Effects of pain on cortical homeostatic plasticity in humans

a systematic review

Zolezzi, Daniela M; Larsen, Dennis B; McPhee, Megan; Graven-Nielsen, Thomas

Published in:
Pain Reports

DOI (link to publication from Publisher):
10.1097/PR9.0000000000001141

Publication date:
2024

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

General Section
Review

OPEN

PAIN REPORTS

Effects of pain on cortical homeostatic plasticity in humans: a systematic review

Daniela M. Zolezzi, Dennis B. Larsen, Megan McPhee, Thomas Graven-Nielsen*

Abstract

Homeostatic plasticity (HP) is a negative feedback mechanism that prevents excessive facilitation or depression of cortical excitability (CE). Cortical HP responses in humans have been investigated by using 2 blocks of noninvasive brain stimulation with a no-stimulation block in between. A healthy HP response is characterized by reduced CE after 2 excitatory stimulation blocks and increased CE when using inhibitory stimulation. Conversely, impaired HP responses have been demonstrated in experimental and chronic pain conditions. Therefore, this systematic review aimed to provide an overview of the effect of pain on cortical HP in humans. Scopus, Embase, and PubMed were searched from inception until November 20, 2023. The included studies (1) compared experimental or clinical pain conditions with healthy controls, (2) induced HP using 2 blocks of stimulation with a no-stimulation interval, and (3) evaluated CE measures such as motor-evoked potentials. Four studies were included, consisting of 5 experiments and 146 participants, of whom 63 were patients with chronic pain and 48 were subjected to an experimental pain model. This systematic review found support for an HP impairment in pain compared with that in pain-free states, reflected by a lack of CE reduction after excitatory-excitatory HP induction over the primary motor cortex. Inhibitory-inhibitory HP induction did not produce a consistent HP response across studies, independent of pain or pain-free states. Standardization of HP induction protocols and outcome calculations is needed to ensure reproducibility and study comparison. Future HP studies may consider investigating sensory domains including nociception, which would further our understanding of abnormal HP regulation in pain conditions.

Keywords: Homeostatic plasticity, Pain, Noninvasive brain stimulation, Plasticity, Corticomotor excitability

1. Introduction

Activity-dependent synaptic plasticity mechanisms enable neurons to integrate and efficiently respond to external stimuli.[1] One of the most well-studied mechanisms is Hebbian plasticity, the widely accepted cellular foundation for learning and memory.[29,59] Hebbian plasticity includes long-term potentiation (LTP), which reinforces synaptic connections that are activated with a given stimuli or experience, and long-term depression (LTD), which downregulates neuronal activity.[43] Given the necessary positive feedback nature of LTP and LTD, there is a risk of destabilizing neuronal activity through excessive positive feedback loops of synaptic strengthening (ie, LTP) or weakening (ie, LTD),[2] which could affect largely the ongoing brain activity.[52–54] Homeostatic plasticity (HP) refers to the negative feedback mechanism that prevents excessive excitation or inhibition and maintains neuronal activity in a physiological range.[35,54] It is currently acknowledged that a healthy HP response prevents destabilization by shifting the threshold for LTP and LTD based on the history of postsynaptic activity, as described by the Bienenstock-Cooper-Munro (BCM) model.[5] The principles of the BCM model have been demonstrated in humans by assessing changes in cortical excitability after 2 blocks of noninvasive brain stimulation (NIBS) (eg, paired associative stimulation [PAS], transcranial magnetic stimulation [TMS], or transcranial direct current stimulation [tDCS]) with a no-stimulation interval between blocks. The protocols for inducing a cortical HP response in humans have varied in methodology, for example, by using different types of NIBS, different no-stimulation interval lengths, and varying durations of stimulation.[56] The HP response is assessed through cortical excitability measures such as motor-evoked potentials (MEPs) or somatosensory-evoked potentials (SEPs), reflecting primary motor cortex and somatosensory cortex activity, respectively.[6,22,29]

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

Center for Neuroplasticity and Pain (CNAP), Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

**Corresponding author. Address: Center for Neuroplasticity and Pain (CNAP), Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Selma Lagerløfs Vej 249, 9260 Gistrup, Denmark. Tel.: +45 9940 9832. E-mail address: tgn@hst.aau.dk (T. Graven-Nielsen).*

PR9 9 (2024) e1141

http://dx.doi.org/10.1097/PR9.0000000000001141

In healthy controls, the HP response has been observed as reduced MEPs after 2 excitatory blocks of primary motor cortex (M1) stimulation with a no-stimulation interval between blocks,[48,56,57] while increased MEPs have been reported when using 2 inhibitory blocks with no stimulation in between.[14,16,57] Thus, in healthy controls, the HP response is characterized by a bidirectional modulation of excitability, depending on the effect of the priming and test NIBS technique.[22] Notably, people experiencing experimental or chronic pain do not exhibit this HP response to the same extent.[50] A deficient HP response may reflect an improper balance between excitation and inhibition and is hypothesized to contribute to disproportionately high synaptic strengthening, aberrant cortical reorganization, increased pain perception, and sensorimotor dysfunction.[8,9,49] It is therefore conceivable that dysfunctional HP regulation might have a role in pain development or persistence,[49,50,58] but this has not yet been systematically assessed. This systemic review aimed to investigate the effect of experimental and clinical pain on the HP response, as reflected by measures of cortical excitability in adults.

2. Methods

2.1. Protocol

The systemic review process followed the guidance of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[28] The protocol was prospectively registered on PROSPERO (CRD42021283696).

2.2. Search strategy and study selection

A systematic search was performed in SCOPUS, PubMed, and EMBASE, which was searched for relevant original research articles up to November 20, 2023, using the following search strings: (pain* OR fibromyalgia OR migraine OR nociception) AND ("noninvasive brain stimulation" OR NIBS OR "transcranial direct current stimulation" OR tDCS OR "transcranial magnetic stimulation" OR TMS OR "paired associative stimulation" OR PAS OR "theta burst stimulation" OR TBS) AND (metaplasticity OR "homeostatic plasticity" OR "neuronal plasticity" OR "cortical excitability" OR "synaptic homeostasis"). No limit or filter options provided by the databases were used. Articles from each database were downloaded and imported to Reference Manager JabRef v5.6 and EndNote X4. In addition, a manual search of references from the included studies and previous systematic reviews was performed. Duplicates were removed in Mendeley Desktop v 1.19.8.

