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Is chronic pain caused by central sensitization? A review and critical point of view

Enrique Velasco [a,b,*], Mar Flores-Cortés [c], Javier Guerra-Armas [c], Laura Flix-Díez [d], Francisco Gurdiel-Álvarez [e], Aser Donado-Bermejo [e], Emanuel N. van den Broeke [f], Laura Pérez-Cervera [b,1], Miguel Delicado-Miralles [b,g,1]

[a] *Laboratory of Ion Channel Research, VIB-KU Leuven Center for Brain & Disease Research, Leuven, Belgium. Department of Cellular and Molecular Medicine, KU Leuven, Belgium*
[b] *Neuroscience in Physiotherapy (NiP), independent research group, Elche, Spain*
[c] *International Doctorate School, Faculty of Health Sciences, University of Málaga, Málaga 29071, Spain*
[d] *Department of Otorrinolaryngology, Clínica Universidad de Navarra, University of Navarra, Madrid, Spain*
[e] *International Doctorate School, Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, 28933 Alcorcón, Spain. Cognitive Neuroscience, Pain, and Rehabilitation Research Group (NECODOR), Faculty of Health Sciences, Rey Juan Carlos University, Madrid 28032, Spain*
[f] *Research Group Health Psychology, KU Leuven, Leuven, Belgium*
[g] *Department of Pathology and Surgery. Physiotherapy Area. Faculty of Medicine, Miguel Hernandez University, Alicante, Spain*

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ABSTRACT

Chronic pain causes disability and loss of health worldwide. Yet, a mechanistic explanation for it is still missing. Frequently, neural phenomena, and among them, Central Sensitization (CS), is presented as causing chronic pain. This narrative review explores the evidence substantiating the relationship between CS and chronic pain: four expert researchers were divided in two independent teams that reviewed the available evidence. Three criteria were established for a study to demonstrate a causal relationship: (1) confirm presence of CS, (2) study chronic pain, and (3) test sufficiency or necessity of CS over chronic pain symptoms. No study met those criteria, failing to demonstrate that CS can cause chronic pain. Also, no evidence reporting the occurrence of CS in humans was found. Worryingly, pain assessments are often confounded with CS measures in the literature, omitting that the latter is a neurophysiological and not a perceptual phenomenon. Future research should avoid this misconception to directly interrogate what is the causal contribution of CS to chronic pain to better comprehend this problematic condition.

1. Introduction

Pain is the main reason for medical consultation (St. Sauver et al., 2013). More specifically, chronic pain is considered an epidemic in developed countries, with prevalence rates ranging from 12 % to 30 % in Europe (Breivik et al., 2006), 20.4 % in the United States (Dahlhamer et al., 2018), and 15.4 % in Australia (Deloitte Access Economics, 2019). Common chronic pain conditions such as low back pain, neck pain, migraine, and osteoarthritis are among the leading causes of disability (Vos et al., 2012). Furthermore, the economic impact amounts to an annual cost of $635 billion in the United States and disrupts work activities in one in four European workers (Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education, 2011).

But what is chronic pain? The International Association for the Study of Pain (IASP) states: *"unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage that lasts for longer than 3 months"* (Raja et al., 2020; Treede et al., 2019). Noteworthy, this definition indicates a temporal criterion (often arbitrary) and makes no reference to the pathophysiological origin of chronic pain, as the biological mechanisms underlying chronic pain are not well understood. Although biological contributors to chronic pain generation and maintenance are readily identifiable in

* Corresponding author at: Laboratory of Ion Channel Research, VIB-KU Leuven Center for Brain & Disease Research, Leuven, Belgium. Department of Cellular and Molecular Medicine, KU Leuven, Belgium.
E-mail address: quique.velascoserna@kuleuven.be (E. Velasco).
[1] Shared last authorship.

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some pathologies, such as abnormal peripheral neuronal activity in cases of neuropathic pain (Baron et al., 2010; Campbell and Meyer, 2006; Choi et al., 2024; Cohen and Mao, 2014; Finnerup et al., 2021; Meacham et al., 2017; Serra et al., 2012), there are scenarios in which identifying relevant contributors to chronic pain is more complicated. Paramount of those is nociplastic pain, defined by the IASP as: *"Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage…"* (Merskey and Bogduk, 1994). As "altered nociception" (which can be interpreted as "increased") is a wide term, an unending list of specific biological processes can be contributing to it, including epigenetics (Buchheit et al., 2012; Denk and McMahon, 2012; Descalzi et al., 2015; Mauceri, 2022), glial activation (Donnelly et al., 2020; Grace et al., 2021; Inoue and Tsuda, 2018; Ji et al., 2019, 2013; O'Callaghan and Miller, 2010), brain function and connectivity alterations (Barroso et al., 2021; Elman and Borsook, 2016; Kregel et al., 2015; Kuner and Flor, 2016; Kuner and Kuner, 2021; Thorp et al., 2018), cognitive and emotional processing (Baliki et al., 2006; Bushnell et al., 2013; Edwards et al., 2016; Hashmi et al., 2013; Malfliet et al., 2017; Yang and Chang, 2019), gut microbiota modulation (Defaye et al., 2020; Freidin et al., 2021; Guo et al., 2019; Lucarini et al., 2022, 2020; Santoni et al., 2021) and peripheral/central sensitization (Berta et al., 2017; Li et al., 2021; Pak et al., 2018; Sluka and Clauw, 2016).

Among these, Central Sensitization (CS), described originally by Clifford Woolf (Woolf, 1983; Woolf et al., 1988, 1994), has gained special attention. The IASP defines CS as *"Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input"* (Merskey and Bogduk, 1994). According to this definition, even in the case of absence of discernible macroscopic tissular damage and with normal peripheral nociceptors functioning, CS could provide a neurobiological explanation for chronic pain (Ji et al., 2003). Although its definition is the one of a phenomenon, its undeniable that some authors and clinicians currently interpretate it as a biological mechanism substantiating chronic pain (Kuner and Kuner, 2021; Woolf, 2011, 2007). In fact, CS was initially proposed as a clinical term, and its currently still used for this purpose in many contexts. For instance, some authors conceptualise CS as the main mechanism underlying pathologies with high social relevance such as fibromyalgia, migraine, irritable bowel disease, among others. These conditions are often referred to as "central sensitivity syndromes" (CSS), a term originally proposed by Yunus (Yunus, 2008), or using related terminology such as "central sensitization syndrome" (Fernández Solà, 2018; Fleming and Volcheck, 2015; Metri et al., 2022; Suzuki et al., 2021) or "central pain syndrome" (Dydyk and Givler, 2024).

Contrarily, referential works and authors adopt a more conservative perspective on CS as a phenomenon correlated to chronic pain, avoiding the inference of CS through pain assessments (Adams et al., 2023; Chapman and Vierck, 2017; Dydyk and Givler, 2024). This posture is reflected in the following cite by Clifford Woolf himself: *"However, because we cannot directly measure sensory inflow […] pain hypersensitivity by itself is not enough to make an irrefutable diagnosis of central sensitization"* (Woolf, 2011).

In fact, the role of CS in the transition between acute and chronic pain, the causal relationship between CS and certain clinical conditions, the misunderstandings and myths surrounding the concept as well as the relevance of this neural phenomenon in clinical practice have recently been addressed by several authors (Cayrol et al., 2021; Cervero, 2014; Fillingim, 2024; Hansson, 2014; van den Broeke, 2018; Van Den Broeke et al., 2024, 2018; Van Griensven et al., 2020). Considering this ongoing debate, a relevant question arises: what is demonstrated about CS contribution to chronic pain? Addressing such a question constitutes the main goal of this work.

This narrative review and critical point of view article first presents how to measure CS and chronic pain, then how to test causality based on clear criteria, using them to execute a review aiming to find studies demonstrating CS causality over chronic pain. Thereafter, the current evidence is examined to determine whether it supports a correlation between CS and chronic pain, and if experimental criteria for establishing a causal relationship, such as sufficiency and necessity, are met. Surprisingly, we were unable to find studies demonstrating such causality, or the presence of CS in humans at all. Afterwards we discuss the clinical and fundamental implications of the state of the evidence, provide advice on what can and cannot be said based on scientific results and propose future experiments to advance the knowledge in the field.

