Metaplasticity and rTMS

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Typical plasticity interventions with TMS

- Repetitive activation of synapses where LTP/LTD is a function of the rate of Ca2+ entry. Low rates promote lTD, high rates promote LTP
  - Eg 1 Hz, 20 Hz rTMS decrease and increase motor cortex excitability
  - Theta Burst protocols such as cTBS (LTD-like) and iTBS (LTP-like)
  - Quadripulse rTMS (QPS): 4 pulses separated by between 1.5 -50ms repeated every 5s.

- Hebbian plasticity: repeated pairing of synaptic input and neural discharge. LTP/LTD is a function of the order of events
  - Paired associative stimulation. EG median nerve stimulation produces synaptic input to motor cortex followed (or preceded) by TMS of motor cortex. If discharge follows input then LTP, if discharge precedes input then LTD
  - Pairing can also involve 2 different, but connected, brain areas (e.g. parietal cortex and motor cortex)

- Motor learning, a natural form of synaptic plasticity

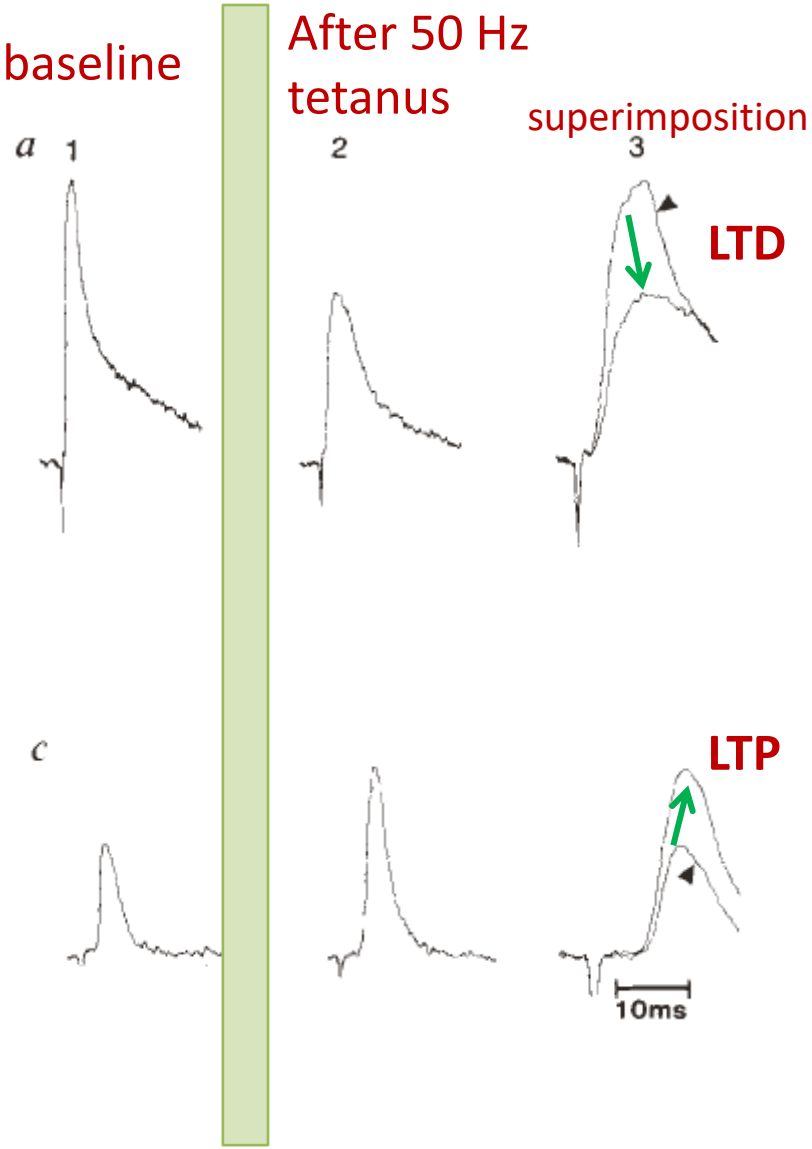
Metaplasticity

- Usually defined as “plasticity of plasticity”…. The ability to change the effectiveness of a synaptic connection is not fixed.
- The results of a given plasticity protocol (such as rTMS, theta burst stimulation, TDCS etc) depend on the *previous history* of activity of a neuron
- A related phenomenon is that plasticity also depends on the level of neural excitability *at the time of* the plasticity protocol.
- Finally, the events *immediately following* a plasticity protocol can interfere with the final result

Changing excitability at the same time as a plasticity intervention

- Initial brain slice experiments showed that depolarisation/hyperpolarisation of a neuronal membrane could affect induction of synaptic plasticity onto the cell. Depolarisation increased effectiveness of LTP.
- Later expts showed that in rat motor cortex it was not possible to induce LTP except when excitability raised by blocking GABA with bicuculline.

- In humans, increasing excitability of motor cortex by deafferentation enhances LTP-like effect of rTMS
- Increasing excitability of motor cortex with simultaneous anodal TDCS enhances motor sequence learning.
- Application with online EEG monitoring of mu rhythm