2.3. Eligibility criteria

The studies were selected according to the following inclusion criteria: (1) peer-reviewed original research article published in English, (2) 2 different groups: (a) healthy adults (older than 18 years) tested when pain-free and when undergoing an experimental pain condition or (b) a group of adults with acute or chronic pain compared with a healthy control group, (3) cortical excitability measures as an outcome (eg, SEPs or MEPs), and (4) NIBS with HP induction protocol including a no-stimulation block between the priming and testing. Exclusion criteria were studies in animals or cells, children or adolescents, and adults with other nonpainful medical conditions. The titles and abstracts of all articles were initially screened by 1 reviewer (D.M.Z.). Two reviewers (D.M.Z. and D.B.L.) then individually assessed the full texts considering the inclusion and exclusion criteria. Disagreements were resolved by a third reviewer (T.G.N.).

2.4. Quality assessment—risk of bias

The Quality Assessment of Before-After (Pre-Post) Studies developed by the National Heart, Lung, and Blood Institute was used in a modified version.[30,56] The quality rating was described as good, fair, or poor by assessing the questions at a study level (**Table 1**). Criteria were then evaluated as "yes," "no," or "cannot be determined/not applicable." This information was used in the data synthesis as an overall strength assessment of the available literature and to make recommendations for future pain-related studies investigating HP mechanisms.

2.5. Data extraction and evidence synthesis

Data on study and sample characteristics (eg, age, sex, pain induction or pain etiology, and study design), excitability measures, NIBS type (eg, time and intensity of stimulation), HP protocol, and study conclusions were extracted from included studies. If sufficient data with homogeneous methods were available (>2 studies using the same methodology and comparable outcomes), then mean group differences in HP response would be extracted for meta-analysis. In the case of insufficient data for meta-analysis, evidence would instead be synthesized qualitatively in text.

3. Results

3.1. Characteristics of included studies

The search retrieved 1873 records from databases (EMBASE, PubMed, and Scopus), of which 659 were duplicates. Following duplicate removal, 1214 studies were screened by title, 988 studies were excluded, and 226 were screened by abstract. Of these, 185 were not retrieved, and 41 studies were assessed for eligibility by full report screening. In addition, 33 studies were identified through citation searching, of which 21 were screened by abstract, and of these, 4 complete studies were obtained for eligibility assessment. In sum, from 45 assessed studies (ie, both from databases and citation searching), 4 fulfilled the eligibility criteria, with 41 excluded (ie, 37 from database search and 4 from citation searching) for the reasons stated in **Figure 1**. A relatively well-known HP study had to be discarded because it investigated a different research question regarding HP (ie, concerning the number of stimuli required for LTP or LTD).[9] Homeostatic plasticity studies in focal hand dystonia[21,36] were also discarded because previous and recent evidence seems to state that pain is not necessarily a symptom of writer cramp dystonia.[4,37]

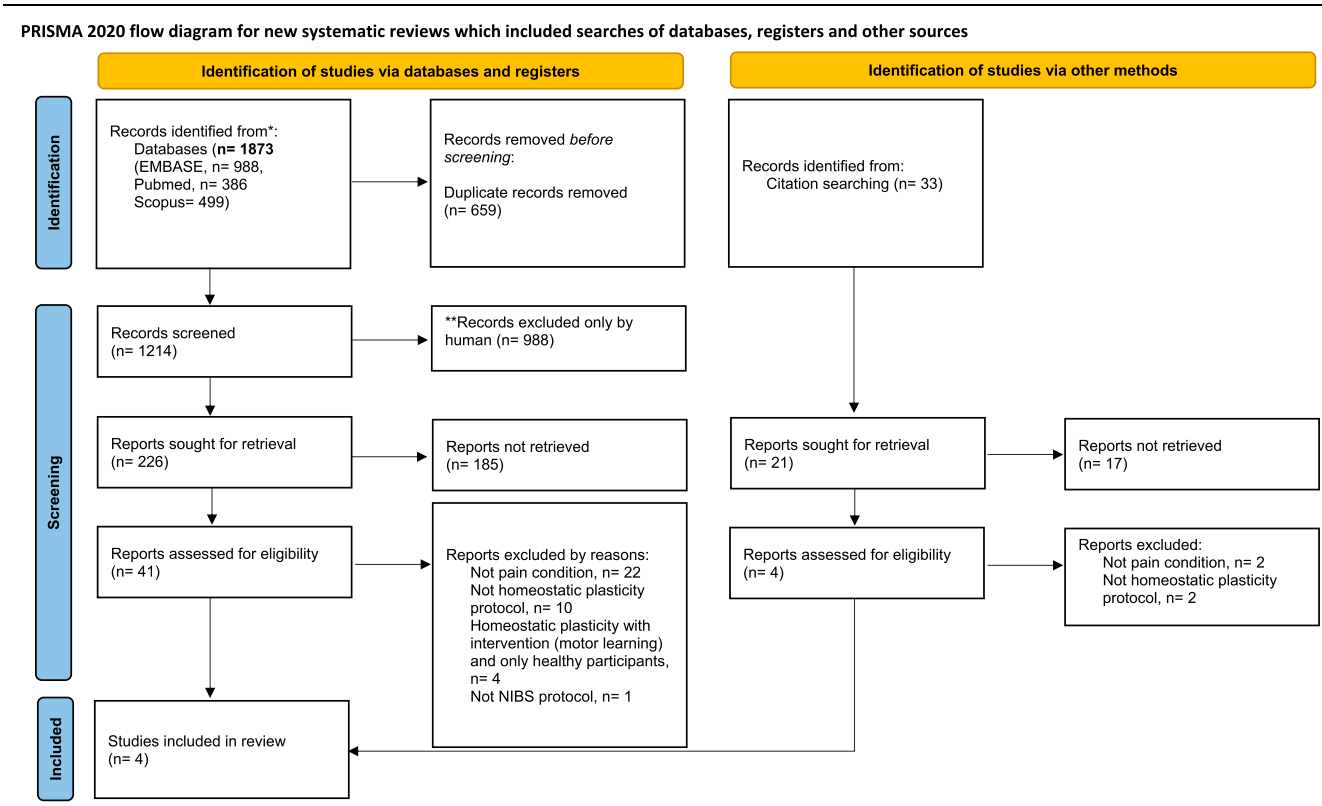
In summary, 4 studies,[3,49,50,58] including 5 experiments and 146 participants, were included in this review (**Table 2**). Of these, 63 participants were patients with chronic pain. Two studies involved an age-matched and sex-matched control group compared with a chronic pain group.[3,49] Two studies included healthy individuals who underwent testing before and during experimental pain models using nerve growth factor (NGF, 21 participants)[50] and a pain model using capsaicin 8% patch.[58] The sample size for each group ranged between 13 and 50 participants, with the included age for healthy controls being a weighted mean for the 4 studies of 31 ± 13 years and for patients with pain 43 ± 16 years. For HP induction (**Fig. 2**), 2 different types of protocols were used: (1) tDCS for 7-minute

Table 1

Quality assessment criteria.

