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The effect of psychological manipulations on the development of secondary hyperalgesia: a critical review

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Abstract

As central sensitization is believed to contribute to persistent pain and psychological factors are increasingly acknowledged to play a role as well, the question arises of whether psychological factors can modulate the development of central sensitization. Secondary hyperalgesia is thought to be a manifestation of central sensitization and can be induced experimentally in humans. To define the state-of-the-art, we critically reviewed the existing evidence that psychological factors can influence the development of experimentally induced secondary hyperalgesia, a proxy of central sensitization. We retrieved 23 studies, 17 aimed at modulating the development of secondary hyperalgesia, 4 at modulating hyperalgesia when already established, and 2 observational studies. The psychological interventions in the 17 included papers focused on placebo/nocebo interventions (N = 5), attention and cognitive load (N = 6, 7 experiments), social support (N = 1), cognitive behavioral therapy (N = 1), threat/fear induction (N = 2), and emotional disclosure (N = 1). Interventions were considered effective if they successfully decreased or increased the magnitude and/or spatial extent of secondary hyperalgesia. Although some psychological manipulations might interfere with the development of secondary hyperalgesia, the number of studies is too low to draw firm conclusions. More studies and replications are needed to determine the impact of psychological factors on the development of secondary hyperalgesia. Factors that should be considered in future studies are (among others) the risk of bias, sufficient statistical power, the measurement of secondary hyperalgesia, the choice of sensitization protocol, the strength of the manipulation, and the role of sex.

Keywords: Central sensitization, Secondary hyperalgesia, Psychological factors

1. Introduction

The International Association for the Study of Pain defines central sensitization as "an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold input."[31] The term derives from animal research demonstrating that intense and/or sustained peripheral noxious input increases the responsiveness of spinal nociceptive neurons.[34] It is believed that central sensitization contributes to persistent pain.[50,57]

On another note, clinical studies have shown that persistent pain is associated with psychological comorbidities such as anxiety and depression.[14,16] These findings raise the question of whether psychological factors can modulate central sensitization. However, studying psychological factors in animals is challenging. Conversely, it is not feasible to record from spinal nociceptive neurons in humans.

Secondary hyperalgesia, the increased pain sensitivity surrounding a cutaneous injury, is considered a manifestation of central sensitization.[2,27,44] Secondary hyperalgesia can also be experimentally induced in humans without causing visible tissue injury (see Quesada et al.[40] for a review) and predominantly affects sharp mechanical stimuli such as mechanical pinprick

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stimuli. This review aims to critically review the existing evidence that psychological factors can modulate the development of secondary mechanical pinprick hyperalgesia as a proxy of central sensitization.

2. Methods

2.1. Study search and organization

Secondary mechanical pinprick hyperalgesia can be assessed in 2 ways: (1) by measuring changes in the perceived pinprick sensitivity before vs after the sensitization protocol and/or compared to a control site or (2) by measuring the size of the area of secondary hyperalgesia. Both ways were considered in the present review.

Some studies use the term pinprick hypersensitivity when referring to increases in pinprick sensitivity. This because under normal conditions, mechanical pinprick stimuli applied to the human skin elicit a sharp needle-pricking sensation but not necessarily a painful percept and thus, the term hyperalgesia (increased pain sensitivity) would not be correct. For this review, we consider any increase in pinprick sensitivity that develops adjacent to the site of conditioning stimulation as a proxy of central sensitization, independent of whether it can be labelled as hyperalgesia. The terms hyperalgesia and hypersensitivity are, therefore, used interchangeably in the present review.

We searched for studies published in English between 2005 and 2024 that have induced secondary hyperalgesia, or hypersensitivity to somatosensory stimuli and that have used (1) a pain model that induces secondary hyperalgesia or secondary hypersensitivity and (2) a psychological manipulation to modulate secondary hyperalgesia. The search was conducted in PubMed and online repositories such as PsyArxiv and OSF, and only studies on healthy volunteers were included. We included studies using mechanical, thermal, and electrical stimuli as outcomes to measure hypersensitivity. We screened studies using psychological manipulations during or around the intervention leading to subsequent somatosensory hypersensitivity and those with at least one control condition, whether the nonsensitized arm, a control group, or a pre–post intervention. However, we discuss in detail only studies that used psychological manipulations to modulate the *development* of mechanical pinprick hyperalgesia/hypersensitivity. We retained studies that (1) manipulated the expectations about the development of secondary hyperalgesia/hypersensitivity and its extent and (2) had a psychological intervention before or during the peripheral noxious (and painful) stimulation protocol responsible for inducing secondary hyperalgesia/hypersensitivity. Studies aiming at modulating already established secondary hyperalgesia/hypersensitivity were not included. The outcome measure of interest was defined as *any* change in secondary mechanical pinprick hyperalgesia/hypersensitivity, that is, both ratings of the intensity elicited by the mechanical stimulation and extent of hyperalgesia/hypersensitivity.

3. Results

We found 23 studies investigating psychological manipulations in the context of the development of secondary mechanical pinprick hyperalgesia/hypersensitivity. Out of these studies, 4 focused on the modulation after hyperalgesia was established, that is, they did not use the intervention to modulate the *development* of hyperalgesia,[17,23,33,56] and 2 were observational studies linking psychological characteristics to hyperalgesia.[39,58] These studies were excluded from the review. **Table 1** provides a summary, in alphabetical order, of the studies included in this review. **Table 2** lists the studies that have modulated hyperalgesia after its establishment, and **Table 3** details the observational studies.

