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PROTOCOLS FOR INDUCING HOMEOSTATIC PLASTICITY REFLECTED IN THE CORTICOSPINAL EXCITABILITY IN HEALTHY HUMAN PARTICIPANTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Homeostatic plasticity complements synaptic plasticity by stabilising neural activity within a physiological range. In humans, homeostatic plasticity is investigated using two blocks of non-invasive brain stimulation (NIBS) with an interval without stimulation between blocks. The aim of this systematic review and meta-analysis was to investigate the effect of homeostatic plasticity induction protocols on motor evoked potentials (MEP) in healthy participants. Four databases were searched (Medline, Scopus, Embase and Cochrane library). Studies describing the application of two blocks of NIBS of the primary motor cortex with an interval of no stimulation between blocks reporting changes in corticospinal excitability by MEP amplitude were included. Thirty-seven reports with 55 experiments (700 participants) were included. Study quality was considered poor overall, with heterogeneity in study size, sample and designs. Two blocks of excitatory stimulation at the primary motor cortex produced a homeostatic response (decreased MEP) between 0 and 30 minutes post protocols, when compared with a single stimulation block. Two blocks of inhibitory stimulation at the primary motor cortex using interval duration of 10 minutes or less produced a homeostatic response (increased MEP) between 0 and 30 minutes post protocols, when compared with a single stimulation block. There were no differences in MEPs when compared with baseline MEPs. In conclusion, homeostatic plasticity induction using two blocks of NIBS with an interval of 10 minutes or less without stimulation between blocks produces a homeostatic response up to 30 minutes post protocol. Improvements in participant selection, sample sizes, and protocols of NIBS techniques are needed.

Abbreviations: NIBS, non-invasive brain stimulation; MEP, motor evoked potentials; LTP, long-term potentiation; LTD, long-term depression; PAS, paired associative stimulation; TMS, transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; SMD, standardized mean difference; CI, confidence interval; STDP, spike-timing dependent plasticity; M1, primary motor cortex; NMDA, N- methyl- D- aspartic acid; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived nerve growth factor.

INTRODUCTION

Synaptic plasticity, which strengthens (i.e. long-term potentiation, LTP) or weakens (i.e. long-term depression, LTD) synaptic transmission, is thought to be the neurophysiological basis of learning and memory[1, 2]. Although synaptic plasticity is an efficient mechanism, its positive feedback nature can affect the stability of neural networks[3, 4]. A variety of regulatory cellular mechanisms, termed homeostatic plasticity, maintain synaptic excitability within a physiological range[3, 5, 6]. Homeostatic plasticity mechanisms control excitability by shifting the threshold for induction of LTP and LTD based on postsynaptic activity[3, 5-7].

Homeostatic plasticity is investigated using a priming-test design, in which priming triggers and test captures the homeostatic response[8]. Homeostatic plasticity has been investigated in humans using two blocks of non-invasive brain stimulation (NIBS) with an interval of no stimulation between blocks[8-10]. NIBS may involve the use of paired associative stimulation (PAS), transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) at the primary motor cortex to induce homeostatic plasticity, and changes in excitability can then be measured by quantifying the amplitude of motor-evoked potentials (MEP)[8, 9]. Studies conducted in healthy participants have reported a homeostatic response of reduced MEP amplitude when a block of excitatory stimulation is primed by another block of excitatory stimulation to the primary motor cortex[11-13]. Interestingly, an enhanced inhibitory effect can be seen post inhibitory NIBS when primed with a block of excitatory stimulation[14]. Further, it seems that a homeostatic response can manifest as a decrease in inhibition or facilitation rather than up-regulation of inhibition or facilitation[8]. Nevertheless, some studies have demonstrated a non-homeostatic response, when using two blocks of NIBS with and interval of no stimulation in-between blocks[15-17].

Protocols used to investigate homeostatic response in healthy participants differ greatly in terms of the type of NIBS, time of application, interval duration between blocks, among others. This may pose a methodological issue since the duration of aftereffects of homeostatic plasticity seems to depend on the protocol employed. The aim of this systematic review was to investigate the effect of homeostatic plasticity induction protocols (excitatory and/or inhibitory priming and test) on MEPs amplitude in healthy participants. Additional analyses aimed to evaluate if interval duration between priming and test stimulation affect homeostatic response and if differences in protocols are related to the length of the aftereffects of the homeostatic plasticity induction protocol.

MATERIALS & METHODS

This systematic review process was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[18] The protocol was registered on PROSPERO (CRD42020162609).

Search methods for identification of studies

The databases Medline, Scopus, Embase and Cochrane library were used to search for relevant studies between 13 and 19 December 2019 (from the date of inception), using a combination of controlled vocabulary and free-text terms (see search strategy in supplementary material, Table S1). Hand search of reference lists of included studies and previously published systematic reviews were also conducted.

Criteria for considering studies and study selection

Studies were eligible for inclusion if they included healthy participants, described the application of two blocks of NIBS at the primary motor cortex with an interval of no stimulation between blocks, assessed corticospinal excitability by MEP amplitude, measured MEPs from any upper limb muscle, and had a full-text publication in a peer-reviewed journal. Studies that included a sample of participants with a clinical condition and a healthy control group were included, but only data from the healthy control group were analysed. Studies that reported a series of experiments were included but only the experiments that followed the eligibility criteria were analysed. All types of study designs were included. Studies that only reported the use of a peripheral stimulation technique were excluded. Reviews, theses, and abstracts were excluded. Firstly, title and abstracts were screened against the eligibility criteria, then two reviewers (PGW & DBL) screened full-texts and in case of discrepancies, the third reviewer (TGN) was asked for a final decision.

Quality assessment

A modified Quality Assessment of Before-After (Pre–Post) Studies developed by the National Heart, Lung, and Blood Institute was used[19]. The criteria “Was the sample size sufficiently large to provide confidence in the findings?” was modified to “Was an *a-priori* sample size calculation performed?”. In addition, a criterion was added to assess the control

for carryover effects in repeated measures studies. Quality assessment criteria available in supplementary material Table S2.

Data extraction and analysis

Data extraction on study and sample characteristics, homeostatic plasticity induction protocol, and results were performed by the first reviewer (PGW) and checked by the other reviewers (DBL & TGN). The primary outcome of interest of this review was the average peak-to-peak amplitude of TMS-induced MEPs. Mean MEP amplitudes and standard deviations from baseline up to 120 minutes post stimulation were extracted from text and tables. When further details were needed, the corresponding author of the study was contacted. When the first two strategies for data extraction failed, data was extracted from available graphs using free online plot digitizing software (https://apps.automeris.io/wpd/). Data were first entered into Excel, then into RevMan for meta-analysis.

Data were analysed separately according to the homeostatic plasticity induction protocol as follows: excitatory priming and excitatory test, inhibitory priming and inhibitory test, excitatory priming and inhibitory test, and inhibitory priming and excitatory test.

The MEP amplitudes were compared between pre- and post-homeostatic plasticity induction (i.e. baseline and after the second block of NIBS) at three time points: early (0 to 5 minutes post test stimulation), mid (6 to 30 minutes post test stimulation) and late (31 to 120 minutes post test stimulation)[20]. If data were available for more than one time point within one of the time points described above, data were combined following the Cochrane Collaboration guidelines[21]. In addition, MEP amplitudes were compared between post homeostatic plasticity induction (i.e. post test stimulation) and post single block of NIBS. Subgroup analysis was conducted comparing studies by the NIBS modality (e.g. tDCS, TMS, PAS or mixed). Given that investigations have pointed towards a critical time window between priming and test stimulation necessary to produce a homeostatic response [8, 10, 11] and that it is essential that the priming stimulus changes cortical excitability, which must persist after the termination of the priming stimulus [3, 8], a second subgroup analysis was conducted to investigate the effect of interval duration between blocks of NIBS. Data from studies using intervals of 10 minutes or less were compared with those that used intervals lasting more than 10 minutes.

