Title

Biophysical modeling of neural plasticity induced by transcranial magnetic stimulation

Authors

Marcus T. Wilson[1], Ben D. Fulcher[2,4,5], Park K. Fung[3], Peter A. Robinson[4,5], Alex Fornito[2], Nigel C. Rogasch[2]*

Affiliations

1. School of Engineering, Faculty of Science and Engineering, University of Waikato, New Zealand
2. Brain and Mental Health Laboratory, School of Psychological Sciences and Monash Biomedical Imaging, Monash Institute of Cognitive and Clinical Neuroscience, Monash University, Australia
3. Department of Ophthalmology, Downstate Medical Center, State University of New York, U.S.A.
4. School of Physics, The University of Sydney, Australia,
5. Center for Integrative Brain Function, University of Sydney, Australia
6. Center for Integrative Brain Function, Monash University, Australia

***Corresponding author**

Nigel C. Rogasch
Monash University
Building 220, Clayton Campus
770 Blackburn Rd.
Clayton, VIC, 3800
Australia
nigel.rogasch@monash.edu

Abstract

Transcranial magnetic stimulation (TMS) is a widely used noninvasive brain stimulation method capable of inducing plastic reorganisation of cortical circuits in humans. Changes in neural activity following TMS are often attributed to synaptic plasticity via process of long-term potentiation and depression(LTP/LTD). However, the precise way in which synaptic processes such as LTP/LTD modulate the activity of large populations of neurons, as stimulated en masse by TMS, are unclear. The recent development of biophysical models, which incorporate the physiological properties of TMS-induced plasticity mathematically, provide an excellent framework for reconciling synaptic and macroscopic plasticity. This article overviews the TMS paradigms used to induce plasticity, and their limitations. It then describes the development of biophysically-based numerical models of the mechanisms underlying LTP/LTD on population-level neuronal activity, and the application of these models to TMS plasticity paradigms, including theta burst and paired associative stimulation. Finally, it outlines how modeling can complement experimental work to improve mechanistic understandings and optimize outcomes of TMS-induced plasticity.

Keywords
transcranial magnetic stimulation; biophysical modeling; plasticity; theta burst stimulation; paired associative stimulation

Abbreviations
TMS, transcranial magnetic stimulation; LTP, long-term potentiation; LTD, long-term depression; rTMS, repetitive TMS; TBS, theta burst stimulation; PAS, paired-associative stimulation; MEP, motor-evoked potential; cTBS, continuous TBS; iTBS, intermittent TBS; NMDA, n-methyl-d-aspartate; CaDP, calcium dependent plasticity; EEG, electroencephalography; MRI, magnetic resonance imaging; STDP, spike timing dependent plasticity; BCM, Bienenstock-Cooper-Munro; GABA, gamma-aminobutyric-acid; ISI, inter-stimulus interval.

1. Introduction

Transcranial magnetic stimulation (TMS) is a powerful tool for studying human brain function (Hallett, 2007). Using the principles of electromagnetic induction, TMS can noninvasively depolarize cortical neurons across the skull and scalp (Rothwell, 1997). When applied using certain patterns of stimulation, TMS can induce plastic increases or decreases in cortical excitability which outlast the period of stimulation, reminiscent of long-term potentiation/depression (LTP/LTD)-like mechanisms observed in vitro (Cooke and Bliss, 2006). The ability of TMS to alter neural activity has resulted in a wide range of uses, from studying the mechanisms of plasticity in humans (Ziemann et al., 2008), to inferring the functional roles of brain regions in behavior (Pascual-Leone et al., 2000), to providing clinical treatments (Lefaucheur et al., 2014). However, the field is facing several challenges, including large interindividual variability in response to TMS (Ridding and Ziemann, 2010), difficulty in optimizing protocols due to nonlinear relationships between stimulation parameters and outcomes (Gamboa et al., 2010), and problems translating the detailed knowledge gained from the motor system to non-motor regions which often lack clearly observable output that can be used to measure the effects of stimulation. (Parkin et al., 2015). At the centre of these challenges is a poor understanding of the cellular and molecular mechanisms underlying TMS-induced plasticity (Müller-Dahlhaus and Vlachos, 2013), which makes it difficult to interpret outcomes at the level of neural populations as measured in human experiments. As such, a general theory that explains how TMS induces plasticity across multiple brain scales and regions is urgently required.

