

University of Groningen

## Central Sensitization and Physical Functioning in patients with Chronic Low Back Pain

Ansuategui Echeita, Jone

DOI:  
[10.33612/diss.211422566](https://doi.org/10.33612/diss.211422566)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2022

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*  
Ansuategui Echeita, J. (2022). *Central Sensitization and Physical Functioning in patients with Chronic Low Back Pain*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.  
<https://doi.org/10.33612/diss.211422566>

### Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

# 9

## General Discussion

The studies in this thesis aimed to contribute to the improvement of the clinical assessment of patients with chronic low back pain (CLBP)<sup>2</sup>, for more effective pain management and rehabilitation. To address this aim, the studies focused on the involvement of central sensitization (CS) in the functioning of patients with CLBP and, additionally, in the measurement methods to assess CS and functioning. In this general discussion, the main findings of the research studies are summarized, their contribution to the body of knowledge described, their implications for the clinical practice discussed, the strengths, limitations and recommendations for future research reported, and the conclusion is presented.

### **Main findings**

**Research Question 1.** *What is the relationship between clinical reference symptoms indicative of CS and functioning measurements in patients with CLBP? Are changes in CS associated with changes in functioning (daily living activities) in patients with CLBP?*

The association between CS and functioning in patients with CLBP was found, although this association was not straightforward (see Table 1 for a summary of the results). The results of the cross-sectional analyses (chapters 4 to 7) revealed very few weak-to-moderate associations between CS and functioning. Moreover, these associations were heterogeneous –differing between the indicators of CS and the functioning measurements– and even contrasting in the studies assessing lifting capacity (chapters 4 and 5). The results of the longitudinal analyses (chapter 4) revealed very few, moderate and diverse associations; and, additionally, differed from the results of the cross-sectional analyses.

**Research Question 2.** *What is the relationship between three measurement methods which assess symptoms indicative of CS in patients with CLBP?*

No association between three different CS measurement methods in patients with CLBP was found (chapter 3). These methods assess symptoms indicative of CS from three very different perspectives –self-reported CS-related symptoms, somatosensory function and autonomic nervous system function–, but showed no significant relationship between them.

---

2. Throughout the General Discussion, patients with CLBP are patients with primary CLBP (International Classification of Diseases 11<sup>th</sup> revision (ICD-11) code MG30.02 - Chronic primary musculoskeletal pain [47]).


**Research Question 3.** Is a maximal cardiopulmonary exercise test feasible and pain tolerable for patients with CLBP? What is the relationship between maximal aerobic capacity acquired by maximal cardiopulmonary exercise test and functioning in patients with CLBP?

The maximal cardiopulmonary exercise test was found to be safe, feasible, pain tolerable and partly associated with functioning in patients with CLBP (chapters 7 and 8). A moderate association between maximal cardiopulmonary exercise test and performance-based functioning –lifting capacity– was found, but not with self-reported measurements.

**Table 1.** Summary of the associations tested between indicators of CS and Functioning measurements.

	Functioning										
	Physical functioning		Pain disability		Work ability		Lifting capacity		Non-organic signs	Aerobic capacity	
<b>CS</b>											
CS-related Symptoms	○	Δ	○	●	○	Δ	○	Δ	●	○	
Somatosensory Function	○	Δ	○	Δ	○	Δ	●	Δ	.	○	
Parasympathetic Function	●	Δ	○	Δ	○	Δ	○	Δ	.	○	
<b>Confounders</b>											
Age	○	Δ	○	Δ	○	Δ	●	Δ	●	○	
Sex	○	Δ	○	Δ	○	Δ	●	Δ	●	○	
Pain intensity	○	Δ	●	Δ	○	Δ	●	Δ	○	○	
Functioning	● <i>Dis</i>	Δ	● <i>Func</i>	Δ	● <i>Func</i>	● <i>ΔLift</i>	○	Δ	● <i>NO</i>	● <i>Dis</i>	
Others	○	● <i>ΔCat</i>	○	Δ	○	Δ	● <i>Clin</i>	● <i>ΔClin</i>	○	● <i>Load</i>	● <i>RR</i>
<b>Chapter number</b>	4		4		4		4		5	6	7

○, not significant association. Δ, longitudinal analysis performed with percentage change from baseline (delta). Abbreviations: *Dis*, Pain disability; *Cat*, Catastrophizing; *Clin*, Clinician observed exertion; *Func*, Physical functioning; *Lift*, Lifting capacity; *Load*, Workload (from cycle ergometer); *NO*, Non-organic signs; *RR*, R-R interval (from heart rate variability); *Work*, Work ability.