50 Hz tetanus

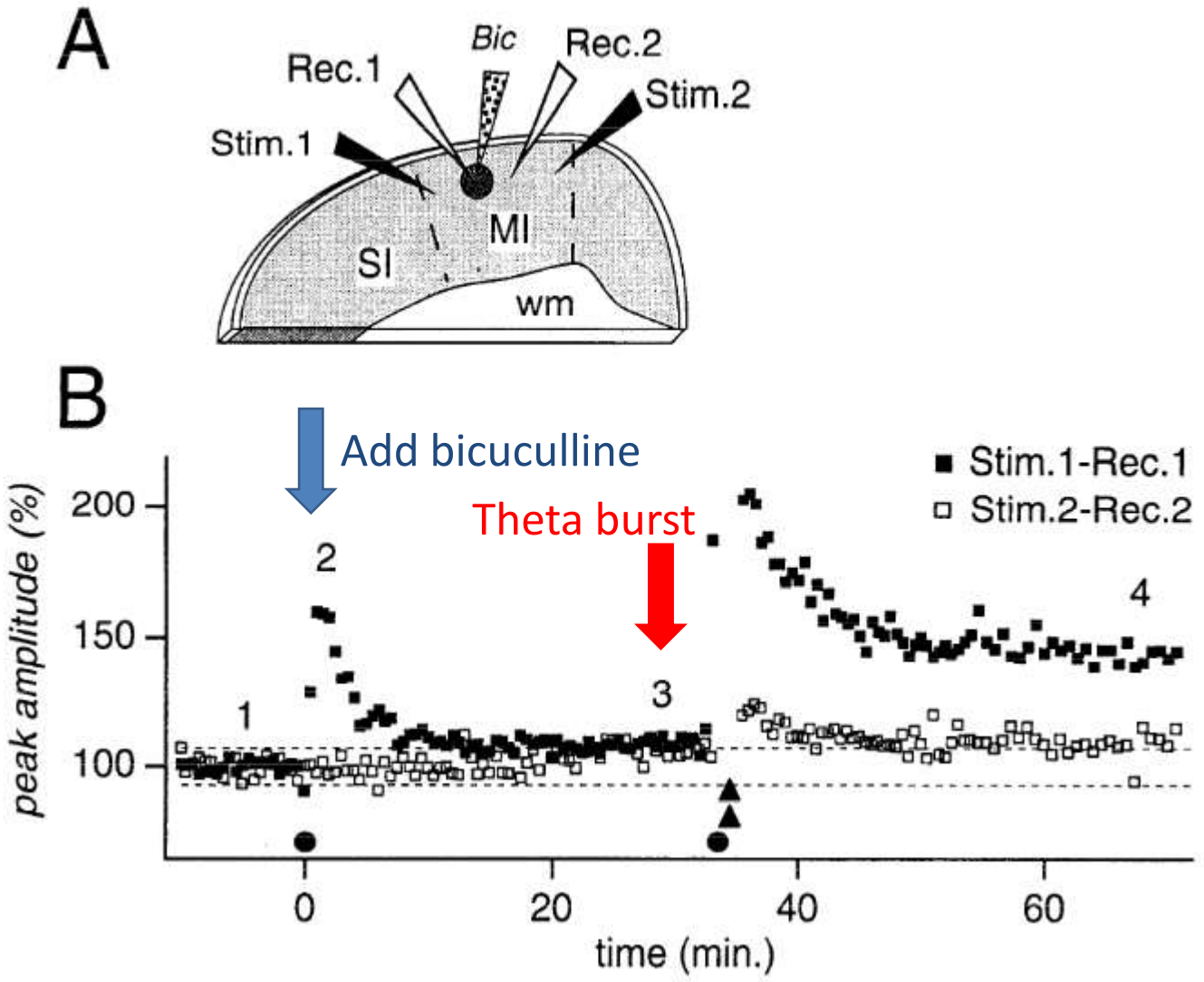
Five 2s trains at 10s intervals

No polarisation

+20mV depolarisation

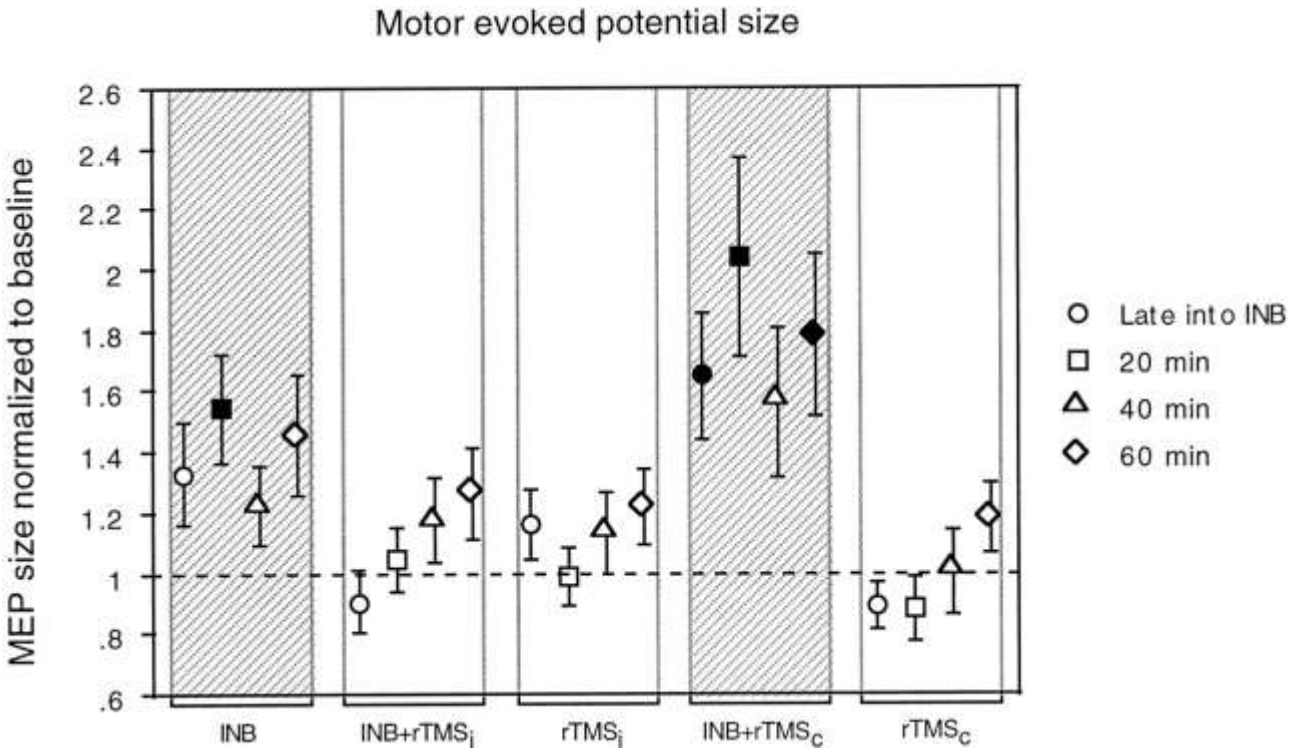
Cortical slices: intracellular recordings from layer II-III of postsynaptic potentials evoked by stimulation in white matter. Polarisation during the 50 Hz white matter tetanus is produced by current injection through electrode

(Artola et al., 1990)



In motor cortex, theta burst stimulation fails to produce LTP unless GABA activity reduced by prior application of bicuculline

Hess et al., 1996



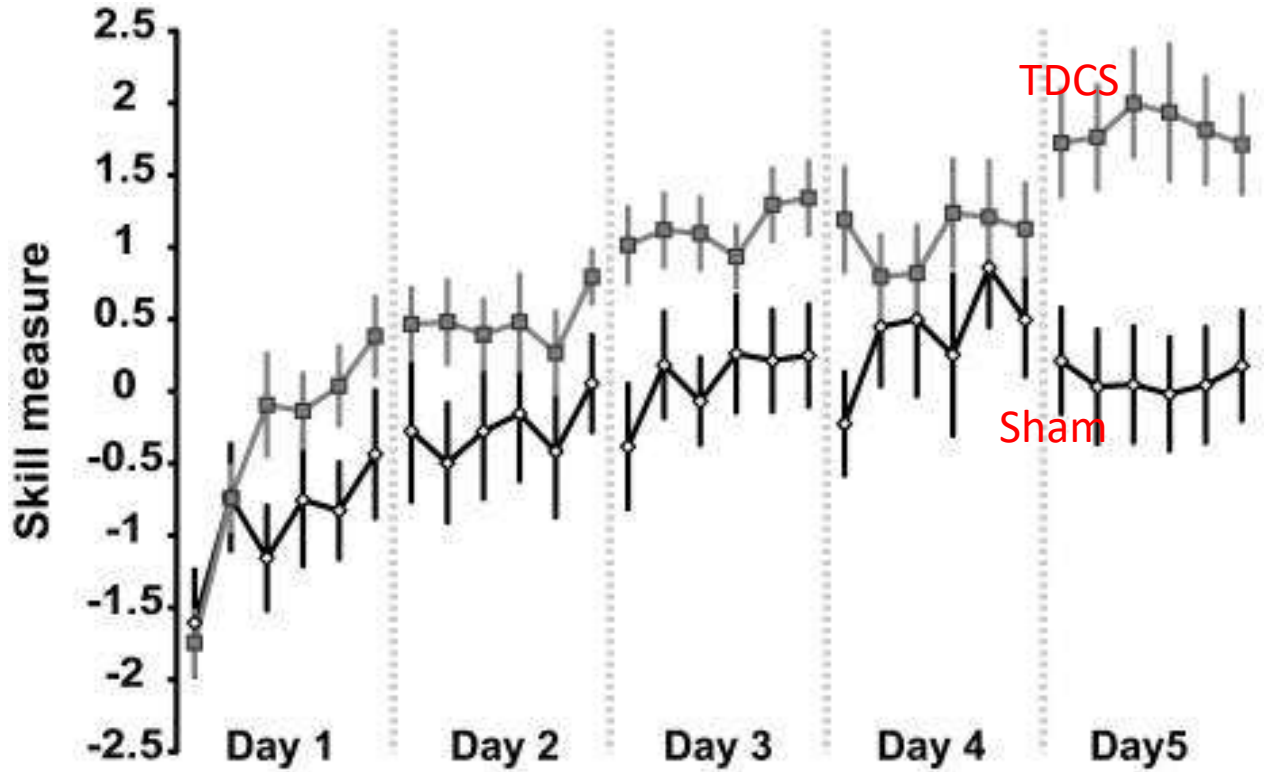
Evidence in human that increased excitability of motor cortex can enhance LTP-like effects of rTMS.

Expt in biceps: increase excitability by ischaemic deafferentation of forearm (increases MEP above baseline)

rTMS is 0.1 Hz and is applied throughout the ischaemia. Test effects ipsilateral and contralateral to ischaemia.

Ziemann et al., 1998

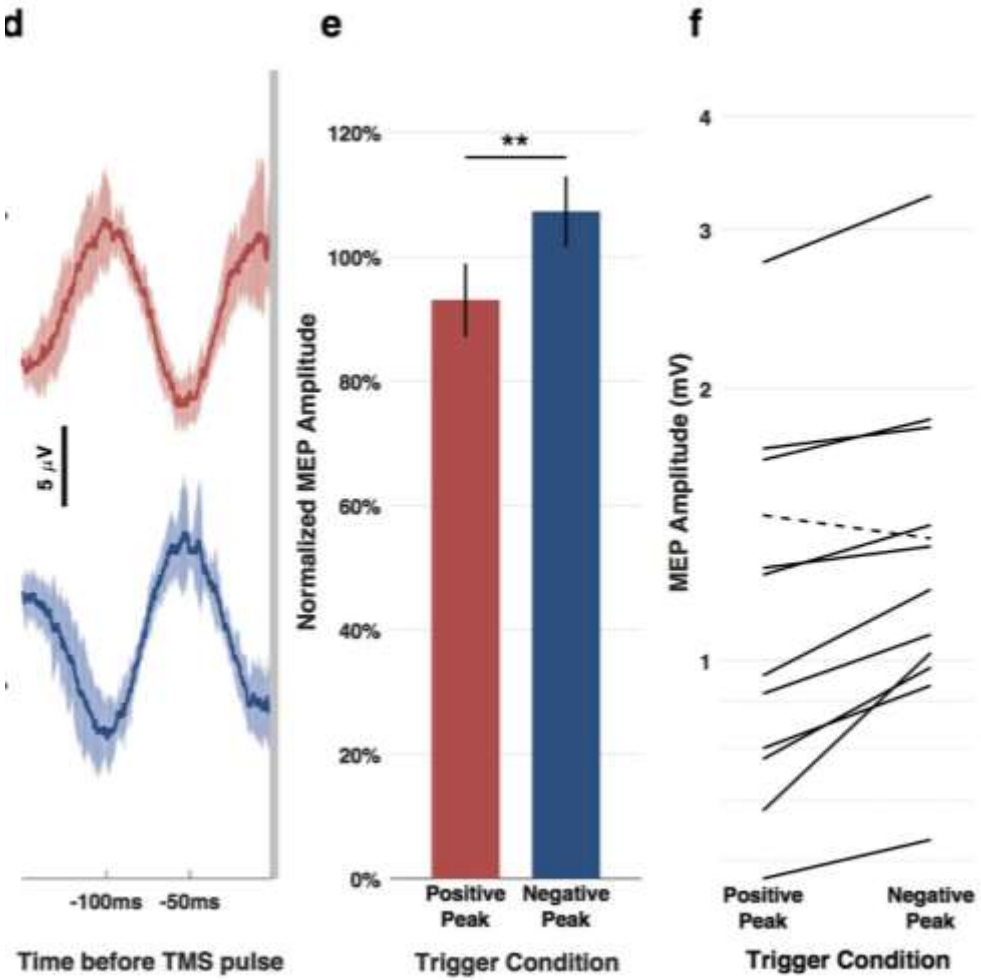
Simultaneous anodal TDCS can boost learning



Learning a complex sequence over 5 days is improved if the practice is delivered with simultaneous TDCS over M1