Psychological manipulations involving changing expectations, attentional manipulations, cognitive behavioral therapy, emotional disclosure, threat/fear induction, and social support were used. In the 17 retained studies, topical capsaicin (6% concentration, N = 1), electrical skin stimulation (N = 14), and repeated heat stimulation (N = 2) were used to induce secondary hyperalgesia. We briefly overview the methods here but refer the reader to more detailed descriptions.[30,40] Capsaicin is the pungent substance in chili peppers and when applied onto the skin typically elicits a burning sensation. The concentration of capsaicin varies across studies. Cutaneous electrical stimulation has been applied with different patterns and frequencies. High-frequency electrical stimulation (HFS) consists of 5 trains of 100-Hz electrical stimuli (each lasting for 1 second) separated with a 10-second intertrain interval. Thus, the total protocol lasts 50 seconds. Low-frequency electrical stimulation (LFS) consists of single electrical stimuli delivered at 2 Hz for 2 minutes. Middle-frequency electrical stimulation (MFS) consists of 12 trains of 42-Hz electrical stimuli separated in a 10-second interval and lasts for 2 minutes. The electrical stimulation is given at an intensity of either 10 or 20 times the detection threshold for a single electrical stimulus and is delivered to the skin via a custom-made concentric electrode. Finally, repeated (painful) heat stimulation is delivered to the skin with a thermode.

3.1. Effects of expectations

Expectations induced by classical conditioning, verbal suggestions, a combination of the 2, or observational learning have been widely studied in relation to acute pain. The literature shows robust and reliable evidence in favor of their modulatory role in shaping individuals' perception of pain.[1,6,9,38] We found 4 studies: 1 study specifically investigating the effect of positive expectations on the development of secondary hyperalgesia,[32] 3 focusing on negative expectations,[14,19,48] and 1 comparing positive and negative expectations.[19]

Matre et al.[32] used a combination of verbal suggestion and classical conditioning to reduce pain induced by the repeated presentation of a noxious heat stimulus (placebo group). The authors showed that compared with a control group, participants in the placebo group reported a lower perceived heat intensity elicited by the heat stimulation and smaller areas of secondary mechanical hyperalgesia and allodynia. However, these results were valid only for a subset of the sample, which included specific criteria (1) completion of the experiment, (2) development of hyperalgesia following 5 minutes of 46°C heat stimulation, and (3) normal heat sensitivity with minimal day-to-day variability in the pinprick scores (<25% variation across days).

van den Broeke et al.[49] aimed to induce negative expectations about pinprick sensitivity as a consequence of HFS using written instructions (nocebo group). More specifically, the aim was to investigate if expectations of increased pinprick sensitivity induced by HFS would lead to more HFS-induced pinprick hypersensitivity compared to a control group that did not receive any suggestion about the increase in pinprick sensitivity after HFS. They found that the nocebo group developed a larger pinprick sensitivity increase than the control group. Unfortunately, the painfulness of HFS and the spatial extent of pinprick hypersensitivity were not assessed. Recently, Jaltare et al.[20] conducted a replication study using the same design and instruction and with manipulation checks. Contrary

Table 1

Overview of the studies investigating the modulation of secondary hyperalgesia.