Strength of the association: 

## **Contribution to the body of knowledge**

The findings of this thesis do not provide a clear straightforward answer on the involvement of CS in the functioning of patients with CLBP. Heterogeneous associations, which differed over time between indicators of CS and biopsychosocial factors, and functioning measurements, were found. These associations may suggest that CS can be a contributing factor to the functioning of patients with CLBP, although it does not seem to be playing a crucial role in hindering functioning. Considerations related to the findings of this thesis are discussed here below.

### *Patient individuality*

Multiple biopsychosocial factors can define the pain and capacity of patients with CLBP to perform activities and engage in society [1,2]. That is, patients with CLBP can be highly variable, because the combination of different factors shapes their pain [3]. It is hypothesized that patient variability can play a role in the heterogeneous associations observed in this thesis; notably the individual and contextual characteristics at the time of the assessment. For example, conflicting results between groups of patients with CLBP on the association between self-reported CS-related symptoms and lifting capacity (chapters 4 and 5) were found. In this case, a group of patients performed a baseline assessment for a pain rehabilitation program (chapter 4) and the other group of patients for a vocational rehabilitation program (chapter 5). It is plausible that the complexity of the cases can vary between the two patient groups. For instance, in personal characteristics such as motivation, behavior, psychological traits, and family, friend and/or work situation. But also, it is plausible that the context, the rehabilitation programs' assessments, can differ in various features such as in clinicians' assessment approach and in intervention goals. The impact of the environment on the functioning assessment of patients has been previously emphasized [4,5]. It is unknown in what way and to what degree, the complexity of patients and the rehabilitation context are involved in the conflicting associations between CS and functioning, and thus far a conjecture that future research may be able to test. Further, the time point of the assessment has been reported to play an important role in the associations between psychological factors and pain intensity, disability and quality of life in patients with CLBP [6]. It is possible that the differences in the results at baseline and over time of the association between CS and biopsychosocial factors, and functioning measurements (chapter 4), could be a reflection of within-patient changes [7]. Altogether, the unique characteristics of patients, and the context and the time of the assessments, are recognized, challenging the generalization of findings, assessments and interventions across patients with CLBP.

### *Underlying factors*

The biopsychosocial framework is based on the understanding of the factors contributing to pain and functioning limitations of patients with chronic pain [1]. However, the effect of these factors on the association between pain and functioning is unclear. It is important to know the effect that different biopsychosocial factors have on an association, as it can assist to define and prioritize relevant targets for the intervention of patients with chronic pain. In particular mediators and moderators are of interest because they can influence an association, respectively by explaining and changing the strength of the association [8]. In such a sense, if underlying (mediating and/or moderating) factors were present in the associations between CS and functioning, heterogeneous associations, also over time, as found in this thesis (chapters 4 to 7), could be expected. Research on underlying factors of the association between pain and disability have been mostly on the mediating effect of psychological factors, and reported no conclusive effects [9–13]. It is recommended to study the underlying biopsychosocial factors involved in the association between pain and functioning, at a later stage CS, and also over time. Future research on underlying factors may help untangle and better understand pain-related disability in patients with CLBP. This research can be used for a better patient-centered design and implementation during pain management and rehabilitation interventions.

