

Interactions between synaptic homeostatic mechanisms: an attempt to reconcile BCM theory, synaptic scaling, and changing excitation/inhibition balance

Tara Keck¹, Mark Hübener² and Tobias Bonhoeffer²

1. Department of Neuroscience, Physiology and Pharmacology, University College London, 21 University Street, London, WC1E 6DE, UK
2. Max Planck Institute of Neurobiology, Am Klopferspitz 18, 82152 Martinsried, Germany

Abstract:

Homeostatic plasticity is proposed to be mediated by synaptic changes, such as synaptic scaling and shifts in the excitation/inhibition balance. These mechanisms are thought to be separate from the Bienenstock, Cooper, Munro (BCM) learning rule, where the threshold for the induction of long-term potentiation and long-term depression slides in response to changes in activity levels. Yet, both sets of mechanisms produce a homeostatic response of a relative increase (or decrease) in strength of excitatory synapses in response to overall activity-level changes. Here we review recent studies, with a focus on in vivo experiments, to re-examine the overlap and differences between these two mechanisms and we suggest how they may interact to facilitate firing-rate homeostasis, while maintaining functional properties of neurons.

Neuronal firing rate homeostasis is essential for proper circuit function. Numerous theoretical models predict that without it, activity levels in the brain would rapidly become extreme, thereby limiting coding and information storage capacity, and potentially resulting in pathological states (1–5). Many synaptic homeostatic mechanisms that could maintain appropriate firing rates have been theoretically proposed, and several of them have been experimentally observed. These include synaptic scaling (6–10), changes in the ratio between synaptic excitation and inhibition (11–17), and a sliding threshold model for the induction of long-term potentiation (LTP) and long-term depression (LTD) (18–23). In addition, non-synaptic homeostatic mechanisms, such as changes in neuronal excitability, either through changes to ion-channel composition (15), or by movement of the axon initial segment (24,25)

have been proposed to alter neuronal firing rates, thereby helping to maintain proper activity levels.

The best-studied homeostatic mechanism is synaptic scaling, where in response to a prolonged increase or decrease in neuronal activity, the weights of all synapses on a cell are thought to scale down or up multiplicatively (8), thus homeostatically adjusting overall synaptic drive and activity levels (Figure 1A). The multiplicative nature of scaling maintains the relative weights of the synapses and thus the information stored in those weights (7). The balance between excitation and inhibition (E/I balance) on a given neuron can also shift accordingly when activity levels increase or decrease for an extended period. This shift can occur through adjusting the number of synapses of each type (12,14,16,26), the relative strength of those synapses (11,13–15)(Figure 1B), or the firing rate of the inhibitory neurons themselves (11,27).

Alternatively, altered activity levels might not directly change overall synaptic weights, but rather modify the synapses' capacity to undergo plasticity in the future. The idea for such a sliding threshold for Hebbian plasticity mechanisms, such as LTP and LTD, was originally proposed in the Bienenstock, Cooper and Munro (BCM) learning rule (28), where decreases in activity were postulated to result in a reduced threshold for the induction of LTP, effectively promoting the strengthening of synapses and making LTD less likely. Conversely, increases in activity were proposed to shift the threshold in the opposite direction to favor LTD. Thus, activity levels would never reach extremes, as synaptic weights would consistently be adjusted to prevent such a scenario, as has been tested experimentally (Figure 1C) (20,21).

The role of the sliding threshold model in firing rate homeostasis has often been examined separately from synaptic scaling and shifts in E/I balance, and the sliding threshold model and synaptic scaling have long been considered to be mechanistically distinct. This is at least partly due to different experimental approaches at the respective times of discovery. Specifically, the spatial scale and precision of the effects are thought to differ, as synaptic scaling observed in reduced preparations seems to occur at all or most synapses (7), while LTP and LTD (in the sliding threshold model) are by and large synapse-specific (22). However, results from more recent experimental approaches suggest that there may be more similarities than differences between these two concepts. Here we discuss the potential areas in which these mechanisms may interact or overlap, particularly in *in vivo* preparations, and

revisit whether the sliding threshold model is necessarily distinct from synaptic scaling and shifts in E/I balance.

How might synaptic scaling and BCM theory overlap?

