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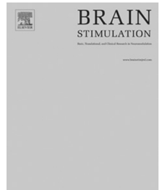

Consensus Paper: Probing Homeostatic Plasticity of Human Cortex With Non-invasive Transcranial Brain Stimulation

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ABSTRACT

Homeostatic plasticity is thought to stabilize neural activity around a set point within a physiologically reasonable dynamic range. Over the last ten years, a wide range of non-invasive transcranial brain stimulation (NTBS) techniques have been used to probe homeostatic control of cortical plasticity in the intact human brain. Here, we review different NTBS approaches to study homeostatic plasticity on a systems level and relate the findings to both, physiological evidence from *in vitro* studies and to a theoretical framework of homeostatic function. We highlight differences between homeostatic and other non-homeostatic forms of plasticity and we examine the contribution of sleep in restoring synaptic homeostasis. Finally, we discuss the growing number of studies showing that abnormal homeostatic plasticity may be associated to a range of neuropsychiatric diseases.

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Throughout life the brain flexibly and quickly adapts to environmental changes while at the same time maintaining a relatively stable equilibrium of neural activity over time. At the neural level, synapses can dynamically express lasting changes in synaptic efficacy, long-term potentiation (LTP) or long-term depression (LTD), in response to a change in presynaptic activity [1]. The threshold for induction of LTP and LTD is flexibly adjusted to the level of postsynaptic activity by homeostatic mechanisms [2]. These adjustments of plasticity prevent excessive expression of LTP or LTD and keep neural activity within a useful dynamic range [3,4].

In humans, a range of non-invasive transcranial brain stimulation (NTBS) techniques has been successfully used to induce cortical plasticity [5–8]. Research has mainly focused on the motor hand area (M1-Hand) and its fast-conducting descending projections to the contralateral hand because M1-Hand can be easily targeted with NTBS due to its relatively superficial position close to the surface of the convexity of the cerebral hemisphere. Moreover, NTBS-induced corticomotor plasticity can be readily probed by measuring the amplitude of motor evoked potentials (MEP) in contralateral hand muscles, although the mechanism of activating corticospinal neurons is complex and not yet fully understood [9]. Several NTBS protocols have been shown to be capable of inducing shifts in corticomotor excitability as indexed by changes in mean MEP amplitude. These changes can outlast the stimulation period for minutes to hours [10], yet both, the magnitude and direction of these excitability changes, display substantial inter-individual variability [11–17]. Depending on the direction of the amplitude changes, these lasting excitability changes have been labeled as

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Definition Box

Metaplasticity: 'plasticity of synaptic plasticity'
Metaplasticity is a higher-order form of synaptic plasticity. The term was originally introduced by W.C. Abraham and M.F. Bear [27]. It refers to synaptic or cellular activity that primes the ability to induce subsequent synaptic plasticity, such as long-term potentiation (LTP) or depression (LTD). The priming event does not necessarily cause a change in the efficacy of normal synaptic transmission. Metaplasticity can be homeostatic or non-homeostatic.

Homeostatic plasticity: 'plasticity stabilizing synaptic plasticity'
The term homeostatic plasticity refers to a range of plasticity mechanisms that stabilize neuronal activity [24]. Homeostatic plasticity counteracts the destabilizing influence of synaptic plasticity and thus, stabilizes neural activity within a physiologically meaningful range. Homeostatic mechanisms can be metaplastic or non-metaplastic.

LTP-like or LTD-like effects [8]. In analogy to homeostatic metaplasticity at the neuronal level, it has been shown that the LTP- and LTD-like changes are subject to homeostatic control. Here, we review the use of NTBS to non-invasively investigate the homeostatic regulation of regional cortical excitability and relate this line of research to homeostatic plasticity described at the neuronal level in invasive non-human animal studies.

Basic principles of synaptic plasticity

The mammalian cortex expresses a wealth of functional and structural mechanisms to change its function in response to experience and use [18]. Functional mechanisms often involve the modification of existing synapses and multiple forms of synaptic plasticity have been demonstrated *in vitro* and in vivo in excitatory and inhibitory cortical synapses [19–21]. Synapses can strengthen (LTP) or weaken (LTD) their efficacy (i.e., synaptic strength) in response to increases or decreases in their activity and in accordance with Hebb's famous principle of cell assembly [22–25]. Synaptic plasticity is complemented by other forms of plasticity, including plasticity of intrinsic cellular excitability [2,26,27]. These functional mechanisms go hand in hand with structural plasticity, including the formation, removal, and remodeling of synapses and dendritic spines [28]. The abundance of plasticity mechanisms in the mammalian neocortex highlights the changeability of cortical neurons. A critical question is how these multiple processes are integrated at the level of a synapse, a single neuron, intracortical microcircuits, and interacting brain systems. The complexity of mechanisms causing synaptic and cellular plasticity renders it difficult to link plasticity-induced change at the regional or system level to specific synaptic or cellular mechanisms. Yet it is likely that plastic processes at the regional or systems level nevertheless follow the same general principles.

Synaptic plasticity provides a mechanism for learning and enables neurons to dynamically modulate their synaptic strength by relating it to other inputs the cell receives at the same time [29]. Synaptic plasticity provides an efficient positive feedback mechanism, which enforces (LTP) or weakens (LTD) synaptic transmission [30]. At many glutamatergic synapses, the magnitude and temporal dynamics of activity-induced Ca^{2+} influx in the post-synaptic neuron determines whether a given level of presynaptic activity induces LTP or LTD. A fast and large increase in Ca^{2+} triggers LTP, whereas a moderate but more sustained Ca^{2+} influx gives rise to LTD [1,31–34]. The existence of distinct thresholds for LTP and LTD induction that are determined by the dynamics of Ca^{2+} concentrations in the post-synaptic neuron has been nicely illustrated by experiments in rat visual cortex: Artola and coworkers pharmacologically manipulated the level of post-synaptic depolarization by local application of the gamma-aminobutyric acid A (GABAa) receptor antagonist bicuculline. The pharmacological manipulation revealed that the same tetanic stimulation protocol induced either LTP or LTD depending on the level of post-synaptic depolarization: LTD was induced when depolarization exceeded a critical level, but still stayed below the threshold for LTP induction [35]. This study showed that the induction and direction of synaptic plasticity depends on the excitability of the post-synaptic neuron at the time of stimulation.

Homeostatic plasticity

The positive feedback nature of synaptic plasticity that allows the 'rich to get continuously richer' in the case of LTP and 'the poor to get poorer' in the case of LTD [30] challenges the stability of neural networks [1–3,24]: "Unsupervised" synaptic plasticity has the inherent risk to induce extreme neural states, causing excessive firing (in the case of uncontrolled LTP) or complete silencing of neural activity (in the case of uncontrolled LTD). An extensive body of research has demonstrated that a multitude of regulatory cellular mechanisms counteracts the 'runaway' effect of synaptic plasticity. Like LTP and LTD induction many of these mechanisms are triggered by an activity dependent change in intra-cellular Ca^{2+} levels [2,3,24,30,36]. This form of plasticity, commonly referred to as homeostatic plasticity, complements synaptic plasticity and plays a role in stabilizing mean neural activity around a set point within a physiologically reasonable dynamic range.

Net neuronal excitability depends on the interaction between intrinsic firing properties of the neuron and synaptic inputs. Therefore, homeostatic plasticity can be achieved by two fundamentally different mechanisms: synaptic homeostasis regulates excitability by up- or down-regulating synaptic strength, whereas intrinsic homeostasis shifts the relationship between synaptic input and firing by controlling intrinsic excitability [30] (Fig. 1). Even though there is ample evidence that both mechanisms coexist, it is not completely clear to what extent they serve different functions in stabilizing neural circuits and how particular firing patterns or activity levels call the appropriate homeostatic mechanism into action [37–39].