### *CS complexity and measurements*

CS is complex, and a substantial diagnostic challenge for clinical practice. There is no defined diagnostic standard nor gold standard to clinically assess CS—only symptoms indicative of CS can be assessed [14,15]. On top of that, the presence and magnitude of CS can manifest diversely across patients with CLBP [14]. It is possible that different manifestations of CS may have been present in the patients with CLBP included in the studies, which were captured with the different CS measurements used in this thesis. But also, these measurements assess CS from different perspectives—self-reported CS-related symptoms, somatosensory function and autonomic nervous system function. The few and heterogeneous associations between CS and functioning—including biopsychosocial factors—(chapters 4 to 7) as well as the lack of associations between the different CS measurement methods (chapter 3); could be attributed to differences in the manifestations of CS and the perspective of CS measurements. These findings challenge the use of a single CS measurement method to detect, quantify and/or assess all contributing aspects related to CS in the clinical practice.

The currently available measurement methods to clinically assess the presence of CS [14] focus on the pain-related sensory and/or psychological symptoms indicative of CS. Pain is a complex multidimensional experience which includes the somatosensory, affective-motivational, evaluative-cognitive and motor control systems [16–18]. The CS measurement methods do not include the motor control or movement dimension in pain. Pain can produce changes in the movement behavior of individuals involving adaptations at multiple levels of the nervous system [19,20], which may contribute to chronification [21,22]. For example, patients with CLBP may move differently to reduce and protect from pain, leading to changes in functioning. In recent years, the need for an integrated multidimensional framework is becoming more and more important to better characterize pain using the concurrent examination of sensory, psychological and motor systems [22,23]. Provided that somatosensory information is a driver of motor control organization, increased somatosensory input such as in CS, along with psychosocial factors, may maintain and contribute to changes in the movement behavior and functioning [24]. Therefore, the integrated multidimensional framework could provide important insights into CS. Future research in the interplay of sensory, cognitive, psychological and motor systems may help in the understanding of pain processing and its association with functioning. Moreover, because movement behavior changes can differ across individuals with CLBP [25], the integrated framework could assist obtain a more accurate characterization of patients and become beneficial for the prevention, assessment and patient-centered intervention.

### *Functioning measurements*

The functioning of patients with CLBP was comprehensively determined with a combination of performance-based and self-reported measurements. These measurements may determine functioning from different perspectives [26], and their outcomes and contributing factors can change with each functioning measurement. Discrepant outcomes between performance-based and self-reported measurements of physical functioning and activity levels of patients with CLBP have previously been reported [26–28]. Furthermore, biopsychosocial factors have been evidenced to differ across performance-based and self-reported functioning measurements [29], and even across different performance-based capacity tests [30]. Consequently, it is reasonable that the maximal cardiopulmonary exercise test was associated with another performance-based functioning measurement –lifting capacity–, but not with self-reported measurements of functioning (chapter 8); and that indicators of CS and biopsychosocial factors, contributed diversely to different functioning measurements (chapters 4 to 7) as found in this thesis. Taken together, these associations underscore the specificity of each functioning measurement and the complex association with their contributing factors, including CS.

### *Machine learning approach*

Contemporary technological innovations allow for more in-depth approaches to data. One of such is machine learning, which aims at detecting patterns in the data [31] and is currently being used more and more for the assessment of patients with chronic pain. This approach can assist better understand pain and be a useful tool for the decision-making of healthcare professionals [32–34]. The analyses of this thesis were planned and executed with conventional statistical analyses aiming to answer the research questions (chapter 2). Seeing the heterogeneity in the associations between CS and functioning (chapters 4 to 7), it is possible that more in-depth approaches may be needed. Machine learning can assist more accurately characterize the functioning of patients with CLBP and the association between CS and functioning. For example, machine learning has been able to analyze gait performance outcomes of patients with CLBP, and recognize gait pattern differences between patients with more self-reported CS-related symptoms and those with less [35]. The combination of both approaches has the potential to be more insightful [33], which can be used to design individualized pain management interventions.

### **Implications for the clinical practice**

The studies in this thesis were performed within the clinical setting and as close as possible to care as usual. Because of that, the findings have important implications in daily clinical practice.