2. How to study if CS causes Chronic Pain?

To determine how to measure causality between CS and chronic pain, first it is necessary to define how to assess each one and establish what criteria experimental studies are required to meet in order to prove a causal relationship between them.

2.1. How to assess chronic pain and CS

CS is a change in the responsiveness of nociceptive neurons to stimuli. Neural activity and its indirect correlates can be measured using several approaches, such as Electroencephalography (EEG), functional Magnetic Resonance Imaging (fMRI), Local Field Potentials (LFP), calcium imaging or single cell recordings (Fig. 1a). All these tools can quantify the neural activity evoked by a nociceptive stimulus and therefore can be used to investigate CS, as CS is a modulation of nociception, which is *the neural process of encoding noxious stimuli* (Raja et al., 2020). Importantly, these approaches are not intended to measure pain itself as an experience, as the IASP clarifies in their pain definition *"Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons"* (Raja et al., 2020).

More specifically, CS is defined as an increase in the evoked activity of nociceptive neurons. Therefore, it necessarily entails a difference between two quantities: usually two time points: before (baseline) and after an event. Consequently, to assess it, it is necessary to; (a) stimulate nociceptive neurons while measuring their response; (b) do it before and after a given event occurs, to confirm an increase in their response, (c) to discard the peripheral activity as the source of the increased responses. The IASP reflects these requirements in its definition of sensitization *"a neurophysiological term that can only be applied when both input and output of the neural system under study are known, e.g., by controlling the stimulus and measuring the neural event…"* (Merskey and Bogduk, 1994). In other words: if a stimulus (a) activates more a central nociceptive neuron before and after a manipulation (b), and this cannot be attributed to a sensitization of peripheral nociceptive neurons (c), then that condition or manipulation is producing CS. As an example, capsaicin-induced sensory hyperalgesia has been investigated using a mixed approach: humans to characterize the psychophysics of secondary hyperalgesia and anesthetized monkeys to associate said psychophysics with changes in peripheral and spinal neurons (Baumann et al., 1991; Simone et al., 1991). In these papers, the authors demonstrate that capsaicin intradermal injection induced both secondary hyperalgesia and increased spontaneous and evoked activity in spinal spinothalamic tract neurons (Simone et al., 1991). Importantly, this was not accompanied by a sensitization of the peripheral nociceptors in the injection area or its surroundings (Baumann et al., 1991).

On the other hand, as pain is an individual experience, the main tool used to assess it in humans, as well as chronic pain, is self-reporting, through analogue scales or questionnaires (Attal et al., 2018; Hjermstad et al., 2011) (Fig. 1b). Further, evoked-pain paradigms are also used to assess pain processing alterations, being particularly useful in subjects unable to report such as children or dementia patients (Beltramini et al., 2017; Lichtner et al., 2014). Similarly, pain is inferred in animals through pain-related behaviours (Turner et al., 2019): withdrawal movements such as tail flick (Carstens and Wilson, 1993) or paw withdrawal tests (Carstens and Ansley, 1993; Chaplan et al., 1994), facial expressions such as the Grimace scale (Langford et al., 2010; Mogil et al., 2020), dynamic weight bearing alterations (Quadros et al., 2015;

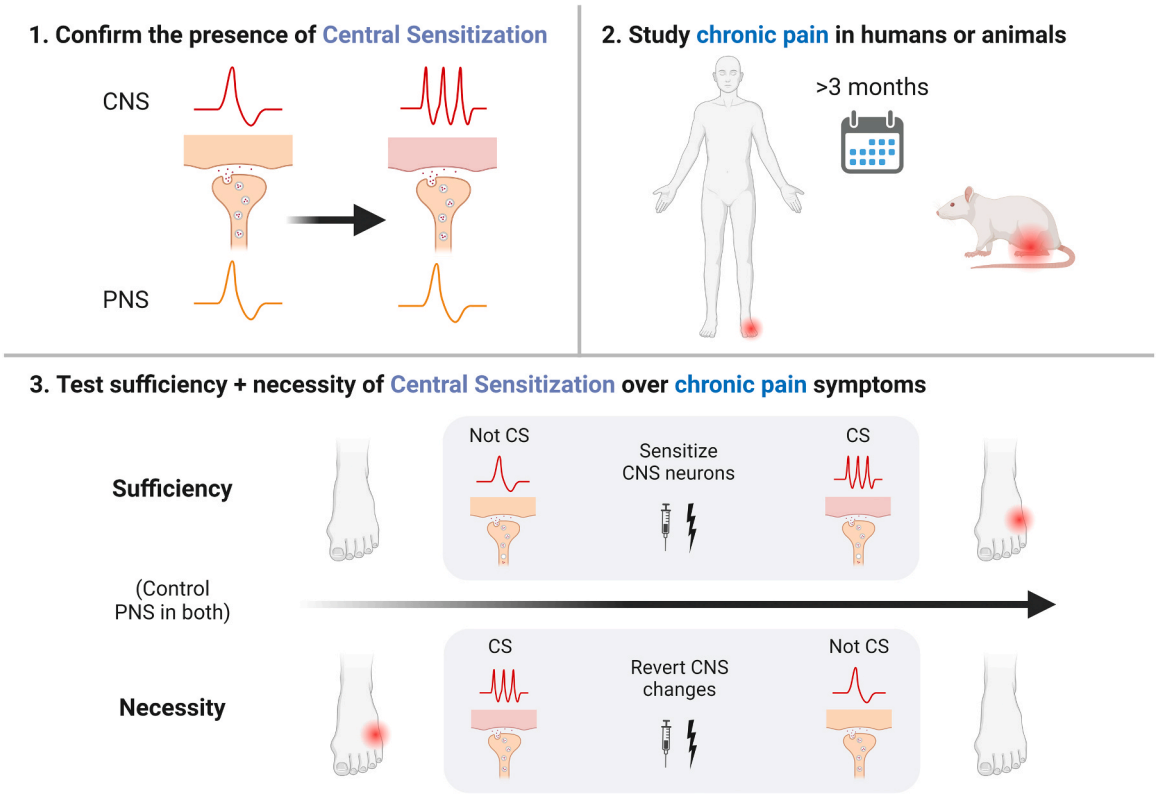

Fig. 1. Measurements of CS and Chronic Pain. Description of the valid approaches to assess CS **(a)** and chronic pain **(b)**. Note that assessing CS entails neurophysiological measurements, while chronic pain is evaluated through verbal, written or behavioural reporting. fMRI: Functional magnetic resonance imaging; PET: Positron emission tomography; EEG electroencephalography; LFP: Local Field Potentials (LFP); QST: Quantitative sensory testing.

Robinson et al., 2012) and other protective actions (Martini et al., 2000), always based on the assumption of this behaviours reflecting pain perception. Although those methods are frequently used, they only capture certain dimensions of the complete pain experience (Gordon, 2015). As a consequence, the field is lately shifting towards multidimensional approaches that consider the interaction of multiple biopsychosocial variables (Haefeli and Elfering, 2006; Seroussi, 2015; Turk et al., 2016; Wijma et al., 2016). In summary, CS is assessed through neurophysiological approaches. Otherwise, pain is evaluated by direct self-reporting or by indirect pain-related behaviours.

2.2. *Criteria to determine CS causality over chronic pain*

A major point that should be taken into account is discerning what constitutes experimental evidence probing CS causality over chronic pain. Although the establishment of causation in science has been the subject of long debates (Gomez-Marin, 2017; Yoshihara and Yoshihara, 2018), for simplicity we will consider in this text that causal evidence is provided by studies demonstrating that CS is necessary and/or sufficient to generate chronic pain (Chao et al., 2013; Thompson, 1994). Taking into account the definitions, reasoning and premises exposed before, we established three necessary conditions that should be met to assert causality between CS and chronic pain (Fig. 2):

(1) Confirm the presence of CS
(2) Ensure a state of chronic pain in humans, or persistent pain in animals*.
(3) Test sufficiency or necessity of CS over chronic pain symptoms.