1. Was the study question or objective clearly stated?
2. Were eligibility criteria for the study population prespecified and clearly described?
3. Were the participants in the study representative of the general or clinical population of interest?
4. Were all eligible participants who met the prespecified entry criteria enrolled?
5. Was the sample size sufficiently large to provide confidence in the findings?
6. Was the intervention clearly described and delivered consistently across the study population?
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?
8. Were the people assessing the outcomes blinded to the participants' interventions?
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?
10. Did the statistical methods examine changes in outcome measures from before to after the intervention?
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time series design)?
12. Was there a control for carryover effects?

priming and 5-minute test block with a 3-minute no-stimulation interval (120 participants)[49,50,58] and (2) a combination of anodal tDCS for 10-minute priming with rTMS test block of varying length (ie, 15 minutes and 20 seconds rTMS).[3] In every experiment, HP induction was performed on the left primary motor cortex. Cortical excitability was assessed through MEPs at various time points (**Fig. 2**): (1) before the priming block,[3,49,50,58] (2) after the priming block (ie, between HP induction),[3,50] (3) immediately after HP induction,[3,50,58] (4) 5 minutes after HP induction,[3] (5) 10 minutes after HP induction,[49,50] and (6) 15 minutes after HP induction[3,58] and 20,[50] 30,[50,58] and 45 minutes after HP induction.[58] Notably, for Wittkopf et al.,[58] post-HP time points at 30 and 45 minutes were after a second HP induction. Motor-evoked potentials were primarily recorded from the first dorsal interosseous muscle,[3,49,58] and one study recorded MEPs from the right extensor carpi radialis brevis muscle.[50] Stimulus intensities used throughout the experiments were based on the resting motor threshold (RMT + 120%) for MEPs (the minimum intensity needed to evoke a peak-to-peak MEP of 50 μV in 50% of trials[3,58]) or a stimulus intensity standardized to elicit peak-to-peak MEPs of 1 mV[49] or 0.5 mV peak-to-peak amplitude.[50]



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram for study identification. The diagram shows the process of identifying studies, screening for eligibility, and giving reasons for exclusion.[34]

Table 2

Characteristics of included studies.

Reference		Pain group	Control group	Priming	Test
Antal et al. 2008[3]	Experiment 1 Experiment 2	n = 13 patients with migraine with aura (3 M, 33 ± 12 y) n = 13 patients with migraine with aura (3 M, 33 ± 12 y)	n = 13 pain-free controls (3 M, 31 ± 10 y) n = 13 pain-free controls (3 M, 31 ± 10 y)	Excitatory Anodal tDCS 1 mA, 10 minutes Inhibitory Cathodal tDCS 1 mA, 10 minutes	Excitatory* 20 seconds rTMS 100 biphasic pulses at 90% of RMT at a constant rate of 5 Hz Inhibitory* 20 seconds rTMS—100 biphasic pulses at 90% of RMT at a constant rate of 5 Hz
Thapa et al. 2018[48]	Experiment 1 Experiment 2	n = 50 patients with chronic low back pain (26 M, 45 ± 16 y) n = 50 patients with chronic low back pain (26M, 45 ± 16 y)	n = 25 pain-free controls (13M, 43 ± 17 y) n = 25 pain-free controls (13M, 43 ± 17 y)	Single tDCS session—to confirm the excitatory response of anodal tDCS 3-minute rest Excitatory Anodal tDCS 1 mA, 7 minutes 3-minute rest	Excitatory Anodal tDCS 1 mA, 7 minutes Excitatory Anodal tDCS 1 mA, 5 minutes
Thapa et al. 2021[50]	Experiment 1	n = 21 healthy individuals (12M, 23 ± 4 y) NGF-induced pain model	n = 21 healthy individuals (12M, 23 ± 4 y) at baseline	Excitatory Anodal tDCS 1 mA, 7 minutes 3-minute rest	Excitatory Anodal tDCS 1 mA, 5 minutes
Wittkopf et al. 2023[58]	Experiment 1	n = 24 healthy individuals (N = 12, 8 M, 25.7 ± 4.6 y) Capsaicin 8% patch-induced	n = 24 healthy individuals (N = 12, 8M, 25.7 ±,2 y) at baseline	Inhibitory Cathodal tDCS 1 mA, 7 minutes 3-minute rest	Inhibitory Cathodal tDCS 1 mA, 5 minutes

* The direction of effects induced by rTMS depend on preconditioning with tDCS. One study included a session where only the priming session was evaluated.[49] Although this is not an HP protocol, it was added to the table because it was part of assessing the HP response.