### *There is no ‘One-intervention-fits-all’ but ‘Custom-made intervention’*

The discovery of and research on CS has given a different understanding of pain and made a paradigm shift in the management of patients with CLBP, and other chronic pain disorders [36]. The suspicion of CS dominating the clinical picture in patients with CLBP calls for a general treatment approach. An approach that may include pharmacological, conservative pain neuroscience education and cognitive behavioral therapy, exercise therapy, and lifestyle – sleep management, stress management, and/or diet– interventions [15,37]. The findings in this thesis emphasize the role of biopsychosocial factors and the integrated multidimensional framework for individualized clinical assessment and rehabilitation of patients with CLBP. For patient centered interventions, where biopsychosocial factors are considered, a general treatment approach such as the one described above [15,37] may be recommended whether there is suspicion of CS dominating the clinical picture or not. On top of that, given the within-patient changes over time, it is recommended that interventions are dynamic –concurrently adjusted to patients’ progression. It may be subject for



future research when and how frequently the assessments should take place during pain management interventions for these to remain patient-centered.

### *Role of CS in rehabilitation programs*

CS has become a focus of attention and a target for clinical practice since it was first described [38]. It has also gained importance because evidence showed that predominant CS pain could predict poor treatment outcomes in patients with chronic musculoskeletal pain [39]. However, the heterogeneous associations between CS and functioning in this thesis, may point towards CS being considered in rehabilitation programs rather than being an important target in them. Reportedly, there is no evidence for including CS as a target in the intervention instead of considering CS in the intervention [15]. Improvements in pain and disability from individualized interventions have not been reported to be parallel to changes in the pain sensory profile [40]. On the other hand, the currently available measurement methods to assess symptoms indicative of CS may collect relevant information to describe patients' pain. The aforementioned collected information can be of use in clinical practice to better differentiate between patients and more precisely characterize patients who experience pain. It is recommended that for patient-centered interventions, the symptoms indicative of CS are taken into account along with biopsychosocial factors, but not be the main focus. For example, if specific indicators of an amplified pain are identified, CS can be explained to patients to enable their self-management of pain and be the foundation for exercise interventions and better functioning [41]. Which would make the inclusion of CS a useful addition in the assessment and pain management and rehabilitation process. The role and extent to which CS is involved in the assessment and intervention for the promotion of functioning of patients with CLBP may be subject of future studies.

### *The performance of a maximal cardiopulmonary exercise test is justifiable*

In routine clinical practice, several self-reported and performance-based measurements are used to assess the functioning of patients with CLBP. Maximal cardiopulmonary exercise test is the gold standard for the assessment of aerobic capacity [42]. This test can be useful as a benchmark and support in the decision-making of the design and implementation of exercise interventions of patients with CLBP. In the studies of this thesis, the maximal cardiopulmonary exercise test was found to be safe, feasible and pain tolerable in patients with CLBP. Moreover, it was related to the performance-based measurement functioning –as expressed by lifting capacity. On top of it, during the conduct of the research, the maximal cardiopulmonary exercise test was reported to be a 'satisfactory'

experience<sup>3</sup> by several participating patients, despite the increase in the intensity of pain essentially in the upper legs. As a result of this thesis, a maximal cardiopulmonary exercise test can be recommended for the assessment of aerobic capacity (a base to rely on in terms of conditioning) of patients with CLBP in clinical practice. Provided patients are willing to perform it and there is availability and compatibility with the program in the usual care.

*Clinicians/assessors are decisive in the assessment of patients*

The influence of clinicians' beliefs on patients' performance during the physical assessment has been recognized [43]. But as it seems, the beliefs of the rehabilitation team –of which the assessor may or may not be part of– also play a role, particularly in the selection of performance-based assessment methods. The assessment of the aerobic capacity of patients with CLBP can illustrate this. Despite a maximal cardiopulmonary exercise test being the gold standard for the assessment of the aerobic capacity [42], in general, patients with CLBP have not undergone this test, because it was believed that pain would limit their performance [44] and/or patients would not be able to manage the consequences. The findings and the experiences collected during the research of this thesis contrast with such a statement. There is some pain response to the maximal cardiopulmonary exercise test assessment but, as shown in this thesis, the test should not be avoided due to the potential pain response. Alternatively, a balanced decision on whether a patient should or should not undergo the test that considers potential pain flares after the test –a response resembling that in able-bodied– is recommended. Through these lines, it is aimed to raise awareness of the influence of clinicians and their beliefs in the assessment of patients even before the assessment begins. Knowledge about the feasibility and tolerance of assessment methods can assist patients and clinicians in making informed decisions for their selection. Future research may consider including feasibility and tolerance within the psychometric properties of performance-based tests to facilitate making an informed decision.