The overall estimated effect size was expressed as standardized mean difference (SMD) using the generic inverse-variance random-effects model. The standard error of the SMD was calculated imputing a correlation coefficient. Correlation coefficients were calculated from raw data when available, or the correlation coefficient from a study with similar design and comparisons was used when data were not available. A sensitivity analysis was conducted when a correlation coefficient was imputed by increasing and reducing the correlation coefficient by 0.1[21]. Heterogeneity between comparable studies was assessed using a standard chi-squared test and I^2 statistics. When chi-squared resulted in a p value < 0.1, statistically significant heterogeneity was considered present. When I^2 > 60%, substantial heterogeneity was considered present.[21]

RESULTS

Characteristics of included studies

The search found 4894 records, of which 1410 were duplicates. Of the 3484 records screened by title and abstract, 68 were potentially relevant and full reports obtained and screened. Of these, 31 reports were excluded with reasons (Fig. 1). Thus, there were 37 reports of studies that met eligibility criteria and were included for review. Several studies reported a series of experiments with different samples, which have been analysed separately. Therefore, a total of 55 experiments (700 participants) were included in the review (Table 1). Study sample sizes were between 6 and 72 participants and mean age of participants ranged from 21.1 and 70.8 years. For priming and test purpose, TMS was used in 29 experiments (334 participants), tDCS was used in 11 experiments (187 participants), PAS was used in four experiments (53 participants) and a combination of techniques was used in 11 experiments (126 participants). Assessment of MEPs were performed at the first dorsal interosseous muscle in 26 studies [11, 12, 14-17, 22-41], at the abductor pollicis brevis muscle in eight studies [13, 42-48], and at the abductor digiti minimi muscle in three studies.[49-51] Four studies used 120% of resting motor threshold as the stimulation intensity to measure MEPS [16, 22, 23, 33], one study used 115% [43], one study used 110% [38], and one study used intensities ranging from 90% to 150% in steps of 10%, as no differences were identified measures were averaged and reported[44]. In 25 studies MEPs were measured using the % of maximal stimulator output intensity which induced an average peak-to-peak MEP of approximately 1 mV at baseline and kept the same intensity

for the rest of the experiment. [11-13, 15, 17, 24-27, 29-31, 34-36, 40, 41, 45-52] The same was done by [28] using an average peak-to-peak MEP of approximately 0.4 mV, by [32] using 0.5 mV, by [37] using amplitudes of 0.8–1 mV, and by [14] using amplitudes of 0.7 – 1 mV. Study details can be found in Tables S3 to S6 in the supplementary material.

Quality assessment

Quality assessment (Table S7) indicated poor quality associated with specification and description of inclusion criteria, representativeness of included subjects, consistency of intervention delivered across the sample, and blinding of participants and outcome assessor. Thirty five of the thirty seven studies did not report a sample size calculation. Thirty two of the thirty seven studies reported measures to control for carryover effects.

Excitatory priming and excitatory test protocols

Thirty-two experiments investigated the effect of excitatory priming and test protocols on MEPs (375 participants, Table 1)[11-13, 15, 22, 23, 25, 28-32, 34, 35, 40-42, 44, 46, 47, 50, 51]. Data could not be pooled from 10 experiments[22, 29, 32, 39, 41, 47, 51]. Overall effects and subgroup effects are illustrated in Fig. 2. Forest plots can be found in supplementary material (Fig. S1-S6).

The early time point (0 to 5 minutes post test stimulation): The overall effect was not significant when comparing MEP amplitude post homeostatic plasticity induction against baseline (SMD = 0.23; 95%CI: -0.06, 0.51; P = 0.12; Fig. 2A). There were no significant subgroup differences in NIBS modality (Chi^2 (3) = 3.89, P = 0.27; Fig. 2A) and interval duration (Chi^2 (1) = 2.13, P = 0.14; Fig. 2A).

There was an overall effect in favour of MEP suppression when comparing MEP amplitude after homeostatic plasticity induction (two blocks) against a single block of excitatory stimulation (SMD = -0.80; 95%CI: -1.16, -0.43; P < 0.0001; Fig. 2B). The test for subgroup differences suggests that tDCS favours MEPs suppression in comparison with TMS and a combination of both (Chi^2 (3) = 7.36; P = 0.06; Fig. 2B). The test for subgroup differences also suggests that studies with an interval of 10 minutes or less intensify the effect of homeostatic plasticity induction in favour of MEP suppression (Chi^2 (1) = 5.33; P= 0.01; Fig. 2B).

The mid-time point (6 to 30 minutes post test stimulation): There was an overall effect in favour of MEP facilitation when comparing MEP amplitude after homeostatic plasticity induction against baseline (SMD = 0.37; 95%CI: 0.07, 0.67; P = 0.01). However, when running a sensitivity analysis in which the imputed correlation coefficient was reduced by 0.1, a non-significant overall effect was found (SMD = 0.28; 95%CI: -0.02, 0.57; P = 0.07 Fig. 2A). The test for subgroup differences suggests (Chi^2 (3) = 9.74; P = 0.02; Fig. 2A) that TMS favours MEP facilitation in comparison with tDCS. The test of subgroup differences comparing the interval duration between priming and test stimulation was not significant (Chi^2 (1) = 0.02; P = 0.88, Fig. 2A).

There was an overall effect in favour of MEP suppression when comparing MEP amplitude after induction of homeostatic plasticity against a single block of excitatory stimulation (SMD = -0.61; 95%CI: -0.96, -0.27; P = 0.0005; Fig. 2B) and no significant subgroup differences for NIBS modality (Chi^2 (3) = 4.48, P = 0.21, Fig. 2B) and interval duration (Chi^2 (1) = 1.89, P = 0.17, Fig. 2B).

The late time point (31 to 120 minutes post test stimulation): The overall effect was not significant when comparing MEP amplitude after homeostatic plasticity induction against baseline (SMD = 0.37; 95%CI: -0.08, 0.82; P = 0.1; Fig. 2A). There were no significant subgroup differences in NIBS modality (Chi^2 (1) = 1.28; P = 0.26; Fig. 2A), and interval duration (Chi^2 (1) = 0.02, P= 0.89, Fig 2A).

The overall effect was not significant when comparing MEP amplitude after homeostatic plasticity induction against a single block of excitatory stimulation (SMD = 0.05; 95%CI: -0.44, 0.54; P = 0.83; Fig. 2B). There were no significant subgroup differences in NIBS modality (Chi^2 (1) = 0.18; P = 0.67; Fig. 2B), and interval duration (Chi^2 (1) = 0.02, P = 0.90, Fig. 2B).

Inhibitory priming and inhibitory test protocols

Twenty experiments investigated the effect of inhibitory priming and test protocols on MEPs (303 participants, Table 1)[11, 14, 15, 17, 25-29, 32-34, 37, 38, 45, 48, 49]. Data could not be pooled from four experiments [29, 32, 38, 49]. Overall effects and subgroup effects are illustrated in Fig. 3. Forest plots can be found in supplementary material (Fig. S7-S11).

The early time point (0 to 5 minutes post test stimulation): The overall effect was not significant when comparing MEP amplitude after homeostatic plasticity induction with

baseline (SMD = -0.05; 95%CI: -0.47, 0.37; P = 0.81; Fig. 3A). The test for subgroup differences suggests (Chi^2 (2) = 7.09, P = 0.03; Fig. 3A) that mixed NIBS favours MEP facilitation in comparison with TMS and tDCS. There were no significant subgroup differences in interval duration (Chi^2 (1) = 3.43; P = 0.06; Fig. 3A).

The overall effect was not significant when comparing MEP amplitude after induction of homeostatic plasticity with single block of inhibitory stimulation (SMD = 0.28; 95%CI: -0.13, 0.70; P = 0.18; Fig. 3B). There were no significant subgroup differences in NIBS modality (Chi^2 (2) = 2.50; P = 0.29; Fig. 3B). Test of subgroup differences suggests that interval of 10 minutes or less modify the effect of homeostatic plasticity induction in favour of MEP facilitation (Chi^2 (1) = 7.72; P = 0.005; Fig. 3B).