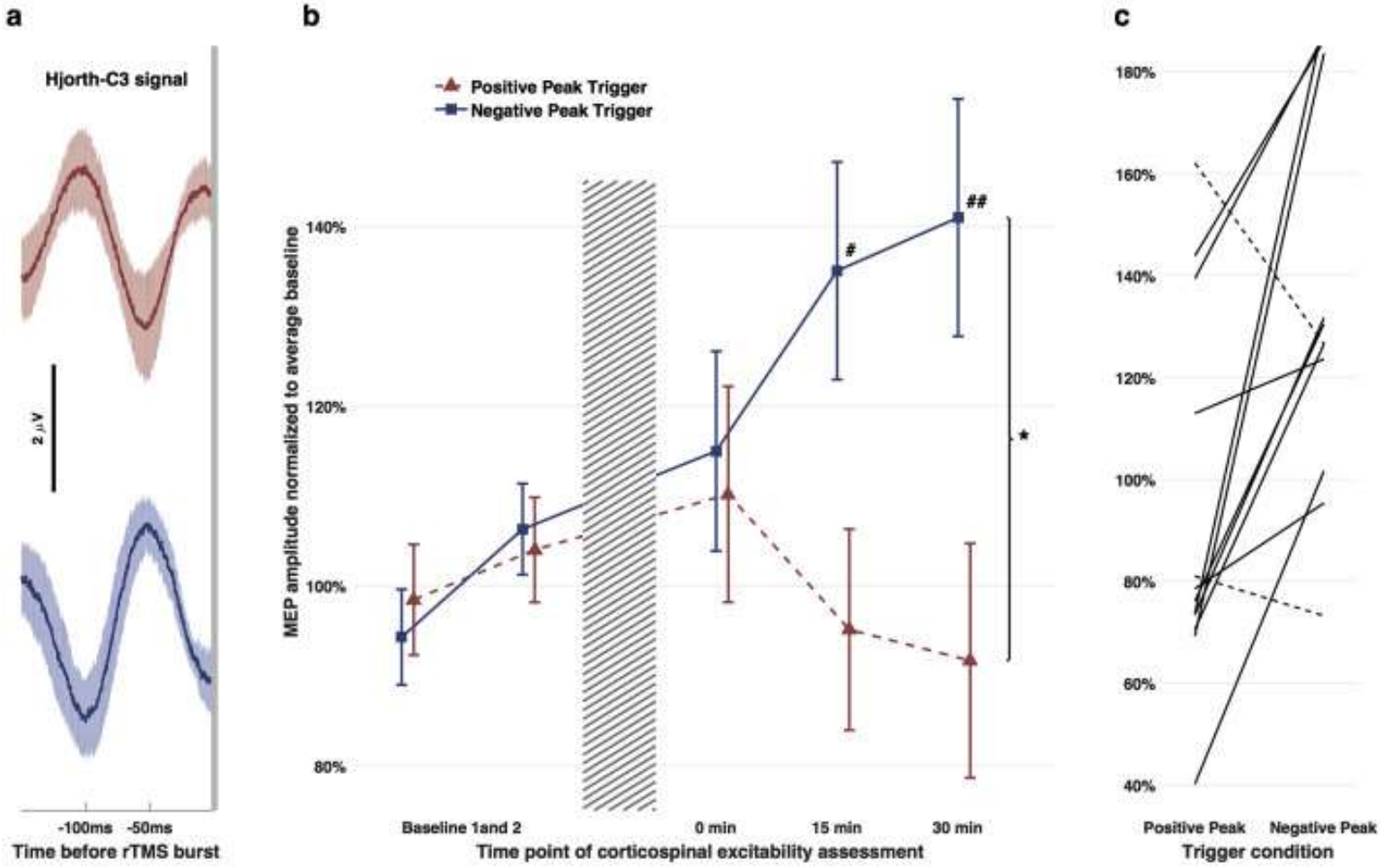
Much of the effect (apart from on-line improvement on day 1) is on between-day consolidation

Reis et al (2010)



Single pulse MEPs are larger when evoked on the downgoing phase of motor cortex alpha (or *mu*) activity (Zrenner et al, Brain Stimulation 2017)

This is true in periods of high alpha (mu) power but the relationship is opposite during periods of low power (Hussein et al, Ccortex 2018)



rTMS effect (100Hz triplets at approx. 1 Hz) also larger if stimulate on negative peak of mu (Zrenner et al, Brain Stimulation 2017).

Similar enhanced response when applied over DLPFC and linked to negative phase of theta rhythm. Increases theta power and theta-gamma coupling and decreases working memory response times (Gordon et al., 2022)

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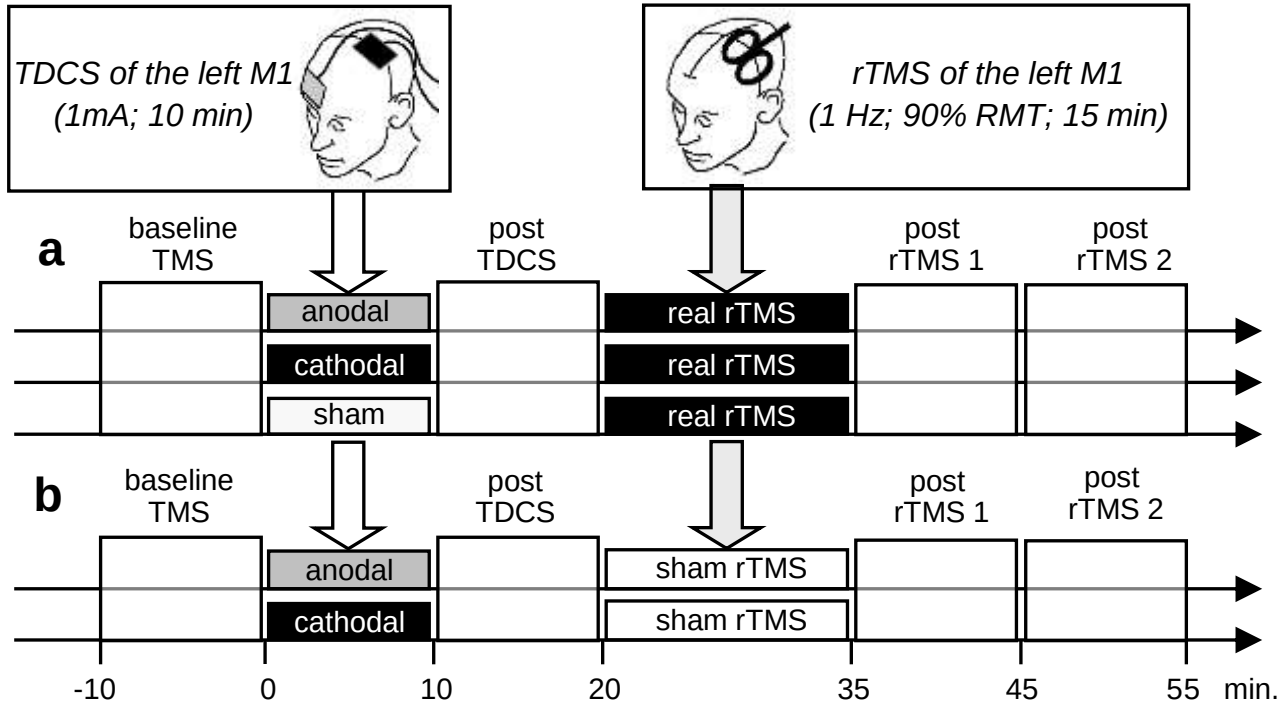
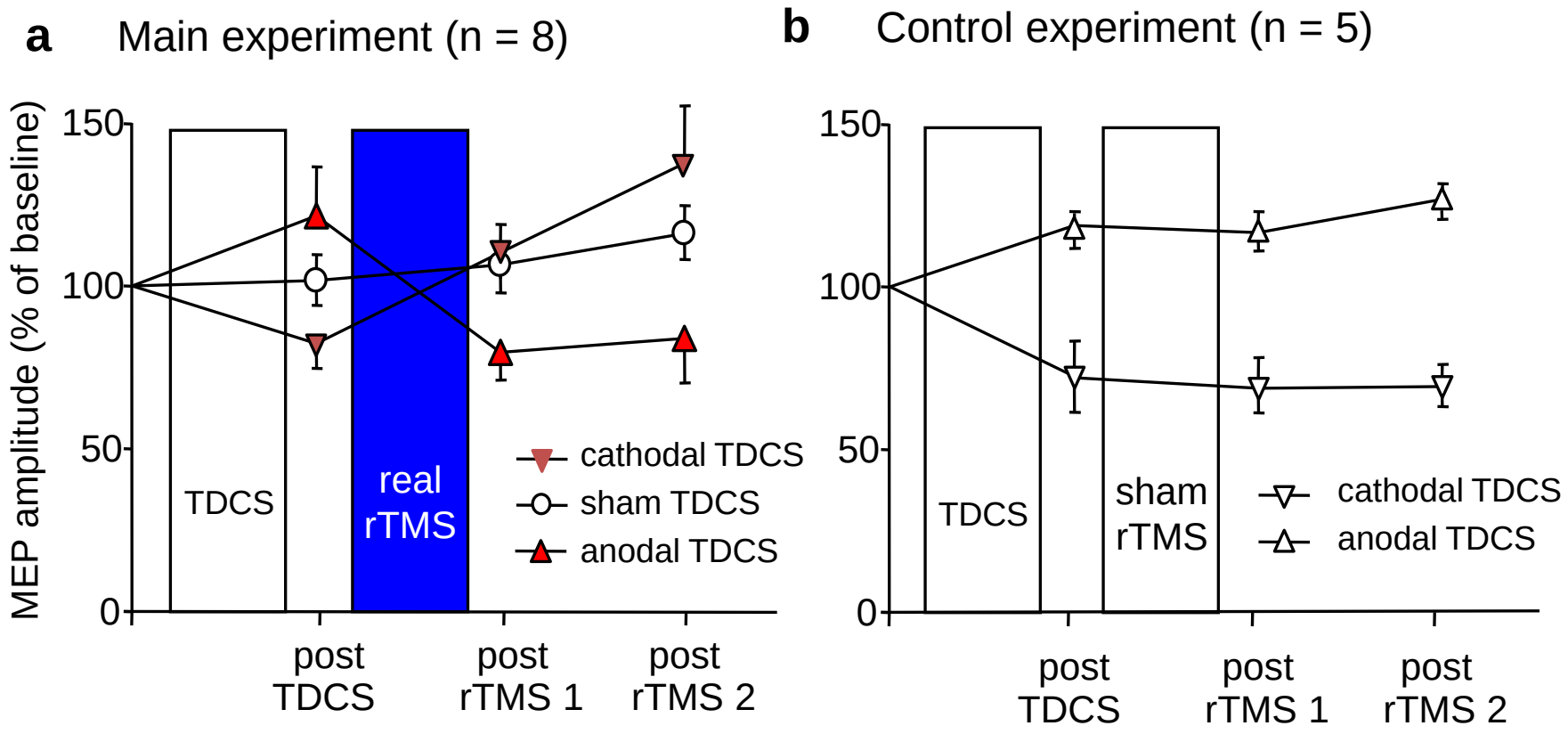
Control of “plasticity” by prior levels of activity