It is relevant to mention that after the presentation of these results to the pain rehabilitation team involved in this research, they will implement the maximal cardiopulmonary exercise test during the assessment of the aerobic capacity of patients with CLBP (when indicated and possible).

---

3. A 'satisfactory' experience is, in this context, the sensation of achievement or the feeling of pride from performing the maximal CPET.

## General considerations: Strengths and Limitations

In chapter 2, the methodology choice and decisions are discussed. In chapters 3 to 8, the strengths and limitations of each of the studies are reported. Therefore, in this section, a general summary is presented.

One of the strengths of this thesis is that it is embedded in the International Classification of Functioning, Disability and Health [45] framework. A Framework that aims to unify and standardize the description of health and health-related states. Another strength of the thesis is that a comprehensive set of CS and performance-based and self-reported measurements of functioning were collected and tested cross-sectionally (with baseline data), and in most of the associations also longitudinally (changes over time). One last strength of this thesis is that the research projects were conducted in a specialized care setting and organized around patients' usual care. The assessments were non-invasive, feasible and compatible with usual clinical practice procedures. Except for the quantitative sensory testing, which was assessed by a trained researcher, all other assessments were performed by healthcare professionals who routinely conducted the assessments.

In hindsight, there is a number of limitations that need to be taken into account. First, the sample size of patients with CLBP is smaller than a priori calculated in the protocol (chapter 2); this has likely contributed to the lower statistical power of analyses. Second, associations between CS, and non-organic signs and aerobic capacity, were only assessed cross-sectionally. Third, the association between CS and physical activity was not examined in this thesis, even though accelerometer measurements were collected for the project (chapter 2). First results with machine learning approach, despite not being part of this thesis, show that the gait pattern of patients with CLBP differed between patients with more self-reported CS-related symptoms and those with less [35]. Fourth, in particular for the pain tolerance to maximal aerobic capacity (chapter 7), pain response measurements were limited to 24 hours after the test, and the comparison to able-bodied individuals is lacking. Fifth, the studies from chapter 5 and 6 are not part of the same protocol. In these studies, only self-reported CS was assessed and certain biopsychosocial factors did not overlap due to the scope of the rehabilitation programs. Lastly, of the CS measurement methods, the assessment of the somatosensory function (quantitative sensory testing) turned out to be methodologically challenging and deviated on several occasions from the original protocol described by the DFNS [46]. As a result of the trade-off, the protocol was adapted to be compatible with usual care and limit the burden for the patients.

## Future research

From the findings of this thesis, a fair amount of speculation and hypotheses have been formulated, based on which several recommendations for future research are proposed.

This thesis described the association between CS and functioning in patients with CLBP using measurement methods that assess different aspects of them. For a more complete overview of the association, future research should overcome limitations presented above. For example, the association between multiple measurement methods of CS and non-organic signs (chapters 5 and 6), the association between CS and physical activity measurements, and/or longitudinal associations between CS and functioning.

Variability in patients with CLBP is high, which stresses the importance of individual characteristics at the time of the assessment. It is interesting for future research to test the involvement of the complexity of patients and the rehabilitation context in the association between CS and functioning. For the interventions to remain patient-centered, these need to be dynamic—continually adjusted to patients' progression. Recurrent re-assessments of patients during the course of the rehabilitation program, allow pain management interventions to remain patient-centered according to the changing needs of patients. Future research should look into when and how frequently during the course of the intervention patients should be re-assessed for this aim. Also, prospective cohort studies could be able to distinguish and profile subgroups of patients with CLBP who may evolve differently during the interventions and for whom different treatment approaches may be needed. Regarding CS, future research should examine its role in the assessment and intervention for the promotion of functioning.