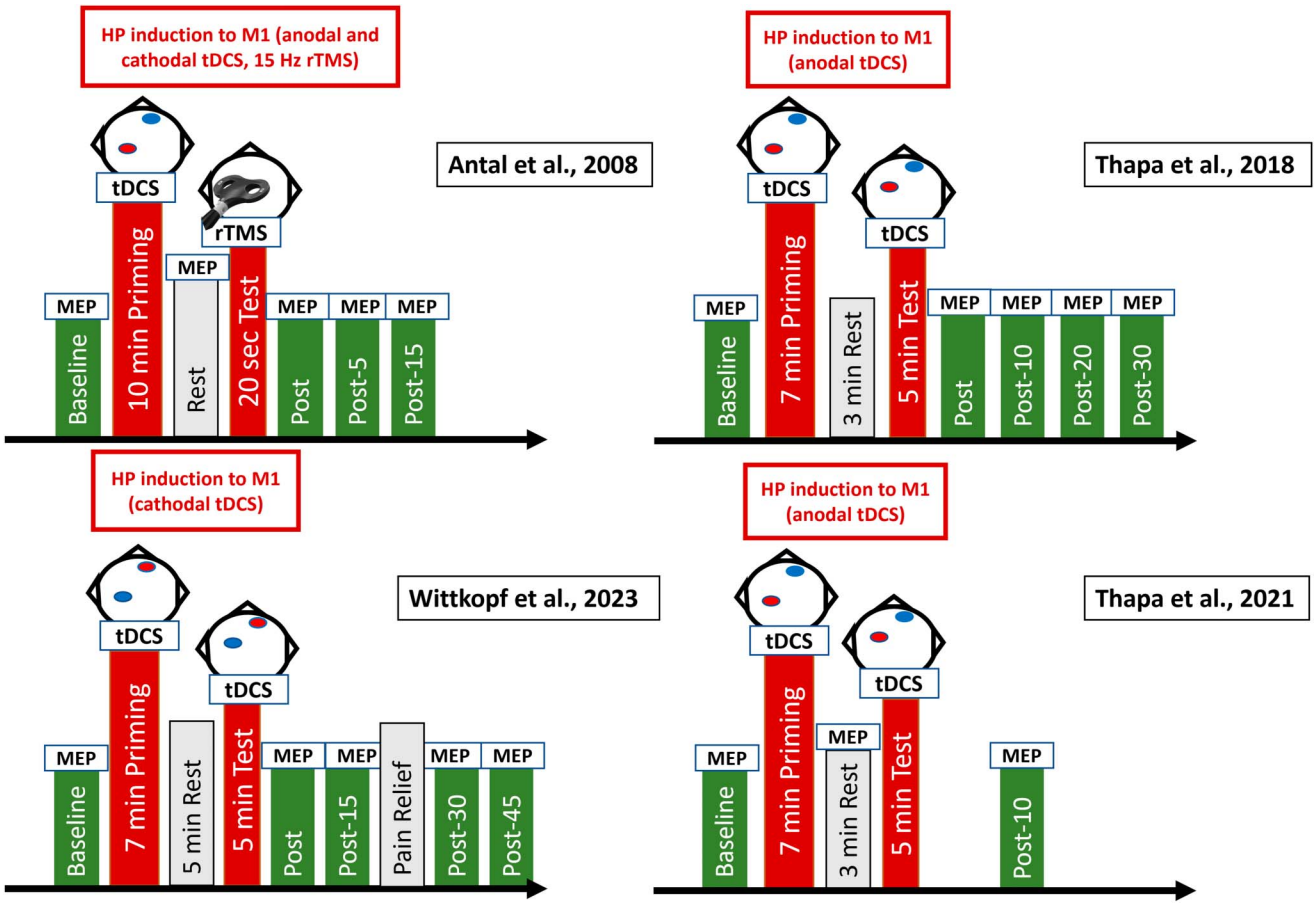


Figure 2. Experimental Procedure for HP protocols and corticomotor excitability (MEP) time points for the 4 studies. One study[3] used tDCS as a priming block and repeated transcranial magnetic stimulation (rTMS) as a testing block. The remaining 3 studies[49,50,58] used an anodal-anodal tDCS HP protocol[49,50] or a cathodal-cathodal tDCS HP protocol.[58] In addition, Wittkopf et al.[58] applied pain relief with ice because the participants were under capsaicin-induced pain and recorded post-HP measures to this pain relief. Two studies[3,50] performed MEPs between the priming and the testing blocks. Antal et al,[3] did not specify the time between tDCS and rTMS. HP, homeostatic plasticity; MEP, motor-evoked potential; tDCS, transcranial direct current stimulation.

3.2. Quality assessment

Quality assessment of the included studies was rated as fair and is summarized in **Table 3**. Most studies lacked clear information on eligibility, sample representation, sample size calculation, blinding, and accounting for dropouts. However, all studies met the criteria concerning the objective statement, consistency of intervention, outcome measurement, statistical methods, multiple time point measurements, and control for carryover effects.

3.3. Effects of priming block

Only one study[49] included a separate session with a single priming block to confirm the presence of an excitatory or inhibitory response. The MEP amplitudes increased compared with baseline after the single anodal tDCS block at all time points (0 minutes, 10 minutes, 20 minutes, and 30 minutes for both groups; 25 pain-free controls and 50 patients with chronic low back pain).[49] Two studies (26 pain-free controls, 26 patients with chronic pain, and 21 healthy participants with experimentally induced pain)[3,50] included measurements between the priming and testing block (ie, a between-block measure). For participants undergoing the NGF-pain model, MEP amplitudes were significantly increased after the 7-minute anodal tDCS priming block on days 0 (no pain), 2, 4 (moderate pain), and 16 (pain resolution).[50] Similarly, a 10-minute priming block of anodal tDCS increased corticomotor excitability for patients with pain and healthy controls.[3] On the contrary, 10-minute cathodal tDCS decreased corticomotor excitability for both healthy controls and patients with pain.[3]

3.4. Excitatory priming and excitatory test—excitatory-excitatory homeostatic plasticity induction

Three studies investigated the effect of pain on the HP response after excitatory priming and test blocks (63 patients with chronic pain, 21 healthy participants with experimentally induced pain, and 38 pain-free controls; **Table 1**).[3,49,50] In pain-free controls, an HP response of reduced MEP amplitudes was found at all time points following HP induction (0 minutes, 10 minutes, 20 minutes, and 30 minutes after HP induction) with anodal tDCS priming and test block.[49] On the contrary, patients with chronic low back pain had no change in MEP amplitudes over time (0 minutes, 10 minutes, 20 minutes, and 30 minutes after HP induction).[49] The progressive development of sustained experimentally induced muscle pain impaired the HP response seen on pain-free days (days 0 and 14).[50] The third study[3] reported an HP response of reduced MEPs after HP induction in control participants (0 minutes, 5 minutes, and 15 minutes), but this inhibition was less pronounced in patients with migraine.

3.5. Inhibitory priming and inhibitory test—inhibitory-inhibitory homeostatic plasticity induction

Two studies (37 pain-free controls and 13 patients with chronic pain) studied the response after an inhibitory priming and test block.[3,58] One study used cathodal tDCS as priming and rTMS as test blocks, at 5 Hz and 1 Hz. The cathodal priming block decreased MEP amplitudes significantly for both controls and migraineurs,[3] which increased significantly relative to the tDCS decrease (ie, not relative to baseline) for controls at 5 minutes after HP induction and for patients immediately after HP induction (0 minutes). The second study applied[58] cathodal tDCS for 7 minutes as priming, a rest of 3 minutes, and 5 minutes of cathodal tDCS as a testing block. The response to the priming block was not assessed, but there was an increased amplitude of MEPs after the HP plasticity induction for healthy individuals. This response was impaired during capsaicin-induced pain and was not restored after pain relief with ice.[58]

4. Discussion

The primary aim of this systemic review was to investigate the effect of experimental and clinical pain on the HP response as assessed through measures of cortical excitability. It has been proposed[3,49,50,58] that an impaired HP response might be a possible cause for the development or persistence of chronic pain due to excessive unregulated excitability. This is the first systematic review to explore this effect.

4.1. Generalizability of findings

The 4 included studies were considered heterogeneous in design (eg, time points to assess cortical excitability and the number of participants in each group) and protocol (eg, NIBS used or polarity of NIBS), which was the primary reason for not performing

Table 3

Quality assessment of studies.