As an example, a study aiming to provide causal evidence must initially measure changes in neural activity before and after the establishment of chronic pain symptoms (Criteria 1 and 2). Additionally, the study must demonstrate that inducing CS generates chronic pain by itself (sufficiency) and/or that impeding CS prevents chronic pain development (necessity) to move beyond correlation and provide causal evidence (Criteria 3).

*In this work we will consider persistent pain animal models as effective chronic pain models, to avoid skipping any relevant study. Nevertheless, it is important to keep in mind that these models can differ from the human condition known as chronic pain. An example is the arbitrary temporal criteria defining what is considered as "chronic": animal models of persistent pain are rarely extending beyond 1 month since pain onset, while the definition for humans states 3 months as a threshold and actual clinical presentations often span several years (Burma et al., 2017; Gregory et al., 2013; Taylor and Ferrari, 2023).

3. Does CS cause chronic pain?

Although this review can be considered a critical narrative review, we followed a systematic approach to assure reproducibility and that every relevant study was taken into account. Two independent groups of two reviewers (totalling 4) have conducted the literature search and performed the trial selection, composed both by clinical experts and neuroscientists, all experts on pain (further methodological details are presented in *Supp. Information 1: Detailed methodology of the reviewing process*). In particular, we tried to be sure not to omit a study effectively demonstrating a causal relationship between CS and chronic pain, as this will drastically change the point of view expressed here as this literature revision was guided by the question: What evidence is available to support the causal relationship between CS and chronic pain?

As a main finding, we were unable to find evidence to prove or disprove a causal relation link between CS and chronic pain because no study met all three criteria (1+2+3). This precludes the formulation of a definitive response to the question regarding the necessity or sufficiency

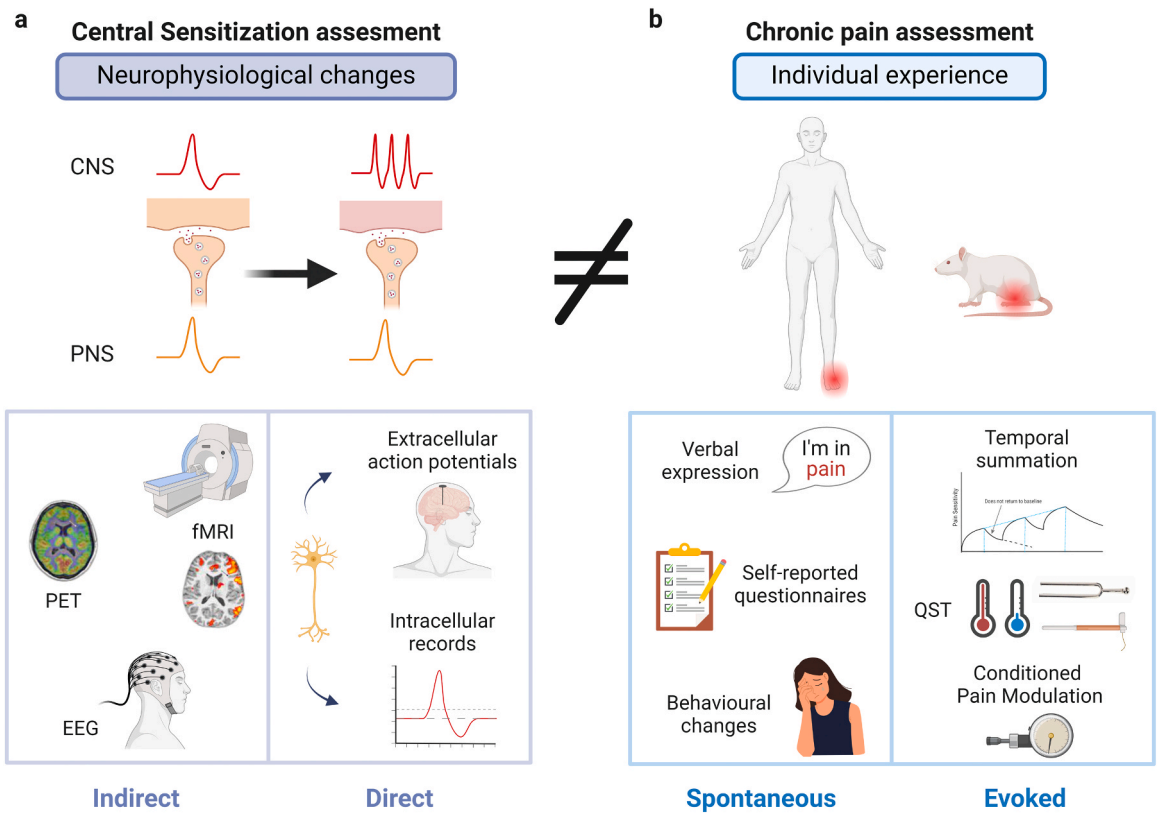

Fig. 2. Criteria for establishing a causal relationship between CS and Chronic Pain. Three necessary criteria should be met (1+2+3): (**1**) Confirm the presence of CS: assess the responsiveness of the CNS both prior and following the chronic pain state development, controlling the peripheral input (PNS). (**2**) Confirm the occurrence of chronic pain, in animals or humans. Valid examples: a neuropathic injury producing sensitization for more than one month in animals, or low back pain with six months evolution in humans (**3**) Test sufficiency and/or necessity of CS over chronic pain symptoms. Fulfilling sufficiency or necessity entails measuring chronic pain through pain-associated behaviour (in animals and humans) or questionnaires (in humans), before and after a CNS manipulation that either induces CS producing chronic pain (sufficiency) or reverts CS disrupting chronic pain (necessity).

of CS in the genesis of chronic pain states, and offering so would be at odds with the prevailing state of the evidence. Moreover, we were unable to find a single study actually demonstrating CS occurrence in humans.

Brazenor et al. conducted a comprehensive review to address whether CS can persist after an injury, inducing persistent pain, a question closely related to ours (Brazenor et al., 2022). Importantly, these authors accepted Quantitative Sensory Testing (QST), the Central Sensitization Inventory questionnaire (CSI) and Conditioned Pain Modulation (CPM) as valid proxies of CS. This widely differs from our approach, as we consider these pain measurements rather than CS assessments, which should be addressed through neurophysiological approaches (this is discussed more in depth in subheading 5 "*Indirect CNS investigations on human subjects*"). Nevertheless, even with this radically different point of view to approach CS, their conclusions are very similar to the ones presented here: there is no evidence directly substantiating that CS lasts after an injury as an autonomous pain generator. To this, our review adds that there is no evidence demonstrating that CS is causally related to chronic pain in any way. Furthermore, based on our results, we conclude that there is no evidence probing the occurrence of CS in humans, neither in patients suffering from pain (chronic or acute) or healthy subjects submitted to experimental pain paradigms.

But if this is the state of the evidence, where is the notion of CS being the cause of chronic pain coming from? Based on the results we obtained, our opinion is that it emanates from two types of studies (1) direct CNS examinations on animal models and (2) indirect investigations on human subjects. In the following, a delineation of select studies that contribute to this perspective will be presented and discussed to highlight why they do not demonstrate a causal relationship between CS and chronic pain. Afterwards, we will present feasible experimental paradigms testing CS causality over chronic pain, and the occurrence of CS in humans, as well as the implications of the current state of the evidence for clinicians and researchers.

4. Direct CNS examinations on animal models

Animal studies have consistently demonstrated a notable augmentation in the nociceptive activity of the CNS on several experimental pain models, encompassing inflammatory (Djouhri et al., 2006; Ikeda et al., 2006; Jakubowski et al., 2007), chemical (Khasabov et al., 2002; Woolf et al., 1994), thermal injury (McMahon and Wall, 1984; Woolf, 1983), spinal nerve ligation (Chao et al., 2021; Djouhri et al., 2006; Rezaee et al., 2019), and electrical pain paradigms (Ikeda et al., 2006; Melzack and Wall, 1965; Thompson et al., 1993; Woolf and Wall, 1986). However, these studies fail to accomplish criterion 1 (demonstrating CS), as they do not assess peripheral sensitization as a potential cause for these CNS increased responses (Khasabov et al., 2002; McMahon and Wall, 1984). Without considering peripheral sensitization, affirming the production of CS becomes challenging, as CNS neurons may exhibit greater responses due to increased input from the periphery rather than being sensitised themselves.

