the acquisition phase, subjects were instructed that painful electrocutaneous stimuli may occur during some movements. In this phase, CS+ movements were paired with the US 80% of the time, whereas no US was paired with the CS– movements. The USs were delivered by means of a variable-interval (VI) schedule that was calculated using half of the mean time required for the subject to reach each of the visual stimulus during the baseline phase. This VI schedule was triggered by the release of the space key. This procedure was repeated 20 times for each side. Finally, during the test phase, subjects were instructed that this set of movements would be just like the previous. In this phase, 10 movements to each of the visual cues were paired 50% of the times with the US^{test}.

Participants were asked to rate pain intensity for each movement immediately after its execution, during the intertrial interval of the acquisition and test phases. After each movement, subjects were asked whether the movement was painful (yes/no) and to estimate their perceived pain intensity using a 0 to 10 visual

analogue scale (VAS) if the answer was positive. This intertrial decision-making was used with the dual function of encouraging participants to stay vigilant during the movements, and to allow us to verify later the effect of the learning history upon the perceptual classification of nonpainful stimuli as painful.

After the acquisition and test phases, some questions for further exploratory analysis were added. The experimenter asked participants whether one movement was more painful than the other, and the participants could answer according to the following options: (1) Neither of the movements were painful, (2) The movement to the right was more painful than the other, (3) The movement to the left was more painful than the other, (4) Both movements were equally painful (pain decision-making measure). Participants were then asked to recall the overall pain felt for each side during the previous set of movements using a 0 to 10 VAS (pain recall [PR]). At the end of acquisition and test phases, subjects were also asked to do a US expectancy rating to each CS by answering the question “To what extent do you expect movements for this side to be painful in the next phase?” on a numerical rating scale ranging from 0 = “I do not expect that movements to this side to be painful” to 10 = “I fully expect movements to this side to be painful.” Subjects were asked to make this judgement after the test phase without knowing that they would not pass through another phase.

2.4. Measures and outcomes

2.4.1. Exit questions

At the end of the experiment, participants answered a number of questions to assess (1) whether they were naive to the purpose of the experiment (ie, blinding check), (2) how they perceived the timing of the electrocutaneous stimuli relative to the movements, and (3) whether they noticed a relationship between the movements CSs and the intensity of discomfort of the electrocutaneous USs (ie, contingency awareness).

2.4.2. Primary outcome

The primary outcome of this study was the percentage of trials during the test phase in which at-pain-threshold electrocutaneous stimuli (US^{test}) were experienced as painful during CS+

Figure 1. Illustration of the basic temporal sequence of a trial during all phases of the experiment.

movements in comparison with CS– movements. For that purpose, the intratrial answers to the question “*Was this movement painful (yes/no)?*” were used.

2.4.3. Secondary outcomes

Two motor behavior measures were assessed: (1) MOL, calculated as the delay between the presentation of the visual CS cue and the beginning of the CS movement (ie, the release of the space key); and (2) CS movement duration (MD), calculated by the delay between the release of the space key and the moment in which the space key was pressed again. The screen used in this experiment did not enable recording of the moment in which it was touched.

Skin conductance response was measured after the appearance of the visual CS cues during baseline, acquisition, and test phases. The SCR amplitudes were determined by manually selecting the difference between the base and the peak of the largest waveform (measured in microsiemens [μS]) in which the onset occurred in a range between 0.5 and 4.5 seconds after the presentation of each visual cue. Waveform was defined as an increase in skin conductance level to a peak followed by a slower recovery period. The minimum response criterion was 0.02 μS . Responses below 0.02 μS were scored as zero and were included in the analysis. Raw SCR values were square-root transformed before the analyses.^{4,31}

The pain decision-making measures for both the acquisition and test phases (see Experimental design) were computed as 0 (neither of the movements were perceived as painful during the previous phase), 1 (the CS+ movements were perceived as more painful during the previous phase), 2 (the CS– movements were perceived as more painful during the previous phase), and 3 (both movements were equally perceived as painful during the previous phase).

3. Statistical analysis

Data were analysed using SPSS 25.0 (IBM SPSS Statistics for Windows, Version 25.0; Armonk, NY). Plots were generated in R v3.4.3 (R Core Team, 2017), in RStudio v1.1.414 (RStudio Team, 2018).

Before analysis, data were checked for normality, outliers, and missing values. When appropriate, nonparametric tests were applied. Post hoc comparisons with Bonferroni adjustment were applied to analyses of variance (ANOVAs) with significant results.

To test whether conditioning was successful, expectancy ratings were analysed by means of 2 separate 2 (Condition: CS+ vs CS–) $\times$ 2 (Phase: acquisition vs test) repeated-measures ANOVAs. The SCRs for each CS during the first and second halves of the acquisition phase were analysed by means of 2 Wilcoxon signed rank tests. These measures were used as an index of learning. In addition, blinding for the study goal and contingency awareness for the CS-US pairings were checked.

To test the main hypothesis that a Pavlovian conditioning procedure would lead to a higher percentage of stimuli at-pain-threshold level being perceived as painful during movements that were previously associated with an US-nociceptive stimulus (CS+ movements) in comparison with movements that were not previously associated with nociception (CS– movements), a binary variable reflecting nonpainful (0) and painful (1) at-pain-threshold trials was computed, based on the intratrial decision-making task. The percentage of US^{test} rated as painful was compared across the conditions CS+/US^{test} and CS–/US^{test} by means of a Wilcoxon signed rank test.

The secondary hypothesis that the conditioning would also lead to higher skin conductance responses to the appearance of the visual CS+ cue in comparison with the visual CS– cue, and higher response onset latency times to the CS+ movement initiation in comparison with the CS– movements was verified by means of Wilcoxon signed rank tests and a 2 (Condition: CS+ vs CS–) $\times$ 3 (Phases: baseline, acquisition, test) RM ANOVA, respectively. A similar ANOVA test was used to examine differential MD. Besides that, a Wilcoxon signed rank test was conducted to compare the pain intensity ratings for the CS+/US^{test} and CS–/US^{test} trials.

The relationship between the primary outcome, SCR, blinding, expectancy, and contingency awareness was explored by means of analyses of covariance (ANCOVAs), with the mean difference of the expectancy ratings and of the SCR at test phase.

4. Results

A total of 40 participants (22 females) were included. Six participants were excluded during the calibration phase because they failed to report the electrocutaneous stimuli within the intensity safety limits as being painful. Therefore, the analyses were conducted with 34 participants (19 females) aged 18 to 58 years (mean = 25.69 $\pm$ 9.66).

4.1. Blinding and contingency awareness

After the experiment, 31/34 (91%) participants were unaware of the actual objective of the study (ie, blinding check), and 19 (55.9%) reported to have noticed that both movements were equally painful during the acquisition phase in the final decision-making task. All participants noticed that the electrocutaneous stimuli occurred during the movements, and 5 (14.7%) reported to perceive some level of causality between pressing the screen and receiving the painful stimulus.

4.2. Manipulation checks

4.2.1. Behavior measures

At baseline, no significant differences were found between the mean MOL ($F(1,66) = 2.12$; $P = 0.14$; CS+ = 0.55; CS– = 0.66) and MD ($F(1,66) = 2.88$; $P = 0.094$; CS+ = 1.21; CS– = 1.37) for both CS movements. Similarly, SCRs did not differ significantly between the CS movements at baseline (CS+ = 0.81; CS– = 0.76; Wilcoxon signed rank test: $Z = -1,274$, $r = 0.15$; $P = 0.2$).

4.2.2. Expectancy ratings

To check whether the conditioning procedure was successful, a 2 (Condition: CS+ vs CS–) $\times$ 2 (Phase: Acquisition vs Test) RM ANOVA was performed on expectancy ratings. This analysis revealed both a significant condition ($F(1,136) = 18.04$; $P < 0.001$; $\eta_p^2 = 0.98$) and phase effect ($F(1,136) = 14.45$; $P < 0.001$; $\eta_p^2 = 0.96$), without a significant condition $\times$ phase interaction.

4.2.3. Skin conductance response

Mean SCR after the appearance of the CS+ movement cue was significantly higher in comparison to the mean SCR after the CS– cue appearance at the first half of the acquisition phase (Wilcoxon signed rank test: $Z = -2.293$, $r = 0.27$; $P = 0.02$), and this difference remained during the second half of the acquisition phase (Wilcoxon signed rank test: $Z = -2.701$, $r = 0.32$; $P = 0.007$).

4.3. Main hypothesis

We tested whether there was a difference between the number of stimuli at-pain-threshold level (US^{test}) being perceived as painful vs nonpainful during CS+ movements in comparison with CS– movements. The Wilcoxon signed rank test revealed a statistically significant CS+/CS– difference (Wilcoxon signed rank test: $Z = -2.65, r = 0.32; P = 0.008$). Participants rated more US^{test} trials as painful during CS+ movements (85%, SD: 25) than during CS– movements (73%, SD: 32).

4.4. Secondary hypotheses

Participants rated the US^{test} as significantly more painful when it occurred during CS+ movements ($M = 2.41$; SD: 1.62) than during CS– movements ($M = 1.96$; SD: 1.49; Wilcoxon signed rank test: $Z = -4.29, r = 0.52; P < 0.0001$).

The test of the response onset latency times revealed a significant Condition $\times$ Phase interaction ($F(2,198) = 51.217; P < 0.001; \eta_p^2 = 1$). Follow-up pairwise comparisons revealed that latency times for both CS movements directed increased significantly from baseline to acquisition as well as from baseline to test (both $P < 0.001$), with higher times to initiate CS+ movements in comparison to CS– movements during the acquisition and test phases (both $P < 0.001$). SCR to both CSs increased significantly from baseline to acquisition ($P < 0.001$) and to test ($P < 0.001$), and decreased from acquisition to test ($P = 0.001$), whereas higher SCR were observed to the appearance of the CS+ cue in comparison to the CS– cue both in acquisition (Wilcoxon signed rank test: $Z = -4.67, r = 0.29; P < 0.0001$) and test (Wilcoxon signed rank test: $Z = -2.419, r = 0.29; P = 0.016$) phases. No statistically significant difference was found between CS+ and CS– movements duration ($F(2,198) = 1.3; P = 0.27; \eta_p^2 = 0.28$). None of these results changed when contingency awareness was added to the analysis as a covariate. The values of these variables across phases are depicted in **Figure 2**.

The ANCOVAs revealed no effect of blinding status, expectancy ratings, and contingency awareness on the percentage of US^{test} trials rated as painful during CS+ movements in comparison to movements to the CS– movements ($P > 0.05$). This means that the main results were not influenced by the participants' knowledge about the purpose of the experiment, conscious expectancy, or by contingency awareness.

4.5. Exploratory analysis

An exploratory analysis was conducted between the first half and second half of the test phase to verify whether extinction of the differences in MOL, SCR, and VAS ratings between CSs occurred. There were no statistically significant differences in these outcomes between the first half and second half of the test phase, although MOL and SCR visually appeared lower in the second half of the test phase (**Fig. 3**).

Given the importance of explicit memory on individual's expectancy ratings, an exploratory analysis was conducted to verify the effect of the conditioning process upon PRs. Pain recalls were significantly higher during the CS+, in comparison to CS– movements both in acquisition and test phases (ANOVA: $F(1,66) = 6.21; P = 0.015; \eta_p^2 = 0.7$ and Wilcoxon signed rank test: $Z = -2.65, r = 0.32; P = 0.008$, respectively). A 2 (Condition: CS+ vs CS–) $\times$ 2 (Phase: Acquisition vs Test) RM ANOVA was performed on pain memory recall ratings. It revealed a significant Condition ($F(1,132) = 7.19; P = 0.008; \eta_p^2 = 0.759$) and Phase ($F(1,132) = 39.87; P < 0.001; \eta_p^2 = 1$) main effects, with no

Condition $\times$ Phase interaction. None of these results changed when contingency awareness was added to the analysis as a covariate ($P > 0.05$), meaning that they were not influenced by the participants' contingency awareness.

To verify the relation between PRs, expectancy, blinding, contingency awareness, and VAS, ANCOVAs were conducted. They revealed a significant effect of VAS at test phase on the PR only ($F(1,59) = 84.92; P < 0.0001; \eta_p^2 = 1$).

5. Discussion

In this study, we examined whether proprioceptive inputs associated with arm voluntary movements can increase the chance of a stimuli at-pain-threshold to be perceived as painful after successive painful associations in healthy participants. We hypothesized that a Pavlovian conditioning procedure would lead to a higher percentage of stimuli at-pain-threshold level being perceived as painful during movements directed to an external visual cue that were previously associated with an US -nociceptive stimulus (CS+) in comparison with movements directed to an external visual cue that were never previously associated with nociception (CS–).

This hypothesis was confirmed because US^{test} stimuli (ie, electrocutaneous stimulus at-pain-threshold) were significantly more likely to be perceived as painful and were also rated as more painful during movements directed to the CS+. These findings are consistent with the data of other studies that investigated the effect of Pavlovian conditioning using vibrotactile and visual stimuli as CSs, and found that painful associations can decrease pain threshold^{21,37,47} and increase its perceived intensity.^{10,12} Together, these studies suggest that pain experience may be modulated through associative learning.

During our study, the association of a specific movement (ie, reaching to touch) and an initial nociceptive stimulus (ie, electrocutaneous stimuli) modulated the pain experience even when the nociceptive stimulus was reduced. This potentially suggests that during movement-related pain episodes, individuals may learn to continuously associate pain to contexts and/or multisensory stimulus that was associated with the initial painful event. In turn, the pain experience remains.

The other secondary hypotheses were that conditioning would lead to higher SCR to the appearance of the visual CS+ cue in comparison with the visual CS– cue (ie, higher arousal), and lead to higher MOLs to the CS+ movement's initiation in comparison with the CS– movements (ie, higher avoidance tendency). These hypotheses were also confirmed because SCRs were significantly higher after the appearance of the visual CS+ cue during the test phase in comparison to the visual CS– cue, and movement onset latencies were significantly higher to initiate the CS+ movements in comparison to the CS– movements during the test phase as well. This increased arousal to the visual CS+ cue, that was also a cue to start the movement, was associated with higher MOL to initiate the CS+ movements in comparison with the CS– movements both in acquisition and test phases, which can be interpreted as a sign of attempted avoidance in a forced choice paradigm. These results are in line with several studies that verified the mechanisms beyond fear of movement-related pain conditioning, in which increased CRs (eg, eye blink response) are observed in predictable movement conditions to the visual cues that predict painful interactions.^{4,15,25,26}

Regarding the secondary hypotheses, one interesting finding of our data, also shown in **Figure 3**, is that although not statistically significant, the visually observed reduction of the SCR

Figure 2. Raincloud plots of the mean difference ([CS+] - [CS-]) and 95% confidence intervals of behavioral measures through phases. MOL, movement onset latency (in sec); MD, movement duration (in sec); SCR, mean skin conductance response (in μ S); VAS, visual analogue scale; Prob(Pain|US), probability of perceive the US^{test} as painful.

and movement onset latencies to the CS+ through the test phase was not accompanied by a full extinction of the perceived pain intensity differences between CS+ and CS-. It seems that behavioral and psychophysiological responses do not always covary with verbal reports, as shown in other experimental

studies.^{24–26} Given these findings, future studies could explore the possible contributions of verbal vs physiological responses in the maintenance of conditioned pain because this information might be relevant for planning clinical interventions that target chronic pain.

Figure 3. Mean movement onset latencies (in sec), skin conductance responses (in μ S), and pain ratings (VAS) from the first half (A) and second half (B) of the test phase. MOL, movement onset latency; SCR, skin conductance response; VAS, visual analogue scale.

The exploratory analysis showed that PR was higher for the CS+ movements during the test phase in comparison to the CS- movements, although both CSs were associated with the same intensity of electrocutaneous stimuli (US^{test}). This finding is consistent with research on memory for bodily symptoms, in which memory recall is relatively inaccurate, and pain is usually overestimated retrospectively.^{1,7,20,43} An interesting finding was that most subjects reported to remember feeling pain during movements toward the CS- after the acquisition phase, although this stimulus was never associated with the US. Given the unpredictability of the acquisition phase, this could be a form of stimulus generalization influencing memory retrieval.^{17,36,38}

Notably, although our experimental design was not designed to exclude the effect of expectancy on pain perception, our findings were not influenced by the participants' blinding status, conscious expectancy, or contingency awareness. Other studies reported similar findings, suggesting that expectations or conscious awareness of learned associations might not be necessary for Pavlovian conditioning to occur.^{10,12,13,37} Furthermore, movement-induced hypoalgesia^{3,18} was observed during the first pilot studies and impaired the conditioning process. However, its effect was reduced with higher US intensities,⁶ which suggests that pain intensity may play a role in conditioned movement-related pain.

5.1. Implications

We speculate that the clinical implications of the present findings are related to the knowledge of the mechanisms by which movement-related pain and associated responses, such as the arousal increase in the presence of a visual cue that predicts painful interactions, could become CRs and modulate pain occurrence and behavior selection to similar motor contexts or future executions of the same movement.

Voluntary movements involve a chain of planning and anticipatory actions that are triggered based on context,⁸ including internal and/or external cues. As such, sensory stimuli that were present during the planning of a given movement may acquire a CS function after the exposure to painful movements, by its capacity to predict pain. In other words, during a movement-related pain episode (eg, shoulder pain during overhead reaching for an object), every stimulus that has a predictive value about the painful experience (eg, height of the object) can become a CS and produce CRs—such as attentional bias to the region of pain,^{2,34} movement-related fear,^{4,25} protective behavioral responses (eg, bracing of shoulder and neck muscles)¹⁶ or, as found in this study,

an increase in arousal and modulation of the pain threshold. The CRs that occur before movement can continue to be evoked during future executions of the same movement.