	Thapa et al. 2021[50]	Thapa et al. 2018[48]	Antal et al. 2008[3]	Wittkopf et al. 2023[58]
Objective	Y	Y	Y	Y
Eligibility	Y	Y	N	Y
Representative	CD	CD	CD	CD
Enrollment	N	N	N	N
Sample size	Y	Y	N	Y
Intervention	Y	Y	Y	Y
Outcome measures	Y	Y	Y	Y
Blinding	N	N	N	N
Follow-up	NA	NA	NA	NA
Statistics	Y	Y	Y	Y
Time point measures	Y	Y	Y	Y
Carryover effect control	Y	Y	Y	Y

The labels are given as stated in Table 1.[30]
CD, cannot be determined; NA, not applicable; N, no; Y, yes.

a meta-analysis. Moreover, the eligibility criteria for included participants were detailed in 3 studies.[49,50,58] As stated in a previous review assessing HP protocols in healthy individuals,[56] ambiguity in eligibility criteria may affect the generalizability of results, and inclusion of demographic (ie, age and sex), personal (ie, mood/affective state, anxiety, depression, and catastrophizing), and lifestyle factors (ie, sleeping patterns and physical activity) should be considered in study design (eg, inclusion and exclusion criteria).[38]

4.2. The influence of homeostatic plasticity induction protocol

The HP response to excitatory-excitatory M1 stimulation was consistently impaired in the clinical or experimentally induced pain conditions while the opposite was true for the healthy controls (**Fig. 3**).[3,49,50] On the contrary, the HP response to inhibitory-inhibitory M1 HP protocol varied in the evaluated studies. An HP response after inhibitory-inhibitory M1 stimulation was observed for healthy participants,[58] and this response was impaired during capsaicin-induced pain. In addition, this impairment was not restored by inducing pain relief with ice.[58] Contrary to this finding, in the study conducted by Antal et al.,[3] there was a decrease in MEP amplitudes in both controls and migraineurs after inhibitory priming but no increase after the testing, indicating a lack of HP response for both groups. The reason for the discrepancy in results when using an inhibitory-inhibitory M1 stimulation protocol may be due to a lack of cathodal tDCS (ie, LTD-like) effect in general, for both controls and pain conditions. Therefore, to induce an HP response, it is important to consider that the effect of tDCS on spontaneous neural activity is driven by its polarity.[26] Anodal tDCS elicits tonic depolarization of the cell membrane while cathodal tDCS induces hyperpolarization.[25,31] Given that tDCS is a subthreshold stimulation that does not directly induce action potentials, the neuromodulatory effect of tDCS is highly influenced by the neuronal state of the cortical region and the initial activity of the stimulated area.[17,27] Moreover, a recent meta-analytical review of 1 session of tDCS[11,12,19,24,31,45] to test polarity effects,[17] found a dual effect (ie, anodal facilitatory, cathodal inhibitory) with a 67% probability of anodal and cathodal electrodes to generate similar effect sizes. Most of the variability in observing anodal and cathodal facilitatory and inhibitory effects between studies was derived from sampling errors, which may, at least partly explain the lack of cathodal HP induction in the included studies.[17] These findings are currently only valid for the motor domain,[32,33] and contrasting evidence is available.[13,46] In addition, the lack of a cathodal priming effect could relate to the difficulty of inhibiting neuronal activity if this is already high, whereas it might be easier to detect increasing facilitation for anodal stimulation.[27] In a previous systematic review and meta-analysis in healthy participants, excitatory-excitatory HP induction protocols were effective in producing an HP response, while inhibitory-inhibitory protocols had inconsistent effects.[56] Therefore, the polarity of tDCS seemingly plays an important role in the design and testing of HP protocols and suggests that excitatory-excitatory HP protocols produce a more pronounced HP response, which differs between pain conditions and healthy controls.

4.3. Calculating homeostatic plasticity—compared with baseline or priming?

Two studies included in this review investigated the priming effect immediately after priming (ie, between priming and

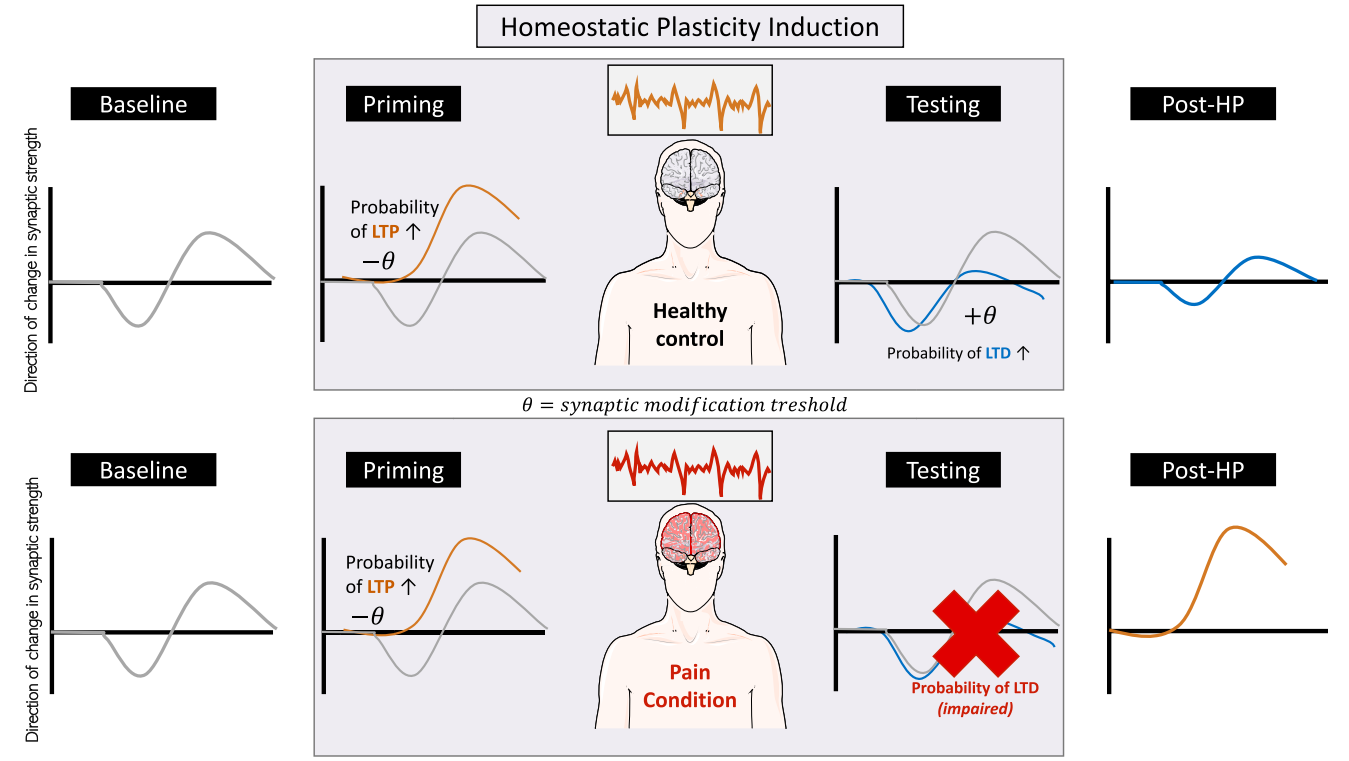


Figure 3. Excitatory-excitatory HP response is impaired in pain conditions. The HP induction protocol is displayed with a priming and testing block that shifts the neuronal membrane threshold probability of LTP or LTD. In a pain-free condition, the included studies showed an HP response that was not found in pain conditions. HP, homeostatic plasticity; LTD, long-term depression; LTP, long-term potentiation.