- Normally, the ability to modulate synaptic effectiveness is carefully modulated
  - Positive feedback nature of LTP can potentially be destabilising, “taking over” synaptic inputs to a neurone
- “Homeostatic plasticity”
  - If time averaged value of post-synaptic activity high then favour development of LTD
  - If value low, then favour LTP
- MAY be possible to investigate in humans
  - Siebner et al: precondition 1 Hz rTMS with a period of DC stimulation
  - Wasserman et al: precondition rTMS with rTMS



Siebner et al., 2004

[TDCS is 1mA direct current polarisation of the cortex through surface electrodes (Nitsche & Paulus, 2002). Give for >5min and leads to after effects on motor cortex excitability lasting several minutes.]



Siebner et al (2004)

“Homeostatic” Plasticity

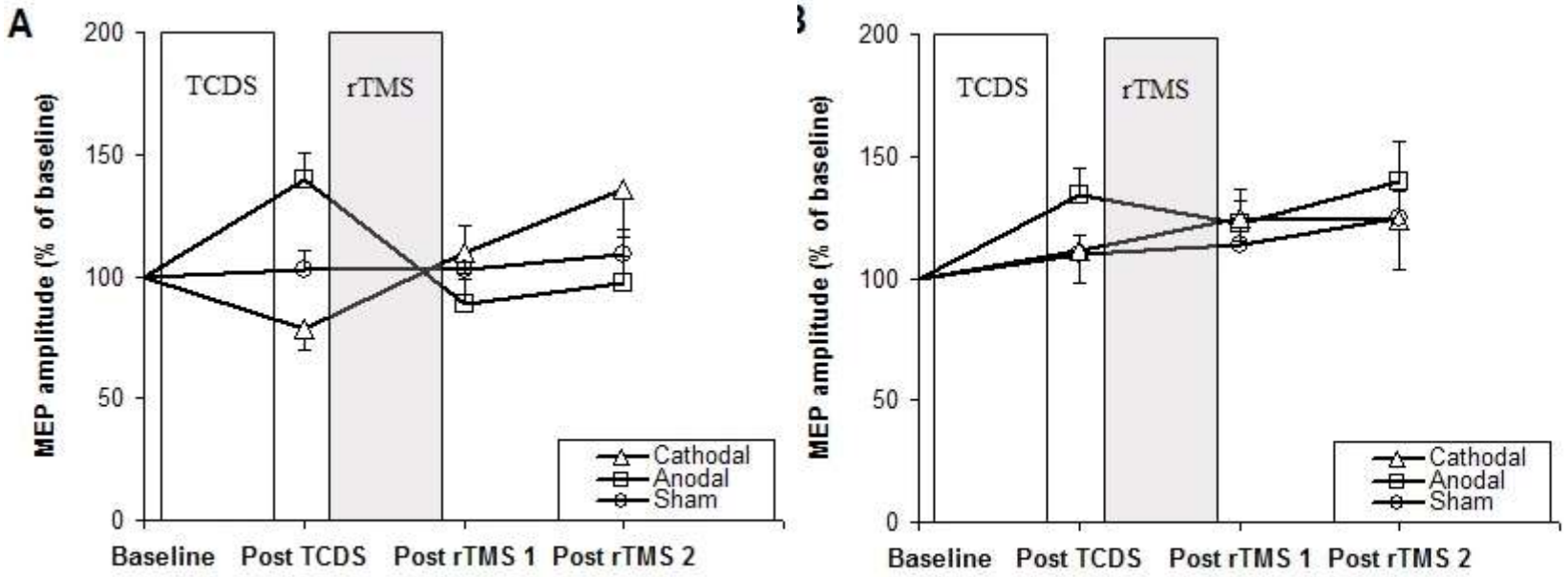
(Siebner et al, 2004)

- Preconditioning the cortex with anodal DC stimulation (usually excitatory) makes the response to 1 Hz rTMS suppressive
- Cathodal DC stimulation (usually inhibitory) makes the response to 1 Hz rTMS facilitatory

- Pathophysiology of homeostatic plasticity: abnormal in dystonia
  - In dystonia plasticity is “stuck” at an abnormally high level

Healthy controls

Hand dystonia

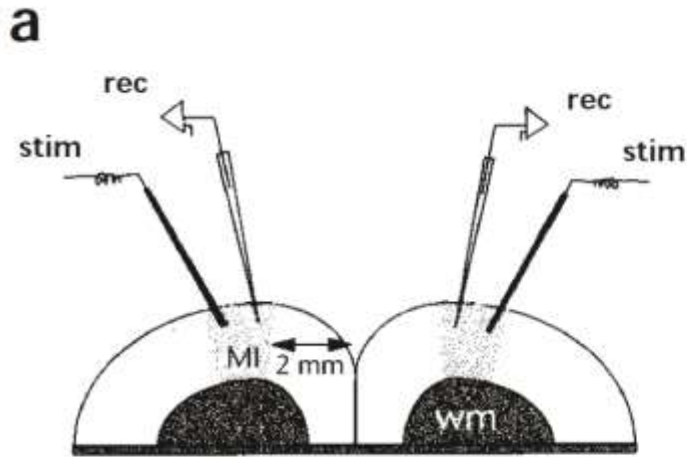


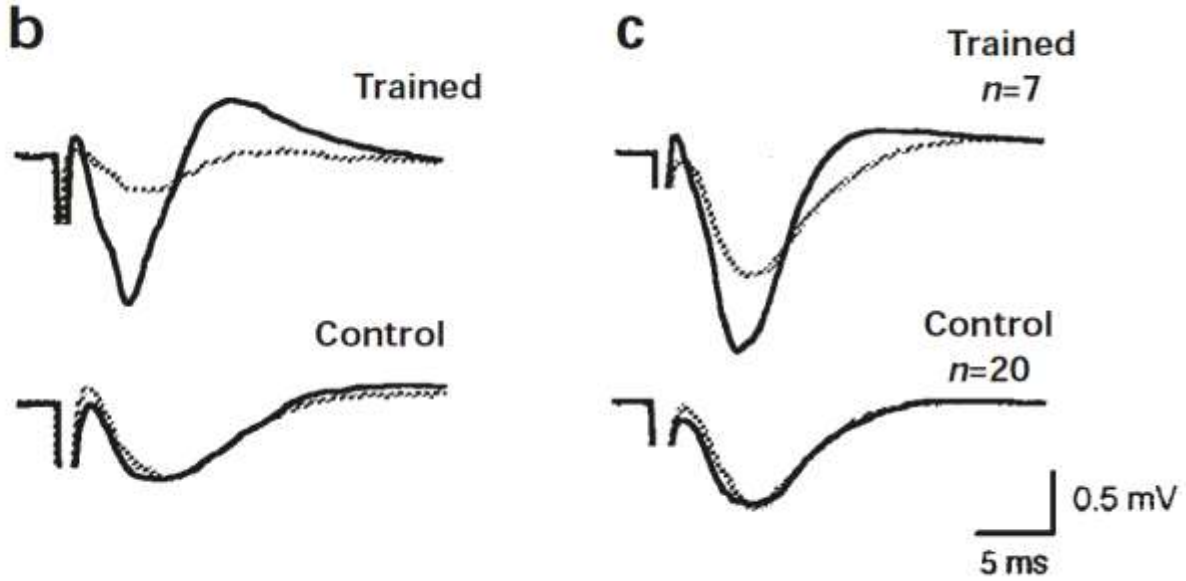
Quartarone et al, 2005

Plasticity produced by motor training interacts with stimulation-induced plasticity

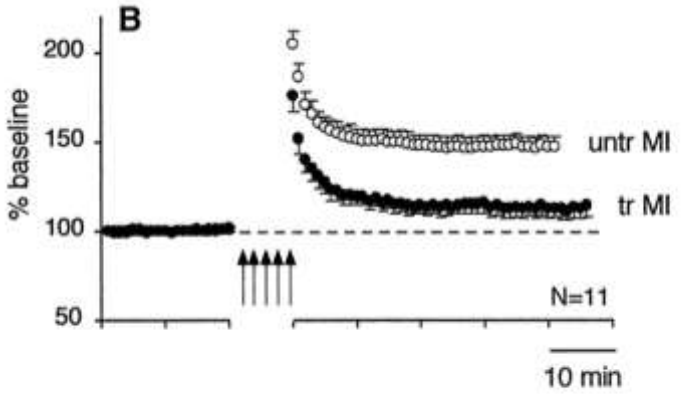
- Rat experiments: 5 days of training potentiates synaptic connections
- BUT reduces stimulation-induced LTP and enhances LTD