A theoretical model for homeostatic plasticity

Over 30 years ago Bienenstock, Cooper and Munro proposed a theory of how Hebbian plasticity is homeostatically regulated depending on experience-dependent modifications in post-synaptic neuronal activity. The Bienenstock–Cooper–Munro (BCM) theory postulates a "sliding threshold" for bidirectional synaptic plasticity [40,41], predicting that the thresholds for induction of LTP and LTD are dynamically adjusted to the integrated level of previous post-synaptic activity. According to the BCM theory, a history of low post-synaptic activity will lower the synaptic modification threshold for future LTP induction and increase the threshold for LTD. Conversely, a history of high synaptic activity will shift the modification threshold favoring the induction of LTD and increase the threshold for LTP (Fig. 2). The BCM theory has become the most influential model of heterosynaptic homeostatic plasticity and has guided experimental work throughout the last three decades. Even though the BCM theory was first introduced to account for experimental observations in the visual cortex, evidence for a 'sliding threshold' regulating the range of synaptic modification has

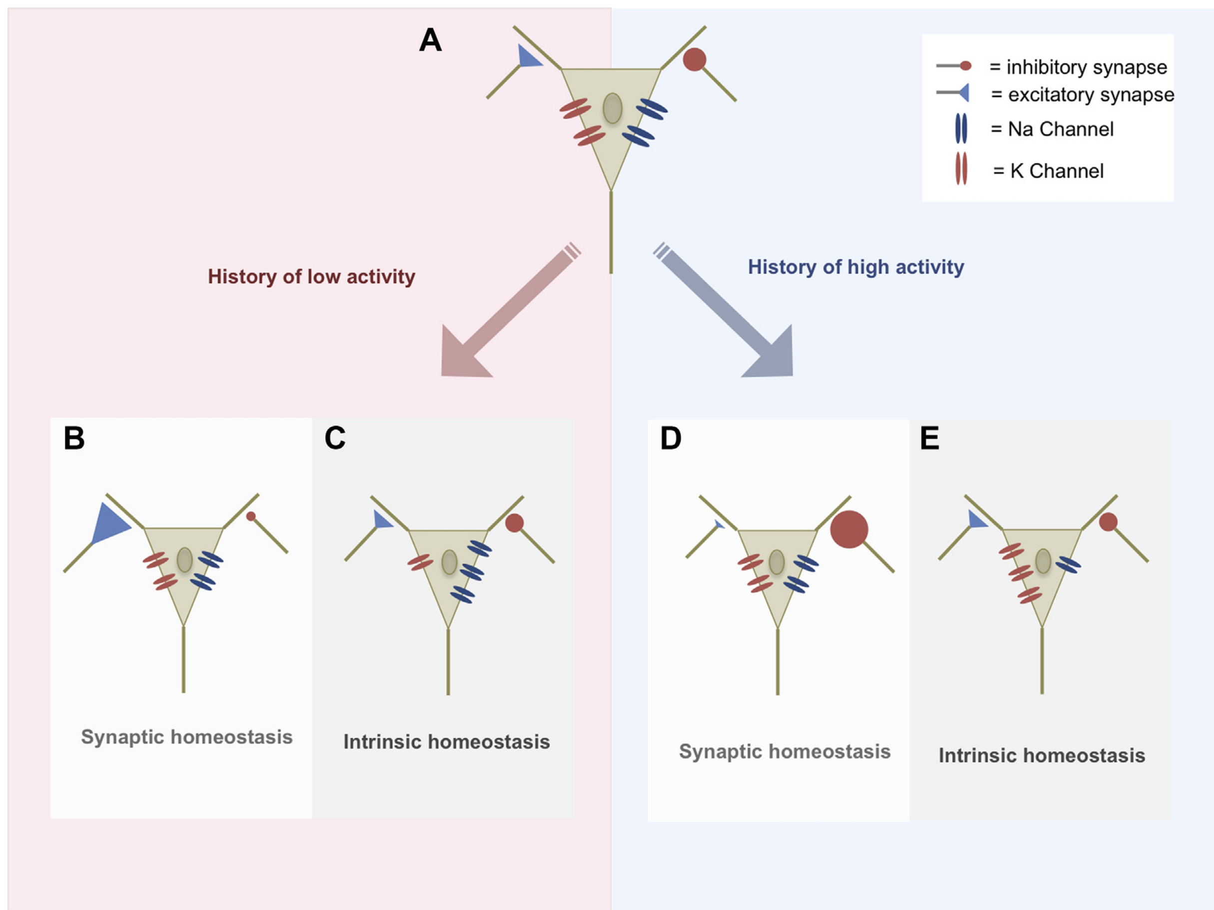

Figure 1. Shows two essentially different mechanisms for the homeostatic regulation. (A) Neuronal activity is governed by both the balance of voltage-gated sodium (Na+) and potassium (K+) channels regulating intrinsic excitability and the weight of excitatory and inhibitory synapses. Neurons react to prolonged sensory deprivation either by increasing the weight of excitatory inputs synaptic homeostasis) (B) or by increasing the amount of inward voltage-dependent currents (intrinsic homeostasis) (C) whereas they react to prolonged sensory activity by increasing the weight of inhibitory inputs (synaptic homeostasis) (D) or by increasing the amount of outward voltage-dependent currents (intrinsic homeostasis) (E).

been obtained in numerous animal and human experiments [42–45] and the rule of a 'sliding threshold' has been established as a key feature of homeostatic plasticity in many brain regions [40].

The threshold for LTP and LTD induction is also modulated under physiological conditions [46,47]. A seminal study by Rioult-Pedotti et al. showed that motor skill learning shares common mechanisms with LTP in the primary motor cortex (M1): when rats had been trained for 5 days on a skilled reaching task, the trained M1 expressed less LTP and more LTD as opposed to the untrained M1 of control rats [48]. This finding shows that the ability to induce LTP and LTD is adjusted by previous learning experience, rendering the induction of LTP more difficult after intensive training.

Approaches to study plasticity in the intact human cortex

The basic mechanisms of plasticity have been primarily investigated *in vitro*. In slice preparations, LTD or LTP are commonly induced by repeated tetanic stimulation of the presynaptic neuron: at many sites, low-frequency stimulation (1–3 Hz) leads to LTD [49] whereas trains of high-frequency stimulation elicits LTP (≥20 Hz) [50]. However, these *in vitro* studies need to be complemented by in vivo studies in animals and humans to probe the functional relevance of synaptic and homeostatic plasticity. This motivates the use of non-invasive transcranial brain stimulation to study plasticity in the intact human cortex.

A range of NTBS protocols have been established over the years to study cortical plasticity [7]. Using stimulation parameters similar to those found effective in slice preparations, both effects reminiscent of early stage LTP and LTD can be observed in the intact human brain [6,51]. Induced plasticity is commonly tested in the fast-conducting corticospinal projections by applying to the M1-Hand. The plasticity is usually probed by measuring the mean amplitude of the motor evoked potential (MEP) with single-pulse transcranial magnetic stimulation (TMS) at constant stimulus intensity before and several times after application of the plasticity-inducing NTBS protocol. Serial measurements of mean MEP amplitude offer a feasible and quantitative way to test changes in excitability levels of the corticomotor output pathway. However, it should be noted that the MEP represents a complex composite measure and its amplitude is influenced by multiple physiological factors including the excitability of neural circuits at both the cortical and spinal level [9]. Finally, MEP measurements before and after a plasticity-inducing NTBS protocol restrict the investigation of cortical plasticity to the M1 and any extrapolation of the observed plasticity patterns to other cortical areas need to be made with great caution.

When applying regular trains of repetitive TMS (rTMS), high-frequency rTMS using frequencies of 5 Hz or higher [52] increase excitability in the stimulated M1 [7,53,54], while low-frequency rTMS at a frequency of around 1 Hz [55] decrease corticomotor