The mid time point (6 to 30 minutes post test stimulation): The overall effect was not significant when comparing MEP amplitude after induction of homeostatic plasticity with baseline (SMD = 0.11; 95%CI: -0.30, 0.51; P = 0.61; Fig. 3A). There were no significant subgroup differences in NIBS modality (Chi^2 (2) = 5.01; P = 0.08; Fig. 3A) and interval duration (Chi^2 (1) = 2.52; P = 0.11; Fig. 3A).

The overall effect was not significant when comparing MEP amplitude after induction of homeostatic plasticity with single block of inhibitory stimulation (SMD = 0.45; 95%CI: -0.13, 1.03; P = 0.53; Fig. 3B). There were no significant subgroup differences in NIBS modality (Chi^2 (1) = 1.26; P = 0.53; Fig. 3B). Test of subgroup differences suggests that interval of 10 minutes or less modify the effect of homeostatic plasticity induction in favour of MEP facilitation (Chi^2 (1) = 6.70; P = 0.01; Fig. 3B).

The late time point (31 to 120 minutes post test stimulation): The overall effect was not significant when comparing MEP amplitude after induction of homeostatic plasticity against baseline (SMD = -0.19; 95%CI: -0.58, 0.20; P = 0.34; Fig. 3A), and against single block of inhibitory stimulation (SMD = 0.45; 95%CI: -0.14, 1.04; P = 0.13; Fig. 3B). Subgroup differences were not considered due to few data points available.

Excitatory priming and inhibitory test protocols

Eighteen experiments investigated the effect of excitatory priming and inhibitory test protocols on MEPs (193 participants, Table 1)[14, 16, 23, 24, 28-30, 33, 34, 37, 48]. Data could not be pooled from six experiments (3 reports)[29, 39, 43]. There was not enough

data for analysis of the late time point (31 to 120 minutes post test stimulation). Furthermore, there was not enough data for subgroup analysis of interval duration between priming and test stimulation. Overall effects and subgroup effects are illustrated in Fig. 4A and 4B. Forest plots can be found in supplementary material (Fig. S12-S13).

The early time point (0 to 5 minutes post test stimulation): There was a significant overall effect in favour of MEP suppression when comparing MEP amplitude post homeostatic plasticity induction against baseline (SMD = -0.42; 95%CI: -0.82, -0.02; P = 0.04; Fig. 4A). There were no significant subgroup differences in NIBS modality (Chi^2 (1) = 3.97; P = 0.05; Fig. 4A).

The overall effect was not significant when comparing MEP amplitude post homeostatic plasticity induction with post single block of inhibitory stimulation (SMD = -0.16; 95%CI: -0.62, 0.30; P = 0.50; Fig.4B). There were no significant subgroup differences in NIBS modality (Chi^2 (1) = 0.05; P = 0.82; Fig. 4B).

The mid time point (6 to 30 minutes post test stimulation): There was a significant overall effect in favour of MEP suppression when comparing MEP amplitude post homeostatic plasticity induction against baseline (SMD = -0.51, 95%CI: -0.97, -0.05; P = 0.03; Fig 4A). However, overall effect was not significant when comparing MEP amplitude post homeostatic plasticity induction with post single block of inhibitory stimulation (SMD = -0.15; 95% CI: -0.72, 0.42; P = 0.61; Fig. 4B). Subgroup differences were not considered due to few data points available.

Inhibitory priming and excitatory test protocol

Eighteen experiments investigated the effect of inhibitory priming and excitatory test protocols on MEPs (226 participants, Table 1)[28, 29, 31, 32, 34-36, 41, 42, 45, 46, 48, 51]. Data could not be pooled from eight experiments (6 reports) [29, 31, 32, 36, 41, 51]. There were not enough data for subgroup analyses. Overall effects are illustrated in Fig. 4C and 4D. Forest plots can be found in supplementary material (Fig. S14 – S16).

The early time point (0 to 5 minutes post test stimulation): There was a significant overall effect in favour of MEP facilitation when comparing MEP amplitude post homeostatic plasticity induction against baseline (SMD = -0.64; 95%CI: 0.25, 1.04; P = 0.001; Fig. 4C). However, overall effect was not significant when comparing MEP amplitude post homeostatic plasticity induction with post single block of excitatory stimulation (SMD =

0.51; 95%CI: -0.12, 1.15; P = 0.11; Fig. 4D). There were no significant subgroup differences in NIBS modality.

The mid time point (6 to 30 minutes post test stimulation):

There was a significant overall effect in favour of MEP facilitation when comparing MEP amplitude post homeostatic plasticity induction against baseline (SMD = 0.50; 95%CI: 0.09, 0.91; P = 0.02; Fig. 4C). However, overall effect was not significant when comparing MEP amplitude post homeostatic plasticity induction with post single block of excitatory stimulation (SMD = 0.08; 95%CI: -0.56, 0.76; P = 0.80; Fig. 4D). There were no significant subgroup differences in NIBS modality.

The late time point (31 to 120 minutes post test stimulation): The overall effect was not significant when comparing MEP amplitude after induction of homeostatic plasticity against baseline (SMD = 0.34; 95%CI: -0.17, 0.85; P = 0.19; Fig. 4C), and against single block of excitatory stimulation (SMD = -0.65; 95%CI: -1.80, 0.49; P = 0.26; Fig.4D).

Heterogeneity in the meta-analysis

Significant and substantial heterogeneity were observed in all comparisons ($p < 0.05$, $I^2 > 61\%$), although the majority of this heterogeneity can be attributed to true variance between study results, rather than within-study error. This was expected, given the known heterogeneity in study sizes, modalities, and protocols.

DISCUSSION

The primary aim of this systematic review was to comprehensively explore the effects of homeostatic plasticity induction protocols, using a NIBS priming-test design, on corticospinal excitability assessed by TMS-induced MEPs in healthy individuals. In addition, this is the first systematic review with meta-analysis to analyse the duration of effects of protocols using a priming-test stimulation and to compare the effect of interval duration between priming and test stimulation on corticospinal excitability. Studies were considerably heterogeneous in design, protocol, and findings, and the majority were considered to have a poor quality due to sample size, subject representativeness, and consistency of intervention delivered. The meta-analysis indicated that excitatory priming and test protocols produced a homeostatic response between 0 and 30 minutes post-test stimulation, when compared with excitatory stimulation. Inhibitory priming and test protocols using interval duration of

10 minutes or less produced a homeostatic response between 0 and 30 minutes post-test stimulation, when compared with a single block of inhibitory stimulation. The excitatory priming and inhibitory test and inhibitory priming and excitatory test protocols showed differences when comparing with baseline but not when comparing with single block of stimulation.

Included studies were in general exploratory, with a diversity of designs and protocols and small sample sizes. In fact, only two out of the thirty-one included studies reported a sample size calculation. One of the main flaws across studies was a failure to appropriately describe and select participants, with few studies reporting detailed eligibility criteria. Although this may seem inconsequential in studies investigating healthy participants, it affects generalisability of results and contributes to heterogeneity in study findings. Given that it is still unknown how various demographic, personal, and lifestyle factors, such as age, sex, and physical activity affect homeostatic plasticity mechanisms, it is important that these factors are taken into account and reported when designing inclusion and exclusion criteria of studies[53].