testing blocks). When the priming block induces an effect (for instance, an increase in MEPs), it may be discussed whether the response from the test block (a decrease in MEPs) could be due to a ceiling or inhibition effect (ie, a saturation of LTD or LTP) instead of actual HP response.[2,22] Thus, conceptually, the priming block should only change the responsiveness of synapses toward LTP or LTD.[25] The latter is possible given that tDCS priming is applied at low current intensity (1–1.5 mA), which may not significantly alter baseline cortical excitability.[25] It may be argued that the study of HP mechanisms also adheres to the BCM principles even if the priming does not directly induce excitability changes[2] because it is highly likely that the response after the testing block is then HP by nature.[22,57] In the studies included in this systematic review, 3 calculated the post-HP response as a reduction or increase of MEPs relative to baseline,[3,49,58] whereas Thapa et al.[50] calculated the HP response relative to postpriming. The appropriate calculation of HP has been previously discussed by Wittkopf et al.,[56] where differences were detected in favor of an HP response when comparisons were made against the priming block. However, the authors noted that calculating the HP response in this way does not technically account for the reversal of excitability but only a decrease or increase in corticospinal excitability after priming.[56] A true HP response would imply a change in the threshold for LTP-like or LTD-like induction,[22] in contrast to a non-HP reversal of synaptic plasticity, where the priming effect is abolished.[2] Nonetheless, the precise polarity effects in cognitive domains (eg, pain perception, sensory perception, and attention) and cortical areas (eg, sensory cortex and frontal cortex) after M1 tDCS are still unknown; thus, it remains a potential necessity to evaluate the priming effect when researching HP responses in other cortical regions after M1 tDCS.

4.4. Role of homeostatic plasticity impairment in different pain conditions

The role of HP impairment in chronic pain is still unclear. For instance, Antal et al.[3] discussed HP impairment in migraineurs as a short-term alteration, playing a permissive role in disorder pathophysiology rather than a causal role. Generally, in migraine, HP impairment has been defined as a generalizable hypersensitivity throughout the cortex that stems from an imbalance between excitation and inhibition.[7,10,44] In chronic low back pain, failure to regulate synaptic plasticity could cause abnormally increased central excitability,[23,55] which may lead to maladaptive reorganization of brain regions.[41,49] Moreover, these cortical excitability changes have been related to pain severity, postural control, and reduced muscle coordination.[18] Other theories suggest that altered HP in the early stages of pain could have a functional role in preventing memory encoding[50] because high levels of LTP impair subsequent learning.[21,39] The longitudinal and experimental study of Thapa et al.[50] established some foundational understanding of HP and its relation to pain development and resolution. The authors reported that the most significant disturbance of HP was on the day of the highest reported pain intensity, while HP was restored when the pain was resolved. Of interest, the HP response was not restored after applying pain relief with ice over a capsaicin-induced pain area (after 45 minutes of pain induction).[58] Taken together, these findings may imply that restoration of HP during pain requires not only a pain-free state but also other cortical/spinal mechanisms affected by the sustained nociception, which may resolve with time.

4.5. Homeostatic plasticity—a localized or generalized mechanism?

In chronic low back pain, a generalized alteration in cortical excitability extends throughout the sensorimotor system, beyond the cortical representation of painful muscles.[42,51] This was confirmed by Thapa et al.,[49] where the disruption of HP in M1 was uncorrelated to the intensity, duration, and location of pain. In migraine with aura, it is well-known that a generalized alteration of cortical excitability extends beyond the visual cortex.[7,10,44] Indeed, due to the possible relevance of HP in other brain functions, primarily those pertaining to pain and perception, studies investigating the somatosensory region have emerged.[6] For instance, theta-burst stimulation protocols can be used to elicit HP responses at the somatosensory cortex level and may affect temporal order judgment.[20] More research on the generalizability of HP is needed to comprehend the role of HP in different cortical regions and their relation to disease impairment, such as sensory function and pain perception.

4.6. Future therapeutic applicability

During the past decade, it has become increasingly important to probe and modulate mechanisms of plasticity in the human cortex because this may aid in unraveling pathophysiological processes of neurological diseases. In this context, studying HP could lead to insights into the mechanisms involved in pain experience and thus reorient toward therapeutically rectifying HP regulation.[49] For example, inducing LTD in focal hand dystonia could be beneficial for reducing symptoms and improving functionality.[40] However, it has also been shown that enhancing synaptic strengthening (LTP-like) should be reconsidered to avoid promoting aberrant synaptic plasticity.[49] These contrasting suggestions open the discussion of what proper cortical excitability balance is if this homeostasis were to be sought. Recent consensus[22,60] and reliability reports[48,57] have been published to standardize HP induction protocols, which will promote quality research into this mechanism and further comprehension of therapeutic potential. If HP has a causal role in chronic pain, targeted treatment to rectify HP would plausibly allow the dissolution of sensorimotor symptoms and dysfunction, but this remains to be further explored.[58]

4.7. Limitations

This review has several limitations. First, although the initial search was extensive, the resulting eligible articles were few, which is low to allow for deductive statements. Thus, the consistency of the conclusions is limited by the heterogeneity, but at the same time, it highlights the need for research on this novel topic. Second, the assessment of risk of bias demonstrated heterogeneity of study protocols, lack of information on enrollment, and blinding, which limit the generalizability of findings. Third, variability in responses to NIBS and assessment techniques is well known,[15] and more than 30% of controls and patients had impaired HP or normal HP, respectively.[49] Given the vast array of NIBS protocols and response variability of NIBS, work on standardization[48,57] allows for critical study design for HP protocols, such as optimizing the time window between priming and testing.[22] Reliable and tested protocols should be considered for future HP study designs to standardize findings. Fourth, HP responses using tDCS were induced with 5 × 7-cm sodium chloride–soaked sponges, which have been reported to stimulate brain areas beyond M1.[47] Future studies may therefore consider using high-definition stimulation techniques to target the intended cortical regions more precisely.

Fifth, there was inconsistency within the 4 studies to adjust the stimulation intensity of TMS for RMT and for the test stimulus of MEPs. Thus, while calculating HP responses, standardization of how to obtain cortical excitability measures (eg, MEPs or SEPs) is also needed to ensure comparability. Furthermore, the effect of pain on HP mechanisms in these studies has only been measured by corticomotor excitability. Whether HP is prevalent or relevant in other cortical areas remains unknown. Studies evaluating sensory and nociceptive responses to HP protocols are needed. Finally, it is critical to establish a consensus on how to define the HP response because the calculations differed among studies, making it difficult to compare findings.