Our aim here is to overview how biophysically-informed modeling approaches can be applied to better understand TMS-induced plasticity, thus addressing the challenges outlined above. Previous discussions have focused on modeling the TMS induced electric field on the cortical surface (Neggers et al., 2015), the generation of motor output following TMS (Triesch et al., 2015), and the neural and behavioural changes following TMS plasticity paradigms (Hartwigsen et al., 2015). We focus primarily on a small, but growing literature interested in modeling the neural plasticity harnessed by TMS. These models aim to explain and predict data observed in TMS plasticity experiments (e.g., changes in cortical excitability) in terms of underlying physiological mechanisms. The central idea is to capture the relevant physiological mechanisms using mathematics, where the variables and parameters of the model equations may be physiological properties such as receptor conductances, membrane potentials, or firing rates. We focus specifically on models of plasticity that have been applied to TMS paradigms, but note that the same models could also be applied to other brain stimulation methods such as transcranial direct current stimulation (tDCS) to complement existing tDCS modeling [for reviews see (Bestmann et al., 2015; Rahman et al., 2015)].

We begin by briefly overviewing the TMS paradigms used to induce plasticity in humans. We then introduce how biophysically-based models, including neural population models, have been used to describe neural plasticity mechanisms. Finally, we overview the application of modeling to TMS plasticity paradigms, discuss how such models can inform the optimization of plasticity-inducing paradigms for TMS, and outline future research directions to further refine our

understanding of the interactions between TMS and plasticity across different brain regions. Modeling will play a key role in resolving many of the seemingly inconsistent and unexpected findings in the field of TMS research. We thus argue for greater integration of modeling and experimentation to guide future research.

2. Plasticity-inducing TMS paradigms

To illustrate the need for models of TMS induced plasticity, we briefly introduce the array of common repetitive TMS (rTMS) paradigms used to induce plasticity in humans. For a review outlining the detail of these TMS plasticity paradigms and the current position of the field, please see (Huang et al., 2017; Suppa et al., 2017, 2016).

'Traditional' rTMS involves the repeated application of stimuli at frequencies typically ≥ 1 Hz (Fitzgerald et al., 2006). For higher frequencies (e.g ≥ 5 Hz), stimulation is often separated in to shorter trains followed by rest periods to avoid coil overheating and for safety considerations (Rossi et al., 2009). More recently, patterned forms of rTMS have been introduced such as theta burst stimulation (TBS), which involves delivering high frequency stimuli (e.g. 50 Hz) nested in lower frequency rhythms (e.g. 5 Hz) (Huang et al., 2005; Suppa et al., 2016). Another form of patterned stimulation involves delivering repeated paired pulses with interstimulus intervals of 1.5 ms (Thickbroom et al., 2006) or 4 pulse bursts at interstimulus intervals ranging from 1.5 to 100 ms (known as quadripulse stimulation) (Hamada et al., 2008, 2007) repeated every 5 seconds. Paired associative stimulation (PAS) is an alternative form of rTMS inspired by spike-timing dependent plasticity, and involves pairing a peripheral nerve stimulus with TMS to the motor cortex (Stefan et al., 2000; Suppa et al., 2017). A more recent variant is cortico-cortical PAS which involves pairing the stimulation of two different cortical areas with dual TMS coils (Arai et al., 2011; Buch et al., 2011).

Most research to assess the capacity of these paradigms to induce plasticity has occurred in the motor system due to the ease of measuring motor outputs. For instance, single TMS pulses given to the motor cortex at suprathreshold intensities result in compound action potentials in the muscle targeted by the stimulated cortical region. This TMS-evoked muscle activity, termed a motor-evoked potential (MEP), can be easily measured using surface electromyography. The amplitude of the MEP is influenced by both excitatory and inhibitory circuits within and outside the motor cortex as well as spinal excitability, but is often used to indirectly infer changes in cortical excitability induced following TMS plasticity protocols (Di Lazzaro et al., 2008). A large body of work over the last several decades has outlined how altering the parameters of these TMS paradigms can change the outcome of stimulation. For instance, applying rTMS at 1 Hz, TBS continuously for 600 pulses (cTBS), or PAS with a 10 ms interval between nerve stimulation and TMS (so that the afferent sensory input arrives at the cortex after the TMS pulse) often reduces MEP amplitude following stimulation. In contrast, applying rTMS at higher frequencies (> 5 Hz), TBS with an intermittent pattern of 2 s of stimulation followed by an 8 s break (iTBS), or PAS with a 25 ms interval between nerves stimulation and TMS (so the sensory input arrives contemporaneously with the TMS pulse) often increases MEP amplitude (Huang et al., 2017). In addition to the frequency and pattern of stimulation, other parameters

such as stimulation intensity, number of pulses, pulse shape, and brain state also influence the outcome of each paradigm, although often in unexpected ways (Pell et al., 2011).