The meta-analysis found no differences comparing corticospinal excitability post-test stimulation with baseline measurements when analysing the excitatory priming and test and inhibitory priming and test protocols. It is possible that due to protocol differences and inter-individual variability in the response to NIBS techniques, protocols did not affect corticospinal excitability overall. In addition, the variability of MEP assessment may affect detection of smaller homeostatic manifestations compared with baseline. However, differences were detected in favour of homeostatic responses when comparisons were made against a single block of stimulation, suggesting that test stimulation reduced the effect of priming stimulation but did not revert excitability. Further studies are needed to investigate and differentiate homeostatic and non-homeostatic responses in humans. For example, as in basic cell studies, it is important to differentiate between a homeostatic response in which the priming stimulus changes the threshold for LTP-like and LTD-like induction as opposed to non-homeostatic reversal of synaptic plasticity, in which the test stimulus abolishes the effect of the priming stimulus without changing the threshold of LTP or LTD induction [3, 8, 54]. Here, it is relevant to point to theories on homeostatic and non-homeostatic plasticity, given the resulting change in corticomotor excitability are similar. For instance, spike-timing dependent plasticity (STDP) is dictated by the timing between pre-

and postsynaptic spike potentials, where Markram et al. [55] demonstrated, in rat hippocampal pyramidal neurons, that presynaptic spike potentials initiated 20 ms before postsynaptic spike potentials caused LTP, and conversely, postsynaptic spike potentials followed by presynaptic spike potentials yielded LTD. A later influential study showed that the critical window for pre- and postsynaptic spike potential induction for LTP or LTD induction may fall within 5 ms [56]. In humans, PAS is utilised to demonstrate these timing-dependent effects by delivering afferent electrical stimulation to the median nerve that precedes stimulation to the primary motor cortex with TMS. When delivered 25 ms before stimulation at the primary motor cortex, corticomotor excitability increases [57], and conversely, if the electrical stimulation precedes stimulation to the primary motor cortex by only 10 ms (i.e. the arrival of sensory input likely happens ~10-15 ms after stimulation to the primary motor cortex), corticomotor excitability reduces [58]. In addition, gating and anti-gating mechanisms may apply when considering changes in corticomotor excitability, where the net change in calcium influx in cortical neurons or activity-dependent changes in intracortical inhibitory circuits may yield overall increases or decreases in corticomotor excitability [59, 60]. However, the most recent position paper on homeostatic plasticity argued that gating mechanisms should be considered non-homeostatic, as the resulting change in corticomotor excitability is not predicated on alteration in threshold for LTP- or LTD induction [8]. Instead, STDP and gating mechanisms (instantaneous changes in corticomotor excitability) are not necessarily bound by the framework of the BCM theory but instead, especially in the case of STDP, may be complementary [61].

When investigating homeostatic mechanisms, the fidelity of homeostatic responses are greater if the priming protocol does not cause detectable change in basal synaptic transmission[3]. On the other hand, when investigating reversal of synaptic plasticity it is imperative that the priming protocol produces overt plasticity[3, 54]. In humans, such investigation faces limitations related to variability in responses to NIBS and assessment techniques[62, 63]. Long-lasting synaptic plasticity is primarily based on LTP- and LTD induction, which in turn are based on changes in NMDA and AMPA receptors function as well as influx and unblocking of Ca^{2+} and Mg^{2+} [64]. In this respect, repetitive TMS can induce LTP- and LTD-like effects by applying high-frequency or low-frequency stimulation, respectively, to a cortical target area. The postulate is that the induction of corticomotor excitability changes is based on synchronisation of firing rates of pre-and postsynaptic

neurons, which weakens or strengthens the basal synaptic efficiency, respectively [65]. Likewise, tDCS can modify synaptic strength by weak-current application to the cortical target area, yet given the subthreshold activation, the induction of motor response is not driven by the same direct mechanisms as TMS [66]. Furthermore, earlier evidence suggests that tDCS application in in-vivo models of mice, that the effects of anodal tDCS on LTP-induction is independent of changes in basal synaptic efficiency (as no changes in input-output curves or paired-pulse ratios were found), but rather on brain-derived nerve growth factor expression (BDNF) [67] which complements earlier studies on the importance of BDNF in relation to tDCS-induced synaptic plasticity [68]. While both types of brain stimulation are predicated on NMDA receptor-dependent glutamatergic transmission, a clear distinction on the underlying neurophysiological effects should be made with respect to the direct activation of corticomotor neurons by e.g. rTMS versus subthreshold axonal membrane potential changes of tDCS [66]. In this meta-analysis, subgroup differences indicate that tDCS may be effective in producing a homeostatic response when using excitatory priming and test protocols but not for inhibitory priming and test protocols. It is possible, that tDCS may work best in inducing homeostatic plasticity because it alters cortical excitability by subthreshold neuronal membrane resting potential modification[69], as opposed to producing neuronal depolarisation and firing within the stimulated region as is the case of TMS[70]. As mentioned, the fidelity of homeostatic responses is higher when the priming stimulation does not induce LTP or LTD so as to not produce a ceiling effect or confound homeostatic with non-homeostatic mechanisms[3, 6, 8]. It is plausible, that the tDCS mechanisms of action and the low current intensities (between 1 and 1.5 mA) used in protocols may prevent such effects contributing to a homeostatic response. However, a number of factors may contribute to the variability observed in the response to NIBS, such as gender, age, history of synaptic activity, and genetic polymorphism[32, 62, 63, 71]. Given the multitude of NIBS protocols available and inter-individual differences in responses to NIBS, further research is still needed to establish a standardised protocol with set evidence-based parameters to investigate and differentiate homeostatic and non-homeostatic mechanisms in humans.

Previous investigations have pointed towards a critical time window in between priming and test stimulation necessary to produce a homeostatic response[8, 10, 11]. In the present review, subgroup differences indicate that intervals of no stimulation between

priming and test stimulation of 10 minutes or less produce a homeostatic response. Within the sliding threshold theory of homeostatic plasticity (see[72]), this critical time window indicates that temporal aspects of changes produced by the priming stimulation on post-synaptic activity is important to shift the threshold in a homeostatic way[3, 7]. It is essential that in homeostatic plasticity induction protocols, the priming stimulus changes neural function, which must persist after the termination of the priming stimulus and alters the response to a subsequent stimulation[3, 8]. Therefore, the test stimulus should be delivered during aftereffects of the priming stimulation. However, this critical time window may differ among different priming NIBS protocols, as NIBS technique, duration, and intensity can affect aftereffects duration[71]. Investigations into the temporal relationship between the priming and test stimulation is crucial for understanding homeostatic mechanisms in humans.

Limitations

An extensive systematic search was undertaken, and further hand-searching for relevant articles was conducted to retrieve as many eligible articles as possible; however, it is still possible that pertinent research was either missed or excluded. The number of studies included in each subgroup varied, some more than others. In addition, false positive significance tests rapidly increase in likelihood as more subgroup analyses are performed. Taken together, these considerations may affect the overall result and statistical significance, and should be interpreted with caution. Factors that may affect the outcome of homeostatic plasticity induction protocols, namely NIBS intensity and intensity of single-pulse TMS for MEPs measurement, were not studied as they were beyond the scope of this review. Anticipating the heterogeneity of protocols, we narrowed our investigation to cortical NIBS and MEPS assessed at the upper limbs, and as such our findings are limited to these parameters. Lastly, data points beyond the three pre-specified time points were not included in the analysis.

CONCLUSION

This systematic review comprehensively explored the effects of homeostatic plasticity induction protocols using a NIBS on corticospinal excitability. The meta-analysis is the first to analyse data investigating the duration of effects of protocols using a priming-test

stimulation and to compare the effect of interval duration between priming and test stimulation on corticospinal excitability. This systematic review and meta-analysis provides tentative evidence that homeostatic plasticity induction protocols using two blocks of NIBS with an interval of 10 minutes or less of no stimulation between blocks produces a homeostatic response of the corticomotor excitability up to 30 minutes post protocol. However, due to poor quality and heterogeneity in designs and protocols of primary studies, we could not find conclusive evidence. Future studies should include clear inclusion and exclusion criteria, sample size calculation and report a standardised protocol of NIBS, possibly including an interval duration of 10 minutes of less between priming and test stimulation. Furthermore, investigations into homeostatic and non-homeostatic mechanisms in health and disease are also needed.

AUTHOR CONTRIBUTIONS

Priscilla Wittkopf: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft, and Writing - Review & Editing. Dennis Larsen: Formal analysis, Writing - Review & Editing. Thomas Graven-Nielsen: Conceptualization, Writing - Review & Editing, Supervision, and Project administration.