Reference	PR	Sample	Blinding	Design and manipulation	Manipulation check	Sensitization protocol (mean stimulation)	Behavioral outcomes	Results (only behavioral)
Bedwell et al., 2022[4]	Yes	N = 26 Median$_{age}$ = 21.00 Range$_{age}$ = 18–55 10 ♂, 16 ♀	Double-blind	Within-subjects: suggestion on skin safety 1) Threat site 2) Safe site	HFS perception Anxiety Threat → Not confirmed	HFS 100 Hz 10× DT M = 1.60 mA	Pinprick sensitivity Spatial extent (128 and 256 mn)	Threat (vs safe site): -Pinprick sensitivity = -Spatial extent =
Della Porta et al., 2022[11]	Yes	N = 67 M$_{age}$ = 23.90 ± 3.70 22 ♂, 45 ♀	Single-blind	Within-subjects: spatial attention task 1) Attended arm 2) Unattended arm	Inclusion based on performance	HFS 100 Hz 10× DT Left arm: M = 2.60 mA Right arm: M = 2.80 mA	Pinprick sensitivity Spatial extent (64 and 128 mn)	Attended (vs unattended): -Pinprick sensitivity = -Spatial extent =
Della Porta et al., 2024[10]	Yes	N = 84 M$_{age}$ = 23.10 21 ♂, 63 ♀	Double-blind	Between-subjects: 1) High load task 2) Low load task	Difficulty Performance → Confirmed	MFS 42 Hz 20× DT 1) M = 3.86 2) M = 3.84	Pinprick sensitivity Spatial extent (128 mn) MFS perception	High (vs low load task): -Pinprick sensitivity = -Spatial extent = -MFS perception =
Filbrich et al., 2020[12]	No	N = 25 M$_{age}$ = 23.10 ± 2.29 Range$_{age}$ = 18–29 9 ♂, 16 ♀	Participants blind to the aims	Within-subjects: spatial attention task 1) Attended arm 2) Unattended arm	Inclusion based on performance	HFS 100 Hz 10× DT Left arm: M = 1.80 mA Right arm: M = 2.00 mA	Pinprick sensitivity Spatial extent (128 mn)	Attended (vs unattended): -Pinprick sensitivity ↑ -Spatial extent: → Proximal-distal = → Medial-lateral ↑
Gousset et al., 2023[15]	Yes	N = 50 M$_{age}$ = 22.74 ± 2.56 25 ♂, 25 ♀	Double-blind	Between-subjects: suggestion on pain from sensitization 1) Nocebo 2) Control	Pain expectations Perceived intensity of single electrical stimulus → Confirmed	HFS 100 Hz Fixed at 3.00 mA	Pinprick sensitivity Spatial extent (128 mN) HFS perception	Nocebo (vs control): -Pinprick sensitivity = -Spatial extent = -HFS perception =
Jaltare et al., 2023[21]	Yes	N = 33 M$_{age}$ = 21.50 ± 3.80 33 ♀	Participants blind to the aims	Within-subjects: 1) Support: handholding with romantic partner 2) Alone	Support Fear of MFS Stress → Confirmed	MFS 42 Hz 10× DT 1) M = 2.60 mA 2) M = 2.69 mA	Pinprick sensitivity Spatial extent (128 mN) MFS perception	Support (vs alone): -Pinprick sensitivity = -Spatial extent ↓ -MFS perception: → Intensity ↓ → Unpleasantness =
Jaltare et al., 2024b[19]	Yes	N = 46 M$_{age}$ = 21.18 ± 4.36 46 ♀	Single-blind	Between-subjects: 1) Support: verbal support from confederate 2) Alone	Support Fear of MFS Stress → Confirmed	MFS 42 Hz 10× DT 1) M = 2.50 mA 2) M = 2.30 mA	Pinprick sensitivity Spatial extent (128 mN) MFS perception	Support (vs alone): -Pinprick sensitivity ↓ -Spatial extent = -MFS perception: → Intensity ↓ → Unpleasantness =
Jaltare et al., 2024a[18]	Yes	N = 60 M$_{age}$ = 21.45 ± 3.99 60 ♀	Single-blind	Between-subjects: suggestion on pain from sensitization 1) Placebo 2) Control 3) Nocebo	Pain expectations → Partially confirmed	HFS 100 Hz Fixed at 3.00 mA	Pinprick sensitivity Spatial extent (128 mN) HFS perception	Placebo vs control vs nocebo: -Pinprick sensitivity = -Spatial extent = -HFS perception = Placebo vs nocebo: -Pinprick sensitivity = -Spatial extent ↓ (placebo) *without outliers
Jaltare et al., 2024c[20]	Yes	N = 60 M$_{age}$ = M = 20.06, SD = 3.32 60 ♀	Double-blind	Between-subjects: suggestion of sensitization 1) Nocebo 2) Control (replication of van den Broeke et al., 2014)	Ratings of expectations →Not fully confirmed	HFS 20× DT 1) M = 5.2 mA 2) M = 4.4 mA	Pinprick intensity Spatial extent (128 mN)	No difference between groups
Matre et al., 2006[32]	No	N = 29 Range$_{age}$ = 20–45 1) 10 ♂, 9 ♀ 2) 7 ♂, 3 ♀	Single-blind	Between-subjects: suggestion of pain from sensitization 1) Placebo 2) Control	—	Thermode 46°C	Heat sensitivity Spatial extent (Von Frey filament 84.4 g/mm^2)	Placebo (vs control): -Heat sensitivity ↓ -Spatial extent ↓
Meyers et al., 2023a[35]	Yes	N = 81 M$_{age}$ = 23.30 ± 4.62 1) 20 ♂, 18 ♀ 2) 21 ♂, 22 ♀	Single-blind	Between-subjects: 1) Low load task 2) High load task	Difficulty Performance → Confirmed	LFS 2 Hz 15× DT 1) M = 3.50 mA 2) M = 3.60 mA	Pinprick sensitivity Spatial extent (128 mN) LFS perception	High load (vs low load): -Pinprick sensitivity = -Spatial extent = -LFS perception =

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Table 1 (*continued*)

Overview of the studies investigating the modulation of secondary hyperalgesia.