The importance of this consideration is elegantly illustrated by a recent study conducted by Chao et al. (Chao et al., 2021). They assessed pain behaviour employing a non-stimulus-evoked pain paradigm, the Conditioned Place Preference (CPP) test in awake and freely moving animals. They found that spinal nerve ligation increased spontaneous activity and evoked firing rates in dorsal horn neurons. The elimination of spontaneous activity in axotomized peripheral neurons lead to a

reduction in the dorsal horn firing rates within a matter of seconds, accompanied by a decrease in pain behaviours. This investigation underscores the contribution of peripheral sensitization to chronic pain symptoms and increased activity in CNS neurons.

Furthermore, many of these studies fail to accomplish criterion 2 (studying chronic pain). Simply, they use acute experimental pain models, excluding chronic pain paradigms. Notably, even the seminal publication by Woolf describing CS did not use chronic pain, but an acute burning injury (Woolf, 1983). Therefore, they are not studying chronic pain paradigms and their findings do not test the neurobiological causes of chronic pain.

A significant part of the studies does not fulfil criterion 3 (testing causality) as they aim to be simply descriptive. The main limitation is the absence of pain behavioral assessments complementing the physiological data demonstrating increased CNS responses. In fact, many of these studies have been performed *in vitro,* employing transverse slices (Randic et al., 1993; Thompson et al., 1993), *in vivo* using decerebrated (McMahon and Wall, 1984; Woolf, 1983; Woolf et al., 1994; Woolf and Wall, 1986) or anesthetized animals (Jakubowski et al., 2007; Khasabov et al., 2005, 2002; Sandkühler and Liu, 1998). Although some of these studies measure flexor withdrawal reflex as a manifestation of allodynia (Mantyh et al., 1997; Rezaee et al., 2019; Woolf, 1983; Woolf and Wall, 1986), it should be noted again that pain is a conscious experience in humans, and we assumed that also in animals. Under this paradigm, unconscious animals cannot manifest pain, precluding from testing if the reversion or induction of CS actually relieves and induces chronic pain symptomatology, respectively. Summarising, none of them manipulate CS to investigate causality, which implies that although they demonstrate that pain models may produce CS, they do not provide evidence of CS producing or being required for pain.

An exemplary study almost fulfilling all three criteria and thus suggesting causality of CS over chronic pain is (Wei et al., 2021). The authors use mice to demonstrate that activating the dorsal hippocampus using chemogenetics, optogenetics or pharmacology produces analgesia in evoked- and spontaneous pain behavioural paradigms (criterion 3). They demonstrate this finding using two neuropathy models: spinal nerve ligation and spared nerve injury (criterion 2). However, despite the relevance of these studies, two drawbacks prevent this evidence from conclusively demonstrating that CS in the hippocampus causes chronic pain. First, this work lacks data demonstrating increased responses of the dorsal hippocampus to noxious stimulation or control of peripheral activity, thus we cannot assure that CS is produced (criterion 1). Second, the specific manipulations performed here (activating the dorsal hippocampus) would need to specifically revert the CS induced in the model to establish causality (criterion 3).

In conclusion, animal studies strongly demonstrate that experimental pain models produce alterations in the responses of CNS nociceptive neurons. However, no study proves that a change in CNS neuronal activity is responsible for symptomatology in animal persistent pain models. To test this hypothesis, it is necessary to induce CS and demonstrate that it evokes chronic pain persisting over time in healthy animals (sufficiency) and that disrupting CS reverts or prevents pain symptomatology in a chronic pain model (necessity).

5. Indirect CNS investigations on human subjects

Studying humans instead of animals presents several advantages. Patients suffering from chronic pain accomplishes our criterion 2 (studying chronic pain) (Berge, 2011; Burma et al., 2017; Taylor and Ferrari, 2023). Furthermore, subjects can provide higher dimensionality through reporting than animal behavioural tests (Breivik et al., 2008; Main, 2016; Smith et al., 1997). Nonetheless, investigating the relationship between CS and chronic pain in humans also presents pitfalls. The main difficulty lies in measuring the presence of CS due to ethical and technical problems (criterion 1). In current literature, we observe three approaches to overcome this problem: to use measurements of neural activity, to use evoked pain paradigms, or to assess CS through the use of questionnaires. In the following, we will discuss why the first one is the only valid one to assess CS and expose why no article satisfies all three criteria. For a detailed analysis of some relevant pieces of the bibliography, please see *Supp. Information 2: Examples of research works investigating CS in humans suffering from chronic pain*.

5.1. Measurements of neural activity in humans

Although it is possible to directly measure single neuron activity in humans, it requires intracranial electrode implantation, an ethically and technically challenging procedure (Shirvalkar et al., 2023; Soyman et al., n.d.). Therefore, the most common approaches to assess CNS activity in humans with chronic pain are non-invasive, such as EEG (Jensen et al., 2013; Ploner et al., 2017), fMRI (Chiu, 2005; Davis et al., 2017; Tanasescu et al., 2016) or Positron Emission Tomography (Šimić et al., 2017). These techniques record signals related with neural activity, i.e., populational electric fields or blood deoxygenation, for EEG and fMRI respectively (Buzsáki et al., 2012; Logothetis and Wandell, 2004). However, as many expert neuroscientists have stated before, alterations in biological processes other than neural spiking activity can influence these readouts, such as volume conduction or activity synchronization for EEG, or alterations in the neurovascular coupling for fMRI (Goense and Logothetis, 2008; Herreras, 2016; Lippert et al., 2010; Logothetis, 2002; Torres et al., 2019).

Therefore, caution should be exerted when interpreting the occurrence of CS from these populational measurements. For instance, Nikos Logothethis highlighted that a single fMRI cortical voxel contains around 5.5 million neurons and the resultant readout reflects the combined blood deoxygenation (Logothetis, 2008). It is then possible that half of these neurons get sensitised by a specific pain-related condition while the other half reduces its activity, and this will result in no change in the fMRI readout for that voxel. Therefore, populational measurements can point out a potential CS but not confirm or discard it.

Importantly, no study using physiological approaches to determine CS fulfilled our three criteria in humans. When criterion 1 (establishment of CS) was not accomplished, it was due to an absence of either peripheral input control or longitudinal measurements. This latter case is especially common, as the most frequent type of study compares the CNS activity of two groups: one with and another without pain. While such studies associate disparities in neural activity with chronic pain, they do not determine whether these changes precede pain chronification (potentially as a causal or risk factor), emerge afterwards as a consequence of chronic pain, or if they contribute to pain experience at all. Moreover, as the possibility of these disparities being there before the pain condition cannot be ruled out, they cannot even be considered a (central) sensitization or increased response. The solution is to design a study to measure before and after a given condition is established. Criterion 3 was often not accomplished, as manipulating the CNS in humans is highly challenging, both technical and ethically.

5.2. Evoked pain paradigms and human-assumed central sensitization

Beyond neural activity assessment, various perceptual proxies are employed to indirectly gauge the presence of central sensitization. Those assessments commonly include temporal summation of pain, conditioned pain modulation, a widespread pattern of pain or the presence of secondary hyperalgesia (Nijs et al., 2023). Then, on the basis of this proposal, the term Human-assumed Central Sensitization has been proposed to describe patients reflecting alterations in evoked pain responses (Schuttert et al., 2022, 2021). This is in accordance with the definition of CS: "*Clinically, sensitization may only be inferred indirectly from phenomena such as hyperalgesia or allodynia*" (Merskey and Bogduk, 1994). Following this perspective, some authors have argued that "*(Clinical) features of central sensitization […] can be assessed in humans and can be assessed by clinicians*" (Nijs et al., 2023).