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Table 1 Included studies characteristics

Reference	Sample	Priming	Test	NIBS
Bastani & Jaberzadeh (2014) - *Experiment i*	n =12 (2M), 21.8 ± 1.4 years	Excitatory	Excitatory	tDCS - current density 0.016 mA/cm^2
Bastani & Jaberzadeh (2014) - *Experiment ii*	n = 6 (0M), 23.2 ± 2.5 years	Excitatory	Excitatory	
Faber et al. (2017)	n = 10 (NR), 25.2 ± 1.5 years	Excitatory Inhibitory	Excitatory Inhibitory	tDCS – current density 0.028 mA/cm^2
Fricke et al. (2010) - *Experiment i*	n = 8 (6 M), 33.5 ± NR years	Excitatory	Excitatory	tDCS – current density 0.03 mA/cm^2
Fricke et al. (2010) - *Experiment ii*	n = 9 (6M), 32 ± NR years	Inhibitory	Inhibitory	
Fricke et al. (2010) - *Experiment iii*	n = 8 (4M), 24.3 ± NR years	Excitatory	Excitatory	
Fricke et al. (2010) - *Experiment iv*	n = 12 (5M), 26.4 ± NR years	Excitatory	Excitatory	
Monte-Silva et al. (2013)	n = 15 (6M), 25.5 ± 3.6 years	Excitatory	Excitatory	tDCS – current density 0.03 mA/cm^2
Monte-Silva et al. (2010)	n = 72 (32M), Range: 18 – 45 years	Inhibitory	Inhibitory	tDCS – current density 0.03 mA/cm^2
Thapa et al. (2918)	n = 25 (13M), 43 ± 17 years	Excitatory	Excitatory	tDCS – current density 0.03 mA/cm^2
Thapa & Schabrun (2018)	n = 10 (5M), 23 ± 5 years	Excitatory	Excitatory	tDCS – current density 0.03 mA/cm^2
Bologna et al. (2017)	n = 11 (7M), 66.7 ± 6.6 years	Excitatory	Inhibitory	Stimulation intensity - 80% AMT iTBS – 3 pulses bursts at 50Hz, trains of 2 s repeated every 10 s- 600 pulses. cTBS – 3 pulses bursts at 50Hz, trains of 10 s repeated at 5Hz.
Do et al. (2018)	n = 20 (6M), 26.4 ± 3.2 years	Inhibitory	Inhibitory	Stimulation intensity - 70% RMT cTBS - 3 pulses bursts at 50Hz repeated at 5Hz for 40 s - 600 pulses.
Doeltgen & Ridding (2011)	n =14 (4M), 24.5 ± 3.1 years	Excitatory	Inhibitory	Stimulation intensity - 80% AMT iTBS – 3 pulses bursts at 50Hz, trains of 2 s repeated every 10 s- 600 pulses. cTBS – 3 pulses bursts at 50Hz continuous for 40 s.
Gamboa et al. (2011) - *Experiment i*	n = 12 (6M), 24.6 ± 2.0 years	Excitatory	Excitatory	Stimulation intensity - 80% AMT iTBS – 3 pulses bursts at 50Hz, trains of 2 s repeated every 10 s- 600 pulses. cTBS – 3 pulses bursts at 50Hz repeated at 5Hz for 40 s.
Gamboa et al. (2011) - Experiment ii	n = 10 (7M), 24.7 ± 1.4 years	Inhibitory	Inhibitory	

Goldsworthy et al. (2012) - Experiment i	n = 12 (5M), 26.3 ± 2.3 years	Inhibitory	Inhibitory	Stimulation intensity - 80% AMT or 70% RMT cTBS – 3 pulses bursts at 50Hz repeated at 5Hz for 40 s.
Goldsworthy et al. (2012) - Experiment ii	n = 6 (3M), 29.7 ± 4.0 years	Inhibitory	Inhibitory	Stimulation intensity – 65% RMT cTBS – 3 pulses bursts at 50Hz repeated at 5Hz for 40 s.
Goldsworthy et al. (2012) - Experiment iii	n = 9 (4M), 22.1 ± 3.7 years	Inhibitory	Inhibitory	Stimulation intensity – 70% RMT cTBS – 3 pulses bursts at 50Hz repeated at 5Hz for 40 s.
Goldsworthy et al. (2013)	n = 14 (7M), 23.8 ± 4.7 years	Inhibitory	Inhibitory	Stimulation intensity – 70% of RMT cTBS – 3 pulses bursts at 50Hz repeated at 5Hz for 40 s.
Hamada et al. (2008)	n = 10 (7M), 38.6 ± 6.9 years	Excitatory Inhibitory Excitatory Inhibitory	Excitatory Inhibitory Inhibitory Excitatory	Stimulation intensity – 90% AMT QPS - 360 trains of four magnetic pulses separated by a certain interstimulus interval (1.5 ms, 5 ms, 10ms, 30 ms, 50ms, 100 ms and 1250 ms) with an inter-train interval of 5 s over 30 min.
Huang et al. (2010) - Experiment i	n = 8 (1M), 33.3 ± 10.3 years	Excitatory Excitatory	Excitatory Inhibitory	Stimulation intensity - 80% AMT iTBS – 3 pulses bursts at 50Hz, trains of 2 s repeated every 10 s- 600 pulses. cTBS – 3 pulses bursts at 50Hz 20 s trains – 300 pulses iTBS and cTBS (150) – same protocol with 150 pulses.
Huang et al. (2010) - Experiment ii	n = 7 (4M), 28.7 ± 3.6 years	Inhibitory Inhibitory	Excitatory Inhibitory	
Huang et al. (2010) - Experiment iii	n = 8 (3M), 32.1 ± 3.8 years	Inhibitory Excitatory	Excitatory Inhibitory	
Iezzi et al. (2011) - Experiment i	n = 10 (6M), 32.0 ± 5.0 years	Excitatory Excitatory	Excitatory Inhibitory	Stimulation intensity - 80% AMT rTMS – 10 trains of 10 pulses, inter-train interval of 1 min. iTBS – 3 pulses bursts at 50Hz, trains of 2 s repeated every 10 s- 600 pulses. cTBS – 3 pulses bursts at 50Hz, trains of 10 s repeated at 5Hz.
Iezzi et al. (2011) - Experiment ii	n= 6 (NR), NR	Excitatory Excitatory	Excitatory Inhibitory	Stimulation intensity - 120% RMT rTMS – 10 trains of 10 pulses, inter-train interval of 1 min. Stimulation intensity - 80% AMT iTBS – 3 pulses bursts at 50Hz, trains of 2 s repeated every 10 s- 600 pulses. cTBS – 3 pulses bursts at 50Hz, trains of 10 s repeated at 5Hz.
Iyer et al. (2003) - Experiment i	n = 16 (10M), 37 ± 8 years	Excitatory	Excitatory	Stimulation intensity - 90% RMT 6Hz and 4-8Hz rTMS – 20 trains, train duration 5 s and inter-train interval 25 s. 600 pulses.
Iyer et al. (2003) - Experiment ii	n = 9 (3M), 26.6 ± 7.4 years	Excitatory	Excitatory	Stimulation intensity - 90% RMT 6Hz and 4-8Hz rTMS – 20 trains, train duration 10 s and inter-train interval 20 s. 1200 pulses.
Mastroeni et al. (2013)	n = 29 (29M), 26.0 ± 3.2 years	Excitatory Inhibitory Inhibitory	Excitatory Inhibitory Excitatory	Stimulation intensity - 80% AMT iTBS – 3 pulses bursts at 50Hz, trains of 2 s repeated every 10 s- 600 pulses. cTBS – 3 pulses bursts at 50Hz repeated at 5Hz for 40 s.