Reference	PR	Sample	Blinding	Design and manipulation	Manipulation check	Sensitization protocol (mean stimulation)	Behavioral outcomes	Results (only behavioral)
Meyers et al., 2023b[36]	Yes	N = 35 M_{age} = 22.00 ± 4.17 35 ♀	Participants blind to the aims	Within-subjects: 1) Low load task 2) High load task 3) Control	Difficulty Performance → Confirmed	MFS 42 Hz 10× DT 1) M = 2 mA 2) M = 1.8 mA 3) M = 1.8 mA	Pinprick sensitivity Spatial extent (128 mN) MFS perception	High load (vs low load vs control): -Pinprick sensitivity = -Spatial extent = -MFS perception =
Salomons et al., 2014[42]	No	N = 34 $Range_{age}$ = 21–38 1) 9 ♂, 8 ♀ 2) 9 ♂, 8 ♀	Double-blind	Between-subjects: 1) Pain-focused training 2) Nonpain focused training	—	Thermode 1) M = 47.90 ± 0.28°C 2) M = 48.30 ± 0.45°C	Heat sensitivity Spatial extent (256 mN)	Pain (vs nonpain): -Heat sensitivity: → Intensity = → Unpleasantness ↓ -Spatial extent ↓
Torta et al., 2020 (exp 2)[45] Torta et al., 2020 (exp 3)[45]	No	N = 19 $Median_{age}$ = 22.00 $Range_{age}$ = 18–40 4 ♂, 15 ♀ N = 21 $Median_{age}$ = 26.00 $Range_{age}$ = 19–36 11 ♂, 10 ♀	Single-blind	Low load task High load task	Difficulty → Confirmed Difficulty → Confirmed	LFS 2 Hz 15× DT M = 7.41 LFS 2 Hz 15× DT M = 8.10	Pinprick sensitivity (128 mN) LFS perception Pinprick sensitivity (128 mN) LFS perception	Pinprick sensitivity ↑ Pinprick sensitivity ↓
Torta et al., 2022[47]	Yes	N = 44 44 ♀	Single-blind	Between-subjects: observation of pain from sensitization 1) Low pain video 2) High pain video	- HFS perception → Confirmed	HFS 100 Hz 20× DT 1) M = 5.20 mA 2) M = 5.60 mA	Pinprick sensitivity Spatial extent (128 mN) HFS perception	High (vs low pain): -Pinprick sensitivity: → Intensity ↑ → Unpleasantness = Spatial extent = -HFS perception ↑
van den Broeke et al., 2014[49]	No	N = 30 $Median_{age}$ = 23.50 $Range_{age}$ = 19–59 11 ♂, 19 ♀	Single-blind	Between-subjects: suggestion of sensitization 1) Nocebo 2) Control	—	HFS 100 Hz 20× DT 1) M = 6 mA 2) M = 5.8 mA	Pinprick sensitivity (256 mN)	Nocebo vs control: -Pinprick sensitivity ↑
You et al., 2014[59]	No	N = 78 78 ♀	Double-blind	Between-subjects: 1) Disclosure group 2) Control group		Topical capsaicin 6%	Pinprick sensitivity Spatial extent Spontaneous pain	Pinprick sensitivity and spatial extent ↑ in women with trauma and emotional disclosure at 1 d after the intervention Pinprick sensitivity and spatial extent ↓ in women with trauma and emotional disclosure at 1 mo after the intervention

We used the term "participants blind to the aims of the study" when there was just one experimenter testing, and we had access to the instructions that the participants received.
DT, detection threshold; HFS, high-frequency stimulation; LFS, low-frequency stimulation; M, mean ± SD; MFS, middle-frequency stimulation; PR, preregistration; PT, pain threshold; VR, virtual reality.

to the results of van den Broeke et al.,[49] they did not see a difference between the nocebo and the control groups in any outcome of secondary hyperalgesia. However, despite not receiving any suggestion in that direction, the control group also expected an increase in pinprick sensitivity after HFS. This unexpected expectation in the control group may have contributed to the lack of observed differences. As van den Broeke et al.[49] did not measure expectations, it is difficult to conclude anything about the role of expectations as a potential explanation for the different results.

Jaltare et al.[19] used a verbal suggestion, reinforced using an inert capsule, that is, a lactose pill, to investigate whether the pill could either increase (nocebo) or decrease (placebo) inflammation and, therefore, HFS pain. The manipulation check revealed lower pain expectations in the placebo compared to the nocebo group but only when 3 outliers reporting no negative expectations in the nocebo group were removed. Yet, pain expectations of both groups did not significantly differ from the control group. Neither the pain elicited by HFS nor HFS-induced pinprick hypersensitivity were affected by the experimental manipulations (placebo and nocebo). However, when the 3 outliers in the nocebo were excluded, the placebo group showed a significantly smaller proximal-distal spread of the area of pinprick hypersensitivity compared to the nocebo group but not compared to the control group. Higher pain expectations across all groups significantly predicted a greater development of pinprick hypersensitivity in all outcomes.

Finally, Gousset et al.[15] used a combination of a short conditioning procedure and verbal instruction to create negative expectations about HFS pain. While their manipulation proved

Table 2

Overview of the studies that modulated secondary hyperalgesia once established.