These initial CRs elicited by the CSs cues that precede motor behavior (eg, height of the object), such as increased arousal and fear, could initially lead the individual to avoid such contexts in a more or less generalized way,³⁸ and for those subjects whose operant contingencies are sufficient to make them not engage in avoidance behaviors (eg, urge to thirst reduction), these same CRs could leave them more primed to feel pain.⁵ The interplay between these CRs (eg, contextual pain threshold modulation during overhead reaching for an object) and operant learning (eg, reinforcement of a maladaptive strategy of movement that fulfill the motor task), in combination with other conscious and nonconscious processes associated to threat processing and movement planning and execution, may enhance and even self-reinforce these processes, which may ultimately play a role in the pathway to pain chronicity.^{5,14,17,44–46}

Knowledge of these mechanisms suggests that for those with movement-related pain, movement may be a key link between body and perception. Thus, although movement is a common and effective trigger for pain experience and persistence, it also offers the most powerful way to access and modify the contextual and behavioral learning processes related to pain chronicity.

5.2. Limitations

The main limitation of this study was the calibration of the US^{test} intensity for the test phase. Assuming that the threshold is a point of uncertainty, we expected that the US^{test} stimuli would be perceived as painful around 50% of the times with differences according to the previous history of learning to each movement. Despite careful calibration, the elevated percentage of US^{test} perceived as painful suggests that, besides the differences found between the CS+/ US^{test} and CS-/ US^{test} in the test phase, a global modulation of the pain thresholds occurred across the experiment. However, this should not have affected the data.

Furthermore, this study used a mechanism-based approach. Its results should only be used to raise hypotheses for further clinical and experimental studies, and not for clinical reasoning and decision-making.

6. Conclusion

This study provides evidence that in healthy subjects, pain can be conditioned to voluntary arm movements. After an acquisition

phase, the percentage of stimuli at-pain-threshold level that were perceived as painful during movements directed to an external visual cue that were previously associated with painful movements in comparison with movements directed to an external visual cue without a history of pain learning was significantly higher, and the stimuli were also perceived as more intense. Furthermore, defensive behavioral responses (ie, SCRs and movement onset latencies) were more pronounced after the appearance of the visual cue that predicted possible painful interactions.

The present data offer support for the current scientific literature suggesting that pain modulation through associative learning may be one of the mechanisms by which persistent pain may occur. The present data also suggest that during a movement-related pain episode, a complex interplay between contextual and behavioral learning takes place, which could be related to clinical processes of avoidance and pain persistence during movement execution.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Chapter 3

Shoulder pain across more movements is not related to more tissue damage in people with chronic shoulder pain diagnosed with subacromial pain syndrome

As movement-related pain reports are often still viewed as an accurate representation of tissue damage ([48](#), [49](#), [51-53](#), [190](#)), a greater number of painful movements or activities is commonly viewed as evidence that more structures might be damaged (e.g. more rotator cuff tendons are damaged in subjects with shoulder pain) or of more severe structural damage (e.g. labral tears in subjects with hip pain). Therefore, the question remains: what are the factors associated with pain occurrence through movements and activities?

The results of Alaiti et al. (2020), described in **Chapter 2**, supports the assumption that pain can be conditioned to movement. However, can pain also be influenced by stimulus generalization? There is experimental data supporting the idea of pain modulation generalization after associative learning ([284](#)). Thus, in order to test the assumption that the precision of pain occurrence through movements could be a by-product learning processes, it is paramount to verify if the pain occurrence through movements and activities might be associated with the number or severity of tissue injuries in people with chronic pain.

Therefore, the aim of this study was to verify if movement-related pain that occurs across a wider variety of activities commonly perceived as painful by people with chronic shoulder pain was associated with the number or severity of rotator cuff radiological findings on a magnetic resonance imaging (MRI). We hypothesized that movement-related pain that occurs across a wider variety of activities would not be associated with the number or severity of rotator cuff MRI findings. In order to verify this hypothesis, this study was designed in three subsequent phases that were aimed at: select the activities commonly perceived as painful; develop and evaluate the measurement properties of a measurement tool that assesses the pain occurrence across clinically-relevant arm movements; and verify the hypotheses of this study through an analysis of the data collected in phase two.

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Shoulder pain across more movements is not related to more tissue damage in people with chronic shoulder pain diagnosed with subacromial pain syndrome

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Abstract

Background: People with chronic shoulder pain commonly report pain during arm movements in daily-life activities. Pain related to movement is commonly viewed as an accurate representation of tissue damage. Thus, when a person reports pain across a variety of movements, this is often understood as indicative of greater damage. We aimed to investigate if movement-related pain that occurs across a wider variety of movements was associated with the number or severity of rotator cuff tendons reported as abnormal on a magnetic resonance imaging (MRI). To answer this question, this study was designed in three phases.

Methods: We recruited 130 individuals with chronic shoulder pain diagnosed with subacromial pain syndrome. Firstly, a list of daily functional activities commonly reported as painful by people with chronic shoulder pain was generated from three well-established outcome measures with 30 individuals and a measurement tool was developed with data from further 100 individuals, which demonstrated to have acceptable content validity, construct validity, internal consistency, inter-rater reliability and structural validity. Multiple linear regression was then used to evaluate the hypotheses of the study. A direct acyclic graph was used to select variables for linear regression modelling.

Results: There was no association between movement-related pain occurrence across movements and the MRI findings.

Conclusion: Our study provides evidence that neither the number of rotator cuff tendons reported as abnormal nor the severity of each tendon imaging finding were associated with pain occurrence across movements and activities commonly perceived as painful by people with chronic shoulder pain.

Keywords: Chronic Pain, Shoulder Pain, Subacromial Pain Syndrome, Rotator Cuff.

INTRODUCTION

People with chronic shoulder pain commonly report pain during daily activities that require arm movements such as reaching to grasp objects or carry weights, which impacts on daily life and is often a reason for care seeking. These symptoms are commonly diagnosed as subacromial pain (formerly impingement) syndrome associated with rotator cuff tendinopathy or tear [59], and clinicians often base their clinical judgements on reports of pain with movement, either looking at patterns of movement and similarities among the painful movements and activities or by doing provocative movements in an attempt to investigate the underlying mechanical causes of pain [8; 23; 26; 28; 44; 57].

Although general measures of shoulder pain intensity are poorly correlated with radiological imaging and pathoanatomical diagnosis [5; 13; 30; 31; 38; 42; 45; 58], the association between tissue damage and movement-related pain in subjects with shoulder pain was not properly investigated. To date, the available studies rely on general pain intensity measures that fail to assess the variability of pain reports during daily life activities of individuals with chronic shoulder pain (i.e. the intensity of the pain across different activities), which would provide a more in depth perception of the pain experience of these individuals. In addition, although the relationship between pain and structural pathology is poor, there is a wide view that more pain or pain in more movements is an accurate measure of more tissue damage (e.g. more rotator cuff tendons are damaged)[6; 11; 12; 21] or more severe tissue damage (e.g. partial or full-thickness tear)[7].

Therefore, the aim of this study was to verify if movement-related pain that occurs across a wider variety of activities commonly perceived as painful by people

with chronic shoulder pain was associated with the number or severity of rotator cuff radiological findings on a magnetic resonance imaging (MRI). Based on the current state-of-the-art, we hypothesized that movement-related pain that occurs across a wider variety of activities would not be associated with the number or severity of rotator cuff MRI findings. In order to verify these hypothesis, this study was designed in three subsequent phases that were aimed at: select the activities commonly perceived as painful; develop and evaluate the measurement properties of a measurement tool that assesses the pain occurrence across clinically-relevant arm movements; and verify the hypothesis of this study through an analysis of the data collected in phase two.

MATERIALS AND METHODS

Study design

A cross-sectional study of three phases was conducted. In phase one, thirty people with subacromial pain syndrome were recruited to determine what would be clinically-relevant arm movements and activities that were most commonly reported and associated with pain during daily life activities. Sixteen movements related to reaching, grasping and hand manipulations with the upper limbs were initially selected from three well-established outcome measures namely, the Constant-Murley [2], Shoulder Pain and Disability Index (SPADI) [29] and American Shoulder and Elbow Surgeons Questionnaire (ASES) [1]. Using a 90% concordance rate of agreement among participants, 10 activities were selected as the most commonly reported and pain provoking activities for people with shoulder pain: unilateral and bilateral reach at 60°, 90° and 120° of flexion; hand to mouth, head and back pocket of the pants; hold 4kg with the affected limb next to the body. From now on, these activities will be referred to as 'clinically-relevant arm movements' for people with shoulder pain.

In phase two, one hundred people with chronic shoulder pain diagnosed with subacromial pain syndrome were recruited to develop and evaluate the measurement properties of a measurement tool that assesses the pain occurrence across clinically-relevant arm selected in the first phase. In phase three, the hypotheses of this study were verified through an analysis of the data collected in phase two. The full description of the content validity conducted in the first phase and of the measurement tool development and properties testing conducted in the second phase is presented in the supplementary materials.

Participants

We included in the study one hundred thirty individuals with chronic shoulder pain (i.e. pain for at least 3 months) located in the antero-proximal region of the shoulder, diagnosed with subacromial pain syndrome by a combination of clinical examination with positive results for 3 out of 5 subacromial pain syndrome tests: 1) Neer; 2) Hawkins-Kennedy; 3) painful arc; 4) pain or weakness resistant to external rotation; and 5) Jobe [36]. Patients in care in the shoulder and elbow medical department of the Orthopedic Institute of the Clinical Hospital of São Paulo (Brazil) aged between 40 and 65 years old, sedentary, symptomatic (i.e. presenting shoulder pain during movements) with a history of traumatic or insidious onset, were consecutively invited over a period of three months to participate in the study.

Exclusion criteria included: Cognitive impairment identified with the Mini-Mental State Examination, use of medications for pain control in the last 24 hours before the evaluation, neurological diseases, limited shoulder passive range of motion (for external rotation $< 30^\circ$ and elevation $< 150^\circ$), previous surgeries in the shoulder and rheumatic diseases.

This study was approved by the Ethics Committee on Human Research of the Psychology Institute [CAAE 49635115.5.0000.5561]. All participants signed the informed consent form.

Outcome Variable

The outcome variable of this study was pain occurrence across clinically-relevant arm movements and activities, assessed by the measurement tool developed during the second phase of this study, named the Movement-related Pain Distribution Scale – Shoulder (MRPDS). The main outcome of the MRPDS is a score based on the pain a person experienced during the execution of 10 different activities commonly reported as painful by people with chronic shoulder pain (e.g. reaching movements, placing the hand in the back pocket of the pants).

The MRPDS gives a general measure of the pain occurrence and intensity across the 10 activities of the scale, indicating whether the occurrence is more widespread across the activities (e.g. pain during most of the activities of the scale) or is more localized to specific movements (e.g. pain during reaching above the head). The closer to 0 the score is, the more widespread are the movement-related pain reports through the 10 activities of the scale (i.e. scores close to 0 indicate that subjects may have experienced pain for most or all of the activities of the scale with similar pain intensities). On the other hand, higher scores indicate that subjects may have experienced pain for few activities with higher differences in pain intensity).

The floor score of the MRPDS is 0, but it has no ceiling as several other ratio scales [48-50]. Measurement properties analyses showed acceptable content validity, construct validity, internal consistency, inter-rater reliability and structural validity. For more details of the MRPDS, see the supplementary material.

Independent Variables

Questionnaires were used to collect sociodemographic data (age, sex, ethnicity, years of study, and working status) and pain-related variables (number of other musculoskeletal complaints, side of the painful limb, symptoms onset, duration of symptoms).

For the assessment of pain intensity, we used a 10 cm Visual Analogue Scale (VAS) with the left extremity labeled as “no pain” and the right as “worst pain possible” [52]. The VAS was administered prior to the MRPDS and the patients were asked to rate their level of overall pain in the shoulder based on their symptoms at the time of the evaluation.

Shoulder imaging findings (number of rotator cuff tendons reported as abnormal on a diagnostic scan and the severity of the long head of the biceps, supraspinatus, infraspinatus and subscapularis tear classified according to the Thomazeau criterion[55] modified by Boileau[3]) were collected and analyzed by one radiologist physician with 14 years of experience from the MRI in the medical profile of each participant. The scale used in the analysis for severity of the cuff tendons tears was normal, tendinopathy, partial thickness tear and full-thickness tear, while the scale used for long head of the biceps pathology was normal, subluxation, dislocation and full-thickness tear.

The MRI reporting was performed as per usual radiological reporting of the shoulder region. This physician was not involved in the study and was blind for the clinical status of these patients. The time elapsed between the performed MRI and study examination ranged from 4 weeks to 3 months.

Statistical Analysis

According to a sample size calculation using G*POWER, 100 participants were needed to be included for a power of 0.80% and 95% of statistical significance ($\alpha=0.05$) to detect a 0.12 effect size among the five shoulder imaging findings defined as independent variables (i.e. number of rotator cuff tendons reported as abnormal, severity of the tendons supraspinatus, infraspinatus, subscapularis and long head of the biceps imaging finding) and the dependent variable in a multiple linear regression analysis. This sample size is also sufficient for the measurement properties analysis (available in the supplementary file) according to recommendations of the “*Quality criteria for measurement properties of health status questionnaires*” [54].

Two multiple linear regression analysis were conducted to estimate the association between the shoulder imaging findings, pain intensity and pain during rest with movement-related pain distribution. The dependent variable was the score of the MRPDS. The two regression models were built according to the conceptual framework depicted in Figure 1.

To estimate the relationship between MRPDS and the other variables, a parameter estimate (β) and confidence intervals (95% CI) were calculated using R Studio v1.1.414 (Rstudio Team, 2018). First, univariate linear regressions were conducted between each of the independent variables and the MRPDS. The collinearity among variables was then assessed, but as no strong correlation between variables was found, all the hypothesized variables were included in the final models.

The adjusted coefficient of determination (R^2), a proportional measure indicating the amount of variation in outcome explained by the models, is presented. Sensitivity analysis were conducted to verify the effect of other measured possible

confounding variables (e.g. sex, age). The homoscedasticity of the final models and models diagnosis (i.e. outliers, aberrant and leverage points) were verified through visual inspection.

Figure 1. Directed Acyclic Graph (DAG) describing the conceptual framework used to construct the multiple linear regression models to verify the hypothesis of this study [5; 13; 40; 41; 43; 56; 58]. The MRPDS was used as a dependent variable. The independent variables of the first model were (1) number of tendons reported as abnormal and severity of the (2) supraspinatus, (3) infraspinatus, (4) subscapularis and (5) long head of the biceps imaging finding. In the second model, the variables (6) pain during rest and (7) pain intensity were added to the variables of the previous model as independent variables, and the model was further adjusted by pain duration and number of musculoskeletal complaints.

RESULTS

The participants' characteristics are presented in TABLE 1 and the β weights of the univariate and multiple regression analyses are presented in TABLE 2. A negative β refers to smaller MRPDS scores (more widespread movement-related pain occurrence across activities), and a positive β refers to higher MRPDS scores (more specific movement-related pain occurrence across activities).

TABLE 1. Summary characteristics of phase two participants (n=100)

	Mean (SD)	N (%)
Age (Years)	55 (8.56)	
Sex (Female)		74
Ethnicity (White)		64
Duration of Symptoms (Months)	76 (24)	
Total Years of Study (Years)	6.48 (4.2)	
Working status		
<i>Employed</i>		35
<i>Unemployed or retired</i>		44
<i>Sick leave</i>		21
Spontaneous Pain at Rest (Yes)		35
Pain Intensity (VAS)	4 (2.3)	
Painful Limb (Dominant)		59
Side of the Complaint (Bilateral)		46
Number of ME Complaints (Two or more)		50
Number of rotator cuff tendons reported as abnormal in MRI		
<i>0 or 1</i>		4
<i>2</i>		25
<i>3</i>		27
<i>4</i>		44
Severity of the imaging finding reported in MRI		
Supraspinatus		
<i>None</i>		13
<i>Tendinopathy</i>		12
<i>Partial-thickness tear</i>		21
<i>Full-thickness tear</i>		54
Infraspinatus		
<i>None</i>		45

Subscapularis	<i>Tendinopathy</i>	16
	<i>Partial-thickness tear</i>	16
	<i>Full-thickness tear</i>	23
<i>Long Head of the Biceps</i>	<i>None</i>	31
	<i>Tendinopathy</i>	17
	<i>Partial-thickness tear</i>	38
	<i>Full-thickness tear</i>	14
	<i>Reduced</i>	45
	<i>Subluxation</i>	9
	<i>Dislocation</i>	8
	<i>Full-thickness tear</i>	38

Note – N = Number; ME = Musculoskeletal; MRI = Magnetic resonance imaging. Duration of Symptoms ranged from 5 months to 10 years.

During the univariate regression analyses, pain intensity ($\beta=-0.2$, $p=0.001$; 95% CI -0.31 to -0.05) and pain during rest ($\beta=-1.53$, $p<0.001$; 95% CI -2.37 to -0.7) were associated with MRPDS. None of the independent variables were associated with the MRPDS in the first multiple regression model (adjusted $R^2= 0.01$), while pain during rest ($\beta=-1.68$, $p<0.001$; 95% CI -2.6 to -0.7) was associated with MRPDS in the second multiple regression model (adjusted $R^2= 0.13$).

Sensitivity analysis suggested that the second multiple regression model was better adjusted than the first model ($F_{1,5}= 3.75$, $p<0.001$) and that adjusting both models for other possible confounding variables was not significant. We further tested the convergent fit indices of the second multiple regression model with Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC), which suggested to select just the variables pain intensity, pain during rest and number of tendons reported as abnormal. We created another multiple regression analysis with these variables as independent variables. This analysis suggested that pain during

rest ($\beta=-1.4$, $p<0.001$; 95% CI -2.2 to -0.59) was associated with MRPDS (adjusted $R^2=0.17$) and no significant difference was found with the second multiple regression model ($F_{1,14}=0.66$, $p=0.79$).