The changes in MEP amplitude observed following the aforementioned TMS protocols are broadly consistent with changes in synaptic efficacy following plasticity mechanisms such as LTP/LTD (Hoogendam et al., 2010). First, the changes in excitability induced by TMS paradigms last beyond the period of stimulation for short periods (~30 min), consistent with synaptic plasticity (Huang et al., 2005; Peinemann et al., 2004; Stefan et al., 2000). Second, the effects of low frequency rTMS, TBS and PAS paradigms are blocked or reversed by NMDA receptor (Fitzgerald et al., 2005; Huang et al., 2007; Stefan et al., 2002) and, calcium channel antagonists in the case of TBS and PAS (Wankerl et al., 2010; Weise et al., 2016). Third, the outcomes of TMS plasticity paradigms are dependent on the history of cortical activation (e.g., past plasticity induced by another TMS protocol or motor learning), consistent with metaplasticity (Iyer et al., 2003; Müller et al., 2007; Todd et al., 2009; Ziemann et al., 2004). In addition to synaptic plasticity, other nonsynaptic mechanisms may also contribute to changes in MEP amplitude, such as changes in membrane excitability, biochemistry, or gene expression (Pell et al., 2011; Tang et al., 2015). However, the contributions of these mechanisms to TMS plasticity are yet to be fully explored.

Despite the widespread use of TMS in research and clinically, a major issue facing the field is the large inter-individual variability in response to TMS plasticity paradigms. Recent studies have demonstrated that only ~50% of participants show the expected plasticity effects following a particular stimulation protocol (Hamada et al., 2013; Hinder et al., 2014; López-Alonso et al., 2014; Maeda et al., 2000; Müller-Dahlhaus et al., 2008). The reasons for this variability are likely complex, involving an interplay between trait and state characteristics (Huang et al., 2017; Ridding and Ziemann, 2010). A major challenge is distilling the enormous parameter space available for delivering TMS to find the optimal combination of parameters for inducing plasticity in a controlled manner within and between individuals. In order to tackle this problem in a principled way, it is essential to develop a detailed understanding of the mechanisms underlying TMS plasticity, both in the motor cortex and other cortical regions. However, it is unclear how the plasticity mechanisms that likely underlie the effects of TMS, such as LTP/LTD, scale from the microscale/synapse level in animal studies to the macroscale/brain region level in human studies (Müller-Dahlhaus and Vlachos, 2013). In order to unify the often disparate results within and between TMS paradigms, we urgently require a framework that structures our results and understanding in terms of putative physiological mechanisms.

3. Mathematical modeling and neural plasticity

Biophysically-based models have the potential to explain patterns in brain-imaging data in terms of the physiological mechanisms that may underlie them. After specifying the mathematical model in terms of known neurophysiology, computers can then be used to simulate TMS-induced plasticity dynamics numerically to produce predictions that can be compared to experimental data. Conversely, given experimental data, the models can be inverted to infer model parameters (which putatively correspond directly to physiological quantities) that best

explain the data. In this way, mathematical models of the brain act as a bridge between macroscale experimental data and the unobserved neurophysiological mechanisms that generate them.

Mathematical models of the brain can be formulated at multiple levels of description, from the microscopic scale of single neurons, through to the complex interplay of macroscopic neural populations that yield whole-brain dynamics (Breakspear, 2017; Deco et al., 2008). The appropriate level of description to include in a model depends on the question of interest and scale of analysis and measurement. Including too much complexity may lead to an under-constrained model that could fit any phenomenon, whereas oversimplifying may obscure important phenomena. In humans, neural activity is commonly measured at the macroscale, e.g., using MRI or EEG, thus reflecting the combined activity of millions of neurons. The electrical stimulation of bulk populations of neurons in the brain by externally applied fields, such as TMS, also typically stimulates a few square centimetres of cortex. Rather than explicitly modeling the complex dynamics of millions of individual neurons, it is more appropriate to simulate the collective dynamics of neurons at this macroscopic scale of stimulation and measurement.