Pain is a personal experience, which involves multiple (interacting) factors and systems that differ between individuals. Future research should study potential underlying (mediating and/or moderating) biopsychosocial factors in the association between pain and functioning, at a later stage CS, and also over time. This may help untangle and better understand pain-related disability, and assist clinicians define and prioritize relevant targets for the intervention of patients with CLBP. Furthermore, future research should also study the interplay of sensory, cognitive, psychological and motor systems for better insights into pain processing, including CS. This integrated multidimensional framework could also assist in the identification and profiling of subgroups of patients with CLBP and their contribution to functioning.

The methods to assess patients' functioning should report sufficient psychometric properties to be useful for pain management and rehabilitation. Feasibility and tolerance of performance-based functioning tests could provide valuable information and assist clinicians in the choice of assessment methods. Future research should consider including these properties within the psychometric studies of performance-based functioning measurements. To better describe the pain tolerance of a cardiopulmonary exercise test, future research should explore pain responses for a period longer than 24 hours after the test, and compare the pain responses between patients with CLBP and matched able-bodied. Given that if CS dominates the clinical picture patients may experience enhanced pain, the potential implication of CS on pain-related tolerance is of interest for future research.

For a more detailed characterization of patients with CLBP and patient-centered interventions the combined use of conventional and machine learning analysis approaches are proposed. It is, however, important to consider the characteristics and requirements of each of the approaches, in addition to the measurement selected, during the design of the study. For example, the machine learning approach is data-driven and, because of this, it needs raw, detailed source data to create reliable algorithms. Based on the design of the research project (chapter 2), most of the measurements were not apt for machine learning. Exceptionally, the collection of large amounts of data from accelerometers was possible, which was afterwards analyzed with machine learning [35]. Awareness is raised for future research to be mindful about the aim of the research and its requirements, in order to design research projects with matching measurements and approaches.

**General conclusion**

The main aim of this thesis was to study the involvement of CS in the functioning of patients with CLBP and, additionally, the measurement methods to assess the indicators of CS and functioning. Indicators of CS and functioning measurements were comprehensively collected in patients with CLBP combining different methods. Results showed few and heterogeneous associations which differed over time between CS and functioning; no associations between CS measurement methods; and a safe, feasible and pain tolerable maximal cardiopulmonary exercise test partly associated with functioning measurements. All things considered, it is concluded that: (1) Pain is a complex, personal, multifactorial and multidimensional experience. The inclusion of the biopsychosocial and integrated (sensory, cognitive, psychological and motor systems) frameworks is crucial for the understanding of CLBP and CS, and for better matching of assessments and interventions to patients' progression. (2) CS is complex and it can be a contributing factor to the functioning of patients with CLBP, although it does not seem to be playing a crucial role in hindering functioning. (3) Maximal cardiopulmonary exercise tests can be recommended for the assessment of aerobic capacity in patients with CLBP in clinical practice.