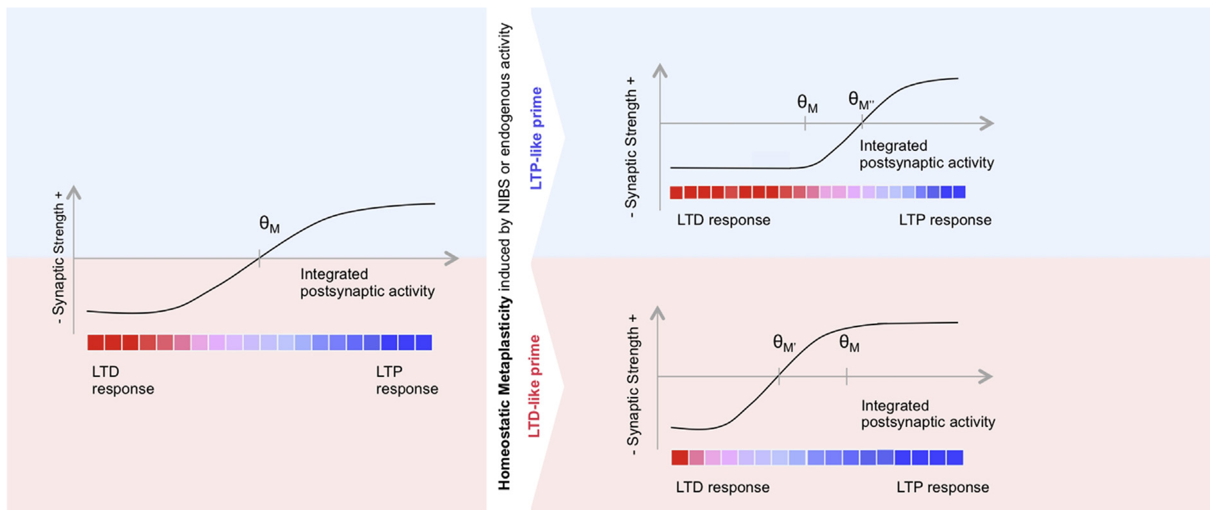

Figure 2. Shows the basic concept of metaplasticity following the BCM theory. The modification threshold (θ_M), the crossover point from LTD to LTP, is not fixed but varies as a function of post-synaptic activity. Using an LTP-like prime will shift the modification threshold ($\theta_{M''}$) to the right along the *x*-axis, while using an LTD-like prime will shift the modification threshold ($\theta_{M'}$) to the left on the *x*-axis. On the color bar, red codes an LTD response while blue codes an LTP response. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

excitability. Patterned rTMS protocols consist of short high-frequency bursts separated by longer inter-burst intervals. They are inspired by patterned burst stimulation protocols applied in cortical slices to induce LTP or LTD [12,46]. Several patterned rTMS protocols have been established, such as patterned paired-pulse protocols [56,57], theta-burst stimulation (TBS) [12,15,58] and quadripulse stimulation [12,15]. The most commonly used TBS protocol applies 50 Hz bursts consisting of three TMS pulses at a burst repetition rate of 5 Hz. TBS of M1 induces generally a lasting increase in MEP amplitude when given intermittently (referred to as intermittent TBS or iTBS), while continuous theta-burst stimulation (cTBS) induced a lasting reduction in MEP amplitude. Quadripulse stimulation (QPS) applies four-pulse bursts at a lower repetition rate than TBS, namely at 0.2 Hz. QPS of M1 at very short inter-stimulus intervals (1.5–10 ms, QPS_{short}) has been shown to increase mean MEP amplitude while QPS of M1 at inter-stimulus intervals of ≥30 ms (QPS_{long}) decreases MEP amplitude [59].

Other repetitive TMS protocols employ associative stimulation of two neural substrates in a temporally coordinated manner. These paired association stimulation (PAS) protocols use a temporal learning rule in analogy to spike-timing dependent plasticity (STDP). For STDP, the direction of plasticity (LTP or LTD induction) depends on the precise timing of pre- and post-synaptic stimulation. The classic PAS protocol pairs peripheral electrical stimulation with single-pulse TMS of contralateral M1 and repeats these stimulus pairs at a low frequency of 0.1 Hz [14,60–62]. More recent cortico-cortical PAS protocols use dual-site TMS targeting two cortical areas [61–64]. Corticomotor excitability increases after classical PAS, if the afferent stimulus reaches M1 before or at the same time as TMS-induced M1 stimulation. Conversely, corticomotor excitability is reduced, if the afferent stimulation reaches M1 after excitation by TMS.

Also, transcranial direct current stimulation (TDCS) can be used to induce lasting bidirectional excitability changes in the human cortex. By applying a constant low current via small electrodes TDCS can either de- or hyperpolarize a neuron's resting membrane potential: anodal TDCS (aTDCS) is thought to depolarize neurons and thereby increases corticomotor excitability, whereas cathodal TDCS (cTDCS) hyperpolarizes the resting membrane, causing a decreased corticomotor excitability [16].

For some but not all of these protocols, it has been shown that changes in MEP amplitude after NTBS of M1 display some features that are reminiscent of LTP or LTD at the synaptic level. The modulation of excitability outlasts stimulation time by at least 30 min, depends on NMDA receptor activity, and originates not from subcortical or spinal excitability changes but from a cortical level [7,53,54]. Therefore the lasting increases or decreases in corticomotor excitability are often called ‘LTP-like’ or ‘LTD-like’ plasticity. It is important to note though that despite the resemblance between NTBS-induced ‘LTP-like’ or ‘LTD-like’ effects and synaptic LTP or LTD, there are apparent differences: TMS activates a substantial number of axons and leads to a massive stimulation of both inhibitory and excitatory cells, whereas synaptic activity is limited to a very small number of connections in classical *in vitro* studies of LTP and LTD [65,66]. Therefore, NTBS-induced plasticity is likely a mixture of plasticity induction in a number of different sets of excitatory and inhibitory synapses. Indeed, a simple equalization of synaptic effects and the NTBS induced after effects is certainly an oversimplification [67]. This is why, in the following text, the terms “inhibitory” (LTD-like) or “facilitatory” (LTP-like) are only describing the final outcome of a protocol on cortical excitability. In fact, a “facilitatory” protocol could be caused by a decrease in inhibition instead of up-regulated excitation. Another important point to note is that the knowledge about LTP- and LTD-like effects is nearly exclusively based on NTBS studies targeting M1 and these effects can not be easily extrapolated to other cortical areas.

Testing homeostatic plasticity with NTBS targeting human M1

The BCM theory predicts that high levels of prior activity favor the induction of LTD, while low levels of prior activity favor LTP [68]. In the human M1, homeostatic patterns have been tested using a priming test design, which consists of a “priming” NTBS protocol that triggers a homeostatic response and a “test” NTBS protocol that captures the homeostatic response (for recent review, [69]). The first study that showed bidirectional homeostatic-like plasticity in M1 combined a TDCS protocol to prime the subsequent response of M1 to a 1 Hz rTMS test protocol: In separate sessions, facilitatory aTDCS, inhibitory cTDCS, or sham stimulation were applied prior to a 15 min treatment session of low-intensity 1 Hz TMS. After a

facilitatory aTDCS priming session, the subsequent 1 Hz rTMS test session had a marked LTD-like effect, causing a reduction in corticomotor excitability. Conversely, inhibitory priming with cTDCS flipped the effect of the very same 1 Hz rTMS test session, which now produced an increase in corticomotor excitability. When preconditioned by sham TDCS, the 1 Hz protocol did not have an effect on corticomotor excitability [70]. This bidirectional modulation of the subsequent 1 Hz rTMS session by the polarity of TDCS strongly suggests that TDCS triggered a homeostatic mechanism in the primed M1 according to the BCM theory. The observation that in the same individual the same NTBS protocol caused either LTP- or LTD-like effects depending on the history of neural activity (manipulated by TDCS priming) questions the validity of a rigid distinction in “facilitatory” or “inhibitory” NTBS protocols, as if these attributes were stable for a given NTBS protocol and robust against the physiological context.

Many other studies have reported similar homeostatic ‘priming’ effects on the plasticity-inducing properties of various NTBS protocols [71–76]. The homeostatic pattern that emerged in these studies showed that the priming NTBS would boost the effect of subsequent test NTBS protocol only if the priming NTBS induced the opposite effect on excitability as the test NTBS. Conversely, the priming NTBS would weaken or reverse the effect of subsequent test NTBS, if it had the same effect on excitability as the test NTBS (Fig. 2). A homeostatic reversal of the excitability effect has also been observed when the same NTBS protocol was applied consecutively [73], when two NTBS protocols were applied simultaneously [74], when doubeling the duration of stimulation [77,78] or when omitting breaks in the stimulation [79].