To date, synaptic scaling and the BCM theory of a sliding threshold have largely been considered separate entities. One potential confound when considering these two mechanisms is the nature of the experiments that have been used to investigate each phenomenon. Many of the experiments examining the sliding threshold model have been done *in vivo* or in acute slice preparations from mice that have previously undergone *in vivo* manipulations of activity levels, for example, by depriving one eye from vision (20,21,29). Until recently, experiments investigating synaptic scaling have mostly been carried out in *in vitro* reduced preparations, where activity can be completely abolished (6–8), or following sensory deprivation *in vivo* (9–11,13,15,30,31), where the exact nature of the changes in activity levels and patterns (15) strongly influences the resulting characteristics of synaptic scaling. Thus, many perceived differences between these models may emerge from differences in activity following deprivation in their respective experiments. Here, we will largely focus on these synaptic scaling experiments following *in vivo* deprivation so as to have the best comparison to experiments investigating the sliding threshold model. Additionally, we will focus on mouse visual cortex, where there have been sufficient experiments addressing both synaptic scaling and sliding threshold plasticity, although many of the properties observed in visual cortex have been found in other cortical areas too (for a review see (32)).

There are some compelling reasons for distinguishing between synaptic scaling and the sliding threshold model for Hebbian plasticity. These include the multiplicative nature of the change, which is key to the concept of synaptic scaling (8), but not to the sliding threshold model, where despite the threshold change occurring cell-wide, individual synaptic weights are altered according to the rules of LTP and LTD (22). There are also differences in the molecular mechanisms involved in these two phenomena (18,22). We will discuss each of these distinctions in turn, examining the experimental results and looking for common ground between the two theories.

The first property that may distinguish synaptic scaling from the sliding threshold for Hebbian plasticity is the fact that scaling is multiplicative. This property of synaptic scaling

was originally observed in electrophysiological measurements of synaptic current amplitudes compared across a population of cells at a single time point, where the pooled synaptic responses increase (or decrease) multiplicatively by a given factor. While multiplicative scaling has been shown to occur in both reduced preparations (7,8) and following *in vivo* deprivation (9,10,13,30,31), this result does not necessarily mean that all synapses are changed by the same factor, as is often implicitly assumed. Especially in *in vivo* preparations, where activity is reduced, but not eliminated during sensory deprivation (11,13,30,33), ongoing LTP and LTD will occur at individual synapses as a result of external stimuli, as well as internally generated neuronal activity. These ongoing fluctuations in synapse strength will ride on top of any synaptic scaling that occurs in response to decreased activity levels. Our own work (13), where we chronically measured synaptic strength using spine size as an *in vivo* proxy (34–39) under conditions of lowered activity levels, shows overall multiplicative scaling both of spine size and mEPSC amplitude (measured with single time point electrophysiology). Yet, not all spines get larger following deprivation, and some spines even decrease in size (13). The overall multiplicative nature of scaling observed in these experiments is due to the fact that even more spines get smaller under control conditions, so when changes are measured across the population and compared between groups, the population as a whole shifts multiplicatively. Thus, multiplicative scaling occurs on the cellular level, but the relative weights of single synapses may change individually. These results are consistent with both, multiplicative scaling of synapse strength, and a shift in the sliding threshold to favor LTP over LTD after deprivation, since fewer individual synapses exhibit a decrease in size typically associated with LTD (40).

The second perceived difference between synaptic scaling and the sliding threshold for LTP/LTD induction rests in the underlying molecular mechanisms. One case in point is the role of tumor necrosis factor (TNF)- α . It has been identified as a key mediator for synaptic scaling, but it does not seem to play a role for the induction of Hebbian mechanisms such as LTP (41–43). However, while it is clear that TNF- α does not affect LTP directly, it remains unexplored, whether it affects the LTP/LTD threshold. Another example is the observation that synaptic upscaling involves the insertion of the GluR2 subunit, while LTP is mediated by GluR1 insertion (44). Similarly, synaptic downscaling can occur via changing the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) unbinding rate from the synaptic scaffold, which has not been implicated in LTD (45). Furthermore, also for LTP and

LTD it is true that several mechanistically distinct forms have been described (46), reflecting different pathways of the same phenomenon. Examples include metabotropic glutamate receptor (mGluR) dependent LTP (47) or N-Methyl-D-aspartate receptor (NMDAR) dependent LTP (48). Therefore, mechanisms associated with synaptic scaling could well represent an additional molecular pathway of homosynaptic plasticity (i.e. LTP and LTD), or a completely distinct form of plasticity.