5. Conclusion

This systematic review is the first to explore the effect of pain on cortical HP in humans. Though limited by the lack of available literature, it provides tentative support for an HP impairment in pain conditions after excitatory-excitatory HP induction in M1, compared with healthy controls. The novelty of the HP mechanism requires some consideration for generalizable research, such as using a reliable and tested HP protocol, including better characterization of demographic and psychological aspects of participants, and ensuring proper HP calculation. More HP research is needed to understand the role of this mechanism in sensory perception and nociception. Finally, targeting treatment to rectify HP in pain could be a potential therapeutic route for resolving painful symptoms and sensorimotor dysfunction.

Disclosures

Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National Research Foundation (DNRF121). The authors have no conflicts of interests to declare.

Article history:
Received 30 August 2023
Received in revised form 9 December 2023
Accepted 28 December 2023
Available online 4 March 2024

References

[1] Abbott LF, Nelson SB. Synaptic plasticity: taming the beast. Nat Neurosci 2000;3(suppl l):1178–83.
[2] Abraham WC. Metaplasticity: tuning synapses and networks for plasticity. Nat Rev Neurosci 2008;9:387.
[3] Antal A, Lang N, Boros K, Nitsche M, Siebner HR, Paulus W. Homeostatic metaplasticity of the motor cortex is altered during headache-free intervals in migraine with aura. Cereb Cortex 2008;18:2701–5.
[4] Avenali M, De Icco R, Tinazzi M, Defazio G, Tronconi L, Sandrini G, Tassorelli C. Pain in focal dystonias—a focused review to address an important component of the disease. Parkinsonism Relat Disord 2018;54:17–24.
[5] Bienenstock E, Cooper L, Munro P. Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex. J Neurosci 1982;2:32–48.
[6] Bliem B, Müller-Dahlhaus JFM, Dinse HR, Ziemann U. Homeostatic metaplasticity in the human somatosensory cortex. J Cogn Neurosci 2008;20:1517–28.
[7] Brighina F, Giglia G, Scalia S, Francolini M, Palermo A, Fierro B. Facilitatory effects of 1 Hz rTMS in motor cortex of patients affected by migraine with aura. Exp Brain Res 2005;161:34–8.
[8] Brighina F, Cosentino G, Vigneri S, Talamanca S, Palermo A, Giglia G, Fierro B. Abnormal facilitatory mechanisms in motor cortex of migraine with aura. Eur J Pain 2011;15:928–35.
[9] Cosentino G, Brighina F, Talamanca S, Paladino P, Vigneri S, Baschi R, Indovino S, Maccora S, Alfonsi E, Fierro B. Reduced threshold for inhibitory homeostatic responses in migraine motor cortex? A tDCS/TMS study. Headache 2014;54:663–74.
[10] Curra A, Pierelli F, Coppola G, Barbanti P, Buzzi MG, Galeotti F, Serrao M, Truini A, Casali C, Pauri F, Cruccu G. Shortened cortical silent period in facial muscles of patients with migraine. PAIN 2007;132:124–31.
[11] Fregni F, Boggio PS, Santos MC, Lima M, Vieira AL, Rigonatti SP, Teresa M, Silva A, Barbosa ER, Nitsche MA, Pascual-Leone A. Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease. Mov Disord 2006;21:1693–702.
[12] Furubayashi T, Terao Y, Arai N, Okabe S, Mochizuki H, Hanajima R, Hamada M, Yugeta A, Inomata-Terada S, Ugawa Y. Short and long duration transcranial direct current stimulation (tDCS) over the human hand motor area. Exp Brain Res 2008;185:279–86.
[13] Galea JM, Jayaram G, Ajagbe L, Celnik P. Modulation of cerebellar excitability by polarity-specific noninvasive direct current stimulation. J Neurosci 2009;29:9115–22.
[14] Gamboa OL, Antal A, Laczo B, Moliadze V, Nitsche MA, Paulus W. Impact of repetitive theta burst stimulation on motor cortex excitability. Brain Stimul 2011;4:145–51.
[15] Guerra A, López-Alonso V, Cheeran B, Suppa A. Variability in non-invasive brain stimulation studies: reasons and results. Neurosci Lett 2020;719:133330.
[16] Hamada M, Terao Y, Hanajima R, Shirota Y, Nakatani-Enomoto S, Furubayashi T, Matsumoto H, Ugawa Y. Bidirectional long-term motor cortical plasticity and metaplasticity induced by quadripulse transcranial magnetic stimulation. J Physiol 2008;586:3927–47.
[17] Jacobson L, Koslowsky M, Lavidor M. TDCS polarity effects in motor and cognitive domains: a meta-analytical review. Exp Brain Res 2012;216:1–10.
[18] Janetzki L, Gussew A, Malessa R, Habenicht U, Reichenbach JR, Strauß B, Borys C. Hirnmetabolische Veränderungen bei chronischem Rückenschmerz. Schmerz (Berlin, Germany) 2016;30:134–40.
[19] Jefferson S, Mistry S, Singh S, Rothwell J, Hamdy S. Characterizing the application of transcranial direct current stimulation in human pharyngeal motor cortex. Am J Physiol Gastrointest Liver Physiol 2009;297:G1035–40.
[20] Jones CB, Lulic T, Bailey AZ, Mackenzie TN, Mi YQ, Tommerdahl M, Nelson AJ. Metaplasticity in human primary somatosensory cortex: effects on physiology and tactile perception. J Neurophysiol 2016;115:2681–91.
[21] Kang J-S, Terranova C, Hilker R, Quartarone A, Ziemann U. Deficient homeostatic regulation of practice-dependent plasticity in writer's cramp. Cereb Cortex 2011;21:1203–12.
[22] Karabanov A, Ziemann U, Hamada M, George MS, Quartarone A, Classen J, Massimini M, Rothwell J, Siebner HR. Consensus paper: probing homeostatic plasticity of human cortex with non-invasive transcranial brain stimulation. Brain Stimul 2015;8:993–1006.
[23] Kregel J, Meeus M, Malfliet A, Dolphens M, Danneels L, Nijs J, Cagnie B. Structural and functional brain abnormalities in chronic low back pain: a systematic review. Semin Arthritis Rheum 2015;45:229–37.
[24] Lang N, Nitsche MA, Paulus W, Rothwell JC, Lemon RN. Effects of transcranial direct current stimulation over the human motor cortex on corticospinal and transcallosal excitability. Exp Brain Res 2004;156:439–43.
[25] Lefaucheur JP, Wendling F. Mechanisms of action of tDCS: a brief and practical overview. Neurophysiol Clin 2019;49:269–75.
[26] Liebetanz D, Paulus W, Nitsche MA. Methods and mechanisms of transcranial direct current stimulation. Klin Neurophysiol 2007;38:136–40.
[27] Miniussi C, Harris JA, Ruzzoli M. Modelling non-invasive brain stimulation in cognitive neuroscience. Neurosci Biobehav Rev 2013;37:1702–12.
[28] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Estarli M, Barrera ESA, Martínez-Rodríguez R, Baladia E, Agüero SD, Camacho S, Buhring K, Herrero-López A, Gil-González DM, Altman DG, Booth A, Chan AW, Chang S, Clifford T, Dickersin K, Egger M, Gøtzsche PC, Grimshaw JM, Groves T, Helfand M, Higgins J, Lasserson T, Lau J, Lohr K, McGowan J, Mulrow C, Norton M, Page M, Sampson M, Schünemann H, Simera I, Summerskill W, Tetzlaff J, Trikalinos TA, Tovey D, Turner L, Whitlock E. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1–160.
[29] Müller-Dahlhaus F, Ziemann U. Metaplasticity in human cortex. Neuroscientist 2015;21:185–202.
[30] National Heart L and BI. Study quality assessment tools. NIH gov; 2021. Available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed July 6, 2023.
[31] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527:633–9.