These experiments point to the importance of the interval between priming and test NTBS. Within the framework of the BCM theory, this implies that the temporal dynamics of the primed change in post-synaptic neural activity is critical to shift the sliding threshold in a homeostatic fashion. Yet only one study has tried to systematically investigate the time dependency of homeostatic plasticity by systematically varying the interval between priming and test NTBS and assess the impact of this manipulation on the induction of a homeostatic response [80]. Fricke and coworkers paired two identical 5 min sessions of TDCS. Priming and test TDCS sessions were separated by 0, 3 or 30 min. When priming and test TDCS were given without a break, the TDCS effect was simply prolonged. If the two TDCS sessions were separated by 30 min, there was no priming effect on the plasticity-inducing effect of the test TDCS. Only when the test TDCS started 3 min after the end of priming TDCS, did the two TDCS protocols interact in a homeostatic fashion [80]. This study stresses that there might be a critical time window during which a homeostatic response pattern emerges after priming NTBS. The importance of the interval between NIBS protocols has also been highlighted by several studies showing a (non-homeostatic) prolongation of the inhibitory effects of cTBS when the cTBS protocol is repeated after a 10–15 min break [58,81]. The studies cited above show that the interval between repeated NIBS protocols could have versatile effects on NIBS-induced plasticity. It is, however, important to keep in mind that critical time windows are likely to differ among different priming NIBS protocols [58,81]. A closely related factor that has never been systematically investigated is the “integration time” for the record of prior activity. This has important implications for both the duration of the prime and the interval between prime and test protocol: Am infinite integration of prior activity would prohibit effects caused by short-term priming protocols, whereas a very short integration time would allow extremely short priming interventions to be effective. A better understanding of the homeostatic integration time might be relevant to understand why some priming-test

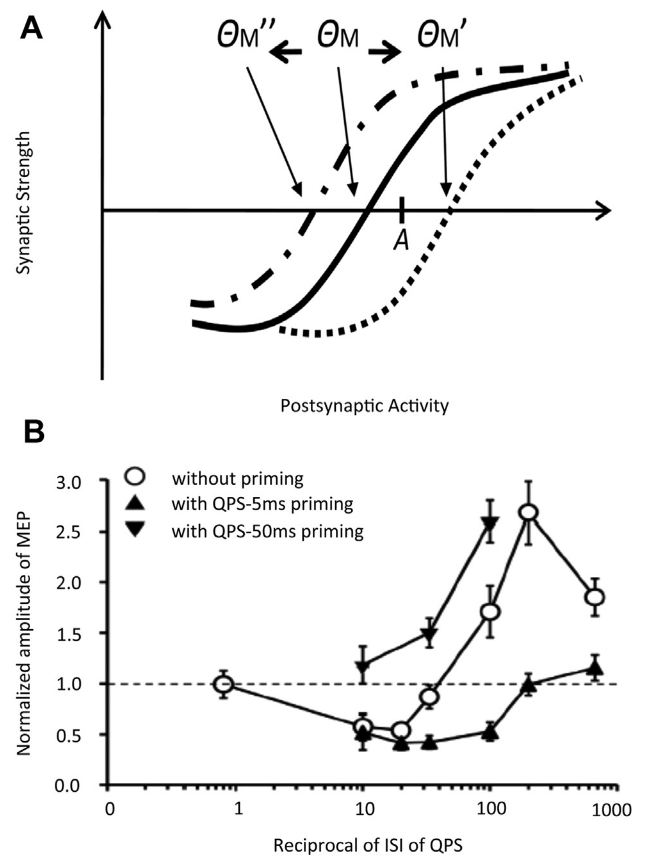

Figure 3. Shows the bidirectional shift of the LTP-LTD induction curve predicted by the BCM theory (A) and induced by a priming QPS session (B). (A) The LTD–LTP crossover point (θ_M) slides to the right on the *x*-axis if the preceding neuronal activity is high ($\theta_{M'}$), and to the left if preceding activity is low ($\theta_{M''}$). (B) QPS with priming over *M*1. The normalized amplitudes of MEP at 30 min post conditioning as a function of the reciprocal of ISI of QPS (in Hertz) with and without priming over *M*1. QPS-5 ms priming over *M*1 resulted in a rightward shift, whereas QPS-50 ms priming produced a leftward shift of the “LTP-LTD induction curve”. The *x*-axis is logarithmically scaled. (Reprinted from Hamada, M. and Ugawa, Y., *Restor. Neurol. Neurosci.*, 28, 419, 2010. With permission from IOS Press and the original authors.)

protocols do not cause homeostatic effects (in these cases the integration time might have been too long).

A relatively new TMS protocol that has proven to be especially helpful for investigating homeostatic effects in M1 is quadruple-pulse stimulation (QPS). QPS induces changes in corticomotor excitability by applying trains of four-pulse bursts with an inter-burst interval of 5 s [59]. Depending on the ISI that separates the four pulses, QPS induces either an LTP-like increase in corticomotor excitability or an LTD-like decrease in corticomotor excitability. An “LTP-LTD induction curve” can be derived by plotting the LTP- or LTD-like effects of the QPS (*x*-axis) against the frequency of the four-pulse burst [15]. Hamada et al. (2008) showed that this LTP-LTD induction curve can be bi-directionally shifted by a priming QPS protocol (Fig. 3B): A priming QPS with an LTP-inducing high-frequency burst (i.e., QPS with a short ISI of 5 ms) switches the “normal” LTP-like effect of most QPS protocols with short ISIs into an LTD-like effect. An LTP-like effect only persisted for the test QPS protocols with the shortest ISIs. In other words, the priming QPS caused a homeostatic rightward shift of the LTD/LTP induction curve. The opposite effect was produced when an LTD-inducing QPS prime with a low-frequency burst (i.e., QPS with a long ISI of 50 ms) was used. In this case, priming QPS switched the “normal” LTD-like effect of most QPS protocols with long ISIs into an LTP-like effect, causing a homeostatic

Table 1
Summarizes the results of different studies of homeostatic and non-homeostatic plasticity.

		Study	Priming/Test	Main findings
Homeostatic plasticity	Primary motor cortex	Siebner et al. (2004) [70]	aTDSC/1 Hz rTMS cTDCS/1 Hz rTMS	Shows a full homeostatic interaction between priming and an inhibitory test protocol.
		Iyer et al. (2003) [71]	6 Hz rTMS/1 Hz rTMS	The facilitatory priming increases the LTD-like effect of the 1 Hz test protocol.
		Lang et al. (2004) [72]	aTDCS/5 Hz rTMS cTDCS/5 Hz rTMS	One of the first studies to show a full homeostatic interaction between priming and an facilitatory test protocol.
		Muller et al. (2007) [73]	PAS_{LTP}–PAS_{LTP} PAS_{LTD}–PAS_{LTP}	A PAS_{LTD} prime increases the LTP-like effect of the test PAS_{LTP}, an PAS_{LTP} prime decreases the LTP-like effect of the test PAS_{LTP}.
		Nitsche et al. (2007) [74]	aTDCS/PAS_{LTP} cTDCS/PAS_{LTP} either as prime/test or *concurrently*	A homestatic effect was only observed when the protocols where given concurrently when given as a prime/test prtocool bith TDCS protocols did increase the facilitatory PAS effect.
		Todd et al. (2009) [75]	2 Hz or 6 Hz rTMS/cTBS iTBS/cTBS	The rTMS priming did not effect the cTBS effect, but the iTBS prime did increase the ingibitory effect of cTBS.
		Ni et al. (2014) [76]	cTBS(short)/PAS_{LTP} cTBS(short)/PAS_{LTD}	The cTBS prime enhanced the PAS_{LTP} facilitation and led to reduced SICI and LICI and abolished the PAS_{LTD} inhibition without change to intracortical circuits.
		Gentner et al. (2008) [77]	Muscle activity/cTBS (20 s) cTBS (40 s)	Short cTBS did only induces an LTD-like effect when primed by muscle activity, when the protocol is prolonged, no activity prime is needed to induce an LTD. like effect.
		Gamboa et al. (2010) [78]	cTBS (double duration) iTBS (double duration)	Both iTBS and cTBS reverse their effect when given for double the standart duration.
		Rothkegel et al. (2010) [79]	5 Hz rTMS protocol with or without breaks	When omitting breaks in a standart 5 Hz protocol the facilitation effect is turned to an inhibition.
		Fricke et al. (2011) [80]	aTDCS/aTDCS cTDCS/cTDCS at different intervals	When the protocols are given without a break (doubling their length) a prolongation of the ‘test’ effect is seen, when the break is 20 min the protocols do not interact but when given with a 3 min break between test and prime there is a homeostatic interaction.
		Hamada et al. (2008) [59]	QPS/QPS	High-freq. QPS priming causes a homeostatic rightward shift of the LTD/LTP induction curve. Low-freq. QPS priming induces the opposite effect (homeostatic leftward shift of the LTP-LTD induction curve).
	Intracortical networks	Doeltgen et al. (2011) [86]	iTBS/cTBS	No effect of priming on SICI and SICF.
		Fricke et al. (2011) [80]	aTDCS/aTDCS cTDCS/cTDCS at different intervals	No effect of priming on SICI and SICF.
		Siebner et al. (2004) [70]	aTDCS or cTDCS/1 Hz rTMS	No effect of priming on SICI and SICF.
		Murakami et al. (2012) [88]	cTBS/cTBS iTBS/iTBS cTBS/iTBS iTBS/cTBS	SICI is only altered when prime and test protocol are identical.
	Interregional cortical networks and outside M1	Potter-Nerger et al. (2009) [89]	1 Hz rTMS/PAS_{LTD} 5 Hz rTMS/PAS_{LTP}	1 Hz rTMS to the dPMC prior to a PAS_{LTD} protocol over M1 increases M1 excitability. 5 Hz rTMS to the dPMC prior to a PAS_{LTP} protocol over M1 suppressed M1 excitability.
		Hamada et al. (2009) [44]	QPS/QPS 1 Hz rTMS/	Homeostatic modulation of M1 excitability when a priming QPS prime is given to the SMA
		Ragert et al. (2009) [90]	1 Hz rTMS/iTBS	Homeostatic modulation of M1 excitability when a priming rTMS prime is given to the contralateral M1.
		Bliem et al. (2008) [91]	PAS/20 Hz HFS	Homeostatic plasticity in primary sensorimotor cortex.
		Gartica Tossi et al. (2014) [92]	5 Hz rTMS/20 Hz HFS	Homeostatic plasticity in primary sensorimotor cortex.
		Bocci et al. (2014) [93]	TDCS/rTMS	Homeostatic plasticity in primary visual cortex.