We disagree with the use of this term. Despite understanding the rationale underlying this perspective, in our view, deducting CS from pain hypersensitivity contradicts its current definition, and such perspective may arise from an oversimplified conceptualization of the neurobiological basis of nociception. Since CS is defined as a potentiation of the response of the nociceptive neurons in the CNS, it does not necessarily imply pain augmentation, i.e. hyperalgesia or allodynia. Indeed, as stated by Treede in 2016 "*Because the CNS contains many interneurons that are not part of the pathway to conscious perception, the consequences of central sensitization may be enhanced nonconscious responses (for reflex interneurons) or even reduced pain sensitivity (for inhibitory interneurons)*" (Treede, 2016), a concept already presented by Sandkühler (Sandkühler, 2009). For example, the potentiation of a neuron participating from endogenous analgesia systems like the OFF cells mediating descending pain inhibition will also fit the definition of CS, but will result in decreased nociception and presumably in pain reduction (Antoine et al., 2000; Chen and Heinricher, 2019; De Felice et al., 2011; Drake et al., 2021). Plasticity can occur at any point of the nociceptive system resulting in increased, decreased or unchanged nociceptive gain, allowing CS to manifest in various forms, paradoxically including the absence of pain. Therefore, from a theoretical point of view, it is illogical to ascribe CS to particular alterations in evoked pain perceptions, and even worse to deduct CS from pain symptomatology.

Evoked pain paradigms present another limitation that further reflect the inconsistency of deducting CS from pain symptoms. As we have previously introduced, the presence of peripheral sensitization can increase the nociception evoked by a determined stimulus. Therefore, it is not possible to conclusively attribute pain hypersensitivity to central sensitization rather than peripheral sensitization, as these measures stimulate peripheral terminals to elicit pain perceptions and is impossible to separate their specific contribution if only pain perception is being measured (i.e. in absence of physiological measurements). In fact, there is specific evidence that can justify a role for peripheral sensitization in every evoked pain paradigm commonly associated with Human-assumed Central Sensitization (Table 1).

This is the case of studies addressing the Nociceptive Withdrawal Reflex (NWR). NWR, previously mentioned in the context of animal studies, can also be measured in humans as an objective measurement of a nociceptive response in contrast to self-reported pain. Moreover, adequate designs in which NWR can be used as a proxy of changes in spinal processing of noxious stimulation have been previously published (Willer et al., 1989). However, a change in NWR can also be due to modifications in the afferent (peripheral sensory neurons) or efferent (motoneurons) arms involved in the reflex. Therefore, to deduct CS from NWR, both the input and the output to the spinal cord should be measured. This can be done, for example, through sensory nerve action potential (SNAP) and H-reflex measurements (Tavee, 2019). Such study is yet to be done.

In conclusion, scientific contributions relying solely on evoked pain paradigms to determine the presence of CS fail to meet our criterion 1 (demonstrate CS) and are inadequate to prove a causal or even a correlative relationship between chronic pain symptoms and CS. At best, these works demonstrate that chronic pain is associated with certain alterations in the perception of standardised noxious stimuli.

5.3. Pain questionnaires

In 2012, a group of researchers led by Robert Gatchel published a questionnaire named Central Sensitization Inventory (CSI) (Mayer et al., 2012). They stated about CSI: "*identifies key symptoms associated with CSSs and quantifies the degree of these symptoms*" being CSSs the central sensitivity syndromes described by Yunus, encompassing many chronic pain conditions such as low back pain and fibromyalgia (Yunus, 2015, 2008). Therefore, the objective of the CSI was not to quantify CS, but how much the symptomatology of a patient coincided with the clinical

Table 1
Peripheral sensitization mechanisms that could produce increased pain responses to QST commonly associated with Human-assumed Central Sensitization.

Symptom	Main findings	Reference
Cold allodynia	*"Our results suggest that cold allodynia is linked to a reduction of IKD [potassium current] in both high-threshold cold thermoreceptors and nociceptors expressing TRPM8"*	González et al., (2017)
	"Block of Kv1 channels [in silent cold-nociceptors] is sufficient to induce de novo cold sensitivity, pointing to the downregulation of these channels during disease as a possible trigger of cold allodynia."	MacDonald et al., (2021)
Heat hyperalgesia	*"TRPV1,[…], plays an important role in the development and maintenance of heat hyperalgesia."*	Pogatzki-Zahn et al., (2005)
	"Haploinsufficiency of Shank3 in mice leads to substantial impairment in TRPV1 function and heat hyperalgesia, and these deficits can be produced by Shank3 deletion in mouse and human sensory neurons.	Han et al., (2016)
	"We demonstrate that secreted Protein disulfide isomerase (PDI) activates TRPV1 channels through oxidative modification of extracellular cysteines of the channel, indicating that PDI acts as an unconventional positive modulator of TRPV1. These findings suggest that PDI in primary sensory neurons plays an important role in development of heat hyperalgesia […]"	Zhang et al., (2022)
Mechanical allodynia	*"Clear evidence of the involvement of an increased expression of the Nav1.7 channel in nociceptive neurons in the development of inflammatory hyperalgesia."*	Yeomans et al., (2005)
	"Our in vivo findings indicate that NaV1.8 mediates mechanical hyperalgesia evoked by activation of PKCε. These results identify Nav1.8 as a direct substrate of PKCε that is important for mechanical hyperalgesia and, together with TRPV1, plays a key role in PKCε-mediated nociceptor sensitization."	Wu et al., (2012)
	"Sensory neurons that express CHRNA3 constitute a subset of peptidergic C-fiber nociceptors that are completely insensitive to mechanical stimuli under normal conditions but become sensitized to such stimuli when exposed to the inflammatory mediator NGF. […] significantly contributes to the development of mechanical hyperalgesia during inflammation."	Prato et al., (2017)
Secondary Hyperalgesia	*"The present study presents some evidence for a nociceptor sensitization probably related both to primary and to secondary hyperalgesia produced by mechanical stimulation."*	Reeh et al., (1987)
Temporal summation	*"In contrast, in 20 of the 25 HTM-A delta units [a type of nociceptor] the Von Frey [mechanical] thresholds markedly dropped in the intervals between […] stimulations"*	Reeh et al., (1987)
Widespread pain / sensitization	**As a global sensitization mechanism**	
	"Extrapolating from the chemosensory function of the circumventricular organs etc. might DRGs be carrying out some as-yet unidentified chemosensory	Devor, (1999)

(*continued on next page*)

Table 1 (*continued*)

Symptom	Main findings	Reference
	function associated with the body's internal milieu?"	
	"The high density of the CD31+ capillaries in the cell body rich area of the dorsal root ganglion (DRG), […] may partly explain why many circulating neurotoxic agents preferentially accumulate and injure cells within the DRG and induce a sensory rather than a motor neuropathy."	Jimenez-Andrade et al., (2008)
	"The results of this preliminary study, the first performed in humans with traumatic Spinal Cord Injury (SCI), suggest a link between changes in the circulating chemokine profile and pain development in subacute SCI stage as well as with severity in a more chronic stage."	Mordillo-Mateos et al., (2019)
	As a pathology that would imply global peripheral alterations	
	"We show for the first time that the majority of fibromyalgia patients have abnormal C nociceptors."	Serra et al., (2014)
	"Our meta-analysis shows that the prevalence of small fiber pathology in fibromyalgia is 49 %."	Grayston et al., (2019)

presentation ascribed to CSS. In other words: identifying a clinical profile.

Worryingly, it is easy to interpret that a questionnaire named "Central Sensitization Inventory" is actually quantifying Central Sensitization, an impossible *desiderata* given the current definition of CS. Following this misunderstanding, stating that a questionnaire named "central sensitization inventory" is identifying key CSSs symptoms can be interpreted as implying that CSSs are caused by CS. According to the results of this review, this is currently not tested, only suspected by association and biological plausibility. Indeed, the validation of the questionnaire was undertaken by comparing groups of patients "*who presumably have different levels of CS impairment*", finding that fibromyalgia patients scored higher than low back pain patients or controls. This argument is based on a flawed circular reasoning: we assume that certain patients have higher CS. Then those patients score higher on the CSI questionnaire. Consequently, we conclude that the questionnaire is measuring something related to CS. As a result, we then assert that individuals with higher scores on the CSI questionnaire have more CS, closing the circle.