Importantly, a majority of experimental work directly compares the mechanisms of synaptic scaling with those underlying the induction of LTP or LTD, but not the those associated with the sliding LTP/LTD threshold. Therefore, an additional important, yet unanswered, question is whether synaptic scaling and the sliding BCM model share common mechanisms. In theory, such mechanisms need not interfere with LTP or LTD directly, so they could be distinct, but they would instead affect the overall likelihood of LTP or LTD induction. Current knowledge of the molecular mechanisms for the sliding BCM model is limited. Numerous studies have suggested that it is caused by a shift in the ratio of synaptic NR2A to NR2B (49–54), which changes the resulting probability of LTP or LTD induction, but additional mechanisms that specifically underlie the sliding threshold in the BCM model remain unexplored. Further experiments that directly compare the molecular mechanisms of synaptic scaling and the LTP/LTD sliding threshold are necessary to determine if they are distinct.

In terms of their common characteristics, as discussed previously (22), both the sliding threshold and synaptic scaling can create conditions that would promote firing rate homeostasis. And despite changes occurring at individual synapses, the spatial scale of the implementation of both synaptic scaling (55) and the sliding threshold model (22) is believed to be cell-wide, but not necessarily evenly across all synapses. Theoretically, synaptic scaling *in vitro* could be an extreme example, where after the complete removal of activity (as is done in reduced preparations) the sliding threshold shifts to promote LTP in most synapses, assuming that LTP can occur in the absence of action potentials.

Separating the two mechanisms is hampered by the fact that they are often observed on similar time scales. Synaptic scaling is generally observed over a period of 24-48 hours (7,13,30), but it can also occur over faster time courses of a few hours (56). For the sliding threshold model, the majority of experimental evidence has been obtained using the paradigm of monocular deprivation (18,20–23). Lid suture causes a decorrelation of activity

and thereby LTD in deprived eye inputs, followed after 24 hours or more by a shift of the sliding threshold that promotes LTP in active, spared eye synapses (18). Whether changes to the sliding threshold model can occur more rapidly, as has been observed for synaptic scaling (56), has yet to be investigated, and the relevant time course for detection of activity changes triggering either synaptic scaling or shifts in the sliding threshold remains experimentally unresolved. Theoretical work has examined the time scales for both the detection of activity changes and the implementation of compensatory mechanisms. It was found that multiple time scales appear to be relevant for both synaptic scaling and the BCM sliding threshold (4,5) to maintain firing rate homeostasis. These results raise a number of questions regarding plasticity time scales that will need to be addressed experimentally, but they confirm that time courses for synaptic scaling and Hebbian mechanisms may prove to be more similar than previously thought. So while synaptic scaling and the BCM theory of a sliding threshold for Hebbian plasticity may have some mechanistic differences, many of their properties are overlapping and as more directly comparable experimental data emerge, particularly *in vivo*, it appears that the two concepts are not necessarily as mutually exclusive as once believed.

Interactions between BCM sliding threshold and E/I balance

The second synaptic homeostatic mechanism that is thought to maintain firing rate homeostasis is a shift in the balance between synaptic excitation and inhibition on a given cell. Whether and how the sliding threshold model for LTP and LTD induction acts on inhibitory synapses onto excitatory neurons is a key determinant of how E/I balance would change (57) and, to date, remains largely unexplored. Following a decrease in activity, the LTP/LTD threshold could shift to promote LTP, as is the case in excitatory synapses. Alternatively, to maintain firing rate homeostasis after deprivation, inhibitory synapses may be more likely to undergo depression. If we consider the experimental data, mainly from mouse visual cortex, a reasonably clear picture emerges. Under normal conditions, levels of synaptic inhibition are balanced with excitatory synaptic drive (58) while ongoing inhibitory plasticity facilitates the maintenance of the E/I balance (59,60). Following deprivation, however, this balance shifts. Electrophysiological studies show that a drop in synaptic inhibitory drive onto excitatory cells occurs within hours to days after deprivation (11–16,61). In line with these results, experiments using chronic imaging to measure synaptic structures also show that both pre- (14,26) and postsynaptic (12,16) components of inhibitory synapses

are decreased in number and size after sensory deprivation. This observation is true for excitatory cells in cortical layer 5 (13,14) and layer 2/3 (11,12,16) and it holds for a number of deprivation paradigms including monocular eyelid suture (12,16,26), binocular retinal lesions (13,14) and monocular enucleation (11). Reduced activity in the presynaptic inhibitory neurons (11,27) is also likely to contribute to a reduction of overall inhibitory drive onto excitatory neurons. Similar decreases in inhibitory synapse number and strength have additionally been observed in somatosensory cortex (for a review, see (32)).