## REFERENCES

1. Waddell G. *The Back Pain Revolution*. 2nd ed. Edinburgh: Churchill Livingstone; 2004.
2. Hartvigsen J, Hancock MJ, Kongsted A, Louw Q, Ferreira ML, Genevay S, et al. What low back pain is and why we need to pay attention. *Lancet*. 2018;391:2356–2367.
3. Fillingim RB. Individual differences in pain: understanding the mosaic that makes pain personal. *Pain*. 2017;158:S11–S18.
4. Ansuategui Echeita J, van Holland BJ, Gross DP, Kool J, Oesch P, Trippolini MA, et al. Association between social factors and performance during Functional Capacity Evaluations: a systematic review. *Disabil Rehabil*. 2018;41:1863–1873.
5. Ansuategui Echeita J, Bethge M, van Holland BJ, Gross DP, Kool J, Oesch P, et al. Functional Capacity Evaluation in Different Societal Contexts: Results of a Multicountry Study. *J Occup Rehabil*. 2018;29:222–236.
6. Scholich SL, Hallner D, Wittenberg RH, Hasenbring MI, Rusu AC. The relationship between pain, disability, quality of life and cognitive-behavioural factors in chronic back pain. *Disabil Rehabil*. 2012;34:1993–2000.
7. Fleeson W. Toward a structure- and process-integrated view of personality: traits as density distribution of states. *J Pers Soc Psychol*. 2001;80:1011–1027.
8. Field-Fote EE. Mediators and Moderators, Confounders and Covariates: Exploring the Variables That Illuminate or Obscure the “Active Ingredients” in Neurorehabilitation. *J Neurol Phys Ther*. 2019;43:83–84.
9. Marshall PWM, Schabrun S, Knox MF. Physical activity and the mediating effect of fear, depression, anxiety, and catastrophizing on pain related disability in people with chronic low back pain. *PLoS One*. 2017;12:e0180788.
10. Costa L da CM, Maher CG, McAuley JH, Hancock MJ, Smeets RJEM. Self-efficacy is more important than fear of movement in mediating the relationship between pain and disability in chronic low back pain. *Eur J Pain*. 2011;15:213–219.
11. Varallo G, Scarpina F, Giusti EM, Cattivelli R, Guerrini Usubini A, Capodaglio P, et al. Does Kinesiophobia Mediate the Relationship between Pain Intensity and Disability in Individuals with Chronic Low-Back Pain and Obesity? *Brain Sci*. 2021;11(6):684.
12. Lee H, Hübscher M, Moseley GL, Kamper SJ, Traeger AC, Mansell G, et al. How does pain lead to disability? A systematic review and meta-analysis of mediation studies in people with back and neck pain. *Pain*. 2015;156:988–997.
13. Edwards RR, Dworkin RH, Sullivan MD, Turk DC, Wasan AD. The Role of Psychosocial Processes in the Development and Maintenance of Chronic Pain. *J pain*. 2016;17:T70-T92.
14. Nijs J, George SZ, Clauw DJ, Fernández-de-las-Peñas C, Kosek E, Ickmans K, et al. Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine. *Lancet Rheumatol*. 2021;3:e383–e392.
15. Nijs J, Leysen L, Vanlauwe J, Logghe T, Ickmans K, Polli A, et al. Treatment of central sensitization in patients with chronic pain: time for change? *Expert Opin Pharmacother*. 2019;20:1961–1970.
16. Melzack R, Casey K. Sensory, motivational, and central control determinants of pain: a new conceptual model. In: *The Skin Senses*. Springfield, IL, US: Charles C Thomas; 1968:423–443.
17. Melzack R. From the gate to the neuromatrix. *Pain*. 1999;Suppl 6:S121–S126.
18. Moseley GL. A pain neuromatrix approach to patients with chronic pain. *Man Ther*. 2003;8:130–140.