Murakami et al. (2012) - Experiment i	n = 9 (7M), 29.2 ± 6.9 years	Excitatory Inhibitory Excitatory Inhibitory	Excitatory Inhibitory Inhibitory Excitatory	Stimulation intensity - 80% AMT iTBS – 3 pulses bursts at 50Hz, trains of 2 s repeated every 10 s- 600 pulses. cTBS – 3 pulses bursts at 50Hz repeated at 4.2Hz for 40 s.
Murakami et al. (2012) - Experiment ii	n = 8 (5M), 27.4 ± 4.7 years	Excitatory Inhibitory Excitatory Inhibitory	Excitatory Inhibitory Inhibitory Excitatory	
Nettekoven et al. (2015) - Experiment i	n = 7 (NR), NR	Excitatory	Excitatory	Stimulation intensity - 70% RMT iTBS – 3 pulses bursts at 50Hz, trains of 2 s repeated every 10 s- 600 pulses.
Nettekoven et al. (2015) - Experiment ii	n = 9 (NR), NR	Excitatory	Excitatory	Stimulation intensity - 80% AMT iTBS – 3 pulses bursts at 50Hz, trains of 2 s repeated every 10 s- 600 pulses. cTBS – 3 pulses bursts at 50Hz repeated at 4.2Hz for 40 s.
Opie et al. (2017) (35) - Experiment i	n = 16 (5M), 22.3 ± 1.0 years	Excitatory Inhibitory	Excitatory Excitatory	Stimulation intensity - 70% RMT iTBS – 3 pulses bursts at 50Hz, trains of 2 s repeated every 10 s- 600 pulses.
Opie et al. (2017) (35) -- Experiment ii	n = 16 (7M), 70.2 ± 1.7 years	Excitatory Inhibitory	Excitatory Excitatory	
Player et al. (2012)	n = 10 (10M), NR	Inhibitory	Excitatory	Stimulation intensity - 80% AMT iTBS – 3 pulses bursts at 50Hz, trains of 2 s repeated every 10 s- 600 pulses.
Tallabs & Hammond-Tooke (2013)	n = 11 (5M), 27.6 ± 7.4 years	Inhibitory	Inhibitory	Stimulation intensity - 80%AMT iTBS – 3 pulses bursts at 50Hz, trains of 2 s repeated every 10 s- 600 pulses.
Tse et al. (2018)	n = 15 (8M), 24.8 ± 4 years	Excitatory	Excitatory	Stimulation intensity - 70% RMT iTBS – 3 pulses bursts at 50Hz, trains of 2 s repeated every 10 s- 600 pulses.
Todd et al. (2009) Experiment i	n = 20 (8M), 25 ± 8 years	Excitatory	Inhibitory	Stimulation intensity - 80% AMT cTBS – 3 pulses bursts at 50Hz repeated at 5Hz for 40 s. Stimulation intensity - 90% RMT or 70% AMT 2-Hz train delivered for 15 s every 30 s, or a 6-Hz train delivered for 5 s every 30 s.
Todd et al. (2009) Experiment ii	n = 8 (4M), 27 ± 10 years	Excitatory	Inhibitory	Stimulation intensity - 80% AMT cTBS – 3 pulses bursts at 50Hz repeated at 5Hz for 40 s iTBS – 3 pulses bursts at 50Hz, trains of 2 s repeated every 10 s- 600 pulses.
Muller et al. (2007)	n = 11 (5M) 27.5 ± 1.6 years	Excitatory Inhibitory	Excitatory Excitatory	225 pairs of PAS – LTP (20+2ms); LTD (20-5ms); CONTROL (alternating LTP/LTD) Electrical median nerve stimulation – three × perceptual threshold (0.25 Hz; square wave, 1 ms duration) TMS stimulation intensity – SI_{1mV} Inter-PAS interval: 30 mins

Muller-Dahlhaus et al. (2015)	n = 12 (6M) 25.6 ± 1.4 years	Excitatory	Excitatory	225 pairs of PAS – LTP (20+2ms) Electrical median nerve stimulation – three × perceptual threshold (0.25 Hz; square wave, 1 ms duration) TMS stimulation intensity – SI_{1mV} Inter-PAS interval: 10 mins, 30 mins, 60 mins, 180 mins
Opie et al. (2017) (41) - Experiment i	n = 15 7(M), 22.9 ± 0.5 years	Excitatory Inhibitory	Excitatory Excitatory	200 pairs of PAS – LTP (20+2ms); LTD (20-10 ms); CONTROL (100 ms) Electrical ulnar nerve stimulation – three × perceptual threshold (0.25 Hz; square wave, 1 ms duration) TMS stimulation intensity – SI_{1mV} Inter-PAS interval: 10 mins
Opie et al. (2017) (41) - Experiment ii	n = 15 (8M), 70.8 ± 1.6 years	Excitatory Inhibitory	Excitatory Excitatory	
Cambieri et al. (2012)	n = 11 4(M), 37 ± 5.5 years	Excitatory Excitatory	Excitatory Inhibitory	tDCS – current density 0.07 mA/cm^2 Stimulation intensity - 120% RMT rTMS – 5 trains of 10 pulses, inter-train interval of 2 min.
Cosentino et al. (2012)	n = 12 (5M), 27.1 ± 2.7 years	Excitatory Inhibitory	Excitatory Excitatory	tDCS - current density 0.04 mA/cm^2 Stimulation intensity - 120% RMT rTMS – 6 trains of 10 pulses inter-train interval of 2 min.
Delvendahl et al. (2010) - Experiment i	n = 14 (7M) 25.07 ± 2.73 years	Inhibitory	Excitatory	200 pairs of PAS – LTP (25ms); LTD (10ms) Electrical median nerve stimulation – three × perceptual threshold (0.25 Hz; square wave, 1 ms duration) Stimulation intensity - SI1mV or 80% RMT rTMS – 1 train of 250 pulses at 0.1 Hz MNS0.1 = SI1mV - 250 stims at 0.1 Hz
Delvendahl et al. (2010) - Experiment ii	n = 12 (5M) 24.25 ± 1.48 years	Inhibitory	Inhibitory	
Delvendahl et al. (2010) - Experiment iii	n = 10 (5M) 25.40 ± 3.06 years	Inhibitory Inhibitory	Excitatory Excitatory	
Lang et al. (2004)	n = 10 (5M), 24.3 ± 1.9 years	Excitatory Inhibitory	Excitatory Excitatory	tDCS – current density 0.03 mA/cm^2 Stimulation intensity - 100% RMT rTMS – 1 train of 100 pulses.
Moloney et al. (2014)	n = 15 (15M), 24.5 ± 63.4 years	Excitatory Inhibitory	Inhibitory Inhibitory	tDCS –current density 0.04 mA/cm^2 Stimulation intensity - 90% RMT rTMS – 1 train of 900 pulses
Ni et al. (2014)	n = 14 (8M) 35.1 ± 3.4 years	Inhibitory Inhibitory Excitatory	Excitatory Inhibitory Inhibitory	180 pairs of PAS – LTP (25ms); LTD (10ms) Electrical median nerve stimulation – three × perceptual threshold (0.25 Hz; square wave, 1 ms duration) Stimulation intensity – 80% AMT cTBS150 – 3 pulses bursts at 50 Hz repeated at 5 Hz for 10s TMS stimulation intensity – SI_{1mV}
Nitsche et al. (2007)	n = 12 (4M) 25 ± 2.5 years	Excitatory Inhibitory	Excitatory Excitatory	tDCS – current density 0.03 mA/cm^2 225 pairs of PAS – LTP (25ms)

				Electrical ulnar nerve stimulation – three × perceptual threshold TMS stimulation intensity – SI_{1mV}
Quatarone et al. (2005)	n = 8 (7M), 46 ± 15 years	Excitatory Inhibitory	Inhibitory Inhibitory	tDCS –current density 0.03 mA/cm^2 Stimulation intensity - 85% RMT rTMS – 1 train of 900 pulses
Siebner et al. (2004)	n = 8 (8M), 35 ± NR years	Excitatory Inhibitory	Inhibitory Inhibitory	tDCS – current density 0.03 mA/cm^2 Stimulation intensity - 85% RMT rTMS – 1 train of 900 pulses

NIBS, non-invasive brain stimulation; n, number of participants; M, male participants; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; iTBS, intermittent theta burst stimulation; cTBS, continuous theta burst stimulation; QPS, quadripulse stimulation; PAS, paired associative stimulation; LTP, long-term potentiation; LTD, long-term depression; RMT, resting motor threshold; SI1mV, Stimulus intensity for inducing motor-evoked potentials of ~1 mV amplitude; NR, not reported. Age is reported as mean and standard deviation unless otherwise specified.