A decrease in the strength and number of inhibitory synapses is reminiscent of LTD in excitatory synapses (40), where a loss of synaptic structures occurs after the induction of synaptic depression. Thus, one possible scenario is that following decreases in activity, the sliding threshold is shifted to favor LTD in inhibitory synapses, consistent with the loss and weakening of inhibitory synapses on excitatory cells. This prediction would suggest a model in which observed shifts in the E/I balance in response to changing activity levels could be achieved through sliding thresholds for LTP and LTD shifting in opposite directions for excitatory and inhibitory synapses on the same excitatory cell (Figure 2). Experimentally, there is evidence for such a relationship. Both endocannabinoids (62,63) and GABA_B-Gi/o protein signaling (60) have been shown to promote LTD at inhibitory synapses when excitatory synapses on the same cell are undergoing LTP. Cannabinoid receptor blockade has also been shown to prevent ocular dominance plasticity in layer 2/3 (64). The confirmation of and exact details of the implementation of these opposite direction sliding thresholds do however require further experimental investigation.

Computationally, opposite direction sliding thresholds for excitatory and inhibitory synapses could be useful for the emergence and maintenance of stimulus selectivity in excitatory cells. Recent evidence shows that neurons maintain their visual response properties, specifically orientation preference and selectivity, following deprivation and recovery during ocular dominance plasticity (65), and inhibition is known to play a key role in shaping these receptive field properties (66–68). One possibility is that the specific subset of inhibitory synapses involved in tuning are maintained throughout deprivation, which may reflect a given subtype of presynaptic inhibitory neurons. Shifting the threshold to promote LTD in individual inhibitory synapses, rather than universally decreasing all inhibitory synapses via a synaptic scaling-like mechanism, would in theory allow for a subset of active inhibitory synapses to be maintained at their pre-deprivation levels. Thus, the specific inhibitory

synapses that play a role in shaping orientation and direction selectivity of the excitatory neurons could be maintained (1,66,68), whereas other inhibitory synapses that are responsible for maintaining the overall inhibitory tone (68), could be depressed to facilitate the shift in E/I balance, in turn helping to homeostatically restore firing rates.

Conclusions

Here we have outlined some commonalities between the BCM sliding threshold model and the synaptic homeostatic mechanisms of synaptic scaling and changing E/I balance and have discussed how they could actually work together. Recent experimental evidence suggests that the often separately considered mechanisms for maintaining firing rate homeostasis may share some properties. Further experiments will be necessary to determine the overlap and interaction between synaptic scaling and BCM sliding threshold for Hebbian plasticity induction, as well as the potential role for BCM theory in changing inhibitory synapses. Finally, in one example we have discussed how the overlapping nature of these concepts may even help explaining how the brain achieves plasticity without losing essential functional properties of neurons.

Figure legends

Figure 1: Different mechanisms of firing rate homeostasis. A) Synaptic scaling. Morphological representation of synapse size before and after activity changes. Increases in activity causes synapses to decrease in size; decreases in activity, cause synapses to increase in size. B) Morphological representation of changes to the E/I balance. Increases in activity cause inhibitory synapses (red) to increase; decreases in activity cause inhibitory synapses (red) to decrease. C) Sliding threshold for LTP and LTD induction. Increases in activity cause the threshold (dashed line) to shift such as to promote LTD induction. Decreases in activity cause the threshold to shift such as to make LTP more easily inducible.

Figure 2: Possible interactions between the sliding threshold model and the shifting E/I balance. A) An increase in activity causes the threshold for excitatory synapses (black dashed line) to shift such that LTD is favored, while the threshold for inhibitory synapses (red dashed

line) shifts to favor LTP. For a decrease in activity the inverse holds true. B) The resulting E/I balance from such sliding threshold shifts.