In fact, assuming that some pain phenotypes, such as fibromyalgia, low back pain, non-fibromyalgia widespread pain and others "have more or less CS than others" is unrealistic from a neurophysiological point of view. CS is not specifically produced in chronic pain conditions, or in CSSs: acute pain models such as capsaicin injection modifies brain activity in rats (Antoine et al., 2000; Jaaks et al., 2022) and humans (Iadarola, 1998). The original paper in which Clifford Woolf described CS used an acute thermal injury model (Woolf, 1983). Moreover, acute, nociceptive and self-resolving painful conditions such as acute eye pain (Yang et al., 2021) or ankle sprain (Terada et al., 2019) involve central alterations. Otherwise, alterations in peripheral activity are also present in these pathologies and could be contributing to pain perception (Pérez-Neri et al., 2023; Staud and Smitherman, 2002). Lastly, as discussed before, CS could in fact result in less pain, so patients with less score in pain symptoms can still have higher CS.

This flawed reasoning has had severe repercussions on the clinical conceptual framework for chronic pain. In order to highlight the current and worrisome message that literature conveys, we performed a brief review of clinical literature using the CSI in the last 5 years to collect some examples of misinterpretations of its results. As a result, Table 2 collects some quotations extracted from peer-reviewed clinical research articles in which patients are diagnosed "suffering from CS" directly with questionnaires.

Table 2
Synthesis of some quotes from recent articles attempting to establish a diagnosis of CS in patients with different pain conditions through the use of questionnaires. Noteworthy, to elaborate this table we only analyzed papers mentioning the use of CSI, only went over the titles and abstracts, and restricted the results to the last 5 years (2019–2024). Therefore, this is only an underestimated sample of how far this misunderstanding actually reaches.

Quotation	Reference
Methods: *"Central Sensitization Inventory (CSI) was used […] to measure the presence and level of central sensitization."* **Conclusions:** *"Central sensitization was common in Irritable Bowel Syndrome and associated with GI symptom severity, but with stronger associations in chronic pain disorders and Inflammatory Bowel Disease"*	Midenfjord et al., (2021)
Title: *"Diagnostic accuracy of the clinical indicators to identify central sensitization pain in patients with musculoskeletal pain"* **Introduction:** *"The identification of central sensitization (CS) is an important aspect in the management of patients with chronic musculoskeletal pain"*	Bittencourt et al., (2021)
Title: *"Duloxetine Reduces Pain and Improves Quality of Recovery Following Total Knee Arthroplasty in Centrally Sensitized Patients: A Prospective, Randomized Controlled Study"* **Methods:** *Patients undergoing TKA were screened for central sensitization preoperatively with use of the Central Sensitization Inventory (CSI)* **Conclusions:** *"A substantial number of patients are centrally sensitized before TKA"* *"Surgeons should consider selective incorporation of duloxetine […] according to the severity of central sensitization"*	Koh et al., (2019)
Aim: *"Patients with chronic nonspecific low back pain with central sensitization"* **Methods:** *"Secondary outcomes were central sensitization…"* Evaluated through CSI	Song et al., (2023)
Title: *"Preoperative education on realistic expectations improves the satisfaction of patients with central sensitization after total knee arthroplasty: a randomized-controlled trial"*	Nam et al., (2023)
Title: *"Diagnosis of Central Sensitization and Its Effects on Postoperative Outcomes following Total Knee Arthroplasty: A Systematic Review and Meta-Analysis"* **Conclusions:** *"CSI is most often used for the diagnosis of CS, and the QST and whole-body pain diagram are also used. CS is closely associated with more severe and persistent pain after TKA"*	Kim et al., (2022)
Introduction: *"patients with chronic musculoskeletal (MSK) pain and central sensitization (CS)"* ***Methods:*** *"enrolling patients ≥18 years of age with chronic MSK pain due to CS"*	Lepri et al., (2023)
Results: *"Participants in the central sensitized group were 3.02 times more likely to belong to the high-level catastrophizing group"*	Koh, H. S et al. (2022)
Title: *"Central sensitization adversely affects quality of recovery following lumbar decompression surgery"* **Methods**: *"We used the Central Sensitization Inventory (CSI) to evaluate CS preoperatively"* **Conclusion**: *"Surgical treatment improved the symptoms of lumbar spinal stenosis regardless of the occurrence of CS preoperatively"*	Mui et al., (2024)

In short, what CSI and the term Human-assumed Central

Sensitization are describing is a specific **pain phenotype**. This phenotype is sometimes defined by clinical features, such as pain catastrophism or widespread pain, and that is what CSI is measuring (Adams et al., 2023). In other occasions, said pain phenotype is defined by alterations in evoked pain responses, such as those elicited by quantitative sensory testing, and that is what Human-assumed Central Sensitization is accounting for (Smeets et al., 2023). Indeed, those two approaches may or may not be assessing the same phenotype depending on different factors, such as the specific pathology being studied (Schuttert et al., 2023; Zanette et al., 2006). But what neither of these approaches is measuring is neurons, and consequently, CS. As an example of this notion, a recent study failed to correlate serum biomarkers of brain plasticity (BDNF) and the severity of Human-assumed Central Sensitization, assessed with pain evoked paradigms (Schuttert et al., 2021). Consequently, research works using pain questionnaires or other self-reported pain variables to assert the presence of CS in humans also fail to demonstrate CS (criterion 1) and therefore cannot provide causal evidence for the relationship between CS and chronic pain. As mentioned at the beginning of this subheading, some examples of these studies and why they do not demonstrate causality of CS over chronic pain can be found in *Supp. Information 2: Examples of research works investigating CS in humans suffering from chronic pain.*

6. Implications for clinical practice and research

Nowadays there is a lack of research evaluating causality between CS in chronic pain. What is more, CS has not been directly measured in humans yet. To guide researchers and clinicians on what can and cannot be affirmed based on evidence, we have created a guide in Table 3 that depicts some statements about pain, chronic pain and CS, and whether they are supported, not supported, or falsified by current evidence. In the following lines, we will discuss the clinical and fundamental implications of the results of this work.

The relevance for clinical practice and research of misconceptions regarding central sensitisation have been previously noted by other authors (Brazenor et al., 2022; Van Den Broeke et al., 2024; Van Griensven et al., 2020). The main clinical implication affects the use of CS as a clinical diagnosis and the cause of pain (Dydyk and Givler, 2024; Fleming and Volcheck, 2015; Suzuki et al., 2021). This is certainly incorrect, as CS is a term confined to describe a physiological phenomenon. Reflecting this, the current International Classification of Diseases (ICD) does not consider CS as a specific pathology (Treede et al., 2015). Classifying patients as "presenting CS" could imply wide-ranging consequences, from the therapeutic approach to the patient experience of its own pathology. In conclusion, considering the available evidence, we strongly advise against labelling patients with CS as a clinical diagnosis.

In a similar way, another misunderstanding widely present in clinical practice and research is the assertion: "*CS is the main contributor to nociplastic pain*". As we have discussed before, CS is not demonstrated in humans and CS is not exclusive to one type of pain. For instance, both neuropathic pain and nociceptive pain do present CS. Conversely, we present the more cautious suggestion of CS being a **phenomenon associated with painful conditions** in animals, that can be potentially

Table 3
Statements about pain, chronic pain and central sensitization and their relationship with current evidence. CNS: Central Nervous System; CS: Central Sensitization.

Affirmation	Current evidence
"Acute and persistent pain models induce Central Sensitization in animals"	Demonstrated
"Humans suffering from pain present alterations in CNS activity and structure"	Demonstrated
"Pain symptoms and nervous system alterations may be correlated"	Demonstrated
"Chronic pain is caused by Central Sensitization"	Not supported
"Central Sensitization has been documented in humans"	Not supported
"Nociplastic Pain is caused by Central Sensitization"	Not supported
"Central Sensitivity Syndromes are caused by Central Sensitization"	Not supported
"Central Sensitization can be assumed in humans using evoked pain paradigms"	Not supported
"Central Sensitization can be assumed in humans through self-reporting pain questionnaires"	Not supported
"Central Sensitization can be assessed in a clinical context"	Not supported
"Treating Central Sensitization cures/ameliorates Chronic Pain"	Not supported
"Central Sensitization occurs specifically in Chronic Pain"	Falsified

occurring in humans suffering pain (Kosek et al., 2016).