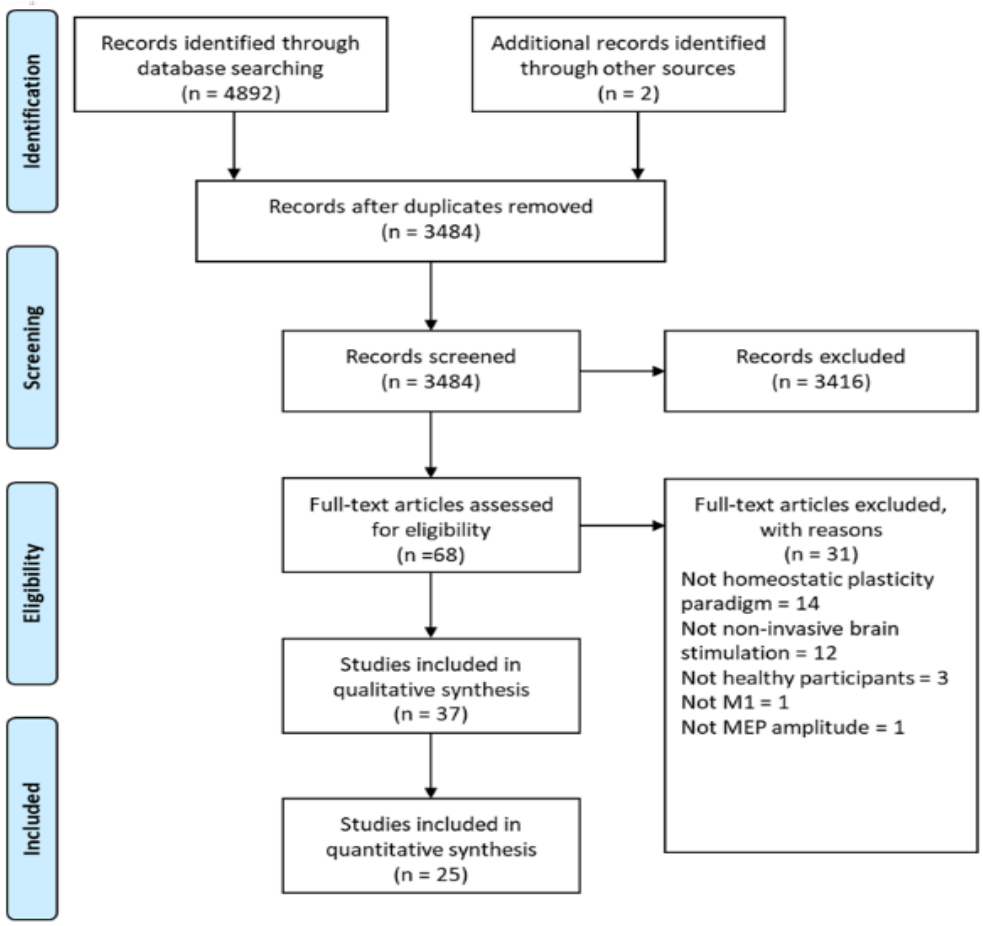

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study identification, screening, eligibility assessment, and inclusion. M1, primary motor cortex. MEP, motor-evoked potentials.

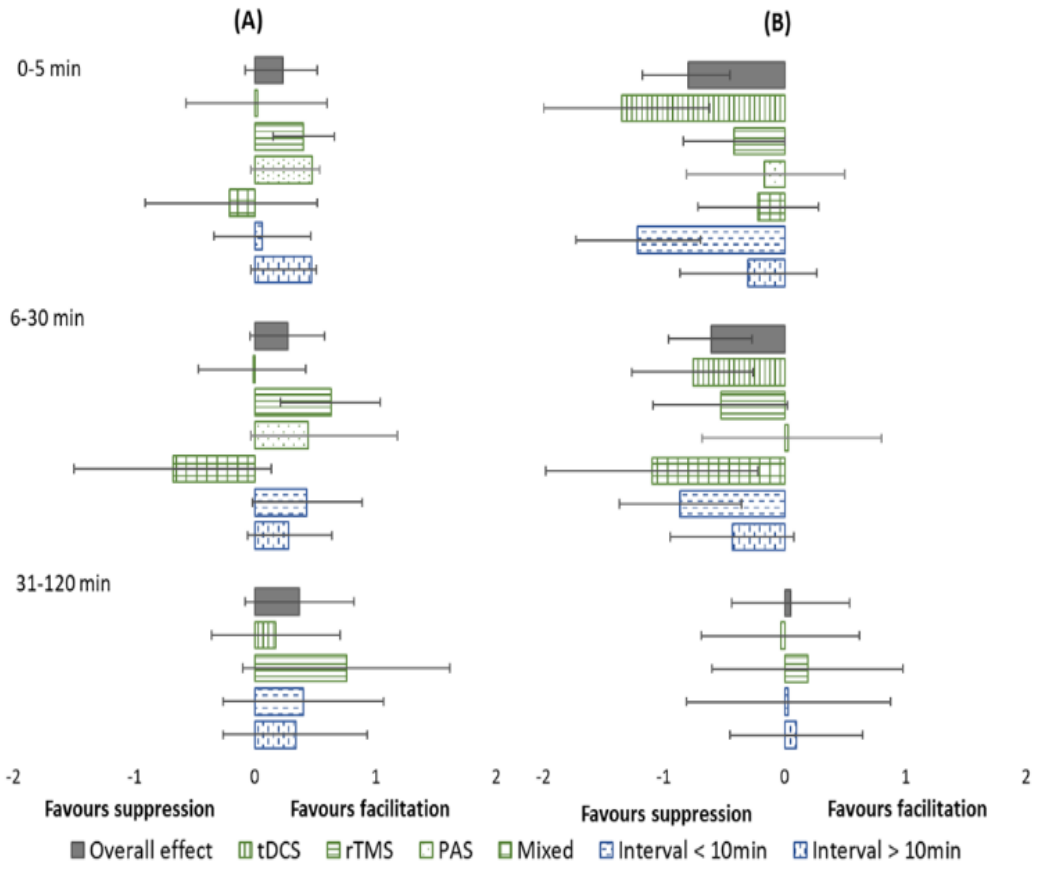

Figure 2. Effect size of comparisons of **excitatory priming** and **excitatory test** protocols at the three time points. (A) Comparisons against baselines. (B) Comparisons against single block of excitatory stimulation. Bars indicate standard mean difference and error bars indicate 95% confidence intervals. Grey bars indicate overall effect. Green bars indicate subgroup comparisons of type of stimulation. tDCS, transcranial direct current stimulation (vertical lines), TMS, transcranial magnetic stimulation (horizontal lines), PAS, paired associative stimulation (dots), mixed (horizontal and vertical lines). Blue bars indicate subgroup comparisons of interval duration. Interval duration of 10 minutes or less horizontal dashes. Interval duration of more than 10 minutes vertical dashes. Forest plots of these comparisons can be found in supplementary material Figures S1 to S6.