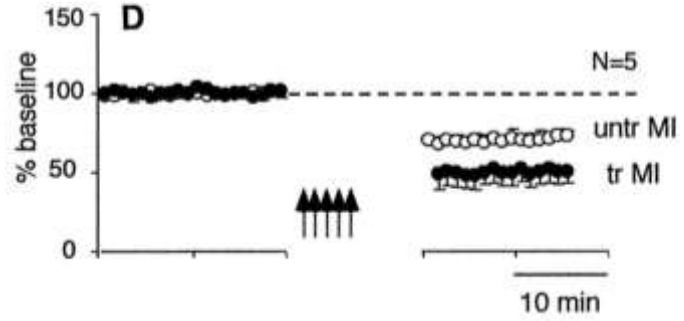
- Human experiments: 30 min training reduces LTP-like response to paired associative stimulation (PAS protocol) and enhances LTD-like effect





Rioult-Pedotti et al, 1998, 2000





Plasticity induced by motor training (not repeated movement) potentiates synaptic connections (LTP) (Left panel).
BUT reduces ability of theta burst stimulation to produce additional LTP, and makes induction of LTD easier (above)

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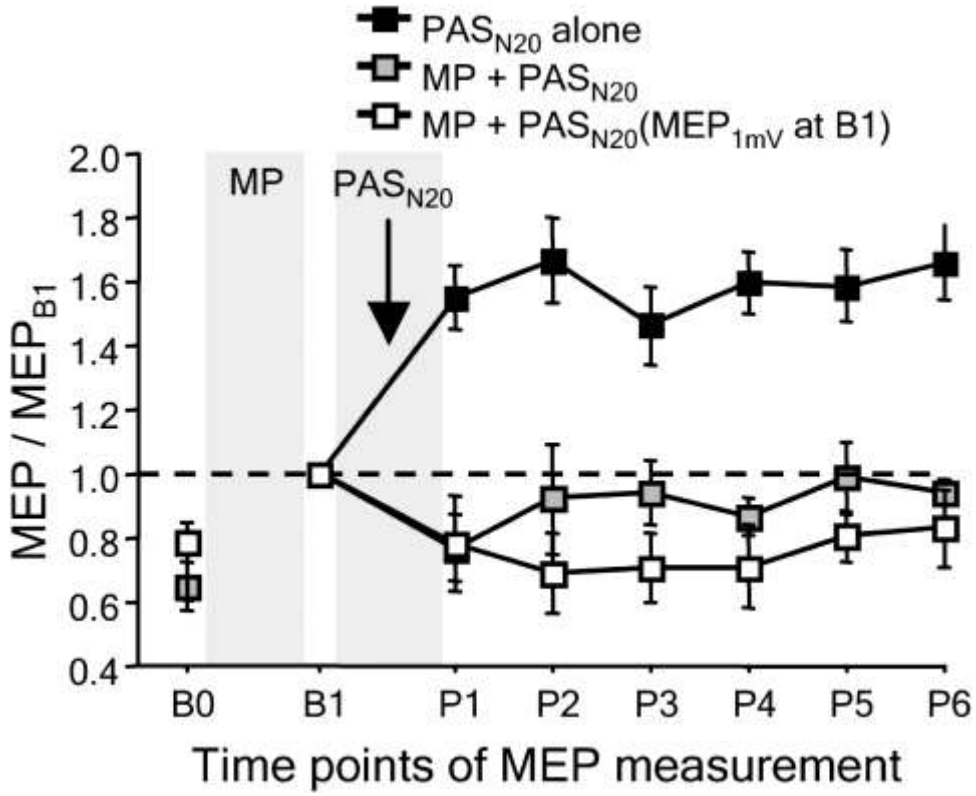
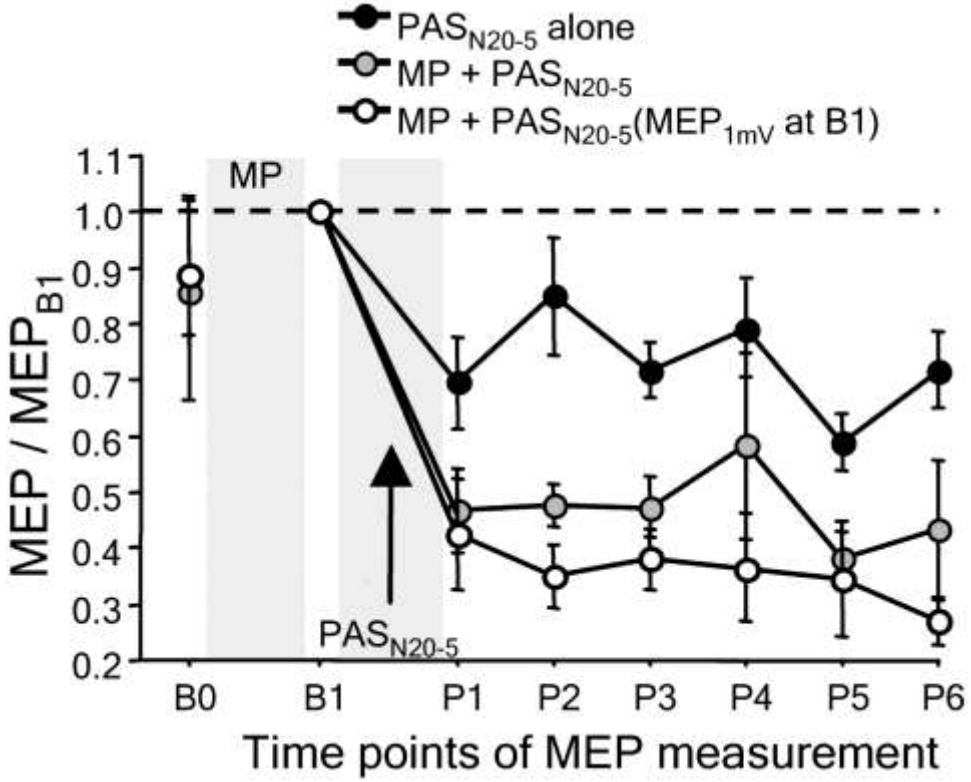
Motor training in humans depresses subsequent LTP-like plasticity but increases LTD-like plasticity





Ziemann et al., 2004

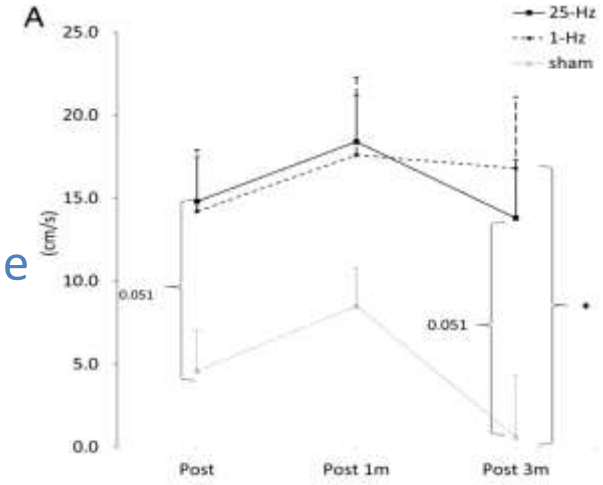
The priming protocol does not itself have to produce any plasticity

- Quadripulse rTMS (QPS: burst of 4 pulses repeated every 5s)
- A short period of QPS (no plasticity) affects response to subsequent QPS in a homeostatic way
- Interareal plasticity (QPS to SMA) can affect response to subsequent QPS of motor cortex

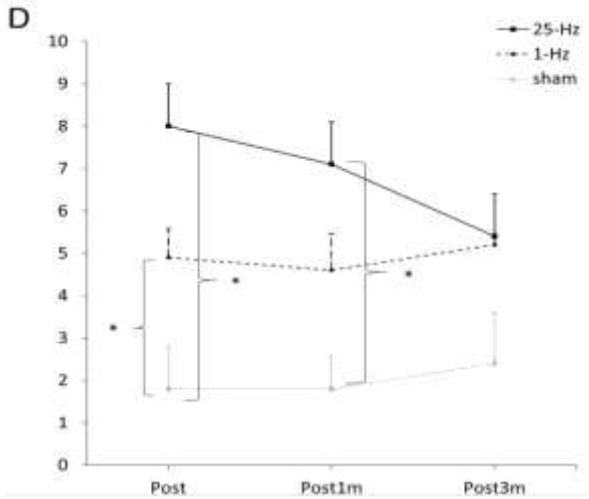
But in the real world……rTMS before training to improve rehabilitation

- Many trials of rTMS to “prime” brain to respond better to a training protocol: stroke, PD, addiction etc
- Rationale is that the increase in excitability produced by rTMS will interact *online* with plasticity developed by training
- But sometimes, training is improved by prior administration of either LTP-like or LTD-like plasticity protocols!
- How to decide which is going to happen?