CS discovery was inspiring and clarifying to understand chronic pain. However, it has been assimilated, as noted above, to the central sensitivity syndromes described by Yunus. As a consequence, treatments aiming to produce relief in chronic pain patients through the modulation of CS are a hot topic nowadays (Nijs et al., 2019, 2014). Nevertheless, studies claiming to measure a treatment-induced reduction are frequently not evaluating CS correctly, as they use evoked pain paradigms or questionnaires, or are measuring changes in CNS activity in animals without accounting for peripheral input (Ferrillo et al., 2022; Lepri et al., 2023; Lluch Girbés et al., 2015; Mohamadi et al., 2020). Therefore, whether treating CS is achievable in a clinical context, or beneficial for chronic pain conditions, remains an open question.

The impressive amount of miscommunication, confusion and bad use of terminology while referring to CS has lead previous authors to propose that its definition was too broad, facilitating misusing the term (van den Broeke, 2018). In fact, Van den Broeke and colleagues have recently proposed to revert the definition of "sensitization" to its original behavioural significance, referring to the phenomenon of pain augmentation in response to sustained or repeated stimulation (Van Den Broeke et al., 2024). Whether a change in the definition of CS is necessary or not is beyond the scope of this work, but what we can affirm is that the current definition is not being correctly used and understood, especially in clinical contexts.

We are aware that there is a clinical necessity to elucidate which mechanisms are altered in a given pain phenotype, and that the term 'CS' has been traditionally used to supply this necessity. However, we encourage the community to use terms reflecting what is actually assessed. When pain manifestations are evaluated (often the case in clinics), terms such as "patients with high sensitivity to pain-inducing stimuli" are appropriate (Cohen et al., 2022). Terms like "facilitated mechanisms", "sensitized nervous system", "increased nociception" should be avoided if those are not being evaluated. This reconceptualization invites to raise awareness on the difference between clinical outputs (measurable in the clinic, such as an altered perception of pain) and potential biological mechanisms (often not measurable in the clinic, such as central sensitization).

7. Implications for basic pain research

Our aim is not defending that there is not a causal relationship between CS and chronic pain. Simply, against the common belief, we argue that this has not been demonstrated. Testing whether CS is the cause of chronic pain is, though ethically and technically challenging, possible with the tools available nowadays. Furthermore, it is worthwhile, since it will allow to ascribe specific neurophysiological adaptations fitting the definition of CS to particular alterations in pain perception.

In animal research the studies should include both neurophysiological measures and pain behavioural assessments. Fig. 3 presents one plausible experimental proposal, though many others would accomplish the same objective. To assess pain behaviour, we recommend employing a non-stimulus-evoked (spontaneous) nociception paradigm, such as the Conditioned Place Preference (CPP) test in awake and freely moving animals (criterion 2). To evaluate CS (criterion 1), studies could use technological advances in electrophysiology, such as chronic recordings through implantation, to longitudinally assess the adaptations produced in the somatosensory system as the pathology is established (i.e. chronic constriction injury in a peripheral nerve).

The main challenge in animal research is to demonstrate causality principles (criterion 3): that preventing CS prevents the development of chronic pain ("necessity") or that inducing CS generates chronic pain ("sufficiency"). The use of circuit manipulations, such as chemo- or

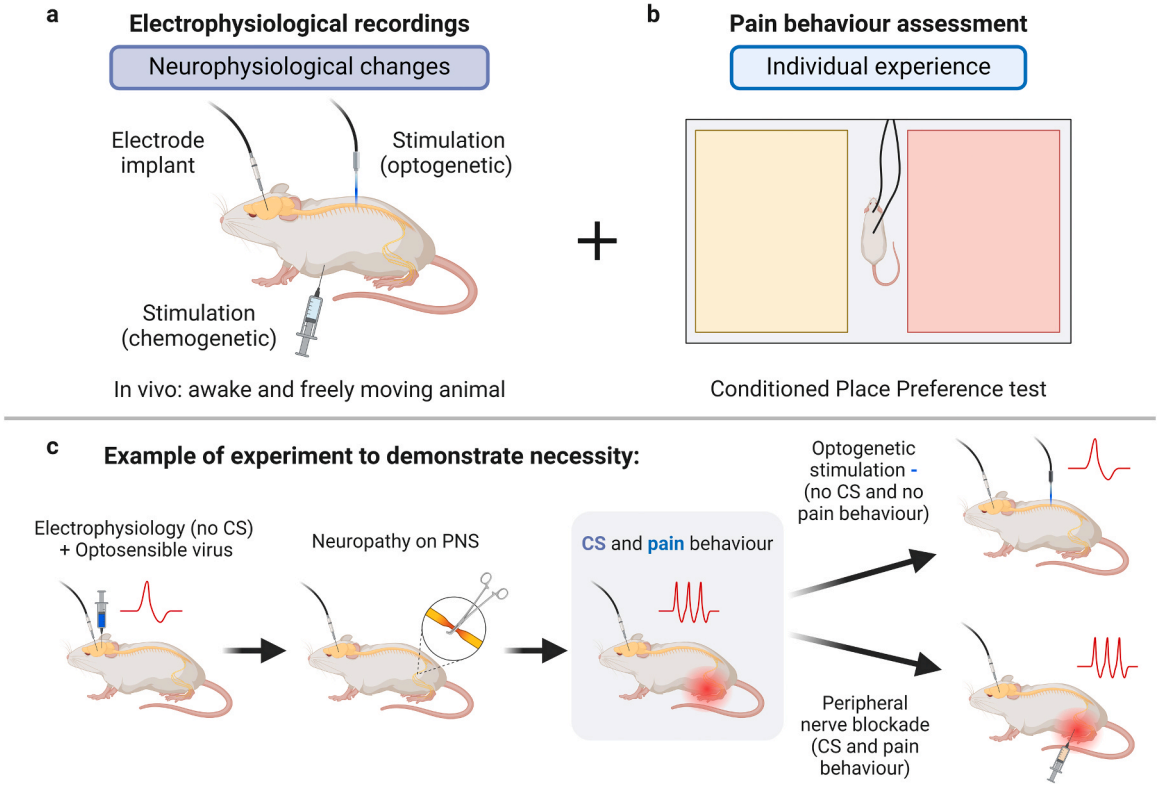

Fig. 3. An experiment proposal to demonstrate CS causality over chronic pain in a neuropathy animal model. Experimental studies should include both neurophysiological measurements, such as chronic intracranial recordings, to confirm CS **(a)** and pain behavioural assessments for pain experience, such as Conditioned Place Preference test **(b)**. Moreover, demonstrating either necessity or sufficiency requires neural activity manipulation, that could be achieved using optogenetics or chemogenetics in a pathological model to determine the link between sensitization of the CNS and chronic pain symptoms **(c)**. Note that the peripheral contribution to chronic pain should be separately tested, either by directly measuring it or by peripheral anaesthetic blockade as in this example.

optogenetics allows to selectively activate and inhibit neuronal subpopulations *in vivo* (Atasoy and Sternson, 2018; Campbell and Marchant, 2018; Carr and Zachariou, 2014). Excitingly, these tools are already being applied to pain research (Cardoso-Cruz et al., 2019; Liu et al., 2019). For instance, to demonstrate that CS is sufficient to cause chronic pain, we could select a group of spinal *substantia gelatinosa* neurons previously identified to be potentiated in a chronic pain model (Uta et al., 2019). Then, their activity could be enhanced using chemogenetics (DREADDs). In the case that the modulation of those neurons is sufficient to produce chronic pain, we could suggest that CS is sufficient to cause chronic pain. Alternatively, we could inhibit these neurons using an inhibitory DREADD in pathological animals to observe if pain diminishes, suggesting necessity.