[32] Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, Paulus W, Hummel F, Boggio PS, Fregni F, Pascual-Leone A. Transcranial direct current stimulation: state of the art 2008. Brain Stimul 2008;1:206–23.
[33] Nitsche MA. Present and future clinical applications of tDCS. Neurologie Rehabil 2016;22:S34.
[34] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
[35] Pozo K, Goda Y. Unraveling mechanisms of homeostatic synaptic plasticity. Neuron 2010;66:337–51.
[36] Quartarone A, Rizzo V, Bagnato S, Morgante F, Sant'Angelo A, Romano M, Crupi D, Girlanda P, Rothwell JC, Siebner HR. Homeostatic-like plasticity of the primary motor hand area is impaired in focal hand dystonia. Brain 2005;128:1943–50.
[37] Rhoad RC, Stern PJ. Writer's cramp—a focal dystonia: etiology, diagnosis, and treatment. J Hand Surg Am 1993;18:541–4.
[38] Ridding MC, Ziemann U. Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. J Physiol 2010;588:2291–304.
[39] Rioult-Pedotti M-S, Friedman D, Donoghue JP. Learning-induced LTP in neocortex. Science 2000;290:533–6.
[40] Schabrun SM, Stinear CM, Byblow WD, Ridding MC. Normalizing motor cortex representations in focal hand dystonia. Cereb Cortex 2009;19:1968–77.
[41] Schabrun SM, Hodges PW, Vicenzino B, Jones E, Chipchase LS. Novel adaptations in motor cortical maps: the relation to persistent elbow pain. Med Sci Sports Exerc 2015;47:681–90.
[42] Schwenkreis P, Maier C, Pleger B, Mansourian N, Dertwinkel R, Malin J-P, Tegenthoff M, Zenz M. NMDA-mediated mechanisms in cortical excitability changes after limb amputation. Acta Neurol Scand 2003;108:179–84.
[43] Seung HS. Half a century of hebb. Nat Neurosci 2000;3(suppl l):1166.
[44] Siniatchkin M, Kröner-Herwig B, Kocabiyik E, Rothenberger A. Intracortical inhibition and facilitation in migraine—a transcranial magnetic stimulation study. Headache 2007;47:364–70.
[45] Stagg CJ, O'shea J, Kincses ZT, Woolrich M, Matthews PM, Johansen-Berg H. Modulation of movement-associated cortical activation by transcranial direct current stimulation. Eur J Neurosci 2009;30:1412–23.
[46] Tanaka S, Hanakawa T, Honda M, Watanabe K. Enhancement of pinch force in the lower leg by anodal transcranial direct current stimulation. Exp Brain Res 2009;196:459–65.
[47] Thair H, Holloway AL, Newport R, Smith AD. Transcranial direct current stimulation (tDCS): a beginner's guide for design and implementation. Front Neurosci 2017;11:641.
[48] Thapa T, Schabrun SM. Test-retest reliability of homeostatic plasticity in the human primary motor cortex. Neural Plast 2018;2018:6207508.
[49] Thapa T, Graven-Nielsen T, Chipchase LS, Schabrun SM. Disruption of cortical synaptic homeostasis in individuals with chronic low back pain. Clin Neurophysiol 2018;129:1090–6.
[50] Thapa T, Graven-Nielsen T, Schabrun SM. Aberrant plasticity in musculoskeletal pain: a failure of homeostatic control? Exp Brain Res 2021;239:1317–26.
[51] Tsao H, Tucker KJ, Hodges PW. Changes in excitability of corticomotor inputs to the trunk muscles during experimentally-induced acute low back pain. Neuroscience 2011;181:127–33.
[52] Turrigiano GG, Nelson SB. Homeostatic plasticity in the developing nervous system. Nat Rev Neurosci 2004;5:97–107.
[53] Turrigiano G. Too many cooks? Intrinsic and synaptic homeostatic mechanisms in cortical circuit refinement. Annu Rev Neurosci 2011;34:89–103.
[54] Turrigiano G. Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function. Cold Spring Harb Perspect Biol 2012;4:a005736.
[55] Wand BM, Parkitny L, O'Connell NE, Luomajoki H, McAuley JH, Thacker M, Moseley GL. Cortical changes in chronic low back pain: current state of the art and implications for clinical practice. Man Ther 2011;16:15–20.
[56] Wittkopf PG, Larsen DB, Graven-Nielsen T. Protocols for inducing homeostatic plasticity reflected in the corticospinal excitability in healthy human participants: a systematic review and meta-analysis. Eur J Neurosci 2021;54:5444–61.
[57] Wittkopf PG, Larsen DB, Gregoret L, Graven-Nielsen T. Prolonged corticomotor homeostatic plasticity – effects of different protocols and their reliability. Brain Stimul 2021;14:327–9.
[58] Wittkopf PG, Boye Larsen D, Gregoret L, Graven-Nielsen T. Disrupted cortical homeostatic plasticity due to prolonged capsaicin-induced pain. Neuroscience 2023;533:1–9.
[59] Ziemann U, Siebner HR. Modifying motor learning through gating and homeostatic metaplasticity. Brain Stimul 2008;1:60–6.
[60] Ziemann U, Paulus W, Nitsche MA, Pascual-Leone A, Byblow WD, Berardelli A, Siebner HR, Classen J, Cohen LG, Rothwell JC. Consensus: motor cortex plasticity protocols. Brain Stimul 2008;1:164–82.