To model the brain at this macroscopic scale, we require a reduced description of the dynamics of a large population of spiking neurons. This can be achieved by taking a population density approach that involves describing the likely distribution of a large number of neuronal states over time. Here we refer to such models as *neural population models*. Neural population models contain equations that define the dynamics of the properties of large populations of neurons, and include parameters that encapsulate physiologically-measurable mechanisms, such as those that may be manipulated using TMS. Different populations (such as excitatory pyramidal neurons and inhibitory interneurons) can be linked together, with weights that represent the number and strengths of synaptic connections between populations, as functions of neural type and location. Once constructed, models can be analyzed mathematically, or simulated numerically with a computer to fit experimental data and generate predictions to guide future experiments (Bojak and Liley, 2010; Deco et al., 2008; Jirsa and Haken, 1996; Nunez, 1974; Robinson, 2005; Robinson et al., 2005, 1997).

A very general class of population-based model is that of neural field models. These models average the properties and dynamics of various neural populations over scales of a few tenths of a millimeter to yield equations for the evolution of average quantities such as firing rate $Q_e(\mathbf{r},t)$ as functions of continuous position $\mathbf{r}$ and time t (i.e., as *fields*). In these models, axons transmit averaged influences between different locations, as activity fields, thereby allowing for time delays and finite ranges of these influences (Breakspear, 2017; Deco et al., 2008; Pinotsis et al., 2014). An important special case of neural field models is to consider the limit in which the activity is spatially uniform; this removes the need to track spatial position, while retaining the effects of axonal ranges and delays, which make essential contributions to system stability and temporal responses. A further approximation is to neglect these delays, which can be valid for low frequency activity whose timescale is much longer than the axonal propagation time across the cortex (i.e., frequencies well below 5 Hz) and whose spatial scales are longer than

corticocortical white matter axonal ranges (several cm). This approximation yields neural mass models, which have been used in some applications, and which essentially shrink the system to a spatial point (Deco et al., 2008). It is worth mentioning that another type of neural mass model has also been discussed, in which populations of neurons have been locally coupled without regard to delays, and then these masses have been taken to represent different values of $\mathbf{r}$ (Breakspear, 2017). In these approaches, the different locations are then coupled together using coupling strengths and time delays that are artificially constructed, or taken from an anatomical ``connectome''. Unless particular care is taken, this latter procedure is not valid – it fails at a very fundamental level because the coupling strengths and delays are not consistent with those implied by the local dynamics in the limit of fine discretization. The most appropriate procedure is to start with a spatially continuous neural field approximation and discretize self-consistently at the desired scale, as is routinely done in spatiotemporal simulations of neural fields, for example.

We now consider some details of neuronal population models. Figure 1A shows an example of a neuronal population model consisting of populations of cortical excitatory and inhibitory cells, driven by TMS. Neuronal populations are represented here by the mean cell body potential, V_i, of neurons which can be simulated from the parametrized set of interactions, time constants and length scales. This mean membrane potential can be related to the mean firing rate, Q_j, through a parametrized sigmoidal function (Fig. 1B) (Freeman, 1975). Some of the other key biophysical parameters of the model, including coupling strengths between populations, ν_{jk} (which specify the strength of excitation or inhibition between populations), and timescales, γ_j (which set the intrinsic timescale of activity for a population), are indicated. Setting these parameters specifies the model; for example, setting $\nu_{ei} < 0$ specifies inhibition from population $i \rightarrow e$, setting $\nu_{ie} > 0$ specifies excitation from population $e \rightarrow i$, and increasing γ_e increases the response timescale for the excitatory population, e. Here, TMS is modelled as an excitatory input to both the excitatory (ν_{ex}) and inhibitory (ν_{xi}) neural populations. To describe interactions between these neural populations, specific parameters quantify the strength of synaptic coupling, and the direction, magnitude, and time course of synaptic input to each population; for example Fig. 1C shows the membrane potential response, V_i, to different forms of synaptic input from excitatory and inhibitory receptors. Furthermore, in neural field models, propagation of activity within a population is described by wave equations with further parameters that govern both spatial and temporal scales.