Interaction of motor learning and homeostatic plasticity		Ziehmann et al. (2004) [8]	Thumb abduction/PAS_{LTP} Thumb abduction/PAS_{LTD}	Motor learning can act as a priming intervention for subsequent NIBS and induce homeostatic effects.
		Lepage et al. (2012) [95]	Motor observation/PAS_{LTP}	Observation of a motor training task is sufficient to prevent subsequent induction of LTP-like PAS effects.
		Rosenkranz et al. (2007) [85]	Novel vs. well-practiced thumb abduction/PAS	The effect of motor learning as a 'primer' depends on the learning phase: homeostatic effects only observed when 'priming' involved a novel motor task.
		Elahi et al. (2014) [98]	PAS/thumb abduction	NIBS can act as a primer on motor learning.
		Jung et al. (2009) [99]	PAS_{LTD}/thumb abduction task PAS_{LTP}/thumb abduction task	PAS given 90 min before the learning task shows a "classic" homeostatic interaction, when given directly before the task both PAS_{LTP} and PAS_{LTD} facilitate learning.
		Teo et al. (2011) [100]	iBTS/thumb abduction	Priming with iTBS boosts performance in a subsequent ballistic motor learning task. The effect of priming iBTS can be blocked by nicotine administration.
		Kuo et al. (2008) [101]	TDCS/serial reaction time task	No homeostatic effect between TDCS and motor learning found.
		Rosenkranz et al. (2014) [111]	Hand immobilization/PAS	Eight hours of hand immobilization significantly reduce the inhibitory effects of PAS-10 ms while enhancing the facilitatory effects of PAS-25ms.
Non-homeostatic plasticity		Nitsche et al. (2003) [102] Anatal et al. (2004) [103] Reis and Fritsch (2011) [105] Stagg et al. (2011) [107]	Concurrent motor learning and TDCS	'Gating': studies have reported reinforcing effects between voluntary motor activity and TDCS when applied *concurrently*.
		Devendahl et al. (2010) [114]	0.1 Hz rTMS/PAS	'Anti-gating': a very low-frequency prime abolished the ability to induce LTP- and LTD-like with subsequent PAS
		Huang et al. (2010) [119]	iTBS/cTBS cTBS/iTBS	The LTP-like effect induced by iTBS is abolished (de-potentiated), when a short train of cTBS followed the protocol. The LTD-like effect induced by cTBS is abolished (de-depressed), if followed by a short train of iTBS.
		Ni et al. (2014) [76]	PAS_{LTP}/cTBS (short) PAS_{LTD}/cTBS (short)	De-potentiating effect of a short inhibitory follow-up.
		Goldsworthy et al. (2014) [120]	cTBS/voluntary contraction	De-depressing effect on a short facilitatory follow up on an inhibitory protocol.
		Cantarero et al. (2013) [96] Cantarero et al. (2013) [97]	Motor learning task/cTBS	Occlusion of LTP-like effect and motor skill retention after short inhibitory protocol.
		Lepage et al. (2012) [95]	Motor observation/PAS_{LTP}	Observation of a motor training task is sufficient to prevent subsequent induction of LTP-like PAS effects.
Homeostatic Plasticity in pathological states	Focal hand dystonia	Quartarone et al. (2005) [138]	TDCS/1 Hz rTMS	The 'homeostatic' response pattern of healthy controls is absent in the affected hand of writer's cramp patients.
		Kang et al. (2011) [139]	PAS_{LTP}–thumb abduction PAS_{LTD}–thumb abduction	In contrast to healthy controls the writer's cramp patients do not show any modulation of learning-dependent plasticity.
	Parkinson's disease	Huang et al. (2011) [148]	TBS	Patients with levodopa-induced dyskinesia showed normal potentiation but were unresponsive to the de-potentiation protocol.

leftward shift of the LTP-LTD induction curve. The bidirectional shifts in the LTP-LTD induction curve nicely demonstrated the existence of a "sliding modification threshold" as predicted by the BCM theory [45]. Table 1 summarizes the results of different studies of homeostatic plasticity and other forms of metaplasticity.

Homeostatic plasticity in cortical networks

Intra-cortical homeostatic plasticity in the motor cortex

The MEP is a complex measure of corticospinal excitability and is influenced by spinal excitability as well as by various intracortical circuits projecting onto the corticospinal motor neurons [9,81,82]. This means that homeostatic plasticity might not only affect corticospinal neurons directly but might also act on intracortical circuits within M1.

Intracortical excitability can be measured by using paired-pulse TMS paradigms, which apply a conditioning (CS) and test stimulus (TS) through the same coil [83]. While several studies have shown motor-training induced plasticity of these intracortical inhibitory circuits [84,85], very few studies have investigated homeostatic effects in intracortical circuits. The results of these studies are not yet fully conclusive: Several studies using facilitatory and inhibitory TDCS primed 1-Hz rTMS [70], facilitatory–facilitatory TDCS and inhibitory–inhibitory TDCS [80] and iTBS primed cTBS [86] found no consistent homeostatic changes in intracortical inhibitory GABAAergic circuits in M1 underlying short interval intracortical inhibition (SICI) [87]. A more systematic investigation of homeostatic effects in intracortical inhibitory circuits demonstrated homeostatic plasticity-like effects on SICI: Murakami and colleagues [88] applied 'facilitatory' intermittent theta-burst stimulation (iTBS) or 'inhibitory' continuous theta-burst stimulation (cTBS) to induce a homeostatic response in intracortical inhibitory circuits. They found that a priming TBS protocol altered the responsiveness of the inhibitory SICI circuits to a test TBS only when the second TBS protocol was identical to the priming protocol (iTBS → iTBS or cTBS → cTBS). The normal direction of TBS-induced SICI after-effects was reversed by priming with identical TBS, suggesting homeostatic regulation of excitability in inhibitory circuits. However, even in that study homeostatic metaplasticity was less consistently expressed in the intracortical inhibitory circuits than in the excitatory corticospinal pathway. In contrast to homeostasis in the corticospinal pathway alternating TBS protocols (the iTBS → cTBS or cTBS → iTBS) failed to trigger a homeostatic response in inhibitory circuits.

Facilitatory circuits within M1 have been even more sparsely studied than intracortical inhibition and no consistent homeostatic effects have been demonstrated so far on intracortical facilitation [80,86]. The few data presently available suggest that homeostatic plasticity is less consistently expressed. Alternatively, homeostatic plasticity in intracortical circuits upstream to the corticospinal motor neuron may simply be more difficult to capture with MEP measurements. Subtle homeostatic changes may have an effect size that remains within the noise level of normal fluctuations in MEP amplitude. More robust homeostatic effects in intracortical circuits are likely to be paralleled by concurrent homeostatic changes in the corticospinal neurons. In that case, the presence of homeostatic changes in MEP amplitude evoked by single-pulse TMS may mask homeostatic effects in upstream intracortical circuits as probed with double-pulse TMS.