During model diagnosis, no aberrant and leverage points were found, the residuals of both models were normally distributed and the error variance was homoscedastic.

TABLE 2. Multiple linear regression for MRPD: $n=100$, adjusted $R^2=0.13$

Univariate Linear Regressions			Multiple Linear Regressions			
		Parameter estimate	Model 1	95% CI	Model 2	95% CI
Number of Abnormal Tendons						
	2	-0.46 ($p=0.45$)	-9.2 ($p=0.14$)	-21 to 3.35	-4.93 ($p=0.45$)	-8.13 to 18
	3	0.32 ($p=0.57$)	-0.2 ($p=.77$)	-1.65 to 1.24	0.08 ($p=0.9$)	-1.29 to 1.46
	4	0.95 ($p=0.1$)	0.83 ($p=0.1$)	-0.15 to 1.82	0.59 ($p=0.21$)	-0.35 to .54
<i>Supraspinatus</i>						
	Tendinopathy	-0.41 ($p=0.38$)	-2.39 ($p=0.23$)	-1.6 to 6.3	-1.9 ($p=0.36$)	-6.12 to 2.26
	Partial thickness tear	0.56 ($p=0.56$)	-1.61 ($p=0.3$)	-4.7 to 1.49	1.46 ($p=.36$)	-1.68 to 4.6
	Full-thickness tear	-0.41 ($p=0.44$)	-0.43 ($p=0.6$)	-1.21 to 2.07	-0.49 ($p=0.57$)	-2.22 to 1.24
<i>Infraspinatus</i>						
	Tendinopathy	-0.25 ($p=0.52$)	2.72 ($p=0.16$)	-1.1 to 6.55	-1.73 ($p=0.39$)	-5.76 to 2.28
	Partial thickness tear	-0.59 ($p=0.2$)	-3.3 ($p=0.1$)	-6.7 to 0.15	0.1 ($p=0.93$)	-2.67 to 2.88
	Full-thickness tear	-0.02 ($p=0.96$)	1.22 ($p=0.24$)	-0.87 to 3.3	0.4 ($p=0.8$)	-2.3 to 1.8
<i>Subscapularis</i>						
	Tendinopathy	0.04 ($p=0.93$)	2.47 ($p=0.17$)	-1.1 to 6.06	-1.85 ($p=0.37$)	-6 to 2.3
	Partial thickness tear	0.55 ($p=0.23$)	-1.47 ($p=0.27$)	-4.1 to 4.18	1.9 ($p=0.37$)	-1.23 to 5.19
	Full-thickness tear	-0.1 ($p=0.82$)	-0.8 ($p=0.88$)	-1.8 to 3	-1.43 ($p=0.17$)	-3.5 to 0.63
<i>Long Head of the Biceps</i>						
	Subluxation	0.52 ($p=0.39$)	0.64 ($p=0.34$)	-0.71 to 2	0.64 ($p=0.35$)	-0.72 to 2
	Dislocation	-0.18 ($p=.87$)	-0.25 ($p=.83$)	-2.7 to 2.1	-0.91 ($p=.46$)	-3.3 to 1.54
	Full-thickness tear	-1.28 ($p=0.39$)	-0.83 ($p=0.58$)	-3.8 to 2.2	-0.97 ($p=0.54$)	-4.1 to 2.19
Pain Intensity		-0.2 ($p=0.001$)**	-	-	-0.04 ($p=0.57$)	-0.19 to 0.1
Pain During Rest		-1.53 ($p<0.001$)***	-	-	-1.68 ($p<0.001$)***	-2.6 to -0.7
Number of Musculoskeletal Complaints						
	1	-0.67 ($p=0.12$)	-	-	-0.41 ($p=0.39$)	-1.3 to 0.55
	>2 or more	-0.01 ($p=0.96$)	-	-	-0.28 ($p=0.44$)	-1.03 to 0.45
Pain Duration		-	-	-	0.001($p=0.83$)	-0.05 to 0.05
R^2			0.01	-	0.13	-

The MRPDS was used as a dependent variable in Models 1 and 2. The independent variables of the first model were (1) number of tendons reported as abnormal and severity of the (2) supraspinatus, (3) infraspinatus, (4) subscapularis and (5) long head of the biceps imaging finding. In the second model, the variables (6) pain during rest and (7) pain intensity were added to the variables of the previous model as independent variables, and the model was further adjusted by pain duration and number of musculoskeletal complaints * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

DISCUSSION

In this study, we investigated if movement-related pain occurrence across clinically-relevant arm movements for people with chronic shoulder pain diagnosed by an orthopedic surgeon as subacromial pain syndrome was associated with the number of rotator cuff tendons reported as abnormal, or the severity of these abnormal findings on a MRI. Based on current literature, we hypothesized that movement-related pain that is reported across a wider variety of activities would not be associated with the number or severity of rotator cuff MRI findings.

Our hypothesis was confirmed. Neither the number of rotator cuff tendons reported as abnormal nor the severity of each tendon finding was associated with the pain occurrence across clinically-relevant arm movements and activities. These findings are consistent with other studies that investigated the association between general measures of pain intensity, disability, and the number and severity of imaging findings in individuals with chronic shoulder pain diagnosed with subacromial pain syndrome, which demonstrated that neither the presence of imaging findings nor the severity of the findings were associated with general measures of pain intensity or disability [5; 13; 37; 58].

Although some of these findings may fall within normal age-related changes, in Brazil, similar to other parts of the world, radiological reporting does not often include that information. Instead, radiological reports often simply described anatomy that differs from what is considered normal and people with shoulder pain are often diagnosed and treated based on these radiological labels.

Despite both pain during rest and pain intensity variables being associated with movement-related pain occurrence across activities during the univariate linear regression models, only pain during rest ($\beta=-1.68$, $p<0.001$; 95% CI -2.6 to -0.7) remained significant during multiple regression analysis. This means that individuals with a more widespread pain distribution across activities (i.e. subjects that reported pain across more activities) were more prone to present pain during rest, regardless of the other variables in the model. Therefore, clinicians should be aware that subjects with pain during rest may be more prone to report pain during more clinically-relevant arm movements. However, this does not imply causation and might happen by other factors that may be common causes for pain during rest and a more widespread pain occurrence through movements.

In summary, the findings of this study demonstrate that movement-related pain that occurs across a wider variety of arm movements in people with chronic shoulder pain diagnosed with subacromial pain syndrome was not associated with the number of rotator cuff tendons reported as abnormal or with the severity of each tendon finding, but it was positively associated with pain during rest.

Implications

The present findings have both clinical and theoretical implications. From a clinical perspective, the results of this analysis provide a deeper understanding about between- and within- individual differences in movement-related shoulder pain presentation. The number or severity of rotator cuff radiological findings on a MRI was not associated with pain occurrence across clinically-relevant arm movements for people with chronic shoulder pain.

This is in contrast with the common view that movement-related pain is an accurate representation of tissue damage [7; 11; 12; 21]. This view is not supported by current evidence [5; 13; 58] and, can in fact instill the belief that the body is damaged and needs protection, leading to fear, avoidance and escalation of care-seeking [51]. Therefore, the results of this study provide further support to recent calls for clinicians to move away from the reductionist pathoanatomical model to explain chronic shoulder pain, towards a multidimensional model [27]. Nevertheless, pathoanatomical factors should not be discarded completely for all shoulder patients, since other complaints (e.g. shoulder instability) may be associated with such factors.

On the theoretical level, our findings that a more widespread pain occurrence across movements is not associated with tissue damage, but with pain and disability (as outlined by our main analysis and during the construct validity presented in the supplementary file) provide insight about a person's protective response to a threat. These findings share similarities with previous research on other protective responses such as pain-related fear and fear of movement-related pain, in which a less precise and more contextual pain has been shown to lead to unbridled fear generalization to safe stimuli and contexts fostering sustained anxiety and excessive avoidance behavior, initiating a pathway toward disability in people with chronic pain [15; 25; 32; 60; 61].

Learning theory can also be used to shed light on the individual variability in movement-related pain in people with chronic pain [16; 32; 60]. Processes of non-associative learning in the form of peripheral or central sensitization were previously identified in people with chronic shoulder pain [4; 9; 39; 46] and could be related to movement-related pain occurrence. The association between the presence of pain during rest with a more widespread pain occurrence across activities found in our

study could be a sign of peripheral sensitization, since spontaneous pain is commonly viewed as a sign of a nociceptive mechanism of pain [47], or central sensitization if accompanied by a diffuse and disproportionate painful experience [39]. This could be adequately investigated in future studies.

Besides that, learned expectancy [53], threat discrimination [19], fear generalization and category-based or conceptual fear conditioning [10; 14; 22; 24; 32] have previously being associated with the contextual modulation of pain experience in healthy subjects and seems to be disturbed in subjects with other chronic pain conditions [17; 18; 20; 33-35]. Future studies should consider the role of these learning processes on explaining movement-related pain and its occurrence through movements in people with chronic shoulder pain.

Limitations

The main limitation of this study is its cross-sectional design. Therefore, it is not possible to infer causation between the associations found. Besides that, the approach to determine what would be the activities that were most commonly reported and associated with pain during daily life activities might not be representative of the role population of people with chronic shoulder pain, as it did not followed a delphi design.

Other activities not assessed by the questionnaires used at phase one to select the activities for the MRPDS might also be clinically important for people with shoulder pain. The only strength assessment in MRPDS, for example, was conducted with the arm to the side of the body. Since people with shoulder pain may report pain when tendons are loaded in other positions (e.g. overhead), this may be a potential limitation of the study.

Besides that, the results in this study are applicable to patients with chronic shoulder pain diagnosed with subacromial pain syndrome (mean duration of symptoms of 6 years), with very few years of study and with the majority being females (74%), not working (65%) and with 50% having 2 or more musculoskeletal complaints. Therefore, we cannot from this study rule out that the association between pain and structural abnormalities could be stronger in a different cohort (e.g. with shorter symptom duration, younger age).

Moreover, the MPRDS was developed for use in a population of patients with subacromial impingement and may not be immediately applicable to shoulder pain from other pathologies.

CONCLUSION

Our study provides evidence that neither the number of rotator cuff tendons or the severity of each tendon reported as abnormal on a MRI was associated with pain occurrence across movements and activities commonly perceived as painful by people with chronic shoulder pain diagnosed with subacromial pain syndrome. This is in contrast with the common view that movement-related pain is as an accurate representation of tissue damage and, therefore, that more pain or pain in more movements is an accurate measure of more tissue damage or more severe tissue damage. These findings provide insight to future research to further investigate which factors are associated with pain occurrence across movements in people with subacromial pain syndrome.

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Supplementary File

The Movement-related Pain Distribution Scale (MRPDS) and score calculation

The MRPDS was developed to assess the movement-related pain distribution in patients with shoulder pain. It is comprised of 10 activities and patients are invited to evaluate their pain during shoulder movements in a comparative way (always considering the score chosen for the last activity). The main outcome of the MRPDS is a number that represents the exponent mathematically modeled by the Stevens Power Law ¹²⁻¹⁵:

$$\psi(I) = kI^a$$

Where I is the intensity or strength of the stimulus in physical units (e.g. energy, weight, pressure, movement, etc.), $\psi(I)$ is the magnitude of the sensation evoked by the stimulus, a is an exponent that depends on the type of stimulation or sensory modality, and k is a proportionality constant that depends on the units used. The score of the MRPDS ranges from 0 to ∞ , which means that there is no maximum score for MRPDS. The closer to 0 the score is, the more widespread are the movement-related pain reports. The full scale can be found as [supplementary file \(S1\)](#).

Supplementary file S1- Movement-related Pain Distribution Scale – Shoulder (MRPDS)

Name: _____

Magnitude Estimation of Movement-Related Pain

Instruction 1: “With your arm relaxed at your side, you are feeling any pain in the shoulder?

Spontaneous pain during rest (yes/no): _____

Instruction 2: “Raise your painful arm to the height of your shoulder (90 degrees of shoulder flexion) in line with your sternum bone and then return your arm to the side of your body (**demonstrate the movement and ask the subject to execute it**). The pain intensity that you felt during the execution of these movements will be represented by the number 100 in a scale that goes from 0 to the infinity. It's important that you understand that this value does not equals 100% of pain”.

Movement 1:

Unilateral reach movement to 90 degrees of flexion in the middle bodyline:

Magnitude estimation: 100

Instruction 3: “Now you will perform the 9 other movements. After you finish each movement, you must judge how painful it was proportionally to the first movement. You can use any number you want to tell me how much of pain you felt in a scale that goes from 0 to infinity. For example, if the pain intensity during the execution of one of the movements was 2 times bigger than our reference movement (the first), the number should be 200. However, if you perceive that the pain intensity during the execution of one of the movements was just half the intensity of the reference movement, the number should be 50. If you do not feel any pain during a movement, the number should be 0.”

Observations: Demonstrate each movement at a time, following the sequence described above. Use an interval of 15 seconds between each movement in order to avoid symptoms sensitization. Request the magnitude estimations after each movement, even if the subject was not able to fulfill it.

Movements:

Movement 2:

Unilateral reach movement to 60 degrees of flexion in the middle bodyline:

Magnitude estimation:

Movement 3:

Unilateral reach movement to 180 degrees of flexion in the middle bodyline:

Magnitude estimation:

Movement 4:

Bilateral reach movement to 60 degrees of flexion in the middle body line:

Magnitude estimation:

Movement 5:

Bilateral reach movement to 90 degrees of flexion in the middle body line:

Magnitude estimation:

Movement 6:

Bilateral reach movement to 180 degrees of flexion in the middle body line:

Magnitude estimation:

Movement 7:

Hand to the mouth with the painful arm

Magnitude estimation:

Movement 8:

Hand to the head with the painful arm

Magnitude estimation:

Movement 9:

Hand to the back pocket of the pants with the painful arm

Magnitude estimation:

Movement 10:

Sustain 4 kg of resistance with the painful arm next to the body

Magnitude estimation:

Instructions on how to use the Movement-related Pain Distribution Scale -

MRPDS

In cases where there is no movement-related pain in the reference movement, the examiner should proceed normally with the assessment until a new reference function is identified. If this is not the case, the exponent of the Power Function Law (MRPDS) is considered 0.

Participants should be encouraged to use any numeric value to make their judgments, but to always keep the notion of proportionality between the intensity of the perceived pain during the course of the last movement and the reference value to make their judgments. These instructions were adapted from other psychophysical studies that used magnitude estimation procedures to evaluate perceptual continuums ¹²⁻¹⁵ and pilot tests were performed with the patient population in order to evaluate their interpretability.

Content Validity

We conducted the pilot study to verify the content validity of the MRPDS. With the main goal of developing a ratio scale capable of assessing movement-related pain distribution across daily activities that require arm movements in a pragmatic way, we performed a ranking procedure among 30 of the first selected subjects to determine what would be the activities that were most commonly associated with painful complaints in their daily lives. Thereby, 16 movements related to reach, grasp and manipulation with the upper limbs were initially selected from three instruments: Constant-Murley ², Shoulder Pain and Disability Index ⁷ and American Shoulder and Elbow Surgeons Questionnaire ¹. After this initial selection, participants were

instructed to confirm if the chosen tasks corresponded to the complaints of movement-related pain faced in their daily lives. Using a 90% concordance rate among participants, 10 activities were selected.

General sample characterization and Statistics

A sample of 100 patients with chronic shoulder pain was enrolled to check for reliability, construct validity, and structural validity. We evaluated 100 patients who fulfilled the eligibility criteria (mean age 55 ± 8.5 years). The statistical analysis was performed using the software Statistica 10 (StatSoft, Inc., USA). A full descriptive analysis for each measurement property can be found below.

Reliability

The reliability assesses the degree to which respondents may be distinguished from each other despite measurement error¹⁷. The inter-rater reliability was verified between two raters and the application of the scale was carried out with a time interval of 15 minutes between the two raters. The short time frame between assessments was adopted to avoid clinical fluctuation of the symptoms and to guarantee clinical stability of the shoulder condition⁹. The inter-rater reliability was calculated by Intraclass Correlation Coefficient (ICC). ICC values above 0.70 were considered acceptable^{17, 18}. We showed acceptable reliability for all functions, with an average ICC of 0.86 (CI95%: 0.82 to 0.9). This finding shows an acceptable reliability for the MRPDS score^{8, 9}.

Internal Consistency

The internal consistency was used to test the homogeneity of the items of the instrument. It was analyzed by means of the Cronbach's alpha coefficient from the numerical magnitude estimations of each movement. We considered Cronbach's alpha values between 0.70 and 0.95 as representatives of acceptable reliability^{8, 9, 17}. The internal consistency analysis using the Cronbach's alpha value was acceptable ($\alpha = 0.79$).

Construct Validity

The construct validity refers to the degree to which the scores of a patient-reported outcome measures (PROM) are consistent with hypotheses based on the assumption that the PROM validly measures the construct to be measured¹¹. Our construct validity hypotheses were: (H1) the MRPDS score should have a weak to moderate correlation with shoulder disability scores (i.e. SPADI disability score) and (H2) with pain intensity scores (i.e. visual analogue scale score and SPADI pain score). The construct validity was investigated by the Pearson Correlation test (r) with the SPADI disability, SPADI pain, and pain visual analogue scale (VAS) scores¹⁷. Correlation was considered weak if $r < 0.30$; Moderate if $0.30 \leq r < 0.60$ and strong if $r \geq 0.60$ ¹⁰.

We confirmed our hypothesis of a moderate correlation between MRDPS and SPADI disability score ($r = -0.41$) and between MRDPS and pain intensity ($r = -0.31$). However, we did not find any correlation between MRDPS vs. SPADI pain domain ($r = -0.28$). Hence, we found supporting evidence for two out of three of our hypotheses raised a priori.