Increase over baseline in maximum velocity



Reduction in motor section UPDRS



Chung et al., 2020

Parkinson's disease gait study

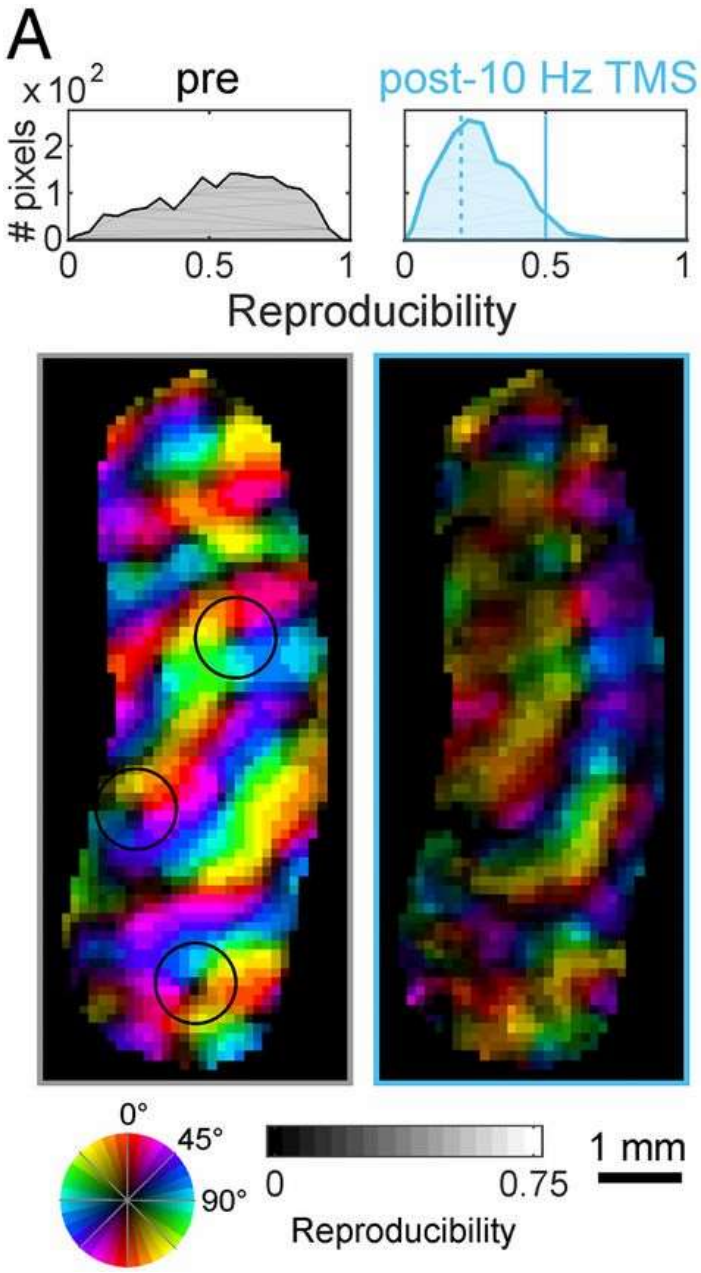
1Hz v 20Hz rTMS (1600 pulses 80% RMT over M1 leg area). 12 sessions over 3 weeks of rTMS plus 30min treadmill training.

Both forms of rTMS increase gait velocity to same extent and reduce motor UPDRS by same amount.

Expt in cats shows that rTMS improves learning by increasing the variability of cortical activity:

10 Hz rTMS increases variability and improves response to orientation training (Kozyrev et al 2018)

- Examine visual orientation maps in V1 before and after rTMS
  - Different areas of visual cortex are preferentially sensitive to particular orientations of straight line
- Variability of maps increases after rTMS
- But the ability of repeated stimulation with a directional grating to change maps is increased after rTMS
  - Many repetitions of the same orientation of visual stimulation increase the amount of cortex that responds to that orientation….a form of plasticity in visual cortex



Variability of response increases after rTMS

Surface map of V1 where colours indicate the preference for lines of a particular orientation.

After rTMS the map is similar but the responses are not as reproducible and are less specific to orientation (they are “noisier”)

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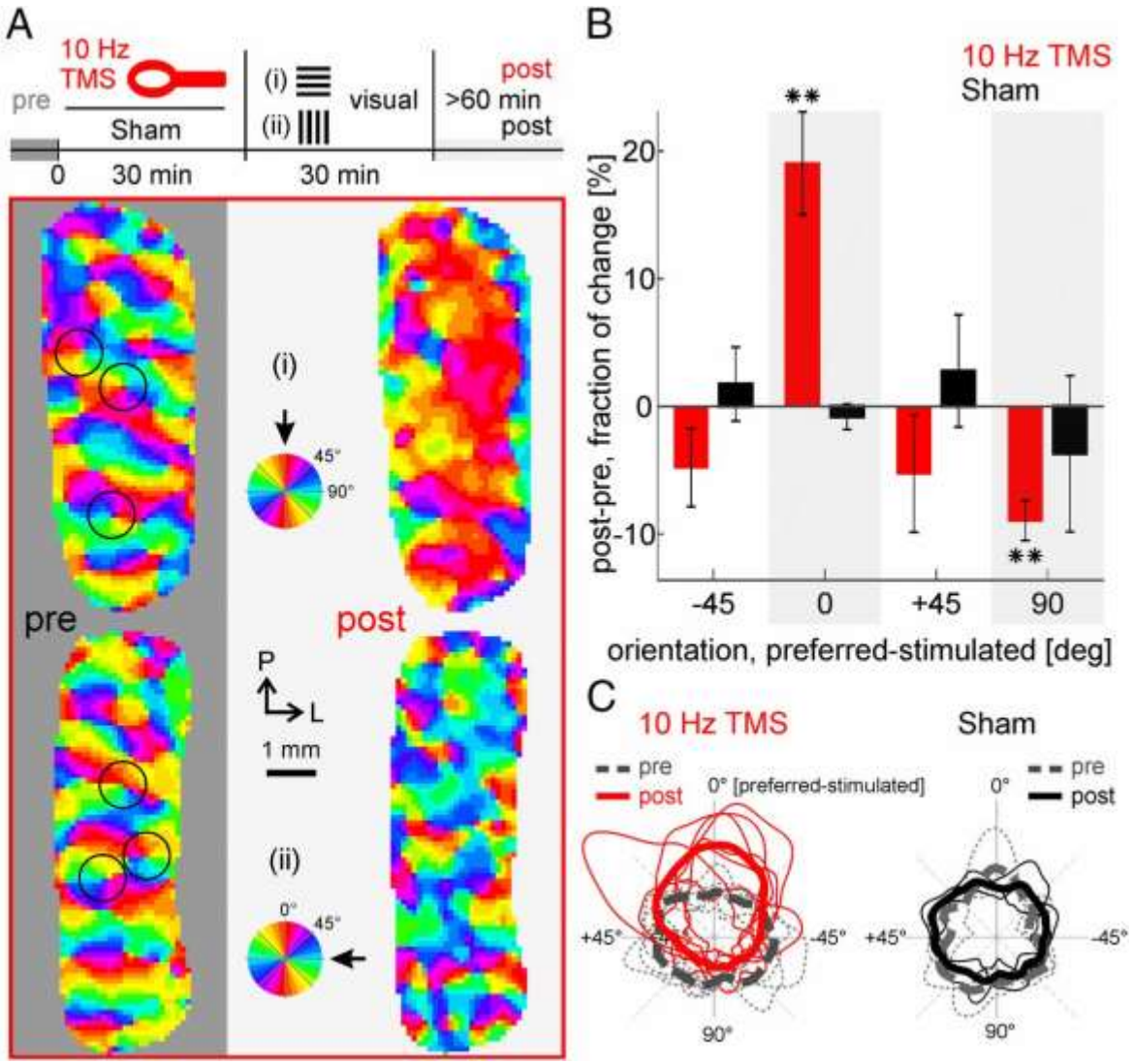

Transient destabilisation of the map makes the circuits more sensitive to repeated orientation (more “plastic”)

Testing the effect of repeated presentation of a vertical grating (red colour on left maps) or horizontal grating (blue colour on left maps).
A short period of presentation usually has no effect on map. BUT after 10 Hz rTMS, the maps change a lot (more red colour on upper map; more blue on lower map)