Plasticity can be incorporated into neuronal population-based modeling both phenomenologically and physiologically. First, it can be included phenomenologically, for example through an adaptation of a pairwise spike timing dependent plasticity (STDP) window (Bi and Poo, 2001) for neuronal populations (Fung et al., 2013; Robinson, 2011; Wilson et al., 2014). The key parametrization is that of the STDP window function describing the time course of STDP (i.e., negative for $t<0$, denoting postsynaptic activity occurring before presynaptic activity, and positive for $t>0$, denoting postsynaptic activity occurring after presynaptic activity). Within this time window, fluctuations in *pre*synaptic activity as a function of time, described through the neuronal population equations, are compared with fluctuations in *post*synaptic activity, to give the rate of change in synaptic weight. An increase in excitatory-excitatory

synaptic weight can then be taken as an approximate measure of change in excitability. STDP requires adaptation to capture spike triplet interactions (such as two presynaptic spikes paired with one postsynaptic spike) which are important when firing rates are high and spikes are close together (Pfister and Gerstner, 2006). Since several hundred presynaptic spikes typically arrive at a given cortical neuron during the integration time for it to produce a postsynaptic spike, population based approaches to STDP are particularly suitable and appropriate (Fung et al., 2013; Robinson, 2011).

The second approach to describing plasticity is through physiological theories that can be formulated in terms of biophysical processes. Calcium Dependent Plasticity (CaDP) theory (Lisman, 1989; Shouval et al., 2002) describes cellular calcium dynamics and its effects on synaptic strength. Broadly, high post-synaptic concentrations of calcium lead to potentiation, and moderate concentrations to depression, although the pattern of stimulation is also important (Yang et al., 1999). CaDP can be captured mathematically by modelling the rate of change of synaptic strength between populations (e.g., equivalent to changes in $\square_{ee}$ in fig. 1A for excitatory-to-excitatory synapses) resulting from changes in postsynaptic calcium concentration. Calcium influx to the neuronal population is provided via voltage-dependent NMDA receptors and is modelled via parameters governing calcium permeability, glutamate binding which is dependent on glutamate concentration resulting from activity of excitatory synapses, and a voltage dependence term which is dependent on the population voltage (e.g., V_e in fig 1A). The calcium concentration levels resulting in depression or potentiation are described through the Ω function (Fig. 1D): where Ω<0.5 gives LTD; Ω>0.5 gives LTP. Figure 1D demonstrates that at very low concentrations, no plasticity is achieved (equivalent to a plasticity threshold). As calcium concentrations increase, LTD is achieved, followed by LTP at higher concentrations, Calcium influx into postsynaptic dendritic spines through NMDA receptors is dependent on both glutamate release due to presynaptic activity and postsynaptic voltage, so CaDP provides a microscopic link between the activity of pre- and postsynaptic populations of cells. Moreover, Graupner and Brunel (Graupner and Brunel, 2010) have shown how *physiological* CaDP can predict plausibly-shaped *phenomenological* STDP windows. Thus both CaDP and STDP can be considered useful and complementary approaches to plasticity, with CaDP providing a physiologically detailed approach.

CaDP theory has been incorporated into neural field models (Fung and Robinson, 2014), The theory has been further expanded to include a Bienenstock-Cooper-Munro (BCM) metaplasticity scheme (Fung and Robinson, 2014). Here, activity-dependent changes in NMDA receptor calcium conductance are assumed to underlie metaplasticity. The rate of change of conductance is described by an equation dependent upon both the instantaneous conductance of the NMDA receptor and the instantaneous excitatory-excitatory synaptic weight. Thus the calcium conductance is dependent upon the history of the synaptic weight. Importantly, the model also includes a metaplasticity timescale parameter, which estimates the time of the protein cascade responsible for altering NMDA receptor conductance. As such, the plasticity signal and expression are separated in time. This means previously high plasticity induction reduces calcium conductance and favors LTD, while previously low induction increases conductance favoring LTP (Bienenstock et al., 1982). As such, the metaplasticity scheme

operates as an activity-dependent sliding window, similar to the BCM postulate, meaning that the requirements for inducing plasticity depend on the history of plasticity induction. Under uniform stimulation a calcium attractor is recovered, with calcium levels converging to the threshold between the depression and potentiation zones during significant stimulation.