Reference	PR	Sample	Blinding	Design and manipulation	Manipulation check	Sensitization protocol	Behavioral outcomes	Results
Hughes et al., 2019[17]	No	N = 15 M_{age} = 25.20 ± 0.47 7 ♂, 8 ♀	Not mentioned	Within-subjects: 1) 3D VR 2) 2D video	—	Topical capsaicin 1%	Capsaicin sensitivity Electrical PT	3D VR vs 2D video -Capsaicin sensitivity ↓ -Electrical PT ↓
Kóbor et al., 2008[23]	No	N = 16 M_{age} = 22.90 $Range_{age}$ = 19–25 11 ♂, 5 ♀	Not mentioned	Within-subjects: 1) Focus on pinpricks 2) Low load task 3) High load task	Performance → Confirmed	Topical capsaicin (concentration not reported) + thermode 45°C	Pinprick sensitivity (Von Frey 180 g/0.98 mm, 300 g/1.09 mm)	High load task (vs focus on pinpricks vs low load task): -Pinprick sensitivity ↓
Mehesz et al., 2021[33]	No	N = 19 M_{age} = 26.70 ± 6.80 12 ♂, 7 ♀	Not mentioned	Within-subjects: 1) 3D VR 2) 2D video	—	HFS 100 Hz 10× DT	Pinprick sensitivity (8, 16, 32, 64, 128, 256, 512 mN)	3D VR vs 2D video: -Pinprick sensitivity ↓
Wiech et al., 2005[56]	No	N = 11 M_{age} = 28.6 $Range_{age}$ = 18–42 8 ♂, 3 ♀	Not mentioned	Within-subjects: 4 groups based on 1) Low vs high pain intensity 2) Low vs high load task	Pain intensity Difficulty	Topical capsaicin 1% + thermode 20°C	Heat sensitivity	High pain (vs low pain) + high load (vs low load): -Heat sensitivity ↓

The blinding was defined as "not reported" if we could not find specific information.
DT, detection threshold; HFS, high-frequency stimulation; M, mean ± SD; PR, preregistration; PT, pain threshold; VR, virtual reality.

successful, that is, the nocebo group perceived single electrical stimuli as more intense, the effects did not generalize to expectations about HFS pain intensity and the perceived pain intensity during HFS. Furthermore, no differences in HFS-induced pinprick hypersensitivity were observed between the 2 groups. Nevertheless, a significant moderate correlation between pain expectations and the perceived painfulness of HFS was found across all participants.

In summary, 2 studies found evidence that placebo interventions targeting peripheral noxious stimulation can reduce secondary hyperalgesia. However, this depends on the comparison made (placebo vs nocebo in Jaltare et al.,[19] but not placebo vs control) and the exclusion of participants (in both Jaltare et al.[19] and Matre et al.[32]). The evidence that negative expectations about secondary hyperalgesia can increase secondary hyperalgesia is inconclusive, as 1 study provided support for this, but a replication study did not.[49] There is no evidence that negative expectations about HFS pain can increase secondary hyperalgesia.[15] Finally, an exploratory correlational analysis suggests that higher pain expectations significantly predict a greater development of secondary hyperalgesia in all outcomes.[19]

3.2. Attentional manipulation

Given the strong tradition of studies on the modulatory role of spatial attention and attention load on the perception of acute brief stimuli in both healthy volunteers and patients suffering from persistent pain conditions,[29,46,48] it is unsurprising that attention has also been investigated in the context of developing secondary hyperalgesia. We found 2 studies examining the impact of spatial attention on hyperalgesia[11,12] and 4 investigating the effects of cognitive load.[10,35,36,45]

Research has shown that directing attention towards the stimulated body part (ie, selective spatial attention) can increase the perception of painful stimuli applied to that body part.[37,41] Following this idea, Filbrich et al.[12] applied HFS on both arms while participants had to perform a (spatial attention) task on 1 of the 2 arms. This resulted in a significantly more extensive medial-lateral spread (but not proximal-distal spread) of the area of HFS-induced pinprick hypersensitivity on the attended arm than the unattended one. However, one cannot conclude whether the effect is due to an enhancement in the attended arm or a reduction in the unattended arm. Notably, these findings were not replicated in a similar experiment performed by Della Porta

Table 3

Overview of observational studies on the association between psychological factors and secondary hyperalgesia.

Reference	PR	Sample	Design and manipulation	Manipulation check	Sensitization protocol	Behavioral outcomes	Results
Pressman et al., 2017[39]	No	N = 38 M_{age} = 25.70 ± 5.30 $Range_{age}$ = 20–42	Observational study	—	Topical capsaicin 10%	Relationship between PCS and hyperalgesia	No moderating effect of PCS High scores at PCS associated with higher capsaicin pain and larger area
You et al., 2016[58]	No	N = 32 M_{age} = 18.70 ± 0.90 32 ♀	Observational study	—	Topical capsaicin	Relationship between stressful life events Pinprick sensitivity Spatial extent Spontaneous pain	More stressful life events predicted a linear increase in the area of hyperalgesia No relationship between stressful life events and intensity of secondary hyperalgesia nor capsaicin pain

M, mean ± SD; PCS, Pain Catastrophizing Scale; PR, preregistration.

et al.[11] In summary, the evidence that selective spatial attention facilitates the development of secondary hyperalgesia remains inconclusive.

Cognitive load refers to the amount of mental effort needed to perform a task. Limited-capacity theories of attention[5,22,28,29] propose that executing a cognitive task during nociceptive stimulation can modulate pain perception by directing attentional resources to the demanding task and reducing the attentional resources allocated to pain.

Torta et al.[45] conducted a series of experiments to explore whether performing cognitive tasks during LFS could prevent the development of LFS-induced pinprick hypersensitivity. They examined the effects of 2 tasks: a low-demand response inhibition task (Experiment 2 in the paper) and a high-demand working memory task (Experiment 3 in the paper). The results showed that participants who performed the high-demanding working memory task during LFS did not develop statistically significant hypersensitivity to mechanical stimuli, indicating a potential protective effect of high cognitive load. Conversely, this protective effect was not observed when participants performed the low-demand task. However, the experiments were conducted sequentially without randomization, meaning the results from different conditions could not be directly compared.