Another important future consideration should be the control of the peripheral input. Clifford Woolf proposed a simple way to grossly gauge the contribution of the peripheral nervous system to pain: to apply local anesthetics (Woolf, 2011). Pain remaining after peripheral blockade can be potentially ascribed to central mechanisms. Alternatively, a more precise approach to reduce the peripheral nociceptive input could be to selectively inhibit peripheral nociceptors through opto- or chemogenetics (Iyer et al., 2016). Of course, the best option would be directly measuring the activity of the peripheral nervous system through electrophysiological recordings, such as single fiber extracellular recordings (microneurography) or compound action potentials (evoked potentials), both approaches being feasible in humans and animals (Mano et al., 2006; Muzyka and Estephan, 2019; Vallbo, 2018). This approach has been previously performed to link capsaicin-induced secondary hyperalgesia to CS, demonstrating that the peripheral fibres innervating the secondary hyperalgesia territory were not sensitized (Schmelz, 2000).

Animal studies will be crucial to determine the contribution of CS to pain, as they allow to compare neural responses before and after the onset of a painful condition in the same individual and directly correlate them to pain-like behaviours. More importantly, they allow for neural circuit manipulation, making possible to contrast if a given alteration classifiable as CS can induce pain by itself (sufficiency), and vice versa, if pain does not occur in the absence of such alteration (necessity). Nevertheless, the main caveat of animal models is that chronic pain is currently non-reproducible in animals. Instead, persistent-pain models are used to infer chronic pain mechanisms implying that they are comparable, a very optimistic assumption, to say the least. Another caveat is that pain in animals is always inferred from behaviour, making impossible to have rich, multidimensional evaluations as we have in humans, and implying another optimistic assumption (pain-like behaviours are a direct readout of pain).

Otherwise, the primary challenge in human research is to acquire direct recordings of the nervous system that can demonstrate the presence of CS and its association with pain. For this, it will be critical to take advantage of invasive neurosurgery for the execution of intracranial recordings in chronic pain patients. In the field of pain research, two referential works have undertaken this approach, producing human intracranial recordings (Shirvalkar et al., 2023; Soyman et al., n.d.). The first work correlates insula activity with the perceived pain intensity (Soyman et al., n.d.), while the second establishes the first prediction of pain intensity in chronic pain patients, based in neuronal activity (orbitofrontal cortex) in patients with refractory neuropathic pain (Shirvalkar et al., 2023).

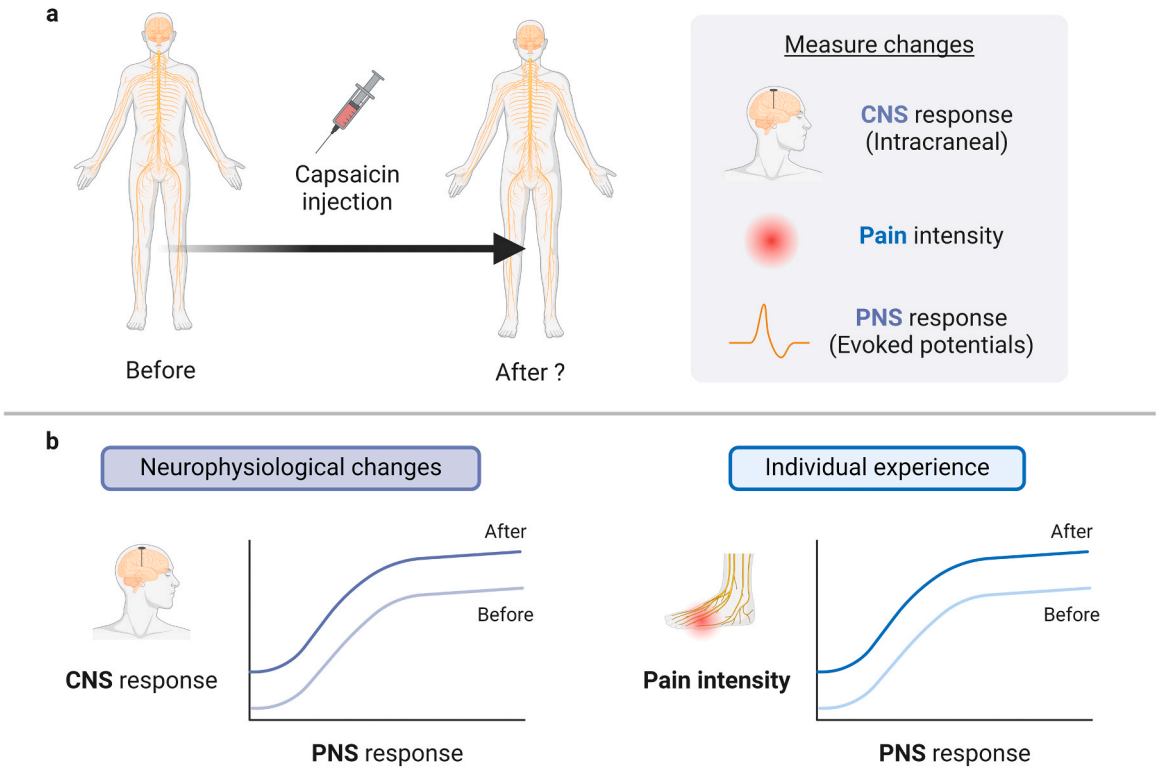

Fig. 4. How to demonstrate CS in humans. CS is yet to be demonstrated in humans, an objective achievable with the experimental tools available nowadays. **(a) Experimental setup**: first, it is necessary to control the peripheral nociceptive input: this can be done finely through microneurographical recordings or the simpler recording of sensory evoked potentials, both neurophysiological approaches to record evoked neural activity, that can be elicited through electrical stimulation, for example. Second, the CNS evoked activity should be measured too: this can be done through direct measurements like intracranial recordings, but non-invasive methods such as EEG are also valid. Then, evoked pain intensity can be assessed using Visual Analogue Scale (VAS). These three variables should be measured before and after the appearance of pain: for example, an intradermal, or topical capsaicin application **(b) Demonstrating CS:** If CS is effectively produced in humans, the same evoked peripheral response should correspond to more CNS activation after the pain-inducing manipulation. **(c) Demonstrating the relation between CS and pain:** To confirm that CS is being translated into increased pain perception, another result to be expected is that the same peripheral nerve activity corresponds to greater pain perception.

However, it is important to mention that those works were not intended to demonstrate CS or its causal role in chronic pain. A proposal for how CS could be assessed in humans is presented in the figure below: ideally, both the peripheral nociceptive activity and a CNS readout should be recorded together with perceived pain intensity, before and after the induction of a sensitising condition or the instauration of a pathological state (Fig. 4). This experiment would offer valuable insights, potentially constituting the first establishment of CS in humans. Of course, while an experimental acute pain model would serve as an initial research stage to demonstrate CS in humans, subsequent steps would be indispensable to study its causal role in chronic pain.

8. Concluding remarks

Nowadays, central sensitization is a correlative finding, a phenomenon occurring in animal pain models. Some suggest that it can be considered a mechanism, likely contributing to pain in general and chronic pain in specific. Nevertheless, while it is proved that experimental models of chronic and acute pain in animals produce central sensitization, the opposite is not: conclusive evidence demonstrating that central sensitization can cause chronic pain is yet to be discovered, as well as direct proof of its presence in humans. This state of the evidence clashes with many common beliefs from researchers, clinicians and patients, as these collectives require a biological explanation, especially in cases in which theorigin of pain is difficult to identify. In an attempt to provide one, central sensitization has been converted into a *deus ex machina,* using it as a justification for what is currently not delineated, generating confusion about what it is and how to measure it. Nevertheless, the harsh truth is that we are lacking such an explanation, and assuming central sensitization as a mechanism causing chronic pain precludes researchers from testing it. We hope this text helps to clarify what is and what is not known and encourages the pain community to tackle this enormously relevant question in clear, specifically designed experiments.

Data availability

No data was used for the research described in the article.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2024.105886.

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