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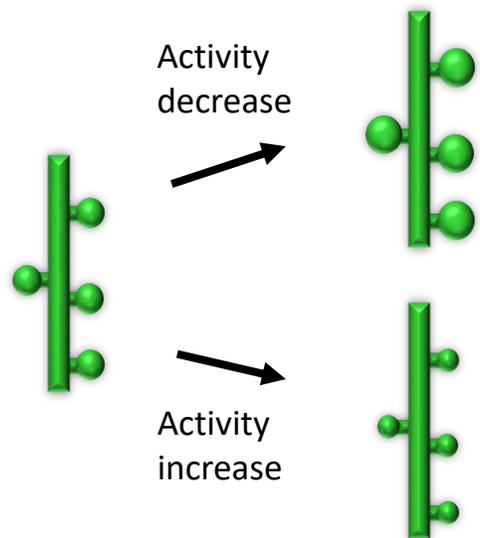
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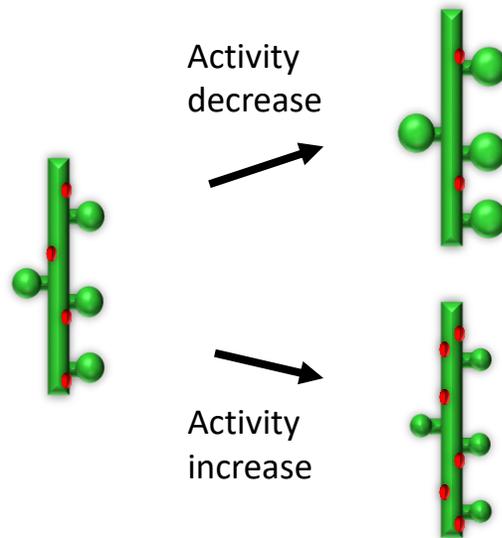
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A

Synaptic scaling

**B**

Excitation/Inhibition balance

**C**

Sliding threshold model

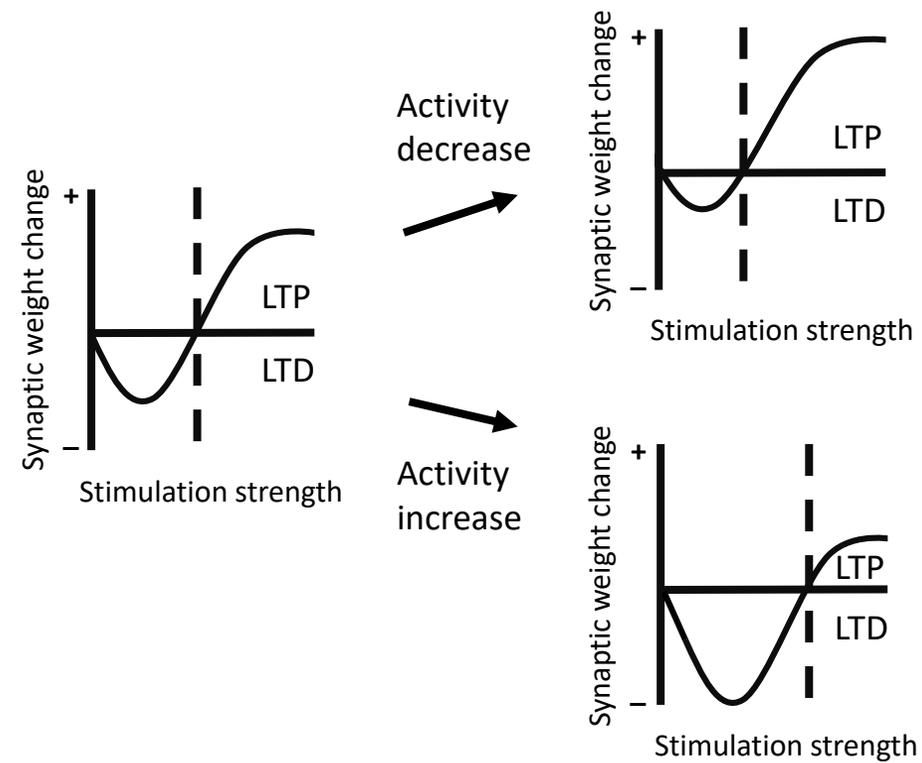
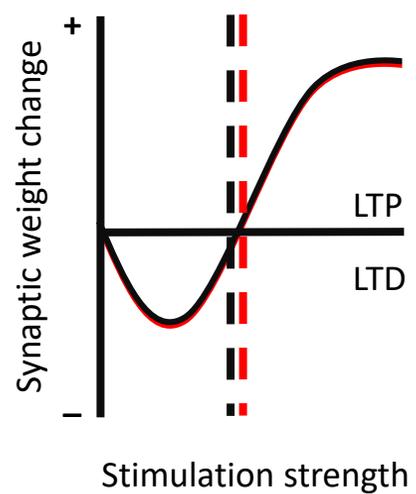