Inter-cortical homeostatic plasticity

Homeostatic interactions can also occur in interregional networks. Several studies have shown that a homeostatic response can be elicited in M1 when the priming protocol is given over a secondary motor area to activate cortico-cortical projections to M1. Potter-Nerger and coworkers demonstrated homeostatic priming on PAS to left M1 after rTMS priming was applied to ipsilateral dorsal premotor cortex (dPMC). Thus, inhibitory 1 Hz rTMS of dPMC prior to an inhibitory PAS protocol over M1 increased M1 excitability, whereas facilitatory 5 Hz rTMS of dPMC prior to a facilitatory PAS protocol over M1 suppressed M1 excitability [89]. Homeostatic modulation of M1 excitability was also demonstrated when a priming QPS session was given to the supplementary motor area [44] or when a priming 1 Hz rTMS was given to the contralateral M1 [90]. Taken together, these findings indicate that homeostatic interactions can be elicited through different input channels in the human M1.

Studies using other measures of cortical excitability, such as somatosensory evoked potentials (SSEP) or visual evoked potentials (VEP), have shown that homeostatic metaplasticity can also be expressed in other cortical areas. SSEP recordings provided evidence for homeostatic plasticity in primary somatosensory cortex [91,92]. Both SSEP applied NIBS before high-frequency (20-Hz) tactile electrical stimulation of the contralateral median nerve in order to demonstrate a homeostatic response in the somatosensory cortex. In primary visual cortex, the VEP revealed a homeostatic reaction to a combined TDCS-rTMS protocol [93]. Identifying additional neurophysiological markers of brain plasticity such as recordings of TMS-evoked cortical potentials with combined TMS-EEG [94] might facilitate investigations into homeostatic effects expressed in other cortical areas.

Homeostatic plasticity and motor learning

Motor learning can induce plasticity under physiological conditions and many studies have shown that brain stimulation and motor learning can interact homeostatically. Early studies showed that a simple motor learning task could act as a 'primer' for subsequent PAS protocols. Ziemann and coworkers [8] showed that motor learning prevented the induction of subsequent LTP-like PAS effects while enhancing subsequent LTD-like effects. More recent work suggests that observation of a motor training task is sufficient to prevent subsequent induction of LTP-like PAS effects [95] and that the temporary occlusion of LTP-like plasticity after motor learning is likely to be a mechanism necessary for successful skill retention. Retention for a simple motor task after learning was proportional to the magnitude of LTP occlusion during a subsequent NTBS protocol and that the amount of occlusion was predictive of resilience against interference of subsequent learning [96,97]. Interestingly, the effect of motor learning as a 'primer' depends on the learning phase: the observed homeostatic effects on subsequent PAS protocols were only observed when 'priming' involved training a novel motor task, while 'priming' with a well-practiced task did not significantly modulate subsequent PAS [85]. Homeostatic interactions between a facilitatory PAS response and a motor learning task can also be seen if the learning task follows the PAS intervention [98].

While these studies clearly demonstrate that learning may have a homeostatic impact on plasticity induced by NTBS, the evidence for a reverse interaction, a homeostatic effect of NTBS on plasticity induced by subsequent motor learning is less consistent. According to the BCM theory, one might expect an inhibitory NTBS protocol to facilitate a subsequent motor leaning task. Jung and Ziemann [99] studied motor learning of rapid thumb abduction movements. The training session was primed with a PAS protocol which ended 0 min or 90 min before training began. When PAS was given directly before training, both the inhibitory and excitatory PAS protocol enhanced motor learning, indicating a non-homeostatic

interaction. However, the same PAS protocols given 90 min before learning gave rise to a "classic" homeostatic interaction. In that condition, excitability-decreasing PAS still had a beneficial effect on motor learning, but excitability-increasing PAS impaired motor learning. These results once again stress the importance of timing between priming and test protocols and suggest that non-homeostatic mechanisms may play a role, especially when the interval between priming stimulation and motor training is short.

Studying homeostatic plasticity in the context of motor learning is difficult, since synaptic strengthening is likely not the only factor influencing the learning rate. A more recent study found that priming with iTBS boosted performance in a subsequent ballistic motor learning task [100]. In that study, the beneficial effect of priming iTBS was blocked by the administration of nicotine. Behavioral analysis and modeling suggested that the iTBS prime facilitated performance by increasing motor output variability. The hypothesis was that the motor system could then explore the task workspace more quickly to find the optimal way to perform the task. The authors hypothesized that nicotine blocked this effect, presumably by reducing the signal-to-noise ratio in cerebral cortex [100]. This and other mechanisms may explain why other studies, which assessed the priming effects of brain stimulation on motor learning, failed to reveal homeostatic effects [101].

Many studies consistently show that NTBS protocols that are sub-threshold for inducing action potentials in the cortex, in particular TDCS, can enhance motor learning when the NTBS protocol is given concurrently with the learning task [102–107]. Although most NTBS protocols that were applied during motor training enhanced motor learning in a non-homeostatic fashion, homeostatic interaction might well occur. However, this should not be called "metaplasticity," because priming and test intervention are not separated in time [3]. An optimal exploitation of homeostatic mechanisms to boost motor learning will require a better understanding of the mechanisms by which the various NTBS protocols modulate motor learning.

It is worth mentioning, that homeostatic interactions between voluntary movement and NTBS are not restricted to motor learning. Several studies have demonstrated plasticity interactions (homeostatic and non-homeostatic) when simple voluntary muscle contractions where performed prior, during or after an NTBS protocol [77,108–110]. Also restricting movement can have a homeostatic influence on NTBS-induced plasticity: 8-h of hand immobilization did significantly reduce the inhibitory effects of PAS-10 while enhancing the facilitatory effects of PAS-25 [111].

Gating vs. homeostatic plasticity

The interactions between motor training and concurrent NTBS often follow non-homeostatic rules (i.e., the priming intervention does not have a homeostatic effect on the test procedure). A complementary mechanism by which NTBS might increase the beneficial effects of motor learning is 'gating'. Many studies have reported gating interactions between voluntary motor activity and NTBS when NTBS was applied *concurrently* with a motor task [102,103,105,107].

Gating mechanisms may also increase the efficacy of NTBS of the M1 to produce LTP-like or LTD-like effects. Gating may be provoked by several mechanisms such as increasing net calcium influx into the targeted cortical neurons, shifting intrinsic excitability of the targeted neurons (e.g. sub-threshold depolarization during anodal TDCS), or transiently suppressing the efficacy of intracortical inhibitory circuits. It has been shown that NTBS can induce acute disinhibition, thereby potentially gate the plasticity-inducing effects of NTBS. For instance, a short period of sub-threshold 5 Hz rTMS can cause a transient suppression of short-latency intracortical inhibition in the stimulated M1-HAND along with a increase in regional cerebral blood flow [52]. Further, a temporary ischemic nerve block of the distal upper limb caused acute disinhibition in the contralateral sensorimotor cortex and boosted training-induced learning of ballistic elbow flexion movements [112]. Together, these studies suggest that "gating" might play a role in determining the efficacy of a given NTBS protocol, but studies are lacking which systematically study the relationship between acute NTBS-induced disinhibition and the efficacy to induce LTP- or LTD-like effects. It is important to point out that gating is a non-homeostatic mechanism, because it does not alter the threshold for expressing LTP or LTD [7]. Yet gating may promote the induction of LTP-like effects in neural circuits targeted by NTBS or learning and indirectly facilitate a homeostatic response.

It is also important to note that not all interactions between consecutively paired protocols depend on homeostatic effects and that several forms of non-homeostatic metaplasticity have been observed using brain stimulation: A very low frequency (0.1 Hz) rTMS prime given to M1 abolished the ability to induce LTP- and LTD-like effects in the primed M1 with subsequent PAS [113,114]. The prime alone did not alter corticospinal excitability as measured by MEP amplitude, but increased short-interval and long-interval intracortical inhibition in the stimulated M1. Increased excitability of intracortical inhibitory circuits caused by the priming protocol might have prevented the PAS protocol from inducing LTP- or LTD-like changes by reducing the ability of afferent volleys, evoked by the peripheral stimulus, to interact with the TMS pulse given over M1-HAND in a Hebbian fashion. If the afferent volley has less "access" to the corticospinal excitability, potentially by reducing the output neurons due to excessive intracortical inhibition, the calcium influx in the corticospinal neurons during PAS [113,114]may drop below the threshold for inducing LTP or LTD-like plasticity. A reduction of the calcium influx caused by increased activity of intracortical inhibitory circuits does not invoke homeostatic regulation because the threshold for LTP and LTD induction is not principally shifted. Such a mechanism rather represents an 'anti-gating' effect that reduces the efficacy of NTBS without shifting the threshold for expressing LTP and LTD [113,114]. However, the notion of 'gating' and 'anti-gating' remains to be thoroughly tested in future studies.