Structural Validity

The structural validity is defined as the degree to which scores of a questionnaire are an adequate reflection of the dimensionality of the construct to be measured ⁹. An Exploratory Factor Analysis (EFA) was used to investigate the structure of the MRPDS (extraction method: maximum likelihood) with promax rotation to obtain the following: Kaiser-Meyer-Olkin test (KMO), Bartlett's Test of

Table S2. Exploratory factor analysis (n=100): factor loading, eigenvalues and Percentage of cumulative variance for items and domains.

Sphericity (BTS), the percentage of explained variance, eigenvalues and factor loadings. The KMO is calculated by the square of the total variable correlations divided by the square of the partial variable correlations, measuring the variance among the items which can be explained by a latent variable ⁶. Hair et al. ⁴ suggested 0.50 as an acceptable level for KMO. The BTS evaluates how much the covariance matrix is similar to the identity matrix by checking the values with zero being indicative of a lack of correlation ⁴. BTS values with $p < 0.05$ indicate that the matrix is factorial ¹⁶. The percentage of explained variance is acceptable at 50% ³. The number of retained factors is the one with eigenvalues higher than one ³. Eigenvalues are variances of the factors that make up a given model ⁵. The items with factor loadings lower than 0.3 should be excluded ³.

The EFA for MRDPS showed acceptable KMO values for MRPDS (0.84) and Bartlett index ($p < 0.001$). The best solution showed two factors for MRPDS scale considering eigen

Tasks	Factor Loading
Unilateral reach with the affected limb at 90° of flexion	0.32
Unilateral reach with the affected limb at 60° of flexion	0.66
Unilateral reach with the affected limb at 120° of flexion	0.63
Bilateral reach at 60° of flexion	0.72
Bilateral reach at 90° of flexion	0.73
Bilateral reach at 120° of flexion	0.71
Hand to the mouth	0.59
Hand to the head	0.66
Hand to the back pocket of the pants	0.46
Sustain 4 kg of resistance with the affected limb next to the body	0.49
Percentage of Explained Variance	42%
Eigenvalue	4.2

values higher than one ³. Whereas the scale showed a low explained variance (43%) when considering the one-factor solution, the items showed acceptable factor loadings (>0.3) in the one-factor structure, hence the unidimensional solution was considered as it supports the conceptual model a priori hypothesized (TABLE S2).

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Chapter 4

Distorted distance perception to reachable points in people with chronic shoulder pain

Perception has evolved to guide action. Since the physiological state of the body and the environment around us are constantly changing over time, perception may work as an adaptive interface to facilitate our interaction with the environment and the selection of behaviors that favor survival ([23](#), [136](#), [341](#)). Therefore, as individuals in pain learn to predict harmful situations and modify their behavior to avoid and/or control symptoms, it would be worthwhile to investigate if perceptual distortions might occur in subjects with chronic musculoskeletal pain.

Researchers have proposed that when people are in pain, spatial distortions may occur to facilitate the selection of safety behavior, although evidence for this is currently mixed ([342-344](#)) and research scarce. Since perception of the environment has significant implications for how and whether we interact with it, the possibility that people in pain could have altered perception has significant implications for understanding behaviors that might contribute to ongoing dysfunction. For example, the FAM posits that avoidance behaviors prevent the extinction of acquired pain-related fear, thus perpetuating a cycle of disuse leading to physical and social dysfunction ([103](#)). One contributor to avoidance may be spatial distortions that result in objects appearing further away. While initially adaptive, this may be subsequently harmful.

In the case of shoulder pain, reaching tasks and overhead actions frequently become predictors of pain. Skewing spatial perception in such a way that objects outside of known pain-free reach appear further away may be advantageous by discouraging reaching into painful range.

The aim of this study was to investigate if patients with chronic shoulder pain have perceptual distortions. We aimed (1) to compare distance perception within and beyond reaching distance between people with and without shoulder pain; (2) to

compare perceived length of the painful limb relative to the non-painful limb and to the control group; and (3) to investigate whether spatial distortion is correlated with the strength of the relationship between pain and movement. We hypothesized that in people with shoulder pain (1) points within and outside reach would appear more distant; (2) that the perceived size of the painful limb would be reduced relative to the pain-free arm and to controls, and (3) that spatial distortions would correlate with the degree that pain is related to movement.

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Original article

Distorted distance perception to reachable points in people with chronic shoulder pain

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ABSTRACT

Perception is not simply a carbon copy of the real world, but is subject to distortions that may reflect protective drive. This study aimed to investigate whether people with chronic shoulder pain show perceptual distortions of space and body that may promote protective behavior. Eighty-four people with shoulder pain and 51 healthy controls participated. Participants estimated (1) distances to points on a cork-board within and outside reaching distance, and (2) the perceived length of their own arms. A novel measure of movement-related pain was also used to determine whether movement-related pain relates to perceptual distortion. Overall, distance and arm length estimates did not differ between groups, nor did participants perceive their arms to be of different length. However, a moderate correlation between movement-related pain and the index of distance perception was found within the pain group, specifically for distance estimates to points within reach. Our results suggest that distorted perception is not a typical consequence of chronic shoulder pain; however, that it may occur in cases where pain is strongly linked to movement. Our findings have implications for understanding avoidance of movement in people with persistent pain.

1. Introduction

Perception has evolved to optimise action, rather than to perfectly represent reality (Hoffman and Singh, 2012; Clark, 2013). Since the physiological state of the body and the environment around us are constantly changing over time, perception may work as an adaptive interface to facilitate selection of behaviors that favor survival (Williams et al., 2012; Hoffman et al., 2015).

Famously, people are known to over-estimate the gradient of terrain during periods of fatigue, when under load, or when in poor physical condition (Proffitt, 2006). This equates to a scaling of spatial perception in accordance with bodily state - an example of what is posited by the economy of action hypothesis (Proffitt, 2006). Some researchers have proposed that when people are in pain, spatial perceptual distortions may occur to promote safety behaviors, such as avoidance of movement (Tabor et al. 2013, 2016), although research on this idea is scarce and

results mixed. Understanding altered spatial perception in people with pain could assist in understanding avoidance behaviors that may contribute to ongoing dysfunction (Vlaeyen et al., 2016).

Following shoulder injury, adaptations to spatial perception that make objects seem to be further away, may initially be advantageous in discouraging movement and promoting rest. In the long term, however, adaptations that continue to discourage movement may contribute to a cycle of disuse and disability. In this study, we aimed (1) to compare distance perception within and beyond reaching distance between people with and without shoulder pain; (2) to compare perceived length of the painful limb relative to the non-painful limb and to the control group; and (3) to investigate whether spatial distortion is correlated with the strength of the relationship between pain and movement. We hypothesized that in people with shoulder pain (1) points within and outside reach would appear more distant; (2) that the perceived size of the painful limb would be reduced relative to the pain-free arm and to

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controls, and (3) that spatial distortions would correlate with the degree that pain is related to movement.

2. Materials and methods

2.1. Participants

A convenience sample of 84 people with shoulder pain (60.7% female, mean age 65 ± 9.4 years old) and 51 healthy volunteers (68.62% female, mean age 57 ± 11.52 years old) participated. A preliminary analysis using G*POWER showed that these sample sizes would be required in order to guarantee 80% of power in the primary statistical analysis. Participants with shoulder pain were consecutively selected from the Shoulder and Elbow Group at the Orthopedic Institute of the Clinical Hospital of São Paulo.

Participants were eligible for the shoulder pain group if they were: right-handed, symptomatic in their dominant shoulder, sedentary for the preceding six months and had shoulder pain for at least the preceding three months. Potential participants were examined by a physician to exclude shoulder complaints resulting from cervical spine dysfunction. Cognitive deficits, use of medications for pain control in the preceding 24 h, neurological diseases, signs of adhesive capsulitis (limited passive range of shoulder motion: external rotation $< 30^\circ$; elevation $< 150^\circ$), previous shoulder surgery, and rheumatic diseases were used as additional exclusion criteria.

Pain-free participants were included in the control group (CG). A history of pain lasting more than three months or pain present at the time of testing were used as exclusion criteria.

2.2. Assessments

Sociodemographic data were recorded on a questionnaire and handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971).

2.2.1. Procedure and apparatus for the distance estimates

Participants used a ratio judgment to estimate the distance between their index finger and nine evenly spaced points on a cork-board. To standardize the position, participants stood facing the cork-board, with their right limb supported in a neutral position with the elbow flexed to 90° and index finger extended. The sternum was aligned with the center of the cork-board, and the height of the board was adjusted such that the subject's elevated arm would point directly at the central point with 90° of shoulder flexion. Depending on the stage of the test, participants were moved such that their index finger was exactly 45 cm or 100 cm from the central point (see Fig. 1).

To introduce the concept of a ratio judgment for distance estimates, all participants performed an initial task in which they were asked to judge the length of a series of lines in proportion to a 5 cm reference line that was always visible. The participants made 10 judgments and the only instruction they had was to use the 5 cm line as a length reference. That is, if they perceived the distance to be equivalent to 4 times the 5 cm reference line, they would estimate the distance as 20 cm. No performance feedback was given during this initial task.

Next, participants were instructed to estimate the distance from the index finger of the dominant hand to each of the nine points in a pseudo-random order.

2.2.2. Pain measurement

Movement-related pain was assessed using another ratio judgment method known as the numeric magnitude estimation procedure (Stevens, 1957, 1958b, 1959, 1960; Stevens, 1958a). The participants were instructed to reach toward the central point of the cork-board, and to consider the associated pain to be of a magnitude of 100 (Alaiti et al., under review a, b). Next, participants reached to each of the remaining points and rated their pain relative the 100 point reference. For

Fig. 1. Participant positioning during the distance judgement task.

example, if reaching to a given point evoked twice the pain of the reference movement, they would rate that pain as 200. The assessment of movement-related pain were made prior to the distance judgments in order to systematize the pain reference that subjects would use to make the estimates. If no pain occurred when reaching to the central point, the test proceeded until a painful movement was experienced. In this way, the first experienced pain formed the 100-point reference value for subsequent ratio judgments. If no movements were painful, the score remained 0.

2.2.3. Arm length judgment

Following the distance judgments, participants estimated the lengths of their arms. To do this, participants were first shown a 30 cm measuring tape as a length reference. The experimenter then touched the participant's right acromion and the tip of the index finger to clarify the anatomical reference points for the subsequent task. Next, the participant raised their right arm to 90° of shoulder flexion with their eyes closed, and were asked to verbalize the perceived length of the right arm. Finally, the participant raised both arms to 90° of shoulder flexion, stated whether they perceived a difference between the size of the two arms (yes/no), and then judged the size of the left arm. Participants were asked if there was a perceived difference first, in order to discourage them from simply reciting the initial estimate.

2.3. Statistical analysis

The statistical analysis was performed using Statistica (v.10, StatSoft, Inc., Tulsa, USA).

Because participants had not been randomly allocated to the groups, a logistic regression analysis was conducted to identify if there was any baseline demographic difference between the groups. Firstly, a univariate logistic regression was used to verify each variable. If one of the variables reached the criterion significance level ($p < 0.2$) a multivariate analyses was to be conducted to further examine interactions between the variables. The analyses were considered statically significant if $p < 0.05$.

The pain ratings corresponding to reaching to the nine spatial points were used to generate an index that expressed the relationship between

pain and movement. We have previously tested and validated this method in people with chronic shoulder pain (Alaiti et al., under review a, b). This index was constructed according to the mathematical model of Stevens's Power Law (Stevens, 1957, 1958b, 1959, 1960; Stevens, 1958a): the pain ratings for the nine movements were first ordered from lowest to highest and then plotted in a power function in order to generate the exponent of the Power Function Law, that will henceforth be referred to as the index of movement-related pain (IMRP).

According to this mathematical model, individuals with a greater number of painful movements and a lower variability of pain will produce lower exponents, while individuals with fewer painful movements, and/or a greater variability of pain across movements, will produce higher exponents. Practically speaking, if an individual's pain hardly varies between different movements, the IMRP will be lower. On the other hand, if an individual reports low levels of pain when reaching to the lower points, but high levels of pain when reaching to the higher points, then they will have a higher IMRP. Thus, the extent to which movement and pain are related can be indexed using the IMRP in a way that is not possible using a simple Visual Analogue Scale.

In order to quantify the overall accuracy of the distance judgments made from 45 cm to 100 cm, we used a mathematical model similar to that used for the relationship between pain ratings and movements to generate an 'index of distortion'. However, in this case the distance estimates were not ordered in an increasing way but were derived by plotting the real distances on the y-axis against the estimates on the x-axis to form a power function in which an exponent of 1 is the most accurate judgment possible. In other words, the closer this index is to 1, the more precise was the judgment. Judgments that were over- or under-estimated would produce numbers greater or less than one, respectively.

The arm size judgments were analyzed by means of two measures. First, an index of perceptual distortion was calculated for the affected arm by dividing the estimated arm size by the actual arm size (from the tip of the index finger to the acromion). Second, the index of perceptual distortion of the affected arm was divided by the index for the healthy arm.

2.3.1. Primary analyses: between-group effects

To test the hypothesis that people with chronic shoulder pain would perceive spatial points as more distant, a one-way ANOVA was conducted using the IMRP at 45 cm and 100 cm as the dependent variable. The Bartlett test of homogeneity of variances was used prior to the ANOVA to test whether a correction should be used.

To test the hypothesis that people with chronic shoulder pain would perceive their affected limb as shorter than their non-painful limb, two independent student t-tests were conducted to test for differences in perceived arm length ('index of distortion') (1) between arms, in the pain group only, and (2) between groups.

2.3.2. Secondary analyses: within-group effects

To test the hypothesis that spatial distortions would correlate with the strength of the relationship between pain and movement, we performed two two-sided Spearman Rank Order correlation analyses between (1) the IMRP and distance estimates, and (2) the IMRP and estimates of upper limb length. Only data from the shoulder pain group were used for these analyses. This non-parametric test was chosen because visual analysis of histogram plots suggested that the data were not normally distributed.

3. Results

3.1. Group characteristics

The logistic regression analysis confirmed that groups were not statistically different at baseline with respect to demographic data. Participant characteristics are presented in Table 1.

Table 1

Group's characteristics.

Variables	Shoulder pain	No pain	p
N	84	51	–
Age	65 ± 9.4	57 ± 11.52	0.2
Sex	60.7% females	68.62% females	0.15
Years of Study	6.76 ± 3.77	9.27 ± 4.9	0.09
Duration of Symptoms	90.61 ± 78.4	0	–
ELD	1 ± 0.19	1 ± 0.16	–
EDP45	1.24 ± 0.55	1.08 ± 0.64	–
EDP100	1.51 ± 0.94	1.71 ± 1.12	–
IMRP	2.21 ± 2.17	0	–
IDPA	1 ± 0.38	1 ± 0.22	–
IDBA	0.99 ± 0.12	0.98 ± 0.07	–

The values represent the mean ± SD unless otherwise indicated. Abbreviations: Duration of Symptoms in months; ELD, exponent of line distortion; EDPs, exponent of distance perception; IMRP, index of movement-related pain; IDPA, index of distortion of the painful arm; IDBA, index of distortion between the arms.

3.2. Primary analyses: between-group effects

One-way ANOVA showed no statistically significant difference between the groups in estimates of the distance to the spatial points ($F(1,132) = 1.28$, $p = 0.259$). Likewise, student t-tests showed no statistically significant difference in perception of arm length between groups ($t[120.15] = 0.4$, $p = 0.68$) or between sides ($t[132.84] = 0.48$, $p = 0.62$).

3.3. Secondary analyses: within-group effects

In the group with shoulder pain, the index of movement-related pain had no correlation with the index of distortion of the painful arm (Spearman's $\rho = 0.13$, $p = 0.22$) and the index of distortion between arms (Spearman's $\rho = 0.05$, $p = 0.65$), but a moderate correlation was found with the index of distance perception (Spearman's $\rho = 0.30$, $p = 0.011$). Notably, this correlation was found only at the standing distance of 45 cm away, and was non-significant at the 100 cm distance (Spearman's $\rho = 0.10$, $p = 0.11$).

4. Discussion

In this study, we aimed to compare distance perception between people with and without shoulder pain, to compare the perceived length of the painful limb relative to the non-painful limb and relative to the control group, and to investigate whether spatial distortion is related to the strength of the relationship between pain and movement. We hypothesized that in people with shoulder pain, points within and outside reach would seem further away, the perceived length of the painful limb would be reduced relative to the pain-free arm and to controls, and spatial distortions would correlate with the strength of the relationship between pain and movement.

The hypothesis that points within and outside reaching distance would appear more distant was not upheld, in that no overall group differences were found for any index of distance perception. The hypothesis that perceived size of the painful limb would be reduced was also not upheld, in that no side or group differences were found. In contrast, the hypothesis that spatial distortions would be more pronounced in people who showed a strong relationship between pain and movement was supported, in that the index of spatial distortion showed a moderate positive correlation with the index of movement-related pain. This suggests that individuals with strongly movement-linked pain tended to overestimate the distance to spatial points. Notably, this relationship was only significant at the 45 cm distance from the board containing the spatial points, and not at the 100 cm distance. This may

indicate that this perceptual distortion is specific to distances to objects that are located within reach.

4.1. Implications

Our results clearly show that distorted perception is not a universal consequence of having shoulder pain. Rather, our results suggest that perception may be distorted in some patients, depending on at least two factors. First, distortion may depend on the behavioral relevance of the target in question. That is, a given distance may be more likely to be overestimated if it is possible to reach to that distance. This suggestion seems plausible, but would need to be verified in future studies that directly manipulate behavioral relevance. Second, distortions may occur only in perceptual domains that are linked to, or can predict, painful interactions. Conversely, when movement is not linked to pain, as in those participants with low IMRP, spatial distortion does not occur.