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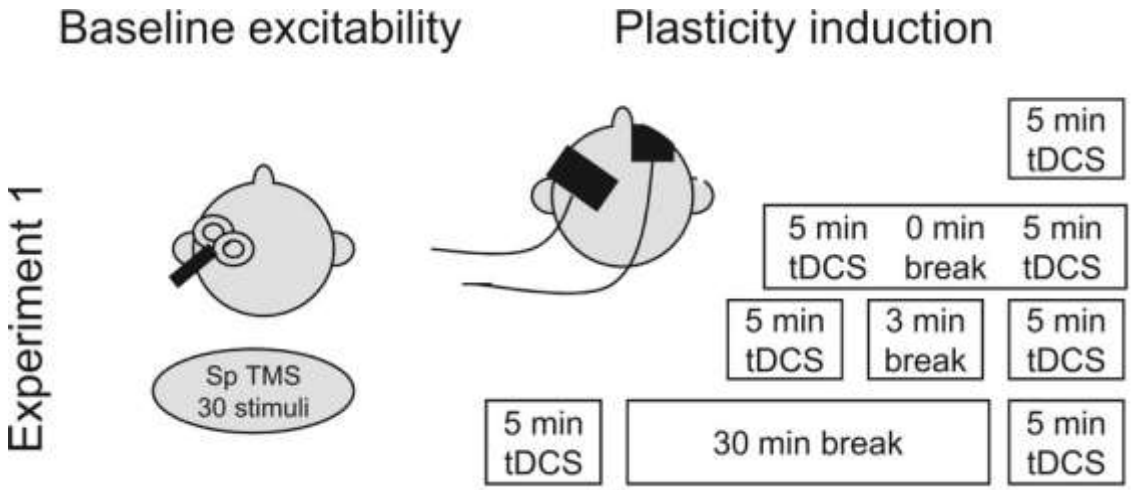
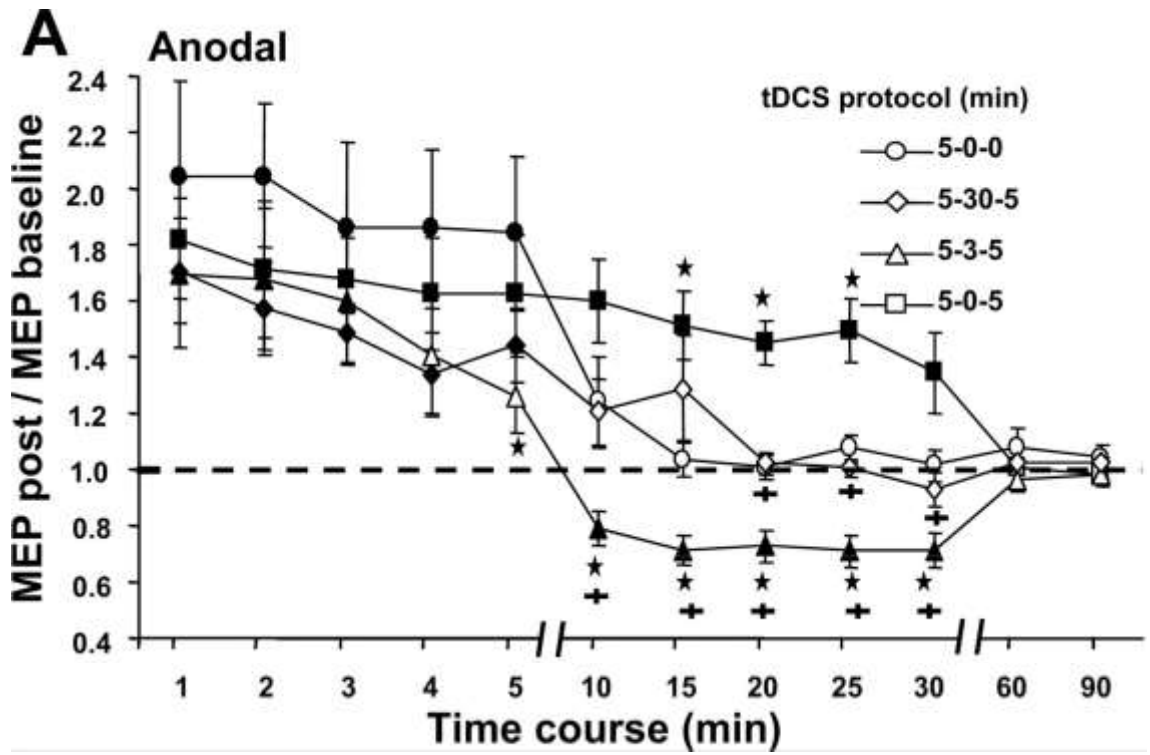
- rTMS makes it much easier to change the orientation map in visual cortex
- It does this by making the synaptic connections more variable, and easier to change

- This is exactly what is needed to interface rTMS with rehabilitation.
- Increased variability will make learning new connections easier and outcomes better.

- Maybe homeostatic interactions are not so important??



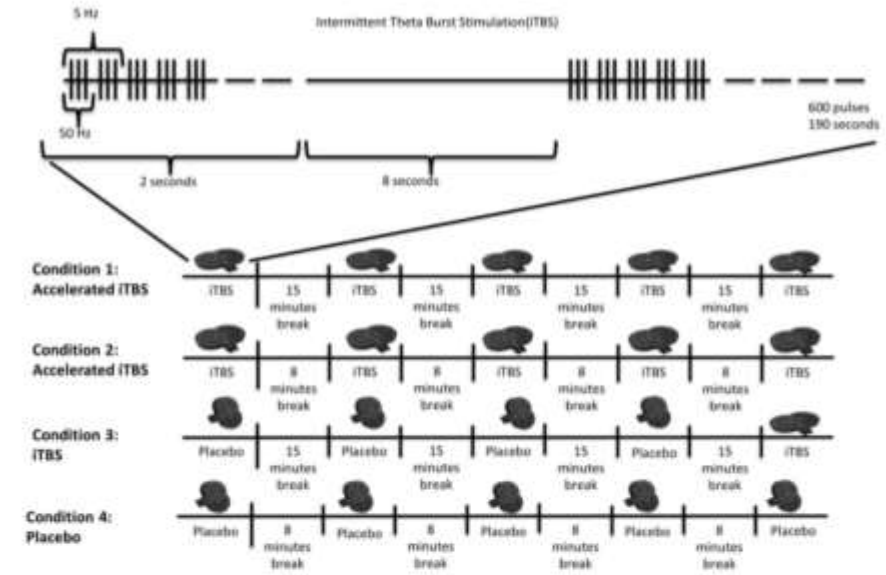


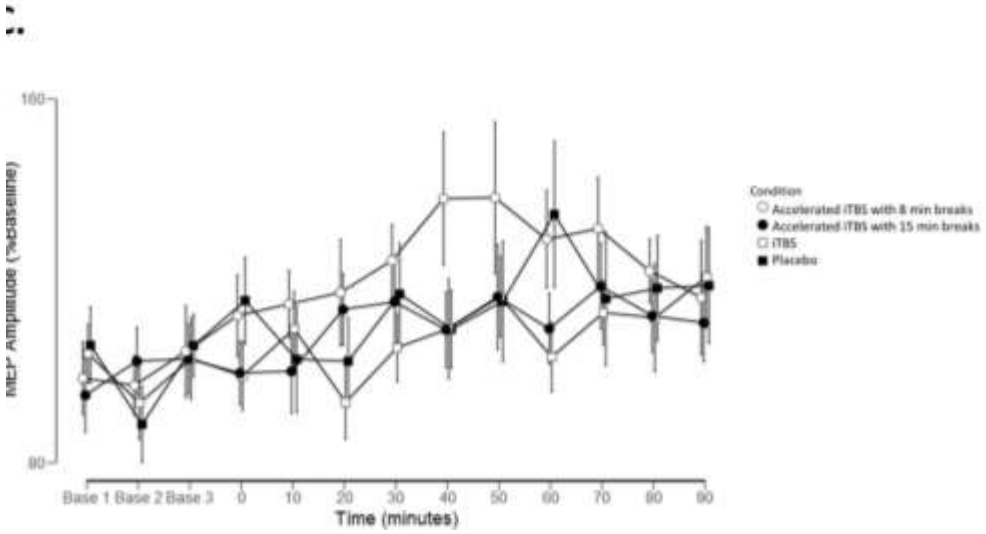
Importance of the interval between priming and test protocols

Fricke et al., 2011

Comparing 10 min of anodal TDCS with two periods of 5min TDCS separated by 3 min or 30 min.

A 3min interval reverses the effect from facilitatory to inhibitory, but a 30min interval has no effect.





Thomson et al., 2019

Metaplasticity and accelerated theta burst protocols?

Accelerated TBS gives 5 sessions of TBS per day for treatment of depression. Is there any effect of a previous TBS application on subsequent ones (homeostatic/reinforcing)?

In this motor cortex study no effect of prior protocols.

Considerations about time

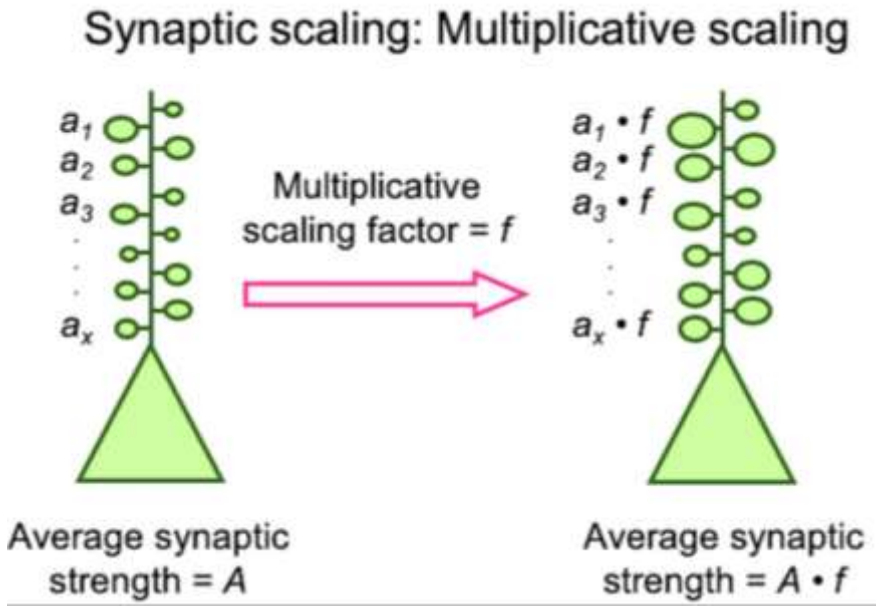
- Standard practice usually says that you can perform two sorts of plasticity intervention without any interaction between them if you leave a day between expts.