Another non-homeostatic form of metaplasticity is de-potentiation (or de-depression). De-potentiation erases previously induced LTP (or LTD) and may be the key mechanism for retrograde inference with learning. There is ample evidence for de-potentiation and de-depression in the animal literature, which implicates this form of metaplasticity as a factor in learning reversal and forgetting [115–117]. Metaplasticity patterns resembling de-potentiation and de-depression were observed in an experiment that combined iTBS and cTBS [118]: The normal LTP-like effect induced by facilitatory iTBS was abolished (de-potentiated), when a short train of inhibitory cTBS followed the iTBS protocol. Vice versa, the LTD-like effect normally induced by a cTBS protocol was abolished (de-depressed), if followed by a short train of facilitatory iTBS. When given alone, the short TBS trains did not change corticomotor excitability. This shows that the de-potentiating (or de-depressing) protocol itself does not need to have any discernable effect when applied alone. Only when given within a certain time window after an LTP- or LTD-inducing protocol are these effects visible. The early phases of LTP and LTD induction are more vulnerable to the effect of interfering stimuli than later phases, when synaptic changes in synaptic efficacy have been stabilized [118]. Other recent studies have confirmed the de-potentiating effect of an inhibitory follow-up on facilitatory NTBS protocols [76] and the de-depressing effect on a facilitatory follow up on an inhibitory protocol [119].

This study also suggests that repeated cTBS application also seems to protect against de-depression: When pairing two cTBS protocols, separated by a 10 min-break, the induced LTD-like effect was resistant against de-depression.

These examples show that there are many non-homeostatic forms of cortical plasticity and metaplasticity that might shape the efficacy of NTBS to induce LTP- or LTD-like effects. Hence, researchers investigating metaplasticity need to be careful when labeling a modulation of NTBS-induced plasticity as "homeostatic." An effect is only likely to be homeostatic, if the priming intervention alters the LTP-LTD induction curve in a way that the changes in LTD-LTP induction threshold favor the induction of plasticity opposite to the priming protocol (Figs. 2 and 3). As mentioned earlier, the temporal relationship between the priming and test protocols is crucial for the induction of both homeostatic and non-homeostatic metaplasticity. Future studies need to explore the interplay between these non-homeostatic and homeostatic forms of cortical plasticity. Currently, there is a growing interest in therapeutic multi-session NTBS applications aiming to extend the duration of excitability changes. When designing such therapeutic protocols it is especially important to better understand possible homeostatic interactions in order to avoid creating an excitability effect in opposition to the therapeutic goal.

Mechanisms regulating metaplasticity

One of the key predictions of the original BCM theory is that the activity dependent threshold is calculated from a running time-average of post-synaptic action potential activity. More recent BCM models have, however, started to question the role of post-synaptic action potentials and focused on the time-averaged free calcium concentration as the biological signal controlling homeostatic metaplasticity [29,120]. Recent *in vitro* experiments confirmed that homeostatic plasticity in the hippocampus did not depend on somatic action potentials, but was determined by calcium release from intra-cellular stores, triggered by muscarinic acetylcholine receptors [121]. In addition to intra-cellular Ca^{2+} stores, Ca^{2+} can also enter the cell via NMDA receptors or via L-type voltage-gated Ca^{2+} channels. Homeostatic modulation of high-frequency tetanic stimulation was also observed when pharmacologically reducing Ca^{2+} via those routes [122–124].

A study combining an acute pharmacological intervention with cTBS showed that the magnitude of Ca^{2+} signaling is also highly relevant for the induction of LTP- and LTD-like phenomena in humans [125]. When the duration of cTBS was shortened from 40 s to 20 s, cTBS was shown to induce a facilitatory effect on corticomotor excitability. These LTP-like effects of short cTBS on corticomotor excitability were reversed when healthy volunteers were treated with nimodipine, an L-type voltage-gated Ca^{2+} channel antagonist. Pharmacological blockade of the NMDA receptor by dextromethorphan did not cause a homeostatic effect, but dextromethorphan abolished both the LTD-like effect of cTBS produced by nimodipine and the normal LTP-like effect of cTBS alone in M1. This study also suggested that the homeostatic effects induced by voluntary activity might be mediated by L-type voltage-gated calcium channels. It is likely that the effects of other interventional NTBS protocols are also strongly influenced by Ca^{2+} dynamics, but might be sensitive to manipulation of Ca^{2+} influx via different routes. This remains a relevant topic for future research.

At the cellular level, a complex machinery of transcriptional as well as pre- and post-synaptic molecular signaling mechanisms can induce and shape homeostatic mechanisms. These mechanisms include secreted molecules such as the brain-derived neurotrophic factor (BDNF) or the tumor necrosis factor (TNF), cell adhesion molecules (e.g. integrins, ephrins, cadherins), different kinases (CaMKs, CaMKII) and transcription factors such as Arg3.1 (for a detailed review on the molecular mechanisms of homeostatic plasticity the reader is referred to [126]).

Synaptic homeostasis and sleep

While we focused on the ability of NTBS to probe and shape homeostatic plasticity in previous sections, this section summarizes the contribution of sleep to homeostatic control and how this can be studied with NTBS. Neurons can undergo specific plastic changes during learning and behavior, they also have many ways to keep overall synaptic weights and post-synaptic activity levels under control. It has been proposed that irrespective of the specific mechanism involved, achieving this control may require the alternation between wakefulness and sleep [127]. Specifically, according to the "synaptic homeostasis hypothesis," the fundamental function of sleep is the restoration of synaptic homeostasis, which is challenged by synaptic strengthening triggered by learning during wakefulness [127]. In this framework, sleep is the price we pay for having a plastic brain that is able to learn and adapt to the ever-changing demands of the environment. Since neurons signal suspicious coincidences and salient events by increasing their firing, learning should happen primarily through synaptic potentiation. Moreover, synaptic potentiation should occur mainly during wakefulness in order to be adaptive, when the brain interacts with the external environment, not during sleep when it is disconnected. Hence, wakefulness is associated with synaptic potentiation and net synaptic weight increases over the wakening hours. Increased synaptic strength during waking has obvious benefits but also various costs at the cellular and systems level; for example, it implies higher energy consumption and demand for the synthesis and delivery of synaptic supplies; in addition, it reduces the selectivity of neuronal responses and saturates the ability to learn. For this reason, neurons must eventually re-normalize total synaptic strength in order to restore cellular functions as well as selectivity. Indeed, the other main tenet of the synaptic homeostasis hypothesis is that re-normalization of synaptic strength occurs primarily during sleep, when the brain is spontaneously active offline, not in wake when a neuron's inputs are biased by a particular situation.

It is important to note that homeostatic plasticity, as described in previous sections, and synaptic sleep homeostasis are related but separate phenomena. Whereas the primary variable regulated by homeostatic plasticity is the level of neural activity [38], sleep homeostasis primarily acts on global synaptic strength. An intriguing hypothesis is that synaptic re-normalization during sleep may be brought about by slow waves and by the underlying alternation between burst firing and neuronal silence. While the relevance and the details of this mechanism remain unknown, experimental studies in animal models show that overall synaptic weights increase during wakefulness but decrease during sleep. For example, structural evidence demonstrates that the strength, the size and number of synapses in the brain of Drosophila flies increase after a period of wakefulness and decrease only when animals are allowed to sleep [128] From a molecular point of view, the levels of GluA1-containing AMPA receptors (a molecular marker of synaptic potentiation) were found to be 30–40% higher after wakefulness than after sleep in rats [129]. Electrophysiologically, the slope of the early (monosynaptic) response evoked by electrical stimulation delivered in the rat cerebral cortex, a classic marker of synaptic strength in vivo, increases with time spent awake and decreases with time spent asleep [130].

In humans, a similar shift of the excitation/inhibition balance toward excitation was documented by two TMS-MEPs studies [131,132] that detected a significant decrease of short-term intracortical inhibition occurring, at the group level, after 24 h of sleep

deprivation. This shift in excitatory/inhibitory balance does also affect efficiency of NTBS-induced plasticity: A systematic comparison of the effect of diurnal rhythm on facilitatory PAS showed that the facilitatory effects of PAS were greater in the evening. This study also confirmed that intracortical inhibition was reduced in the evening [133]. While providing some information on the nature of cortical plastic changes, these NTBS studies confirm the idea that in humans, sleep may contribute to keep the overall weight of cortical synapses under control.