In contrast to what has previously been shown for pain in other body regions (Moseley et al., 2012; Gilpin et al., 2015), we did not find distortions in the perceived length of the symptomatic upper limb relative to the unaffected arm and to pain-free controls. This may relate to the nature of the painful conditions studied, which may involve altered sensory perception to differing degrees.

That the perception of the external environment might be influenced by bodily state is consistent with the economy of action hypothesis. This theory suggests that conscious perception is an inference that can be optimized to serve protection and energy efficiency. The theory has previously been explored in other domains (Proffitt, 2006; Witt et al., 2004; Tabor et al., 2013, 2015, 2016). Interestingly, previous experimentation in clinical populations has so far failed to support theoretical predictions of the economy of action hypothesis in people with persistent pain. Tabor et al. (2016) asked people to estimate distance to a series of target cones to which they were to walk. Participants with various chronic pain conditions were found to estimate the distances similarly to their pain-free peers. Critically, in the current study, participants made judgments about the distances to the spatial points without the intention to interact with those points. That the current study found spatial distortions when measuring judgments towards inert spatial points, suggests that distortions might be present prior to the intention to act.

The current findings are relevant to understanding perception-related clinical complaints and the processes that underlie avoidance behaviors in some patients with chronic shoulder pain. Previous studies have demonstrated that avoidance is a major component in subjects with chronic pain (Vlaeyen and Linton, 2012) and a number of mechanisms may contribute to it, such as catastrophizing beliefs (Vlaeyen et al., 2016), classically conditioned fear (Meulders et al., 2016), operant conditioning (Meulders et al., 2016) and vicarious learning (Goubert et al., 2011). Altered spatial perception may also play some role in the perpetuation of avoidance behaviors, although our data suggests this might be limited.

Besides that, uncommon verbal reports about subjective sensations may occasionally occur in clinical practice, such as abnormal body sensations in patients with fibromyalgia (Martínez et al., 2018). Knowledge of these processes may help clinicians to reassure their patients during the rehabilitation process, thus deconstructing potentially confusing beliefs about perception-related clinical complaints that may incite fear and anxiety about their clinical condition.

4.2. Limitations

The current study has several limitations. Most notably, the cross-sectional nature of this study does not allow us to test for causative relationships between movement-related pain, perceptual distortions and avoidance behaviors in subjects with chronic pain complaints. Further, we can only posit the possible mechanisms underlying our

results. Finally, the lack of between-group effect for the primary analysis reduces our confidence when inferring meaning from the secondary analysis and, as such, some caution is required when drawing conclusions.

5. Conclusion

In this study, we aimed to investigate the accuracy of distance perception between the painful arm and points within and outside reaching distance, in people with chronic shoulder pain. Further, we aimed to investigate whether the extent of spatial distortion is dependent on how strongly movement and pain are related. Our hypothesis that people with chronic shoulder pain would show distorted spatial perception relative to controls was not supported. However, within the patient group, spatial distortions did correlate with the strength of the relationship between pain and movement, suggesting that spatial distortions may occur when pain is strongly linked to movement. Notably, this relationship was only significant when estimating the distance to points within reaching distance, suggesting that perceptual distortions depend on behavioral relevance. These findings may assist in understanding the mechanisms underlying phenomena such as avoidance behaviors and learned non-use behaviors in some patients with persistent shoulder pain.

Conflicts of interest

This study was approved by the Ethics Committee on Human Research of the Psychology Institute of the University of São Paulo and follows the statements of the Declaration of Helsinki. Conflicts of Interest: There are no conflicts of interest.

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Chapter 5

Mechanisms of Action of Cognitive-Behavioral and Exercise-Based Interventions for Pain and Disability in People with Chronic Musculoskeletal Pain

The first step of evidence-based practice is to choose among the available evidence-based treatments for the targeted health condition ([325](#)). Although active interventions such as exercise or cognitive-behavioral approaches are all effective on reducing pain and disability in people with chronic musculoskeletal pain, effect sizes are often small ([20](#), [333-336](#)). This raises the question if available approaches are targeting the right mediators of effect, or if there are common mechanisms that explain the small mean effects of all these treatment approaches. One way to answer this question is to better investigate how pain interventions work (or not).

Mediators (i.e. a variable by which one intervention affects an outcome ([345](#))) studied from randomized clinical trials provide information about the mechanisms by which an intervention works ([346](#), [347](#)). Systematic reviews of mediation studies do exist for chronic low back pain ([348](#), [349](#)), but to our knowledge, no other study tried to systematize the mechanisms of action of cognitive-behavioral and exercise-based interventions for people with chronic musculoskeletal pain as a whole.

This review aimed to systematically identify and synthesise studies that conducted mediation analyses of randomized controlled trials that test or estimate indirect effects of cognitive-behavioral and exercise-based interventions for pain and disability in people with chronic musculoskeletal pain.

This chapter is currently under review at Pain. Alaiti RK, Castro J, Lee H, Caneiro JP, Vlaeyen JWS, Kamper SJ, Costa MF.

What are the Mechanisms of Action of Cognitive-Behavioral and Exercise-Based Interventions for Pain and Disability in People with Chronic Musculoskeletal Pain? A Systematic Review and Meta-analysis of Mediation Studies from Randomized Controlled Trials

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Abstract:

This systematic review examined studies that used mediation analysis to investigate the mechanisms of action of cognitive-behavioral and exercise-based interventions for pain and disability in people with chronic musculoskeletal pain. We searched five electronic databases for articles that conducted mediation analyses of randomized controlled trials to either test or estimate indirect effects. We found 40 studies (n=8354), including 193 mediation models examining the role of 39 putative mediators on pain or disability, of which 19 partially mediated treatment effect; 15 had mixed results and 5 did not mediate treatment effect. The conditions studied were chronic whiplash-associated pain, osteoarthritis, chronic headache, fibromyalgia, chronic temporomandibular disorder, chronic low back pain and mixed group of chronic pain. Unstandardized regression coefficients of the indirect effect, treatment-mediator, mediator-outcome and total effects were transformed to standardized correlation coefficients and pooled when homogeneity was considered sufficient. We conducted one meta-analysis estimating the mediating role of self-efficacy on disability in exercise-based interventions and 5 meta-analyses estimating the mediating role of acceptance, fear-avoidance beliefs and psychological flexibility on disability and of psychological flexibility on pain in cognitive-behavioral interventions. We found no evidence of mediating effects of these putative mediators. Methodological limitations were common. There are substantial gaps with respect to understanding how cognitive-behavioral and exercise-based interventions work to reduce pain and disability in people with chronic musculoskeletal pain.

Keywords: Chronic Pain, Mediation, Mechanisms of Action, Exercise, Cognitive-Behavioral.

1. Introduction

Chronic pain is among the most burdensome health conditions worldwide [45]. Since 1990, chronic low back pain and other chronic painful musculoskeletal conditions have been the leading causes of years lived with disability in most countries [45; 66]. Although active treatment approaches, such as cognitive-behavioral and exercise-based interventions, are effective in reducing pain and disability for people with chronic musculoskeletal pain [8; 14; 58; 71], most interventions are not superior to each other and the effects sizes are often small [1; 30; 38]. A possible explanation is that most interventions do not sufficiently target relevant mediators, or may work through similar mechanisms despite their complex proposed mechanisms of action [4]. Better understanding of the underlying mechanisms of cognitive-behavioral and exercise-based treatment effects is important for the optimisation and refinement of these complex interventions [34].

Studying the role of mediators in randomized clinical trials can generate evidence about the mechanisms by which an intervention causes an outcome [32; 67]. Although systematic reviews of mediation studies exist for chronic low back pain [36; 44], no review has tested the mechanisms of cognitive-behavioral and exercise-based interventions for chronic musculoskeletal pain in general. Understanding treatment mechanisms would save valuable research resources by identifying more promising clinical hypotheses to be tested in randomized clinical trials. Further, better understanding of mechanisms of action would allow interventions for pain conditions to precisely target mediators of treatment effect, based on empirical evidence rather than presumptive theories about how interventions work. Finally, a review with a broader scope might provide insights about shared mechanisms of action across interventions and conditions.

This review aimed to identify and synthesise the results of studies that conducted mediation analyses of randomized controlled trials that test the indirect effects of cognitive-behavioral and exercise-based interventions for pain and disability in people with chronic musculoskeletal pain.

2. Methods

2.1. Protocol and Registration

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement [47; 51]. The review protocol was prospectively registered on PROSPERO (CRD42020198188), accessible at

https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020198188, and on the Open Science Framework (<https://cutt.ly/4xwuBIL>). Deviations from the pre-registered protocol are documented in the following sections.

2.1. Eligibility Criteria

We included randomized controlled trials of cognitive-behavioral and exercise-based interventions on pain and disability in subjects with chronic musculoskeletal pain that conducted mediation analyses. Studies that included individuals 18 years or older with chronic musculoskeletal pain longer than 3 months, including neck pain, headache, temporomandibular disorders, low back pain, shoulder pain, hip pain, knee pain, osteoarthritis and fibromyalgia were included. Studies that included patients with specific pathology (e.g. fracture, cauda equina syndrome, malignancy, full thickness rotator cuff tear or spinal stenosis) were excluded. Studies with mixed populations and varying pain duration were only included if 75% or more of the participants met the condition and duration criteria.

Interventions that used cognitive-behavioral (including cognitive behavioral therapy, acceptance and commitment therapy, cognitive functional therapy, graded activity, operant therapy, graded exposure, exposure in vivo, respondent therapy, lifestyle interventions and mindfulness-based interventions) and exercise-based approaches (including general or specific exercises, motor control exercises, McKenzie, Yoga, Pilates, stretching), in comparison to passive or active controls, for pain or disability in subjects with chronic musculoskeletal pain were included. Education was defined as a cognitive-behavioral intervention if it pertained to cognitive and psychological aspects associated with pain such as knowledge, beliefs, fear, stress or relaxation, with a didactic mode of delivery (e.g. a lecture or a session).

We included studies that formally conducted a mediation analysis (eg, product of coefficient test, difference in coefficient test, Baron and Kenny's causal steps of mediation, structural equation modelling, causal mediation analysis) or significance tests of mediation (eg, Sobel's first-order test). We did not exclude studies based on the mediators that were studied.

Studies that did not conduct formal mediation analyses, studies without a control group and non-standard randomized designs (e.g. stepped wedged designs), studies not written in English or studies that did not test or estimate indirect effects were excluded. Only studies published in peer-reviewed journals were included. Conference proceedings, preprints, dissertations and non-original research were excluded.

2.3. Search Strategy

On October 1, 2020, an electronic search was conducted in the following databases: PubMed, CINAHL (via EBSCOhost), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and PsychINFO (via EBSCOhost). All databases were searched from their inception. The search strategies outlined by the Cochrane Back Review Group were used to identify studies including low back pain and neck pain. The search strategy of other systematic reviews were used to identify studies including other painful conditions [19], cognitive-behavioral interventions [26; 71], exercise-based interventions [23], and studies that conducted mediation analyses [5; 33]. The full search strategy is available in the supplementary file.

The search results were downloaded into EndNote (EndNote X9 Thomson Corporation) and duplicates were removed. R.K.A. and J.C. independently screened titles and abstracts and selected articles for full-text review using the inclusion/exclusion criteria and independently reviewed the full texts to determine eligibility. R.K.A. and J.C. resolved disagreements through discussion and reaching consensus. H.L. was consulted for consensus if disagreements persisted. Furthermore, we hand-searched the reference lists of included studies for eligible articles.

2.4. Data Extraction

Two reviewers (R.K.A. and J.C.) independently extracted data using a data extraction form developed for the study. We extracted information about the study, including year of publication, journal and sample size; participant characteristics (age, gender, pain condition and duration); characteristics of the intervention (type and content); mediators and outcome variables (construct, measurement tool, time of measurement); mediation analysis approach; measures taken to control for confounding; testing of moderated mediation paths; standardized or unstandardized coefficients, precision of estimates and significance levels of the relevant paths (treatment-mediator, mediator-outcome, total, direct and indirect effects); and the authors' conclusion(s).

2.5. Data Synthesis and Analysis

The beta-coefficients of the indirect, treatment-mediator, mediator-outcome, and total effects were synthesized. Before pooling, we organised the data by type of intervention (exercise-based, cognitive-behavioral or combined), time frames (short-term; ≤ 2 months, intermediate; between 2 and 12 months and long-term; ≥ 12 months), outcome (pain or

disability), mediator and condition. We pooled data when more than one study reported on the same mediator and outcome and were assessed by similar measurement tools at similar time points. We only pooled studies that controlled for possible confounding variables. Before pooling the data, the scoring method of each measurement tool were analyzed for potential differences in signs across instruments.

Analyses were performed in R (The R Foundation for Statistical Computing) with the metacor package [16]. The beta-coefficients for individual studies were transformed to correlation coefficients [53] using the esc package [41], and subsequently pooled using random-effects meta-analysis. For each analysis, we used standardized correlation coefficients and sample sizes to calculate a pooled effect size for the indirect, treatment-mediator, mediator-outcome, and total effects [3; 53]. We assessed heterogeneity using the I^2 statistic and assigned thresholds of 25%, 50% and 75% to reflect low, moderate, and high heterogeneity [27].

2.6. Study Quality Assessment

The quality of the included studies were assessed via criteria outlined by Mansell et al. [44]. Two independent reviewers (R.K.A. and J.C.) scored each of the 7 criteria: 1 (yes) or 0 (no). The sum of these scores were used to reflect the overall quality for each study.

3. Results

3.1. Study Selection

A total of 17,552 records were identified through the database search and hand searching of reference lists (Figure 1). After duplicate removal, a total of 15,639 records were screened. After title and abstract screening, 55 studies remained for full text-screening, 40 studies met the inclusion criteria and were included in the systematic review (Figure 1). A description of the characteristics of excluded studies is provided in Tables S1 in the supplementary file.

Figure 1. PRISMA flowchart.

3.2. Description of Studies

From 40 included studies (n=8354), 7 studies, comprising 1395 participants, estimated the effect of exercise-based interventions on pain and disability through 6 putative mediators in 3 different conditions [2; 20-22; 46; 56; 59]; 27 studies, comprising 3312 participants, estimated the effect of cognitive-behavioral interventions on pain and disability through 32 putative mediators in 8 different conditions [6; 9-12; 17; 18; 25; 29; 31; 37; 39; 40; 48-50; 52; 54; 57; 59; 61-63; 68-70]; and 9 studies, comprising 3647 participants, estimated the effect of a combined (exercise-based plus cognitive-behavioral interventions) approach on pain and disability through 12 putative mediators in 4 different conditions [7; 13; 15; 42; 43; 55; 59; 60; 64]. In total, these studies tested 193 mediation models examining the role of 39 putative mediators on pain or disability in different time frames, of which 19 partially mediated treatment effect; 15 had mixed results and 5 did not significantly mediate treatment effect. Characteristics of the included studies are provided in Tables 1, 2 and 3.

Insert table 1 here

Two studies included subjects with chronic whiplash-associated pain [54; 69], 6 studies included subjects with osteoarthritis [2; 15; 20; 22; 46; 60], 2 studies included subjects with chronic headache [10; 29], 11 studies included subjects with fibromyalgia [12; 25; 40; 48; 49; 52; 55; 57; 63; 64; 68], 2 studies included subjects with chronic temporomandibular disorders [11; 62], 9 studies included subjects with chronic low back pain [7; 13; 21; 37; 42; 43; 50; 56; 59] and 8 studies included subjects with chronic musculoskeletal pain [6; 9; 17; 18; 31; 39; 61; 70].

Insert table 2 here

Thirty of the mediators were psychological constructs, nine studies estimated the mediating role of physical, lifestyle and social constructs. Summary of the estimated mediators and of the results of mediation analysis (treatment-mediator, mediator-outcome and indirect effects) are provided in Tables S2, S3 and S4 in the supplementary file.

Insert table 3 here

3.3. Meta-analyses

3.3.1. Self-efficacy as a mediator of exercise-based interventions for short-term disability

The pooled estimate of the indirect effect of self-efficacy for short-term disability was not significant ($r=-0.07$; 95% CI= -0.2 to 0.06), while the pooled estimates of treatment-mediator effect ($r=0.27$; 0.14 to 0.39), mediator-outcome effect ($r=-0.4$; -0.6 to -0.17) and total

effect ($r=-0.18$; -0.3 to -0.05) were all significant. Heterogeneity was low for the indirect effect ($p=0.99$, $I^2=0\%$), total effect ($p=0.96$, $I^2=0\%$) and treatment-mediator effect ($p=0.6$, $I^2=0\%$), and high for mediator-outcome effect ($p=0.03$, $I^2=0.77\%$).

3.3.2. Acceptance as a mediator of cognitive-behavioral interventions for intermediate disability

The pooled estimate of the indirect effect of acceptance for intermediate disability was not significant ($r=-0.04$; -0.18 to 0.1). The estimates of the treatment-mediator, mediator-outcome and total effects were not available from all studies. Heterogeneity was low for the indirect effect ($p=0.61$, $I^2=0\%$).

3.3.3. Fear-avoidance beliefs as a mediator of cognitive-behavioral interventions for short-term disability

The pooled estimate of the indirect effect of fear-avoidance beliefs short-term disability was not significant ($r=0.01$; -0.14 to 0.16). The estimates of the treatment-mediator, mediator-outcome and total effects were not available from all studies. Heterogeneity was moderate for the indirect effect ($p=0.18$, $I^2=41.5\%$).

3.3.4. Psychological Flexibility as a mediator of cognitive-behavioral interventions for intermediate pain

The pooled estimate of the indirect effect of psychological flexibility for intermediate pain was not significant ($r=-0.06$; -0.14 to 0.03). The estimates of the treatment-mediator, mediator-outcome and total effects were not available from all studies. Heterogeneity was low for the indirect effect ($p=0.97$, $I^2=0\%$).