In a follow-up study, Meyers et al.[36] compared the effects of a low- and high-load working memory task but did not find differences in LFS-induced pinprick hypersensitivity between the 2 groups. In a third follow-up study, Meyers et al.[35] employed a within-subjects design to investigate further the effects of cognitive load on the development of secondary hyperalgesia, using medium-frequency stimulation at 42 Hz. Unlike their earlier study,[36] this study introduced an inactive control condition (no task performed) and modified one of the tasks to include a nonworking memory condition. Despite these methodological changes and the addition of the inactive control, no significant differences in pinprick hypersensitivity were observed between the conditions. More recently, Della Porta et al.[10] investigated the effects of cognitive load during HFS using a between-subjects design. The study compared a high-demand working memory task with a low-demand cognitive task during HFS. The working memory task was explicitly modified to align with the timing of the electrical stimulation (HFS). Yet, consistent with the findings of Meyers et al.,[35,36] no differences in pinprick hypersensitivity were observed between the high-load and low-load cognitive tasks. In summary, 3 out of 4 studies show a lack of effect of cognitive load during noxious electrical stimulation on the development of secondary hyperalgesia, suggesting that the effect is either weak or absent.

3.3. Social support

A supportive social environment can reduce the perception of experimental pain.[8,26] Moreover, attachment styles appear to moderate the effect of social support on pain.[24,25,54] While highly anxiously attached individuals seem to benefit from social support during pain, avoidantly attached individuals report more pain with social support.[24,54] Social support can be operationalized in different ways: by verbal support, by hand-holding, and by affective touch. Two studies investigated the role of social support in developing secondary hyperalgesia, 1 using a hand-holding procedure and 1 verbal support from a stranger.

Jaltare et al.[21] examined whether handholding by the romantic partner during peripheral noxious electrical stimulation at MFS buffered against the development of pinprick hypersensitivity compared to an alone situation. They observed that this was the case as participants in the handholding condition had a smaller area of pinprick hypersensitivity compared to the alone situation. The ratings for pinprick stimulation were not different in the 2 conditions.

In a follow-up study, Jaltare et al.[18] investigated the potential beneficial effects of a supportive verbal confederate during MFS. They found a smaller increase in the pinprick ratings after MFS compared with the control condition (alone situation) but no differences in the size of the area of pinprick hypersensitivity. In summary, both studies investigating the effect of social support on secondary hyperalgesia found a reduction of secondary hyperalgesia but on different outcomes; one found a smaller area of pinprick hypersensitivity while the other found a smaller increase in pinprick ratings compared to control.

3.4. Negative affect and emotions

Negative affect and emotions have a significant impact on pain perception and are frequently associated with various clinical conditions.[14,16] One study targeted negative affect by using cognitive behavioral therapy,[42] 1 emotional disclosure,[59] and 2 tried to induce an increase in fear or threat perception.[4,47]

Cognitive behavioral therapy focuses on reducing negative affect by targeting maladaptive cognitions.[3] Salomons et al.[42] developed a brief cognitive–behavioral intervention to reduce pain perception and the development of secondary hyperalgesia. Participants were randomly allocated to a regulate group or a control group. The regulate group was given a pain-focused training aimed at reducing negative emotions and cognitions associated with pain. Their results revealed that the pain-focused intervention reduced the perceived unpleasantness of the peripheral thermal noxious stimulation compared to the control group and the area of secondary hyperalgesia.

Emotional disclosure, a practice where individuals write about a traumatic or stressful experience, is believed to enhance emotional regulation and potentially improve pain coping.[59] You et al.[59] conducted a study involving participants with and without a history of trauma who underwent either a written emotional disclosure intervention or a control intervention, in which they were asked to write about their time management. Their results revealed that in the emotional disclosure group, participants with a trauma history initially exhibited a greater area of capsaicin-induced secondary hyperalgesia compared to participants without a trauma history (control group). However, after 1 month, the opposite effect was observed: Participants with a trauma history displayed a smaller area of capsaicin-induced secondary hyperalgesia compared to those without a trauma history. These findings suggest that emotional disclosure may have a negative short-term effect but positive long-term consequences for secondary hyperalgesia in individuals with a trauma history.

Bedwell et al.[4] investigated the influence of threat on the development of secondary hyperalgesia induced by HFS in a within-subject, double-blinded experiment. They exploited a previously successful experimental manipulation,[55] suggesting that some areas of the skin were more sensitive than others, leading to a moderate risk of injury. Unfortunately, however, despite promising results in the pilot study, the manipulation check in the main experiment showed that the intervention did not work because participants did not develop more fear of tissue damage in the threat condition. As the intervention did not work, no conclusions can be drawn regarding secondary hyperalgesia.