An important practical implication is that synaptic sleep homeostasis needs to be taken into account whenever interventional NTBS protocols are given over consecutive days or weeks. In these studies, the sleep quality might have substantial impact on the emergence of cumulative NTBS effects.

Homeostatic plasticity in pathological states

Synaptic homeostasis has been demonstrated to be a fundamental mechanism within brain circuits, operating in different species including humans [2,38,127,134–136], but much less is known about the significance of dysfunctional homeostatic plasticity for the pathogenesis and pathophysiology of brain diseases. In this review, we focus on a series of experiments, which have used NTBS to probe homeostatic plasticity in focal dystonia and discuss the future potential of NTBS to study homeostatic plasticity in neuropsychiatric disorders.

Focal dystonia

Using TDCS as conditioning protocol and low-frequency (1 Hz) rTMS as test protocol, Quartarone et al. found that the 'homeostatic' response pattern of healthy controls was absent in the affected hand of writer's cramp patients [137,138]. In dystonic patients, aTDCS to M1 increased MEP amplitude as in normal controls, but the subsequent 1 Hz rTMS did not produce an LTD-like effect. Thus despite producing an LTP-like effect, aTDCS failed to trigger a homeostatic response that sensitized M1 to the LTD-inducing effect of 1 Hz rTMS.

A subsequent study addressed the question whether patients with focal hand dystonia would show an enhancement of motor learning induced plasticity after priming with an excitability-reducing NTBS protocol as previously shown in healthy individuals [99]. While the healthy control group showed a homeostatic enhancement of learning-dependent plasticity following an excitability-reducing prime and a homeostatic suppression of learning-dependent plasticity following an excitability-increasing prime, the writer's cramp patients did not show any modulation of learning-dependent plasticity and the lack of homeostatic modulation was correlated with the clinical severity of the dystonia [139]. These results suggest that focal hand dystonia is associated with a dysfunctional homeostatic regulation of plasticity, which might set the frame for aberrant sensorimotor plasticity. Several NTBS studies have shown that patients with focal hand dystonia show excessive sensorimotor plasticity with lack of somatotopic specificity [140,141]. However, due to the large variability of PAS responses, both in patients and healthy subjects, there is considerable overlap between patient and healthy data. The questions the validity of excessive, non-focal PAS effects as a general 'dystonic fingerprint' [142]. Large multicenter studies and a stronger focus on individual plasticity profiles will help to clarify the role of dysfunctional homeostatic plasticity in dystonia.

Additionally, it should be noted that focal dystonia is also characterized by deficient inhibition within intracortical circuits [143]. This might explain that also the response to NTBS protocols such as iTBS, which are not involving a sensorimotor component, is abnormal in these patients. However, iTBS induced plasticity is absent or reduced in focal dystonia, not excessive and non-focal as for PAS [144]. Deficient intracortical inhibition might also produce an abnormal "gating" of the LTP-inducing effects of NTBS and hereby introduce a bias toward producing LTP-like rather than LTD-like effects in M1.

Parkinson's disease

There is ample evidence for altered LTP- and LTD-like plasticity in Parkinson's disease (PD) [145–147] and recent research suggests that abnormalities in plasticity may depend on disease state and l-DOPA administration [145]. Despite the relatively large number of NTBS studies investigating synaptic plasticity in PD, homeostatic plasticity has not been systematically investigated. Huang et al. studied non-homeostatic metaplasticity in patients with and without levodopa-induced dyskinesia (LID). PD patients without LIDs had normal potentiation and de-potentiation, when they took their full dose of levodopa. Patients with levodopa-induced LIDs were studied while being on half their usual dose of levodopa to prevent emergence of overt dyskinesias during testing. LID patients showed normal potentiation but were unresponsive to the de-potentiation protocol [148]. Given this altered non-homeostatic metaplasticity in LID patients, it is possible that homeostatic plasticity might also be affected in PD.

Psychiatric disorders

Several lines of research suggest that both the NMDA- and GABA-ergic transmitter systems that participate in cortical plasticity are also involved in the pathophysiology of various psychiatric disorders such as schizophrenia (SCZ), major depressive disorder (MDD) and bipolar disorder [149–153]. Except for dysfunctional GABA and glutamatergic neurotransmission, key features of these disorders are abnormalities in the expression of several proteins which are important for synaptic plasticity and homeostatic plasticity (e.g. BDNF, dybindin, neurexin) [154–156].

Disrupted plasticity is an established part of the pathophysiology in schizophrenia (SCZ), and several neurophysiological experiments using a range of plasticity-inducing NTBS protocols have shown that LTP- and LTD-like effects are reduced in SCZ [152,157,158]. SCZ patients also demonstrate less use-dependent plasticity. By measuring the spontaneous direction of TMS-induced thumb movements before and after 30-min training in thumb abduction, Daskalakis and coworkers [159] found that M1 excitability was affected less in SCZ patients than healthy controls. Impaired cortical plasticity has also been reported in patients with major depressive disorder (MDD) who have reduced plasticity in response to TMS [160] and visual evoked potentials [161].

As in PD although there is ample evidence for altered LTP- and LTD-like plasticity in SCZ and MDD, direct examples of impaired homeostatic plasticity are rare. On a molecular level, evidence exists linking various psychiatric diseases such as SCZ, MDD and other disorders to dysfunctional homeostatic synaptic plasticity involving a wide array of genes and molecules required for homeostatic synaptic plasticity [155,156]. However, even though these molecular findings have led to a conceptual framework that places homeostatic dysfunction at the heart of a wide array of neurologic and psychiatric diseases there is, to the authors knowledge, no direct investigation of homeostatic regulation in psychiatric patient populations. Considering the links between the pathophysiology of a variety of psychiatric disorders and synaptic processes necessary for homeostatic control, it will be a future challenge to understand how these mechanisms work together in the intact human brain.

A systematic investigation of homeostatic plasticity in various psychiatric disorders will help to start understanding how homeostatic responses orchestrates systemic functions in the brain.

Dysfunctional synaptic plasticity and homeostatic plasticity in various disorders could have an impact on the design of future clinical trials. At the moment, treatment trials for several psychiatric disorders involve the application of plasticity-inducing NTBS protocols to counteract hypo- or hyperactivity of different brain areas. If, indeed, plasticity in these disorders is fundamentally changed, we cannot assume that the plasticity-enhancing effect of brain stimulation techniques, observed in healthy subjects, can be directly translated to patient populations. Indeed Barr et al. showed that one session of 20 Hz rTMS had opposing effects in SCZ patients and healthy volunteers: rTMS inhibited gamma–oscillatory activity in patients, who had a greater activity at baseline, while the same rTMS protocol potentiated gamma–oscillatory activity in healthy controls with relatively lower oscillations at baseline, suggesting a homeostatic interaction [162].

Conclusions and perspectives

Homeostatic metaplasticity plays a critical role in stabilizing neural activity around a set point and is defined by inducing a shift in the stimulus–response curve of the firing neuron and is controlled by the intra-cellular Ca^{2+} levels. The use of NTBS allows homeostatic effects to be investigated on a systems level and in interaction with physiological conditions. Since NTBS activates a massive number of neurons, inducing action potentials in a mixture of inhibitory and excitatory cells, NTBS-induced plasticity cannot be equated with *in vitro* studies on synaptic plasticity. Additionally, the traditional measure of NTBS-induced excitability, the MEP, has confined most investigations of homeostatic effects in the intact human brain to the primary motor cortex.

In the future a combination of NTBS with other brain mapping techniques will allow investigation of homeostatic phenomena to expand to cortical areas outside M1. A careful investigation of the network effects and the combination of NTBS with neuroimaging, pharmacology and animal studies will help to reveal more insights into the neural mechanisms underlying homeostasis at a systems level.

Systematic investigation of individual differences in NTBS response will, in the future, allow researchers to move toward the use of individually adjusted protocols that take relevant neurophysiological state markers into consideration. These custom made protocols may decrease inter-individual variance and make NTBS an even more powerful tool. The study of homeostatic plasticity in patients with neurological and psychiatric diseases is still very limited and future research should tackle this issue since it might give some insight into contribution of dysfunctional regulation of cortical plasticity to these conditions.

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