3.3.5. Psychological Flexibility as a mediator of cognitive-behavioral interventions for short-term disability

The pooled estimate of the indirect effect of psychological flexibility for short-term disability was not significant ($r=-0.09$; -0.27 to 0.1). The estimates of the treatment-mediator, mediator-outcome and total effects were not available from all studies. Heterogeneity was low for the indirect effect ($p=0.74$, $I^2=0\%$).

3.3.6. Psychological Flexibility as a mediator of cognitive-behavioral interventions for intermediate disability

The pooled estimate of the indirect effect of psychological flexibility for intermediate disability was not significant ($r=-0.06$; -0.15 to 0.02), as well from the treatment-mediator effect ($r=0.49$; -0.26 to 0.87) and b ($r=-0.59$; -0.92 to 0.24). The estimates of the total effect were not available from all studies. Heterogeneity was low for the indirect effect ($p=0.96$, $I^2=0\%$) and high for treatment-mediator effect ($p<0.001$, $I^2=98.5\%$) and mediator-outcome effect ($p<0.001$, $I^2=98.8\%$).

Insert table 4 here

3.4. Quality assessment

All included studies cited a theoretical framework. Only 2 studies reported a sample size calculation, and 10 studies reported the psychometric characteristics of the mediator and outcome measures. Most of the studies controlled for confounding (32/40) and used measures of the exposure that preceded the mediator (27/40) and used measures of the mediator that preceded the outcome (30/40). The quality assessment ratings are presented in Table 5.

Insert table 5 here

4. Discussion

This systematic review identified 40 studies, including 8354 participants, which included a total of 193 mediation models examining the role of 39 putative mediators on pain or disability. Nineteen mediators partially mediated treatment effect; 15 had mixed results and 5 did not significantly mediate treatment effect. Most studies (30/40) assessed psychological mediators, while nine studies investigated physical, lifestyle and social constructs. Five meta-analyses were conducted and no compelling evidence of mediating effects of self-efficacy, acceptance, fear-avoidance beliefs and psychological flexibility were found.

There were relatively few studies that conducted mediation analyses on exercise-based interventions (7) compared to combined or cognitive-behavioral interventions (9 and 27 respectively). This discrepancy may reflect the long tradition of psychological science to investigate how interventions work. Evidence-based psychological interventions rely on theoretical assumptions and conceptual models for explaining how interventions exert their effects [24; 28]. These findings are supported in the reviews by Mansell et al. [44] and Lee et al. [36], where most putative mediators for low back pain were psychological constructs.

We observed that several of the studies included in our systematic review identified similar mechanisms of action, even between different interventions (eg., self-efficacy was identified as a mediator for pain and disability by studies of exercise-based, cognitive-behavioral and combined interventions [56; 60; 62]). These observations corroborate those of Mansell et al [44]. Their review revealed that increased self-efficacy, reduced pain catastrophizing, accurate pain beliefs, increased pain coping, increased psychological flexibility and reduced fear-avoidance and distress were important mediators for all psychological interventions for low back pain. Nevertheless, our meta-analyses found no evidence of mediating effects of the putative mediators so far assessed.

Poor methodological quality of the available research was identified by this review, since most of the included studies were at high risk of bias. Although most of the studies controlled for possible confounders (32/40) and ensured temporal precedence (intervention-mediator: 27/40, mediator-outcome 30/40), sample size estimations and psychometric properties of the measurement tools were rarely reported (2/40 and 10/40 respectively). Besides that, the conduct and reporting of mediation analysis were highly heterogeneous between studies, which is in line with what has been described by Vo et al. [65].

This systematic review presents preliminary evidence about the mechanisms of action of cognitive-behavioral and exercise-based interventions so far, with meaningful opportunities to move the field forward by establishing strengths and limitations of the field. Our results suggest that there is serious publication bias and better studies are needed if we are to inform policy and practice with mechanistic studies. Better evidence of causal mechanisms of interventions can help to develop more fine-grained clinical hypotheses to be tested in randomized clinical trials, which could ultimately lead to more effective interventions.

4.1. Strengths and Limitations of this Review

This review has several limitations. It is possible that post hoc mediation analyses were only conducted in studies that showed a significant treatment effect, and that primarily those

with statistically significant results were published. Study heterogeneity is another important issue. We may have fostered heterogeneity during the meta-analyses by pooling together different interventions and conditions. However, we think that this is also the main strength of this study. We were able to identify and summarize, in a single paper, the evidence of the mechanisms of action for very different interventions, which gave us a glimpse of the field. Other strengths of this review included: preregistration [35]; a comprehensive search strategy; use of two reviewers that independently screened, extracted the data and evaluated the studies.

5. Conclusions

There are substantial gaps with respect to understanding how cognitive-behavioral and exercise-based interventions work for pain and disability in people with chronic musculoskeletal pain. We found a total of 193 mediation models examining the role 39 putative mediators on pain or disability, of which 19 partially mediated treatment effects; 15 had mixed results and 5 did not significantly mediate treatment effect. Five meta-analyses were conducted and no compelling evidence of mediating effects of self-efficacy, acceptance, fear-avoidance beliefs and psychological flexibility were found. Methodological limitations were common and most of the included studies were at high risk of bias.

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Table 1. Exercise-based interventions study characteristics

Study	N analysed	Condition	RCT number of arms	Intervention	Mediators (measure)	Mediator time of measurement	Outcome (measure)	Outcome time of measurement	Identified Mediator	Analysis method; significance test;	Single/Multiple mediator models; confounders;
Bandak et al [1]	33	KO	Two arms	Exercise vs Waitlist	Muscle Perfusion (Dynamic Contrast Enhanced MRI)	12 weeks	Pain (KOOS Pain)	12 weeks	Muscle perfusion for pain at 12 weeks	Causal Mediation Analysis; bootstrapping	Single; Controlled
Smeets et al [43]	103	CLBP	Four arms	Aerobic + Strengthening vs Training vs Waitlist	Catastrophizing (Pain Cognition List)	10 weeks	Pain (VAS) and Disability (RMDQ)	12 weeks	Catastrophizing for pain and disability at 12 weeks	Baron and Kenny; Sobel or bootstrapping	Multiple; Controlled
Hall et al [16]	102	CLBP	Two arms	Tai chi vs Waitlist	Catastrophizing (CSQ)	10 weeks	Disability (RMDQ)	10 weeks	Catastrophizing for disability at 10 weeks	Baron and Kenny; bootstrapping	Single; Controlled
Hall et al [15]	97	KO	Two arms	Strengthening vs Waitlist	Strength (Knee Extensors Strength)	3 months	Pain and Disability (WOMAC)	3 months	Strength for pain and disability at 3 months	Baron and Kenny; regression	Single; Controlled
Hall et al [17]	488	RAH	Two arms	Strengthening + Mobility vs TAU	Strength (Full Hand Grip Strength)	4 months	Disability (MHOQ)	4 months	Strength for disability at 4 months	Baron and Kenny; SEM	Single; Controlled
Mihalko et al [31]	454	KO	Three arms	Exercise + Diet vs Diet.	Self-efficacy (Walking Efficacy Scale and Activity-specific Balance Confidence Scale)	18 months	Pain and Disability (WOMAC)	18 months	Self-efficacy for pain and disability at 18 months	Baron and Kenny; Sobel	Single; Uncontrolled
Sherman et al [41]	118	CLBP	Three arms	Yoga vs Self-care Book; Stretching vs Self-Care book	Self-efficacy (ASS), Sleep (RMDQ Sleep Quality Question) and Physical Activity (Self-Reported)	6 weeks	Disability (RMDQ)	3 months	Self-efficacy and sleep for disability at 3 months for both interventions	Product of coefficients; bootstrapping	Single; Controlled

KO, knee osteoarthritis; CLBP, chronic low back pain; RAH, rheumatoid arthritis of the hand; CSQ, coping strategies questionnaire; RMDQ, roland moris questionnaire; WOMAC, western ontario and mcmaster universities osteoarthritis index; VAS, visual analogue scale; KOOS, knee injury and osteoarthritis score; MHOQ, michigan hand outcomes questionnaire; ASS, arthritis self-efficacy scale; TAU, treated as usual; CBT, cognitive behavioral therapy.

Table 2. Cognitive-Behavioral study characteristics

Study	N analysed	Condition	RCT number of arms	Intervention	Mediators (measure)	Mediator time of measurement	Outcome (measure)	Outcome time of measurement	Identified Mediator	Analysis method; significance test;	Single/Multiple mediator models; confounders;
O'Neill et al [35]	117	CLBP	Two arms	CFT vs Exercise + Education	Self-efficacy (PSES), Stress (DASS-7), Fear (FABQ), Coping (CSQ), Depression, Anxiety and Sleep (SHCI), Catastrophizing (Pain Cognition List)	6 months	Pain (NRS) and Disability (ODI)	12 months	Self-efficacy for pain and disability at 12 months	Causal Mediation Analysis; bootstrapping	Single models; Controlled
Smeets et al [43]	100	CLBP	Four arms	CBT vs Waitlist;	Pain (VAS), Anxiety and Depression (HADS), Fear (TSK), Self-efficacy (PSES) and Psychological Flexibility (PISP)	10 weeks	Pain (VAS) and Disability (RMDQ)	12 weeks	Catastrophizing for pain and disability at 3 months	Baron and Kenny; Sobel or bootstrapping	Multiple; Controlled
Wicksell et al [51]	20	WAD	Two arms	ACT + TAU vs TAU	Pain (VAS), Anxiety and Depression (HADS), Fear (TSK), Self-efficacy (PSES) and Psychological Flexibility (PISP)	2 months	Disability (PDI)	2 and 6 months	Psychological flexibility for disability at 2 and 6 months	Baron and Kenny; bootstrapping	Single models, Uncontrolled
Turner et al [46]	115	CTD	Two arms	CBT vs Education	Self-efficacy (PSS), Pain Beliefs (SPA), Catastrophizing (PCS), Coping (CPCI)	6 months	Pain (GPCS) and Disability (MFIQ)	12 months	Self-efficacy and catastrophizing for pain and disability at 12 months	Baron and Kenny; Sobel	Single models; Controlled
Cederberg et al [4]	64	Chronic Pain	Two arms	ACT vs Applied Relaxation	Acceptance (CPAC), Anxiety and Depression (HADS),	7 weeks	Disability (ÖMPQ)	6 and 12 months	Acceptance, anxiety and depression for disability at 6 months	Causal Steps; bootstrapping	Single models; Uncontrolled
DasMahapatra et al [6]	492	Chronic Pain	Two arms	CBT vs Print Material	Coping (CPCI), Emotional Functioning (DASS)	2, 3 and 6 months	Pain (BPI)	2, 3 and 6 months	Depression and stress for pain at 3 and 6 months	McKinnon, glmm	Multiple models; Controlled
Day et al [7]	24	Primary Chronic Headache	Two arms	Mindfulness-based Cognitive Therapy vs TAU	Acceptance (CPAQ), Catastrophizing (PCS), Self-efficacy (HMSES)	2 months	Pain (BPI)	2 months	Acceptance for pain at 2 months	Baron and Kenny; bootstrapping	Single models; Uncontrolled
Durá-Ferrandis et al [8]	72	CTD	Two arms	CBT + TAU vs TAU	Psychological Distress (BSI), Catastrophizing (PCS), Perceived Control (SPA), Distraction, Mental Self-control and Insomnia (CPQ)	3 months	Pain (GCPS)	3 months	Psychological distress, catastrophizing, perceived control, distraction, mental self-control and insomnia for pain at 3 months	Product of Coefficients; bootstrapping	Multiple models; Uncontrolled
Edinger et al [9]	61	Fibromyalgia	Three arms	CBT + TAU vs TAU	Insomnia (Insomnia Severity Index)	2 and 6 months	Pain (MTPS)	2 and 6 months	Insomnia for pain at 2 and 6 months	Causal Mediation Analysis; bootstrapping	Single models; Uncontrolled

Galarud et al [12]	95	Chronic Pain	Two arms	Mind-body Therapy + Mindfulness vs Support Group	Positive Psychology Function (Latent Variable)	2 months	Pain (BPI)	2 months	Positive psychology function for pain at 2 months	Path Analysis; Chi Square	Multiple models; Controlled
Galarud et al [13]	115	Chronic Pain	Two arms	Mind-body Therapy + Mindfulness vs Support Group	Reinterpretation of pain sensations (CSQ), non-reactivity (FFMQ), Reappraisal (CERQ)	2 months	Pain (BPI)	2 months	Reinterpretation of pain sensations and non-reactivity for pain at 2 months	Path Analysis; Sobel	Multiple models; Controlled
Herdman-Lagerlöf et al [19]	140	Fibromyalgia	Two arms	Exposure Therapy vs Waitlist	Avoidance Non-reactivity (FFMQ), Worry (PRS)	10 weeks	Disability (FIQ)	10 weeks	Avoidance, non-reactivity and worry for disability at 10 weeks	Baron and Kenny; bootstrapping	Multiple; Controlled
Holthoyd et al [22]	169	CTTH	Four arms	CBT Stress Management Therapy with Antidepressants or Placebo vs Antidepressants or Placebo	Self-efficacy (HMSSES)	2 months	Pain (Headache Diary) and Disability (HDI)	8 months	Moderated mediation for mood disorders and severity of the CTTH on self-efficacy for pain and disability at 8 months	Moderated mediation; bootstrapping	Single; Controlled
Leeuw et al [25]	85	CLBP	Two arms	Exposure in vivo vs Operant therapy	Perceived Harmfulness of Activities (PHODA) and Catastrophizing (PCS)	12 months	Disability (QBPDs)	12 months	No mediation	MacKinnon; Joint Significant Test	Multiple; Controlled
Lin et al [26]	302	Chronic Pain	Three arms	ACT vs TAU; Unguided ACT vs TAU	Psychological Flexibility (CPAQ)	9 weeks	Pain (NRS) and Disability (BPI)	6 months	Psychological flexibility for pain and disability at 6 months for both groups	SEM; bootstrapping	Multiple; Controlled
Luciano et al [27]	156	Fibromyalgia	Three arms	ACT vs Waitlist; Pharmacological Treatment vs Waitlist	Acceptance (CPAQ)	2 months	Pain (VAS) and Disability (FIQ)	6 months	No mediation	Path Analysis; bootstrapping	Single; Controlled
Wicksell et al [50]	40	Fibromyalgia	Two arms	ACT vs Waitlist	Psychological Flexibility (PISP)	12 weeks	Disability (PDI)	3 months	Psychological flexibility for disability at 3 months	Product of Coefficients; bootstrapping	Single; Controlled
Molinari et al [33]	47	Fibromyalgia	Two arms	Positive Affect Intervention vs Diary	Affect (PANAS), Expectations about Future Events (Subjective Probability Task), Depression (BDI)	1 month	Disability (FIQ)	1 month	Depression for disability at 1 month	Regression-based approach; bootstrapping	Multiple; Uncontrolled
Montero-Marín et al [34]	42	Fibromyalgia	Two arms	Attachment-based Compassion	Psychological Flexibility (AAQ)	2 months	Disability (FIQ)	3 months	Psychological flexibility for disability at 3 months	Path Analysis; bootstrapping	Single; Controlled

Table 3. Combined interventions study characteristics

Study	N analysed	Condition	RCT number of arms	Intervention	Mediators (measure)	Mediator time of measurement	Outcome (measure)	Outcome time of measurement	Identified Mediator	Analysis method; significance test;	Single/Multiple mediator models; confounders;
Cheing et al [5]	76	CLBP	Two arms	Motivational Enhanced PT vs PT	Pain (VAS), Working Alliance and Outcome Expectancy (PRES)	2 months	Disability (RMDQ)	2 months	No mediation	Path Analysis; Chi Square	Multiple models; Uncontrolled
Smeets et al [43]	109	CLBP	Four arms	Aerobic + Strength + Problem-Solving Training vs Waitlist	Catastrophizing (PCL)	10 weeks	Pain (VAS) and Disability (RMDQ)	12 weeks	Catastrophizing for pain and disability at 12 weeks	Baron and Kenny; Sobel or bootstrapping	Multiple; Controlled
Fordham et al [10]	701	CLBP	Two arms	CBT + Exercises vs Exercises	Self-efficacy (PSES), Physical Activity and Mental Function (SF-12), Fear (FABQ)	3, 6 and 12 months	Pain (MKVp) and Disability (RMDQ)	3, 6 and 12 months	Self-efficacy and physical activity for pain and disability at 3, 6 and 12 months, mental function for pain at 3, 6 and 12 months	SEM	Multiple models; Controlled
Foy et al [11]	1756	KO	Two arms	Intensive Lifestyle Intervention vs Support and Education	Weight (Kg) and Fitness (Metabolic Equivalents at 80% of Maximum HR)	12 months	Pain and Disability (WOMAC)	12 months	Weight and fitness for pain and disability at 12 months	Baron and Kenny; Sobel	Multiple models; Controlled
Mansell et al [28]	138	CLBP	Two arms	PIPT vs Current Best Care	Pain-related Distress (Latent Variable) and Pain intensity (Latent Variable)	4 months	Disability (RMDQ)	4 months	Pain-related distress and pain intensity for disability at 4 months	SEM; bootstrapping	Multiple models; Controlled
Mansel et al [29]	240	CLBP	Two arms	PIPT vs TAU	Fear (TSK)	2 months	Disability (RMDQ)	2 months	Fear for disability at 2 months	Product of Coefficients; bootstrapping	Multiple models; Controlled
Serrat et al [40]	169	Fibromyalgia	Two arms	PNE + Exercise + CBT + Mindfulness + Nature Exposure + TAU vs TAU	Fear (TSK) and Catastrophizing (PCS)	6 weeks	Pain (VAS) and Disability (FIQ)	3 months	Fear and Catastrophizing for pain and disability at 3 months	Path Analysis; bootstrapping	Multiple models; Controlled
Taylor et al [44]	300	KO	Two arms	Physical Activity + CBT + Weight Management vs TAU	Self-efficacy (ASES), Coping (CSQ) and Catastrophizing (PCS)	6 months	Disability (WOMAC)	12 months	Self-efficacy and coping for disability at 2 months	Product of Coefficients; Sobel	Multiple models; Controlled
Van Koudil et al [49]	158	Fibromyalgia	Three arms	CBT + Exercise vs Waitlist [PA]; CBT + Exercise vs Waitlist [PP]	Fear and Avoidance (PCI) for PA and Activity Pacing (CPCI) for PP	2 months	Disability (Credibility/Expectancy Questionnaire)	2 months	Fear and avoidance for PA and activity pacing for PP for disability at 2 months	MacKinnon; Joint Significance Test	Single models; Controlled

CLBP, chronic low back pain; KO, knee osteoarthritis; CBT, cognitive behavioral therapy; TAU, treated as usual; PT, physical therapy; PIPT, psychologically informed physical therapy; PRES, pain rehabilitation expectancies scale; PCL, pain cognition list; PSES, pain self-efficacy scale; FABQ, fear and avoidance beliefs questionnaire; TSK, Tampa scale of kinesiophobia; PCS, pain catastrophizing scale; ASES, arthritis self-efficacy scale; CSQ, coping strategies questionnaire; PCI, pain coping inventory; CPCI, chronic pain coping inventory; RMDQ, Roland Morris disability questionnaire; HR, heart rate; VAS, visual analogue scale; WOMAC, western ontario and mcmaster universities osteoarthritis index; FIQ, fibromyalgia impact questionnaire; MKVp, Modified Von Korff Scale for pain; PA, pain-avoidance; PP, pain persistence.