Torta et al.[47] tried to manipulate fear through an observational learning paradigm by using videos. In this study, participants, before undergoing HFS, observed either a video portraying

a model in high pain or low pain during fake HFS. The actual pain ratings during HFS were significantly higher in the high-pain group compared with the low-pain group. Furthermore, a significant 3-way interaction (time × arm × group) was found for pinprick sensitivity, suggesting a difference in pinprick sensitivity between the HFS and control arm after HFS between the 2 groups. However, no post hoc test was significant. This suggests that the effect of the manipulation is either due to chance or lack of statistical power. Fear ratings, however, were not significantly different between the 2 groups, suggesting that the possible effect of watching somebody in high pain on pain and secondary hyperalgesia may not be mediated by fear.

In summary, 1 study found that reducing negative emotions and cognitions about pain reduces the perception elicited by heat stimulation and the area of heat-induced secondary hyperalgesia. Emotional disclosure seems to have a dual effect on capsaicin-induced secondary hyperalgesia, depending on the presence of trauma and the time point investigated (close or far from the emotional disclosure). In the short term, it seems to enlarge the area compared with control, but in the long term, it shows smaller areas. Finally, watching a video of a person in high pain resulted in higher pain scores during HFS compared to watching a person showing lower pain. The effect on secondary hyperalgesia needs replication.

3.5. Moderating and mediating effects

In many previously described experiments, psychological states and traits were assessed as potential mediators or moderators in the psychological modulation of secondary hyperalgesia. State fear, measured before peripheral noxious electrical stimulation, was found to correlate with the magnitude of secondary hyperalgesia[35,36] and was also found to be linked to participants' expectations.[19] In addition, fear of pain, assessed through questionnaires, was predictive of a greater proximal-distal spread of hyperalgesia,[35] when outliers were included, and was identified as a moderator in the relationship between pain expectations and secondary hyperalgesia, with higher fear scores significantly amplifying the connection between expectations and hyperalgesia.[19] However, Della Porta et al.[10] found no significant moderating effect of fear on increased pinprick sensitivity.

In the study by Salomons et al.,[42] individuals who experienced reduced pain catastrophizing also showed the greatest decrease in the area of secondary hyperalgesia. The studies of Meyers et al.[35] and Jaltare et al.[19] also conducted secondary analyses to test whether scores on the Pain Catastrophizing Scale predicted the development of secondary hyperalgesia but found no significant associations.

Finally, in both studies by Jaltare et al., attachment styles influenced the development of secondary hyperalgesia, in Jaltare et al.[21] higher attachment avoidance scores were associated with a smaller width and a smaller increase in the sensitivity of the stimulated arm. In the follow-up study of Jaltare et al.,[18] attachment anxiety and avoidance moderated the self-reported intensity in the support group in the sense that individuals with higher attachment anxiety and avoidance scores reported lower intensity ratings.

Importantly, some of these analyses were exploratory, and even when preregistered, they were mostly secondary outcomes. There is, therefore, a possibility that the studies were not sufficiently powered for these analyses. In this case, further replications and data aggregation will help to corroborate the findings.

4. Discussion

The number of studies investigating if and how psychological factors influence the development of secondary hyperalgesia has substantially grown in the last years, indicating a surging interest in this line of research's theoretical and clinical implications.

In this narrative review, we identified 23 studies on the topic in the last years, 17 of which specifically targeted the development of secondary hyperalgesia. The psychological interventions focused on placebo/nocebo manipulations (N = 5), attention and cognitive load (N = 6, 7 experiments), social support (N = 1), cognitive behavioral therapy (N = 1), threat/fear induction (N = 2), and emotional disclosure (N = 1). All these modulations have proven successful for modulating the perception elicited by acute painful stimuli. However, there is less evidence for modulating of the development of hyperalgesia. The studies on spatial attention are inconclusive, with 2 studies reaching opposite results; the ones on cognitive load reveal a weak, most likely absent effect. Mixed results are observed for placebo/nocebo interventions. Studies targeting "negative affect" and those on social support have demonstrated a modulation of the development of secondary hyperalgesia. Further replications of these studies are encouraged. In short, the number of studies is too low to draw firm conclusions and run meta-analytic studies. On the methodological side, the risk of bias cannot be excluded in some cases since the assessor was not (or could not) be blind to the condition, not all studies were preregistered, and the number of participants was not always based on a (correct) sample size calculation of the outcome variable. This does not per se undermine the relevance of the results, but in the case of positive findings, it might have boosted the observed effects.[43] In the cases of (partial) replications, single vs double blinding could have played a role in Filbrich et al.,[12] vs Della Porta et al.,[11] and in van den Broeke et al.[49] vs Jaltare et al.[20] In contrast, double vs single blinding did not lead to different results for cognitive load studies.[10,35,36]

4.1. Measurement of secondary hyperalgesia

Across the different studies, different methods are used to quantify changes in secondary hyperalgesia. For instance, the area can be measured along 8 axes, or only along the proximal-distal and medial-lateral axes, or only along the proximal-distal axes. A previous study has found that the forearm and the proximal-distal axes are more reliable than the medial-lateral axes.[7] However, this was not compared with an 8-axes area size estimation.[7] Moreover, it is yet unknown which pinprick intensity identifies the area most reliably. What can also be debated is the control condition for assessing changes in perceived pinprick intensity. The choice of method for data analysis may significantly influence the results, emphasizing the need for consensus on a standardized approach to analyzing secondary hyperalgesia outcomes. Another challenge is the substantial variability in baseline ratings elicited by mechanical pinprick stimulation. When the variability is large, differences between groups need to be large to be able to detect a significant difference. This variability underscores the importance of carefully selecting measurement and analysis methods to ensure consistency and reliability across studies. Agreement across scholars about which measures to take and report is critical to enhancing comparability and robustness in future research.