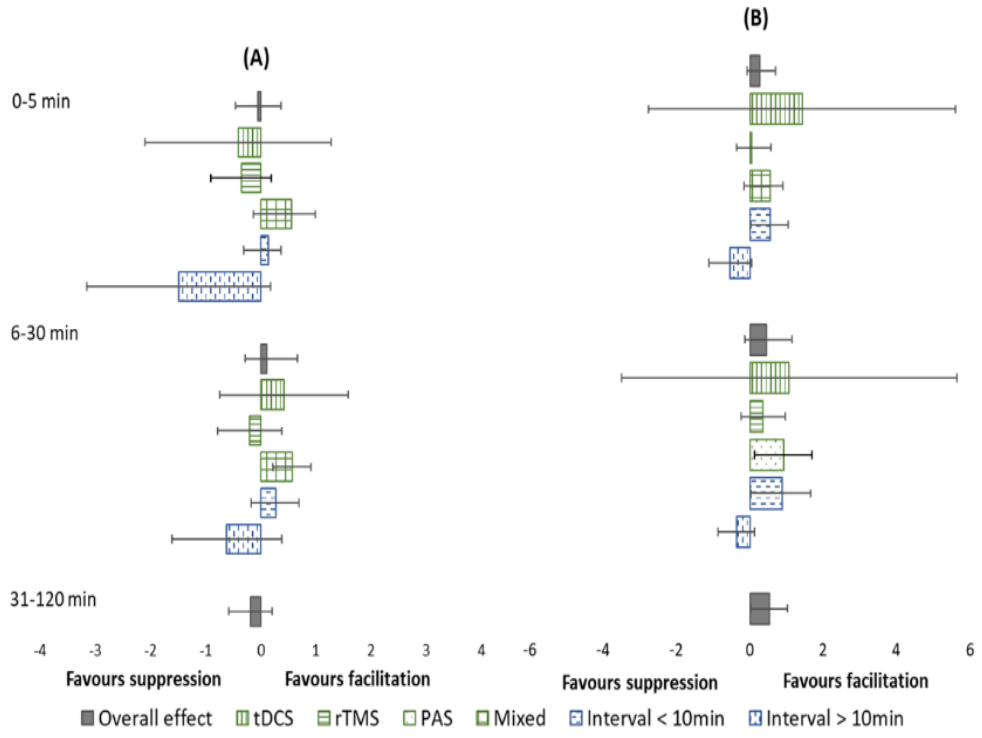

Figure 3. Effect size of comparisons of **inhibitory priming** and **inhibitory test** protocols at the three time points. (A) Comparisons against baselines. (B) Comparisons against single block of excitatory stimulation. Bars indicate standard mean difference and error bars indicate 95% confidence intervals. Grey bars indicate overall effect. Green bars indicate subgroup comparisons of type of stimulation. tDCS, transcranial direct current stimulation (vertical lines), TMS, transcranial magnetic stimulation (horizontal lines), PAS, paired associative stimulation (dots), mixed (horizontal and vertical lines). Blue bars indicate subgroup comparisons of interval duration. Interval duration of 10 minutes or less horizontal dashes. Interval duration of more than 10 minutes vertical dashes. Forest plots of these comparisons can be found in supplementary material Figures S7 to S11.

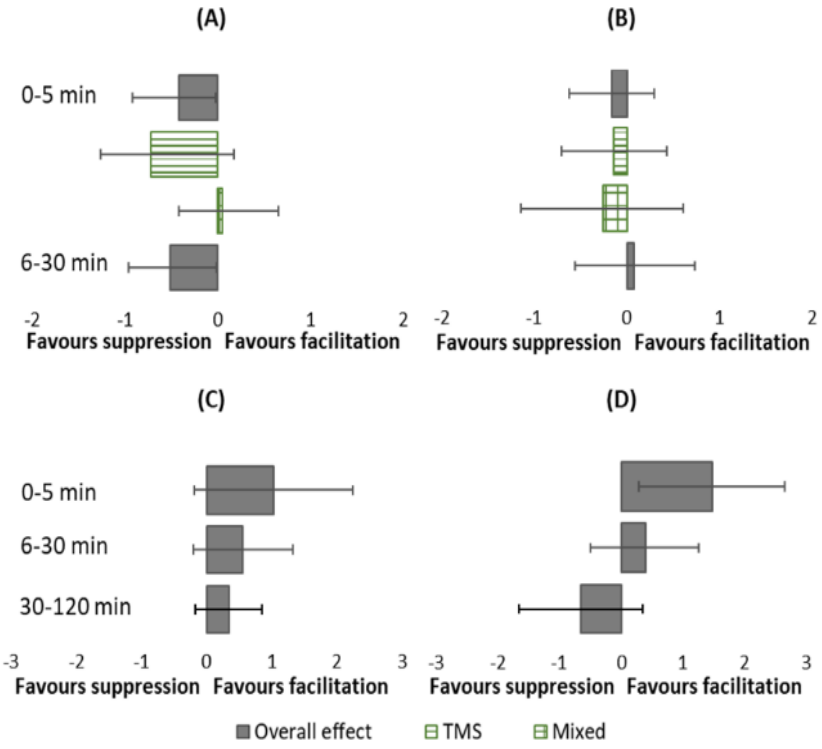

Figure 4. Effect size of comparisons of **excitatory priming** and **inhibitory test** (top) and **inhibitory priming** and **excitatory test** (bottom) protocols. (A) and (C) Comparisons against baselines. (B) and (D) Comparisons against single block of stimulation. Bars indicate standard mean difference and error bars indicate 95% confidence intervals. Grey bars indicate overall effect. Green bars indicate subgroup comparisons of type of stimulation. TMS, transcranial magnetic stimulation (horizontal lines), mixed (horizontal and vertical lines). Forest plots of these comparisons can be found in supplementary material Figures S12 to S16.

PROTOCOLS FOR INDUCING HOMEOSTATIC PLASTICITY REFLECTED IN THE CORTICOSPINAL EXCITABILITY IN HEALTHY HUMAN PARTICIPANTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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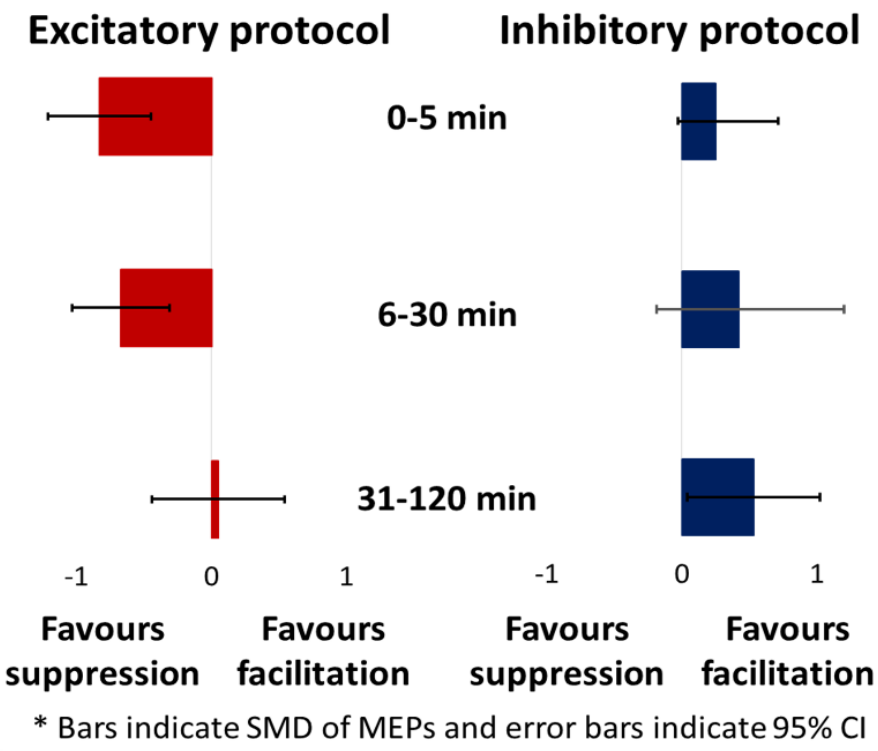

* Bars indicate SMD of MEPs and error bars indicate 95% CI

A meta-analysis of 25 studies indicated that two blocks of excitatory non-invasive brain stimulation at the primary motor cortex produced a homeostatic response between 0 and 30 minutes post protocols, when compared with a single-stimulation block. In contrast, two blocks of inhibitory non-invasive brain stimulation did not produce a homeostatic response. Protocols used to investigate homeostatic response differ greatly in terms of the type of non-invasive brain stimulation, time of application, and interval duration between blocks.