Table 5. Quality Assessment

	1. Theoretical framework	2. Report of Psychometric characteristics	3. Power calculation for mediation analysis	4. Were acceptable statistically methods of data analysis used?	5. Changes in exposure precedes changes in mediator?	6. Changes in mediator precedes changes in outcome?	7. Controlled for confounding?
Bandak et al [2]	1	1	0	1	0	1	1
Smeets et al [59]	1	0	0	1	1	1	1
Hall et al [21]	1	0	0	1	1	1	1
Hall et al [20]	1	0	0	1	1	1	1
Hall et al [22]	1	0	0	1	1	1	1
Mihalko et al [46]	1	0	0	1	1	1	0
Sherman et al [56]	1	0	0	1	1	1	1
Cheing et al [7]	1	0	0	1	0	1	0
Fordham et al [13]	1	0	0	1	0	1	1
Foy et al [15]	1	0	0	1	1	1	1
Mansell et al [42]	1	0	0	1	1	1	1
Mansel et al [43]	1	0	0	1	1	1	1
Serrat et al [55]	1	0	0	1	1	1	1
Taylor et al [60]	1	0	0	1	1	1	1
Van Kouilil et al [65]	1	0	0	1	0	0	1
O'Neill et al [50]	1	0	0	1	0	0	1
Wicksell et al [70]	1	1	0	1	0	0	0
Turner et al [63]	1	0	0	1	0	0	1
Cederberg et al [6]	1	0	0	1	0	0	1
DasMahapatra et al [9]	1	0	0	1	0	0	1
Day et al [10]	1	0	0	1	1	1	0
Durá-Ferrandis et al [11]	1	0	0	1	1	1	0
Edinger et al [12]	1	0	0	1	1	1	0
Galard et al [17]	1	0	0	1	1	1	1
Galard et al [18]	1	1	0	1	1	1	1
Herdman-Lagerlöf et al [25]	1	1	0	1	0	0	1
Holhoyd et al [29]	1	0	0	1	0	0	1
Leeuw et al [37]	1	0	0	1	0	0	1
Lin et al [39]	1	0	0	1	1	1	1
Luciano et al [40]	1	1	0	1	1	1	1
Wicksell et al [69]	1	0	0	1	1	1	1
Molinari et al [48]	1	0	0	1	1	1	0
Montero-Marín et al [49]	1	1	0	1	1	1	1
Pérez-Aranda et al [52]	1	1	0	1	1	1	1
Robinson et al [54]	1	1	0	1	1	1	1
Simister et al [57]	1	1	0	1	1	1	1
Trompeter et al [61]	1	1	0	1	1	1	1
Van Gordon et al [64]	1	0	0	1	0	0	0
Williams et al [71]	1	0	1	1	1	1	1
Kemani et al [31]	1	0	1	1	1	1	1

1, did the study cite a theoretical framework?; 2, were the psychometric characteristics of the mediator and outcome variables reported? (Computed from the present study or a reference provided); 3, did the study report a power calculation? If so, was the study adequately powered to detect mediation?; 4, were statistically appropriate/acceptable methods of data analysis used? This includes the product of coefficient approach with bootstrapped confidence intervals, structural equation modelling, path analysis, latent growth modelling, and causal mediation analysis; 5, did the study ascertain whether changes in the exposure variable preceded changes in the mediator variable?; 6, did the study ascertain whether changes in the mediating variables preceded changes in the outcome variables?; 7, did the study control for possible confounding factors, eg, baseline values?

Supplementary File

Search Strategy

PUBMED

1. "Chronic Pain"[Mesh]
2. (Musculoskeletal pain)
3. (Musculoskeletal diseases)
4. (Musculoskeletal disorder*)
5. "Back pain"[Mesh]
6. "Sciatica"[Mesh]
7. (Cervicogenic)
8. "Shoulder Pain"[Mesh]
9. (subacromial impingement syndrom*)
10. "Fibromyalgia"[Mesh]
11. (Fibromyalgia)
12. (Arthritis)
13. (Joint disease)
14. "Neck pain"[Mesh]
15. (Spin* Pain)
16. (Hip Pain)
17. "Osteoarthritis, Hip"[Mesh]
18. (Arthralgia)
19. (Knee Pain)
20. (Patellofemoral pain syndrome)
21. "Osteoarthritis, Knee"[Mesh]
22. "Osteoarthritis"[Mesh]
23. (Ankle Pain)
24. (Frozen Shoulder)
25. "Headache"[Mesh]
26. (Joint Pain)
27. (Myalgia)
28. or/1-27

29. "Exercise"[Mesh]
30. "Resistance Training"[Mesh]
31. (Strength*)
32. (Exercis*)
33. (Train*)
34. (Physical activity)
35. (Physical exercise)
36. (Isometric)
37. (Aerobic exercise)
38. (Pilates)
39. (Motor control)
40. "Yoga"[Mesh]
41. "Physical Therapy Modalities"[Mesh]
42. (Physical therapy)
43. (Physiotherapy)
44. (Exercise therapy)
45. (McKenzie*)
46. (Cognitive Functional Therapy)
47. "Psychotherapy"[Mesh]
48. "Psychology"[Mesh]
49. (Psycholog*)
50. "Behavior Therapy"[Mesh]
51. (Biofeedback)
52. Acceptance and commitment therapy)
53. (Cognitive Behavio* Therap*)
54. (Behavio* therap*)

55. (Cognitive therap*)
56. (Relax* technique*)
57. (Meditat*)
58. (Psychotherap*)
59. (Psychological therap*)
60. (Exposure in vivo)
61. (Graded exposure)
62. (Operant therap*)
63. (Graded activity)
64. (Pain neuroscience education)
65. (Pain education)
66. (Explain pain)
67. (Psycho-education*)
68. (Mind and body relaxation technique*)
69. (Virtual reality)
70. (Imagery)
71. or/29-70

72. (Structural Equation Modeling)
73. (Modeling, Structural Equation)
74. (Structural Equation Modelings)
75. (Baron and Kenny)
76. (Product of coefficient)
77. Difference in coefficient)
78. (Process of change)
79. (Causal pathway)
80. (Causal mediation analysis)
81. (Indirect effect)
82. (Intermediate)
83. (Process variable)
84. (Process evaluation)
85. (Mediation analysis)
86. (mediat*)
87. (path)
88. (MacKinnon)
89. (sobel*)
90. (mechanism)
91. (SEM)
92. or/72-91

93. (randomized controlled trial)

94. (controlled clinical trial)
95. (comparative study)
96. (clinical trial)
97. (randomized)
98. (placebo)
99. (randomly)
100. (trial)
101. (groups)
102. (RCT)
103. (secondary analys*)
104. or/93-103

limit to Humans

Table S1. Studies excluded with reasons

Study	Condition	Intervention	Reasons for Exclusion
Van der Maas et al. [48]	CLBP	Psychomotor therapy + TAU vs TAU	Wrong outcome
Mansell et al. [27]	CLBP	Pain Education + TAU vs TAU	Wrong population: >50% were people with acute pain
McKnight et al. [28]	KO	Exercise + self-management vs self-management	Wrong predictor
Montero-Marin et al. [31]	Fibromyalgia	Attachment-based compassion therapy vs Relaxation	They broke treatment allocation for mediation analysis
Stevens et al. [43]	CLBP	Multifaceted intervention	Wrong study design
Ter Kuile et al. [45]	CH	Cognitive self-hypnosis vs autogenic training	Wrong method for mediation analysis
Knoop et al. [20]	CMP	Cognitive behavioral therapy vs TAU	Wrong method for mediation analysis
Knoop et al. [21]	KO	Joint Stabilization + endurance + daily activities vs endurance vs daily activities	Wrong method for mediation analysis
Carmody et al. [2]	CMP	Telephone CBT vs Telephone Pain Education	Wrong method for mediation analysis
Schemer et al. [37]	CLBP	Exposure in vivo vs CBT	Wrong method for mediation analysis
Voerman et al. [51]	CNP and CSP	Myofeedback + ergonomic counseling vs ergonomic counseling	Wrong method for mediation analysis
Rejeski et al. [35]	KO	Aerobic exercise vs resistance exercise vs health education	Wrong outcome and method for mediation analysis
Spinhoven et al. [42]	CLBP	Operant-behavioral therapy + cognitive coping skills vs group discussion	Wrong outcome
Whittle et al. [52]	SLBP	Usual GP care vs minimal psychosocial intervention	Wrong population
Graham et al. [13]	CMP	Written anger expression vs write about their goals	Wrong intervention

KO, knee osteoarthritis; CMP, chronic musculoskeletal pain; CH, chronic headache; CLBP, chronic low back pain; CNP, chronic neck pain; CSP, chronic shoulder pain; SLBP, sub-acute low back pain; TAU, treated as usual; GP, general practice.

Table S2. Summary of mediation models from exercise-based interventions assessed in included studies

Study	Intervention vs comparator	Path a	Mediator	Path b	Outcome	Indirect Effect
Bandak et al [1]	Exercise vs Waitlist	NR	Muscle Perfusion	NR	Pain at 3 months	+
Smeets et al [41]	Aerobic + Strength	NR	Catastrophizing	NR	Pain at 10 weeks	+
	Training vs Waitlist	NR	Catastrophizing	NR	Disability at 10 weeks	+
Hall et al [15]	Tai chi vs Waitlist	NR	Catastrophizing	NR	Pain at 10 weeks	+
		NR	Catastrophizing	NR	Disability at 10 weeks	+
Hall et al [14]	Strengthening vs Waitlist	NR	Knee Extensor Strength	NR	Pain at 3 months	+
		NR	Knee Extensor Strength	NR	Disability at 3 months	+
Hall et al [16]	Strengthening + Mobility vs TAU	NR	Hand Grip Strength	NR	Disability at 4 months	+
Mihalko et al [29]	Exercise + Diet vs Diet	NR	Self-efficacy	NR	Pain at 18 months	+
		NR	Self-efficacy	NR	Disability at 18 months	+
Sherman et al [39]	Yoga vs Self-Care Book;	+	Physical Activity	-	Disability at 3 months	-
		+	Self-efficacy	+		+
		+	Sleep	+		+
	Stretching vs Self-Care book	+	Physical activity	+	Disability at 3 months	-
		+	Self-efficacy	+		+

TAU, treated as usual;

Table S3. Summary of mediation models from cognitive-behavioral interventions assessed in included studies

Study	Intervention vs comparator	Path a	Mediator	Path b	Outcome	Indirect Effect
O'Neill et al [33]	CFT vs Exercise + Education	+	Anxiety	+	Pain at 12 months	-
		+	Coping	+		-
		+	Depression	+		-
		+	Fear	+		-
		-	Self-efficacy	-		+
		+	Sleep	+		-
		+	Stress	+	Disability at 12 months	-
		+	Anxiety	+		-
		+	Coping	+		-
		+	Depression	+		-
		+	Fear	+		-
		-	Self-efficacy	-		+
Smeets et al [41]	CBT vs Waitlist;	NR	Catastrophizing	NR	Pain at 10 weeks	+
		NR	Catastrophizing	NR	Disability at 10 weeks	+
Wicksell et al [54]	ACT + TAU vs TAU	-	Anxiety	-	Disability at 2 months	-
		+	Depression	+		-
		+	Fear	-		-
		+	Pain	-		-
		+	Psychological Flexibility	-		-
		-	Self-efficacy	-		-
		-	Anxiety	-	Disability at 6 months	-
		-	Depression	+		-
		+	Fear	-		+
		+	Pain	+		+
		-	Psychological Flexibility	+		-
		-	Self-efficacy	-		-
Turner et al [47]	CBT vs Education	NR	Catastrophizing	NR	Pain at 12 months	+
		NR	Coping	NR		-
		NR	Pain Beliefs	NR		+
		NR	Self-efficacy	NR		+
		NR	Catastrophizing	NR	Disability at 12 months	+
		NR	Coping	NR		-
		NR	Pain Beliefs	NR		+
		NR	Self-efficacy	NR		+
Cederberg et al [3]	ACT vs Applied Relaxation	NR	Acceptance	NR	Disability at 6 months	+
		NR	Anxiety	NR		+
		NR	Depression	NR		+
		NR	Acceptance	NR	Disability at 12 months	-
		NR	Anxiety	NR		-
		NR	Depression	NR		-
DasMahapatra et al [5]	CBT vs Print Material	NR	Coping	NR	Pain at 2 months	-
		NR	Anxiety	NR		-
		NR	Depression	NR		-
		NR	Stress	NR		-
		NR	Coping	NR	Pain at 3 months	-
		NR	Anxiety	NR		-
		NR	Depression	NR		+
		NR	Stress	NR		+
		NR	Coping	NR	Pain at 6 months	-
		NR	Anxiety	NR		-
		NR	Depression	NR		+
		NR	Stress	NR		+
Day et al [6]	Mindfulness-based Cognitive Therapy vs TAU	NR	Acceptance	NR	Pain Interference at 2 months	+
		NR	Catastrophizing	NR		-
		NR	Self-efficacy	NR		-
Durá-Ferrandis et al [7]	CBT + TAU vs TAU	+	Catastrophizing	+	Pain at 3 months	+
		+	Distraction	+		+
		+	Distress	+		+
		+	Mental self-control	+		+
		+	Perceived control	+		+
Edinger et al [8]	CBT + TAU vs TAU	NR	Insomnia	NR	Pain sensibility at 2 months	+
		NR	Insomnia	NR	Pain sensibility at 6 months	+

Galard et al [11]	Mind-body Therapy + Mindfulness vs Support Group	+	Positive Psychology Health	+	Pain severity at 2 months	+
Galard et al [12]	Mind-body Therapy + Mindfulness vs Support Group	+	Coping	+	Pain severity at 2 months	+
		+	Non-reactivity	+		+
		-	Reappraisal	-		-
Herdman-Lagerlöf et al [17]	Exposure Therapy vs Waitlist	-	Avoidance	+		+
		+	Non-reactivity	+	Disability at 10 weeks	+
		+	Worry	+		+
Holhoyd et al [18]	CBT Stress Management vs Placebo	+	Self-efficacy	+	Disability at 8 months	+
	CBT Stress Management + antidepressant vs antidepressant	+	Self-efficacy	+	Headache severity at 8 months	+
Leeuw et al [22]	Exposure in vivo vs Operant therapy	+	Catastrophizing	+		-
		-	Perceived harmfulness	-	Disability at 12 months	-
Lin et al [23]	ACT vs TAU	+	Psychological Flexibility	+	Pain at 6 months	+
	Unguided ACT vs TAU	+	Psychological Flexibility	+	Disability at 6 months	+
		+	Psychological Flexibility	+	Pain at 6 months	+
		+	Psychological Flexibility	+	Disability at 6 months	+
Luciano et al [24]	ACT vs Waitlist	NR	Acceptance	NR	Pain at 6 months	-
		NR		NR	Disability at 6 month	-
Wicksell et al [53]	ACT vs Waitlist	-	Psychological Flexibility	-	Disability at 3 months	+
Molinari et al [30]	Positive Affect Intervention vs Diary	+	Positive affect	-		-
		+	Negative affect	-		-
		+	Depression	-	Disability at 1 month	+
		-	Positive expectation	-		-
		-	Negative expectation	-		-
Montero-Marín et al [32]	Attachment-based Compassion Therapy vs Relaxation	+	Psychological Flexibility	+	Disability at 3 months	+
Pérez-Aranda et al [34]	Mindfulness-based Stress Reduction + TAU vs TAU;	+	Mindfulness facet	+		+
		+	Psychological flexibility	+	Disability at 12 months	+
Robinson et al [36]	Exposure in vivo + Information Booklet (IB) vs waitlist	+	Fear of movement-related pain	+	Disability at 1 month	+
Simister et al [40]	Online ACT + TAU vs TAU	NR	Fear	NR	Disability at 3 months	+
		NR	Acceptance	NR		-
		+	Catastrophizing	-		-
	Online ACT vs waitlist	+	Psychological Flexibility	+	Pain intensity at 6 months	+
		+	Catastrophizing	+		+
		+	Psychological Flexibility	+	Pain interference at 6 months	+
		+	Catastrophizing	-		-
	Online ACT vs Expressive Writing	+	Psychological Flexibility	+	Pain intensity at 6 months	+
		+	Catastrophizing	+		+
		+	Psychological Flexibility	+	Pain interference at 6 months	+
Van Gordon et al [49]	Meditation Awareness Therapy vs Group CBT	+	Civic engagement	+		+
		+	Non-attachment	+	Disability at 2 months	+
Williams et al [55]	Telephone-based HLC+ Education and Behavioral	-	Diet	-		-
		-	Pain beliefs	-		-
		-	Physical activity	-	Pain at six months	-
		-	Weight	-		-