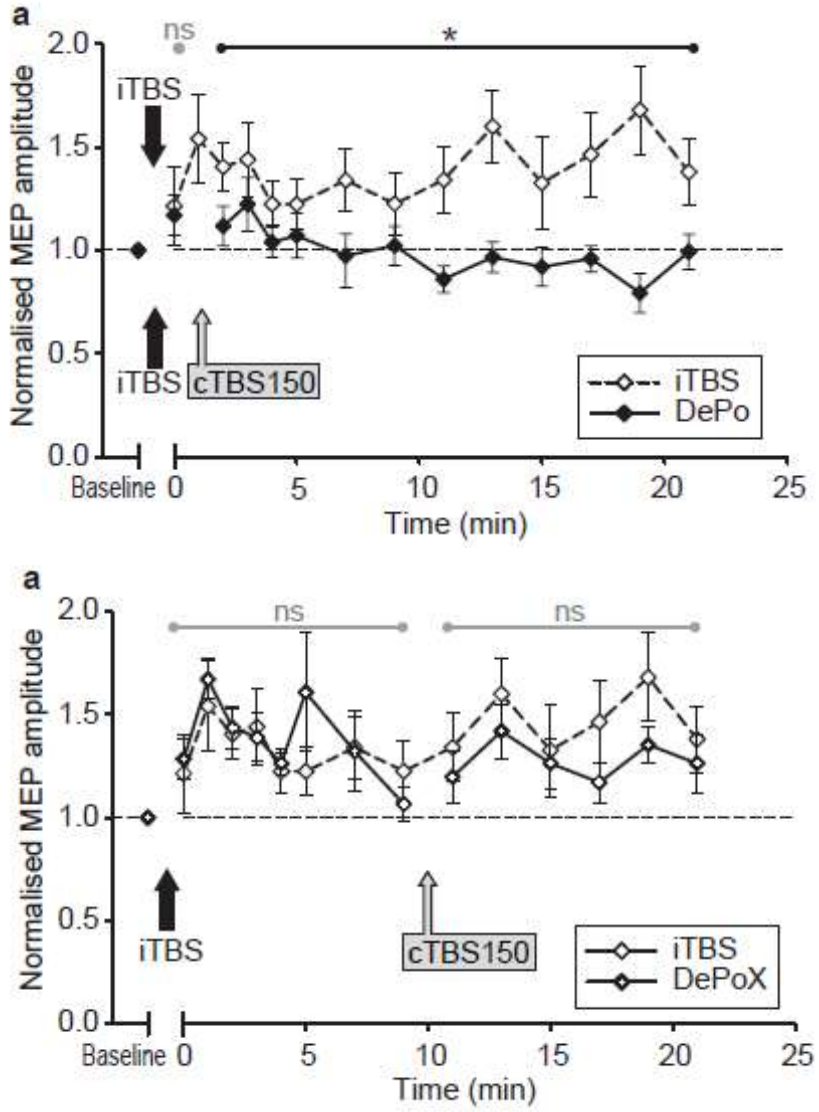
- WHY?

- **Theoretically** because of “synaptic scaling”: the mean firing of a neuron is controlled over time to stay within a narrow band.
- This can involve reducing/increasing the effectiveness of all synaptic contacts onto the neuron so that the relative weights of different synaptic inputs remains constant

A **simple** model of synaptic scaling. If there has been an overall LTD-like effect on synaptic activity in one set of connections, (e.g. a3 versus a1) then the average activity of the neuron will decline.

A multiplicative synaptic scaling, raising the effectiveness of all synapses can compensate without losing the relationship between the strength of a1 and a3



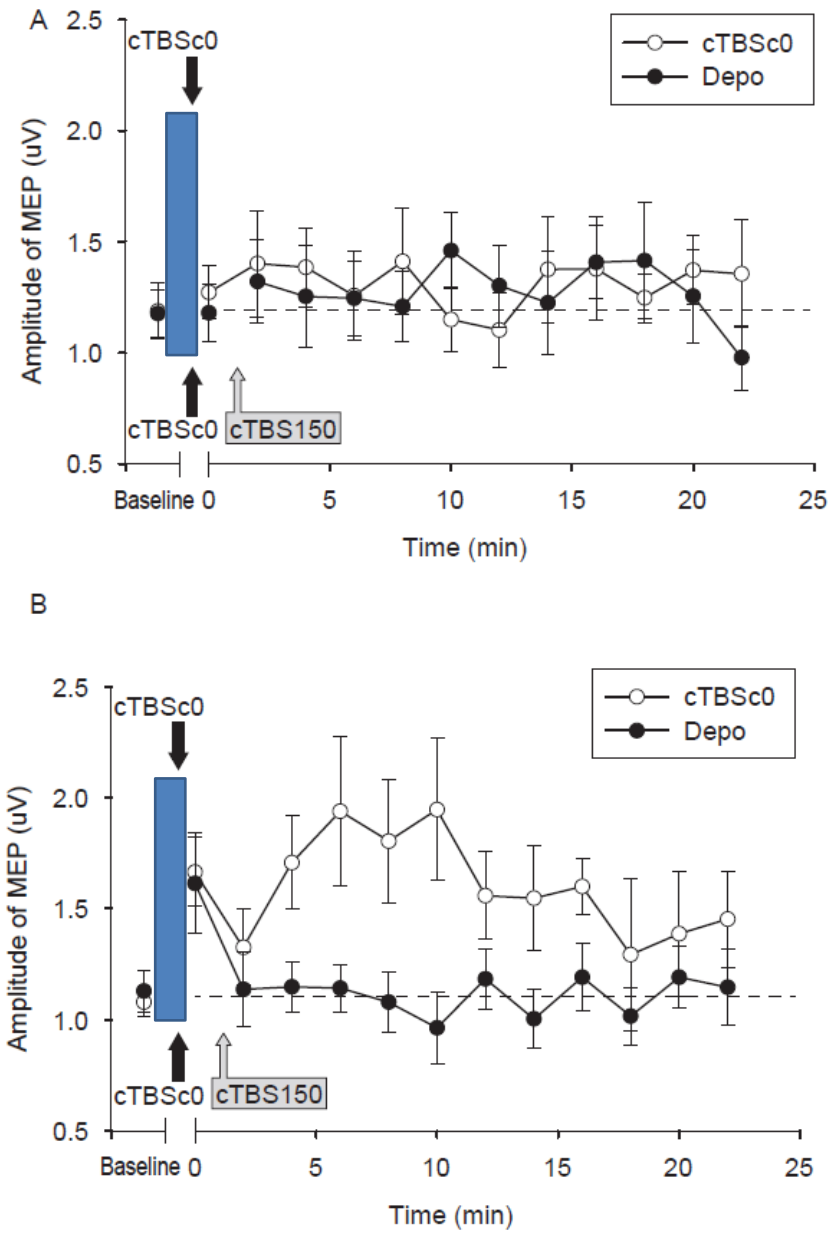


De-potentiation and De-depression

The response to a plasticity intervention can be abolished if an opposite subthreshold intervention is applied within a short period of time

The Expected LTP or LTD is abolished

Huang et al., 2010

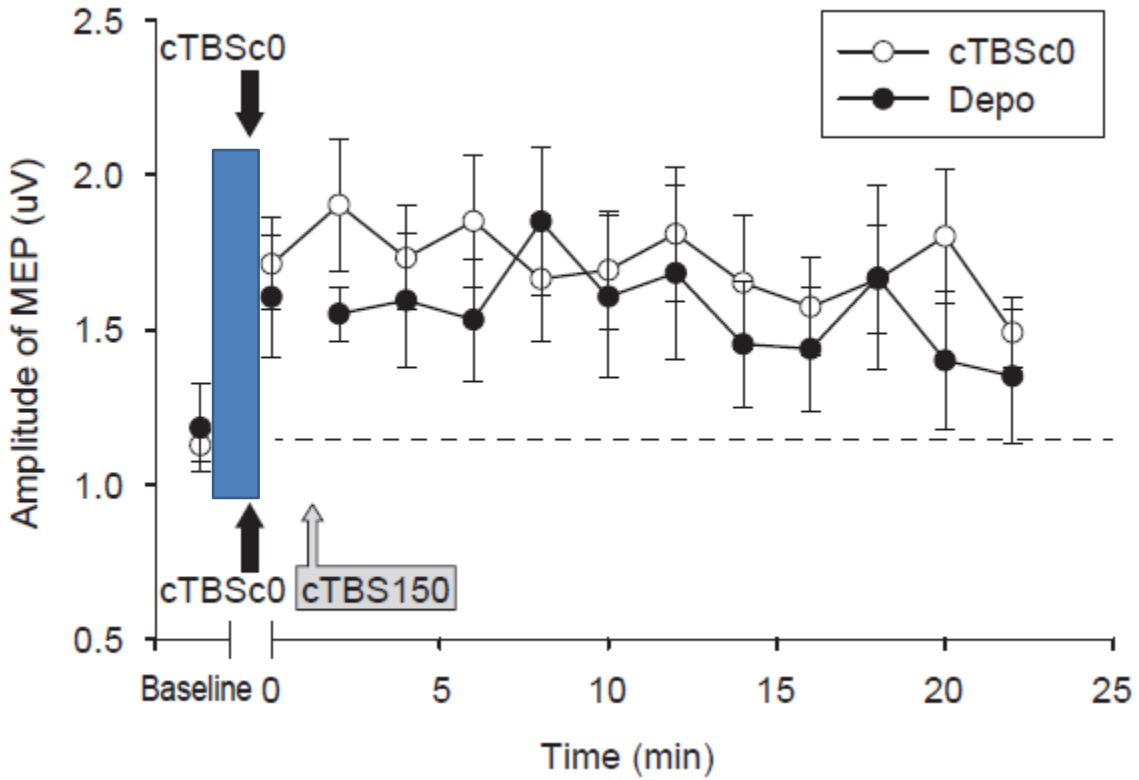


Pathology of plasticity in Parkinson's disease

When patients with PD are OFF therapy they show no LTP-like and no effect of the depotentiation protocol.

When non-dyskinetic patients with PD are ON therapy they show good LTP-like plasticity which can be depotentiated by a short conditioning stimulation (so long as it is applied within 5 min of the original LTP protocol).

(Huang et al Brain 2011)



Patients who have dyskinesias show good LTP-like plasticity BUT no response to the depotentiation protocol.

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Take-home messages

- Metaplastic effects are well-described in animal expt
- BUT transferring these conclusions to human non-invasive brain stimulation is complicated
  - Animal expts can isolate effects of individual synapses on single neurons
  - Human stimulation affects many categories of neuron, and an overall excitatory effect is likely to result from a mixture of underlying effects
  - We need to know more about the interval between prior activity and present plasticity and the time span over which prior activity is relevant, and whether to prioritise online versus history effects.