19. Hodges PW, Tucker K. Moving differently in pain: A new theory to explain the adaptation to pain. *Pain*. 2011;152:S90–S98.
20. Tsao H, Galea MP, Hodges PW. Reorganization of the motor cortex is associated with postural control deficits in recurrent low back pain. *Brain*. 2008;131:2161–2171.
21. Nijs J, Daenen L, Cras P, Struyf F, Rousset N, Oostendorp RAB. Nociception affects motor output: a review on sensory-motor interaction with focus on clinical implications. *Clin J Pain*. 2012;28:175–181.
22. Meier ML, Vrana A, Schweinhardt P. Low Back Pain: The Potential Contribution of Supraspinal Motor Control and Proprioception. *Neuroscientist*. 2019;25:583–596.
23. Butera KA, Fox EJ, George SZ. Toward a Transformed Understanding: From Pain and Movement to Pain With Movement. *Phys Ther*. 2016;96:1503–1507.
24. Hodges PW, Smeets RJ. Interaction between pain, movement, and physical activity: short-term benefits, long-term consequences, and targets for treatment. *Clin J Pain*. 2015;31:97–107.
25. van Dieën JH, Reeves NP, Kawchuk G, van Dillen LR, Hodges PW. Motor Control Changes in Low Back Pain: Divergence in Presentations and Mechanisms. *J Orthop Sports Phys Ther*. 2019;49:370–379.
26. Brouwer S, Dijkstra PU, Stewart RE, Göeken LNH, Groothoff JW, Geertzen JHB. Comparing self-report, clinical examination and functional testing in the assessment of work-related limitations in patients with chronic low back pain. *Disabil Rehabil*. 2005;27:999–1005.
27. Wittink H, Rogers W, Sukiennik A, Carr DB. Physical Functioning: Self-Report and Performance Measures Are Related but Distinct. *Spine*. 2003;28:2407–2413.
28. van Weering MGH, Vollenbroek-Hutten MMR, Hermens HJ. The relationship between objectively and subjectively measured activity levels in people with chronic low back pain. *Clin Rehabil*. 2011;25:256–263.
29. Schiphorst Preuper HR, Reneman MF, Boonstra AM, Dijkstra PU, Versteegen GJ, Geertzen JHB, et al. Relationship between psychological factors and performance-based and self-reported disability in chronic low back pain. *Eur Spine J*. 2008;17:1448–1456.
30. Smeets RJEM, van Geel AC, Kester AD, Knottnerus JA. Physical capacity tasks in chronic low back pain: What is the contributing role of cardiovascular capacity, pain and psychological factors? *Disabil Rehabil*. 2007;29:577–586.
31. Dhar V. Data science and prediction. *Commun ACM*. 2013;56:64–73.
32. Lötsch J, Ultsch A. Machine learning in pain research. *Pain*. 2018;159:623–630.
33. Rajula HSR, Verlato G, Manchia M, Antonucci N, Fanos V. Comparison of Conventional Statistical Methods with Machine Learning in Medicine: Diagnosis, Drug Development, and Treatment. *Medicina*. 2020; 56(9):455.
34. Matsangidou M, Liampas A, Pittara M, Pattichi CS, Zis P. Machine Learning in Pain Medicine: An Up-To-Date Systematic Review. *Pain Ther*. 2021;10:1067–1084. A
35. Zheng X, Reneman MF, Ansuategui Echeita J, Schiphorst Preuper HR, Kruitbosch H, Otten E, et al. Effect of Level of Sensitization on Gait in Chronic Low Back Pain: Insights from a Machine Learning Approach. *J Comp Bio Med*. 2022;144:105329.
36. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011;152:S2–S15.
37. Nijs J, Malfliet A, Ickmans K, Baert I, Meeus M. Treatment of central sensitization in patients with “unexplained” chronic pain: an update. *Expert Opin Pharmacother*. 2014;15:1671–1683.
38. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature*. 1983;306:686–688.



39. Nijs J, Goubert D, Ickmans K. Recognition and Treatment of Central Sensitization in Chronic Pain Patients: Not Limited to Specialized Care. *J Orthop Sport Phys Ther.* 2016;46:1024–1028.
40. Palsso TS, Christensen SWM, De Martino E, Graven-Nielsen T. Pain and Disability in Low Back Pain Can be Reduced Despite No Significant Improvements in Mechanistic Pain Biomarkers. *Clin J Pain.* 2021;37:330–338.
41. Foster NE, Anema JR, Cherkin D, Chou R, Cohen SP, Gross DP, et al. Prevention and treatment of low back pain: evidence, challenges, and promising directions. *Lancet.* 2018;391:2368–2383.
42. Tran D. Cardiopulmonary Exercise Testing. In: *Methods in molecular biology.* 2018;1735:285-295.
43. Lakke SE, Soer R, Krijnen WP, van der Schans CP, Reneman MF, Geertzen JHB. Influence of Physical Therapists' Kinesiophobic Beliefs on Lifting Capacity in Healthy Adults. *Phys Ther.* 2015;95:1224–1233.
44. Duque IL, Parra J-H, Duvallet A. Aerobic fitness and limiting factors of maximal performance in chronic low back pain patients. *J Back Musculoskelet Rehabil.* 2009;22:113–119.
45. World Health Organization. International classification of functioning, disability and health: ICF. World Health Organization. 2001.
46. Rolke R, Baron R, Maier C, Tölle TR, Treede R-D, Beyer A, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *Pain.* 2006;123:231–243.
47. Nicholas M, Vlaeyen JW, Rief W, Barke A, Aziz Q, Benoliel R, et al. The IASP classification of chronic pain for ICD-11. *Pain.* 2019;160:28–37.