Figure 1

A

Activity decrease



Activity increase

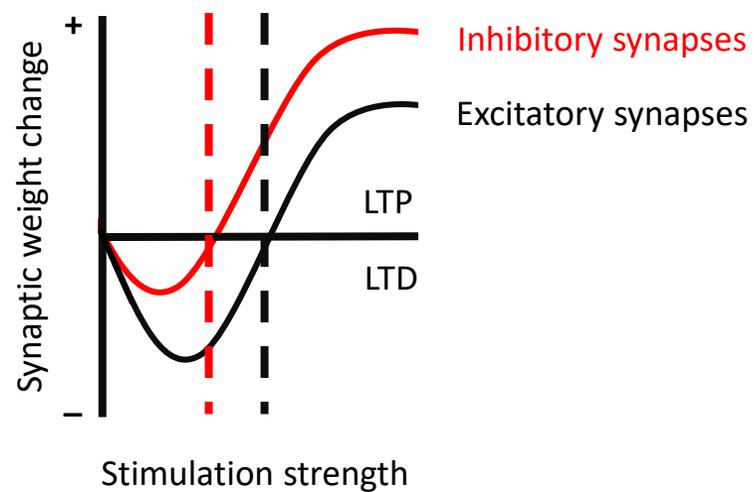
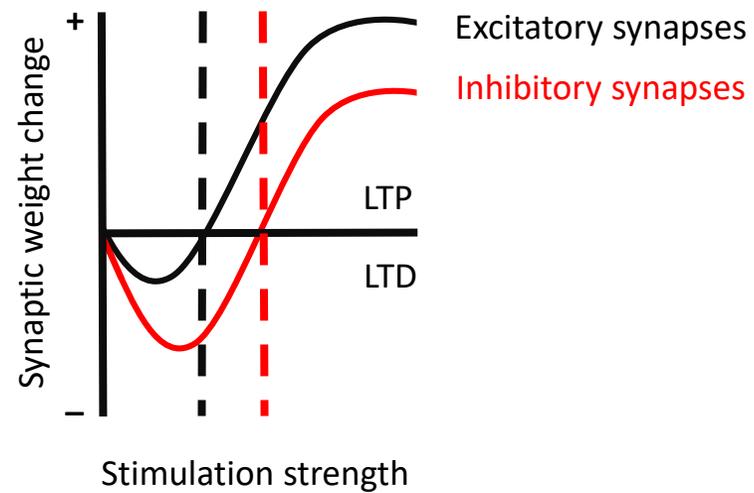
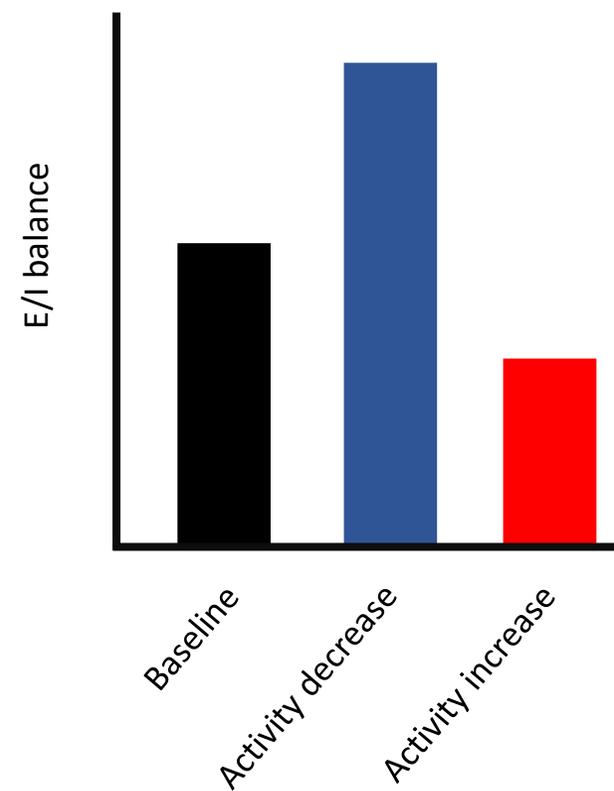
**B**

Figure 2