Kemani et al [19]	Change vs Waitlist	-	Diet	-	Disability at six months	-
		-	Pain beliefs	-		-
		-	Physical activity	-		-
		-	Weight	-		-
	ACT vs Applied Relaxation	+	Catastrophizing	-	Pain interference at 3 months	-
		-	Pain	-		-
		+	Psychological flexibility	+		+

ACT, acceptance and commitment therapy; CBT, cognitive behavioral therapy; TAU, treated as usual;

Table S4. Summary of mediation models from combined interventions assessed in included studies

Study	Intervention vs comparator	Path a	Mediator	Path b	Outcome	Indirect Effect
Cheing et al [4]	Motivational Enhanced PT vs PT	+	Outcome expectancy	+	Physical function at 2 months	-
		-	Pain	+		-
		+	Working alliance	+		-
Smeets et al [41]	Aerobic + Strength + Problem-Solving Training vs Waitlist	NR	Catastrophizing	NR	Pain at 10 weeks	+
		NR		NR	Disability at 10 weeks	+
Fordham et al [9]	CBT + Exercises vs Exercises	NR	Fear	NR	Pain at 3 months	-
		NR	Mental functioning	NR		-
		NR	Physical activity	NR		+
		NR	Self-efficacy	NR		+
		NR	Fear	NR		-
		NR	Mental functioning	NR	Disability at 3 months	-
		NR	Physical activity	NR		-
		NR	Self-efficacy	NR		-
		NR	Fear	NR		-
		NR	Mental functioning	NR	Pain at 6 months	-
		NR	Physical activity	NR		+
		NR	Self-efficacy	NR		+
		NR	Fear	NR		+
		NR	Mental functioning	NR	Disability at 6 months	-
		NR	Physical activity	NR		+
		NR	Self-efficacy	NR		+
		NR	Fear	NR		-
		NR	Mental functioning	NR	Pain at 12 months	-
		NR	Physical activity	NR		+
		NR	Self-efficacy	NR		+
		NR	Fear	NR		+
		NR	Mental functioning	NR	Disability at 12 months	-
		NR	Physical activity	NR		+
		NR	Self-efficacy	NR		+
		NR	Fear	NR		+
		NR	Mental functioning	NR		+
Foy et al [10]	Intensive Lifestyle Intervention vs Support and Education	+	Weight	+	Pain at 12 months	+
		+	Weight	+	Disability at 12 months	+
Mansell et al [25]	PIPT vs Current Best Care	+	Pain	+	Disability at 4 months	+
		+	Pain-related distress	+		+
Mansel et al [26]	PIPT vs TAU	+	Fear of movement-related pain	+	Disability at 2 months	+
Serrat et al [38]	PNE + Exercise + CBT +	+	Catastrophizing	+	Pain at 3 months	+
	Mindfulness + Nature	+	Fear	+		+
	Exposure + TAU vs TAU	+	Catastrophizing	+	Disability at 3 months	+
Taylor et al [44]	Physical Activity + CBT + Weight Management vs TAU	-	Catastrophizing	-	Disability at 12 months	-
		+	Coping	+		+
		+	Self-efficacy	+		+
Van Kouilil et al [50]	CBT + Exercise vs Waitlist [PA];	+	Activity pacing	NR	Disability at 2 months	+
	CBT + Exercise vs Waitlists [PP]	+	Fear	NR		+

PT, physical therapy; CBT, cognitive behavioral therapy; TAU, treated as usual; PNE, pain neuroscience education; PIPT, psychologically informed physical therapy.

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Chapter 6: Discussion and Concluding Remarks

Chronic musculoskeletal pain is among the most prevalent, disabling and costly sources of human suffering world-wide. However, current evidence is unable to precisely explain the causes of this burden, as chronic musculoskeletal pain seems to be associated with a complex interplay of several biopsychosocial factors. Nevertheless, the lack of understanding by researchers, clinicians and the general population of what is pain and how to deal with it can lead to ineffective advice with a rapid escalation of care by healthcare professionals, and be a great source of unhelpful health behaviors among people with pain.

There are still several gaps of knowledge in the literature regarding the possible underlying mechanisms associated with pain persistence and recovery. Therefore, the main focus of this thesis was to contribute to bridge some of this gaps by further exploring the possible mechanisms underlying pain persistence through the lens of learning theories and by systematizing current evidence on the mechanisms of action of exercise-based and cognitive-behavioral interventions for pain and disability in people with chronic musculoskeletal pain. I believe that this thesis will assist to move the field forward by providing new evidence and insights to questions that were not properly answered by the scientific literature so far.

One of the main gaps addressed during this thesis was related to explain how exactly movements may become and remain painful in people with chronic musculoskeletal pain. Two research questions were based on this gap:

1. *Can pain be conditioned to movement through associative learning?*
2. *The precision of pain occurrence through movements and activities is associated with the number or severity of structures reported as damaged in people with chronic musculoskeletal pain?*

Chapter 2 aimed at addressing the first research question. This chapter described a study that aimed at investigating whether proprioceptive inputs associated with arm movements can increase the chance of a stimuli at-pain-threshold to be perceived as painful after successive painful associations in healthy participants (i.e. an increased

chance of perceiving pain during movements in the presence of nociception). We hypothesized that a Pavlovian conditioning procedure would lead to a higher percentage of stimuli at-pain-threshold level being perceived as painful during movements that were previously associated with an US-nociceptive stimulus (CS+ movements) in comparison with movements that were not previously associated with nociception (CS- movements).

Furthermore, we hypothesized that pain conditioning would also lead to higher pain intensities during the CS+ in comparison with the CS- movements and higher defensive responses, including higher skin conductance responses (SCRs) (ie, measure of sympathetic arousal ([340](#))), and higher movement onset latency (MOL) (ie, measure of avoidance tendency), before the CS+ movement initiation in comparison with the CS- movements. We found that the stimuli at-pain-threshold level were more likely to be perceived as painful and were also rated as more painful during the CS+ movements. Movement onset latency and skin conductance responses were significantly higher in anticipation of the CS+ movement as compared to the CS- movement. These findings suggest that pain can be conditioned to voluntary movements.

The role of associative learning in pain persistence was hypothesized by the Imprecision Hypothesis of Chronic Pain (IH) ([137](#)), and previously investigated by several studies using different stimuli as CSs ([250](#), [278](#), [280-283](#)). However, none of the previous studies in the literature have investigated if pain can be conditioned to movements, which is one of the major points of the first assumption of the IH (i.e. Pavlovian conditioning may be the behavioral base by which other processes associated with pain persistence take place). The findings described in **Chapter 2** strengthen this assumption by providing evidence that pain, and associated defense behaviors in anticipation of a threat, can be conditioned to voluntary movements in healthy subjects. Future studies should consider to replicate this study and investigate if pain conditioning might also occur in other movements and tasks besides reaching to touch.

Chapter 3 aimed at addressing the second research question. This chapter described a study that aimed to verify if movement-related pain that occurs across a wider variety of activities commonly perceived as painful by people with chronic

shoulder pain was associated with the number or severity of rotator cuff radiological findings on a magnetic resonance imaging (MRI).

Based on the current state-of-the-art, we hypothesized that movement-related pain that occurs across a wider variety of activities would not be associated with the number or severity of rotator cuff MRI findings. In order to verify this hypothesis, this study was designed in three subsequent phases that were aimed at: select the activities commonly perceived as painful; develop and evaluate the measurement properties of a measurement tool that assesses the pain distribution across clinically-relevant arm movements; and verify the hypotheses of this study through an analysis of the data collected in phase two.

The results of this study provided evidence that neither the number of rotator cuff tendons reported as abnormal nor the severity of each tendon imaging finding were associated with pain occurrence across movements and activities commonly perceived as painful by people with chronic shoulder pain. These findings are in contrast with the common view that movement-related pain is as an accurate representation of tissue damage and, therefore, that more pain or pain in more movements is an accurate measure of more tissue damage or more severe tissue damage, which strengthen the second assumption of the IH that suggest that pain distribution through movements may be a by-product of learning processes (i.e. stimuli generalization), and not a precise sign of tissue damage.

Stimulus generalization ([239](#), [255](#), [257](#)) is an adaptive learning process because it enables individuals to extrapolate the predictive value of one stimulus to novel stimuli based on perceptual resemblances and conceptual knowledge without the necessity to learn anew. According to the IH, this would imply that pain itself, once conditioned, can generalize to other classes of movements based on perceptual similarity or conceptual knowledge, following the principle of stimulus generalization ([284](#)). However, experimental findings of pain generalization in healthy individuals are scarce ([284](#)), and experimental data in chronic pain populations are lacking ([156](#), [162](#), [164](#), [169](#), [177](#)) to support such proposition. Although challenging because of factors such as the lack of experimental control over confounders to infer learning processes, further investigating the hypothesis of movement-related pain generalization in a clinical scenario is certainly worthwhile. To evaluate this hypothesis, future studies

should consider the role of learned expectancy ([234](#)), threat discrimination ([289](#)), fear generalization and category-based or conceptual fear conditioning ([239](#), [245](#), [257](#), [263](#), [350](#)) on movement-related pain and its distribution through movements in people with chronic pain.

Another gap addressed during this thesis was related to verify if pain anticipation and the prioritization of pain-related information observed in people with chronic pain ([25](#), [139](#), [156](#), [238](#), [267](#), [271-273](#), [351](#), [352](#)) might influence other perceptual *continuums* related to painful movements that could foster avoidance behaviors. One research question was based on this gap:

3. *How does the previous history of movement-related pain influence the way people with chronic musculoskeletal pain perceive other perceptual continuums associated with movements?*

Chapter 4 aimed at addressing this research question. This chapter described a study that aimed to investigate if patients with chronic shoulder pain have perceptual distortions. We aimed to compare distance perception within and beyond reaching distance between people with and without shoulder pain; to compare perceived length of the painful limb relative to the non-painful limb and to the control group; and to investigate whether spatial distortion is correlated with the strength of the relationship between pain and movement. We hypothesized that in people with chronic shoulder pain, points within and outside reach would appear more distant; that the perceived size of the painful limb would be reduced relative to the pain-free arm and to controls, and that spatial distortions would correlate with the degree that pain is related to movement.

The results of this study showed that distance and arm length estimates did not differ between groups, nor did participants perceive their arms to be of different length. However, a moderate correlation between movement-related pain and the index of distance perception was found within the pain group, specifically for distance estimates to points within reach. These results suggest that distorted perception is not a typical consequence of chronic shoulder pain. However, that it may occur in cases where pain is strongly linked to movement. These findings may have implications for

understanding avoidance of movement in people with persistent shoulder pain, which should be further investigated in future studies.

Finally, one important gap in the literature is related to explain how pain interventions work to reduce pain and disability in people with chronic musculoskeletal pain. One research question was based on this gap:

4. *What are the mechanisms by which active interventions may work to reduce pain and disability in people with chronic musculoskeletal pain?*

Chapter 5 aimed at addressing this research question. This chapter described a systematic review that aimed to identify and synthesise studies that conducted mediation analyses of randomized controlled trials that test or estimate indirect effects of cognitive-behavioral and exercise-based interventions for pain and disability in people with chronic musculoskeletal pain. The results of this systematic review suggest that there are still substantial gaps with respect to understanding how cognitive-behavioral and exercise-based interventions work for pain and disability in people with chronic musculoskeletal pain.

We found 40 studies (n=8354), which included a total of 193 mediation models examining the role 39 putative mediators on pain or disability, of which 19 partially mediated treatment effects; 15 had mixed results and 5 did not significantly mediate treatment effect. Methodological limitations were common in several of the studies found and there was no consensus between studies on how to conduct and report mediation analysis. Due to the heterogeneity of the included studies, we conducted one meta-analysis to verify the mediating role of self-efficacy on disability in exercise-based interventions, and five meta-analyses to verify the mediating role of acceptance, fear-avoidance beliefs and psychological flexibility on disability, and of psychological flexibility on pain in cognitive-behavioral interventions. Nevertheless, our results suggest that thus far, there is no evidence of mediating effects of these putative mediators.

The findings described in **Chapter 5** presents preliminary evidence about the mechanisms of action of cognitive-behavioral and exercise-based interventions so far, with meaningful opportunities to move the field forward by establishing strengths and limitations of the field. Its results suggest that there are still substantial gaps with

respect to understanding how these interventions work for pain and disability in people with chronic musculoskeletal pain. There is serious publication bias and better studies are needed if we are to inform policy and practice with mechanistic studies.

Better evidence of causal mechanisms of interventions can help to develop more fine-grained clinical hypotheses to be tested in randomized clinical trials, which could ultimately lead to more effective interventions or to the optimization of current interventions. Researchers should bridge this gap by including mediation analysis with adequate statistical methods in their randomized clinical trials protocols, and by designing clinical trials to answer mechanistic questions (i.e. measuring relevant mediators with adequate measurement tools in adequate time points to conduct a mediation analysis).

As chronic musculoskeletal pain complaints may share similar drivers of pain and disability, the investigation about the mechanisms of action of pain interventions would also probably benefit if putative mediators to be investigated were not selected just by the proposed explanation of how each intervention works, but by current knowledge of pain science and its multidimensionality. Particularly, researchers should look for the mediating effect of processes driven by learning (e.g. sensitization, threat anticipation, expectancy, learned defense and pain behaviors) in the effect of pain interventions. This might be a promising direction to discover better mediators of effect.

Concluding Remarks and Future Directions

Although the results of this thesis offer new insights, they also raise some questions and opportunities for further research. After extensively reviewing the scientific literature and based on the results of the studies presented during this thesis, I personally believe that learning theory can be used to shed light on how exactly movements may become and remain painful and in the understanding of individual variability in movement-related pain reports in people with chronic musculoskeletal pain ([25](#), [116](#), [239](#)).

Processes of non-associative learning in the form of peripheral or central sensitization and the dysfunction of endogenous pain modulatory mechanisms are clearly associated with several chronic musculoskeletal painful conditions ([142](#), [169](#),

[199-202](#), [208](#), [209](#), [213-215](#)), and might be good putative mediators for pain and disability to be investigated among pain interventions that are known or hypothesized to address this mechanisms in this population (e.g. exercise therapy ([353](#))).

There is also compelling evidence suggesting that pain beliefs and behaviors may influence the transition from acute to chronic pain and associated outcomes, such as disability ([119](#)) and sick leave ([124](#)), with plenty experimental data suggesting that these factors may be associated with the maintenance of chronic disabling pain in people with chronic musculoskeletal pain ([25](#), [26](#), [142](#), [143](#), [251-254](#), [354-356](#)). The mediating role of relevant cognitive and behavioral variables for pain and disability should be properly investigated among pain interventions that are known or hypothesized to adress this mechanisms in people with chronic musculoskeletal pain (e.g. operant therapy and pain neuroscience education).

Finally, the role of associative learning in movement-related pain persistence, clinical presentation and improvement should also be further investigated. The interplay of pain conditioning with other very known processes driven by associative learning, such as fear of movement-related pain and expectancy, might offer new insights about how interventions targeted at modifyng threat anticipation during tasks and movements (e.g. exposure therapy) may work.

Through a better understanding of what is pain and what are the mechanisms associated with its persistence, we may start raising more promising clinical hypothesis to be investigated about what may be the best interventions to improve pain and disability in people with chronic musculoskeletal pain. Understanding treatment mechanisms of action would also save valuable research resources by allowing pain interventions to target the right mediators of effect, based on empirical evidence rather than presumptive theories about how interventions work (or not). As current evidence-based pain interventions usually have small effects for this population ([332](#), [357](#), [358](#)), the whole field would benefit if more effective interventions were developed.

Meanwhile, clinicians should use the available evidence about mechanisms to optimize treatment prescription with caution. Clinicians commonly try to use mechanism-based knowledge to make sense of the complexity and uncertainty in chronic pain treatments to create a rationale for their clinical decision-making.

Although this seems intuitive, there are some problems with this approach.

Clinicians should be aware that evidence of mechanism is not a proof of treatment efficacy, no matter how much it makes sense (e.g., hyaluronic acid injections has been shown not to be superior to placebo for hip osteoarthritis, despite existing *in vitro* evidence show otherwise ([359](#))). Similarly, evidence of efficacy does not necessarily reflect the mechanisms by which the intervention affects the outcome (e.g., motor control exercises for people with low back pain does not work through changes in deep muscles activation patterns ([112](#), [113](#))). Therefore, clinicians should choose among the available evidence-based treatments and use good conceptual models and the available evidences of mechanisms of action to choose what may best work for whom, and to explain to patients what is pain and the possible underlying mechanisms through which the chosen interventions may or may not work. This may help people with chronic pain to better understand their clinical condition and deal with it.

Finally, science disseminators and health institutions should provide better information about current evidence of what is pain and how to deal with it to the general population, according to modern concepts of pain science. As long as pain continues to be understood as an accurate sign of tissue damage, we can expect that it will continue to be overdiagnosed and overtreated. Through a better understanding about the mechanisms underlying movement-related pain persistence and recovery in subjects with chronic musculoskeletal pain, we may be on a better track to understand how to lessen its burden.

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