4.2. Choice of protocol

The choice of the protocol used to induce secondary hyperalgesia (HFS, LFS, capsaicin or heat) can influence whether an

effect of a psychological variable on pain and secondary hyperalgesia is observed. For instance, when the aim is to investigate whether a psychological variable can increase pain, the noxious stimulation intensity should not be too high (eg, high-intensity HFS), as this may result in a ceiling effect, limiting the variability in pain ratings. Conversely, if the goal is to examine a reduction in pain, the stimulation should not be too weak, as this may cause a floor effect, making it difficult to observe changes. Regardless of the aim, the noxious stimulation intensity must be sufficient to reliably induce secondary hyperalgesia.

Each stimulation method has its strengths and limitations. Electrical stimulation offers precise control over intensity, onset, and duration. However, it is not a natural stimulus and may not replicate real-world pain experiences. In contrast, heat stimulation and capsaicin application are more natural stimuli but can induce peripheral sensitization, which may complicate the interpretation of the results. The topical application of capsaicin has additional challenges, as its effects are variable across participants due to factors like skin absorption.

Therefore, the choice of stimulation protocol should be guided by the research question and the specific outcomes being measured, with careful consideration of potential ceiling or floor effects and the reliability of secondary hyperalgesia induction. Balancing these factors is essential to ensure the validity and generalizability of findings.

4.3. Strength of the manipulation

Another crucial factor that can determine whether an effect will be observed is the strength of the manipulation. Stronger manipulations make it easier to detect and measure an effect. Moreover, to ensure that the intervention effectively influenced the psychological variable of interest, it is essential to include manipulation checks in the experiment.

4.4. Sex differences

The role of sex in the effect of psychological factors on secondary hyperalgesia is underinvestigated but may be important. For instance, acute stress has been shown to have opposite effects on pain between males and females.[13] Therefore, future studies should investigate the role of sex as they could provide valuable insights into potential sex-specific mechanisms and contribute to the understanding of individual differences in pain. Many available studies have either focused on 1 sex (female) or did not conduct different analyses. Only Meyers et al.[36] made a first attempt at this regard, not revealing sex differences in the effects of cognitive load, similar to what had been reported in Torta et al.[45] Nevertheless, sex studies need very large samples, and none of the available studies might have been sufficiently powered to disclose small differences.

4.5. Increasing vs decreasing secondary hyperalgesia

Studies aimed at reducing the development of hyperalgesia have yielded more positive results compared to those attempting to increase it. One explanation may be that some protocols may induce a negative bias in control group participants,[20] leading them to expect negative outcomes. This expectation can diminish the effects of the experimental protocol aimed at increasing the development of secondary hyperalgesia. Conversely, one could argue that an intervention causing a large area of hyperalgesia is inherently more likely to be reduced, as its effects may already be at their maximum.

4.6. The conundrum of attention

One notable finding is that attention appears to have minimal to no impact on the development of hyperalgesia, at least with the current methodology. One important issue is that none of the studies can definitively conclude that they sufficiently engaged participants. Performance at the task and perceived difficulty have been used as manipulation checks to confirm the successfulness of the intervention, but in principle participants can be very engaged and have a poor performance and vice versa. In addition, the theoretical framework is grounded in limited capacity theories, which propose that the more attention is allocated to a task, the less attention remains available for a stimulus. While this perspective provides valuable insight, it likely represents only part of the story. Other factors, such as fatigue, motivation, and the pleasantness of the task, may also play crucial roles in modulating attention[51–53] and its influence on the perception of pain and secondary hyperalgesia. Another assumption of the limited capacity theory would be that the development of hyperalgesia is at least partly dependent on attention. However, we do not have enough evidence of how much *focusing* attention on the electrical stimulation contributes to hyperalgesia, as results are contradictory.[11,12]

It remains also elusive whether reducing the pain experienced during the sensitization procedure is a prerequisite for decreasing secondary hyperalgesia. This has been observed in some studies[21,32,42,47] along with a small but significant correlation between the pain during the sensitization procedure correlated and the magnitude of hyperalgesia developed.[36,45] Importantly, these correlations cannot be solely explained by the use of the scale (eg, participants who rate the pain of the sensitizing stimulus higher also rate the mechanical stimulation higher), as they were also obtained on the "absolute increase," that is, taking into account also the ratings for stimuli applied before the intervention, on the control arm.

5. Conclusion

The growing body of research on the role of psychological factors in the development of secondary hyperalgesia highlights increasing interest in both the theoretical and clinical significance of this field. Current evidence suggests that factors such as positive expectations, emotional regulation, disclosure, and social support may attenuate the development of hyperalgesia, but the findings await further independent replications. Moving forward, the field should prioritize rigorous, well-powered studies with robust experimental designs, standardized protocols, and clear reporting practices. Addressing these gaps will not only enhance the reliability and validity of findings but also facilitate the translation of this research into clinical applications, ultimately improving pain management strategies for diverse populations.

Disclosures

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