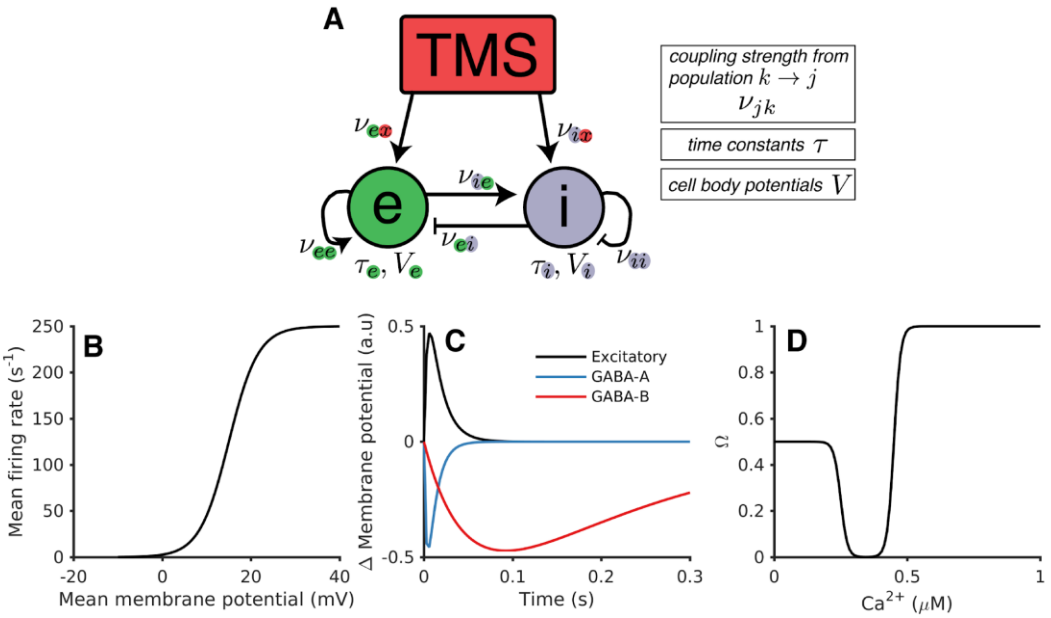

Figure 1. Three examples of how physiological relationships can be approximated in models of macroscale brain activity, as demonstrated in (Wilson et al., 2016). (A) Populations annotated with some relevant parameters, including coupling strengths between populations, ν_{jk}, timescales, τ_j, and cell body potentials, V_j. (B) The relationship between mean cell body (membrane) potential V_j and mean firing rate within a neural population can be described with a sigmoid function (Freeman, 1975). (C) Changes in membrane potential V_e across time resulting from a single input of an excitatory population synapsing onto dendritic excitatory receptors (black line), and an inhibitory population synapsing onto dendritic $GABA_A$ (blue) and $GABA_B$ (red) receptors. The amplitude of the change in membrane potential has been scaled to illustrate differences in peak change between receptor types. The $GABA_A$ and $GABA_B$ curves describe the dynamics of the inhibitory connections i→e and i→i of part (A); the excitatory curve describes the dynamics of the excitatory connections e→e and e→i. (D) The Ω synaptic plasticity function codes the direction of change of synaptic strengths v_{ee}. Neural firing results in calcium influx to the cell, the concentration of which determines whether synaptic strength decreases (Ω < 0.5; LTD) or increases (Ω > 0.5; LTP).

4. Modeling of TMS plasticity paradigms

The models described above provide useful tools for understanding the effects of TMS on plasticity. We now consider in more detail how such models have been applied to TMS plasticity paradigms. For mathematical detail of the models below, readers are directed to the original sources.

Theta burst stimulation protocols were first considered from a theoretical perspective by Huang et al. (Huang et al., 2011). They proposed a neural mass model of plasticity based on 'facilitatory' and 'inhibitory' agents. Both were driven by postsynaptic calcium concentration; however, the former depended upon the *rate* of increase of calcium while the latter depended on the *accumulated* concentration of calcium. By using the difference between the concentrations of the facilitatory and inhibitory agents as a measure of plasticity effect, many of the canonical TBS results could be explained in this manner. cTBS (600 pulses) was ultimately depressive due to the accumulation of postsynaptic calcium, which favoured inhibitory activity over excitatory activity. Conversely, iTBS was potentiating since the breaks in pulses allowed for calcium levels to decay between bursts, resulting in larger increases in excitatory activity relative to inhibitory activity. Other phenomena were also captured – for example a 300 pulse cTBS protocol did not produce enough calcium for the inhibitory effects to dominate and was hence potentiating, in line with experimental results. However, when a prior muscle contraction was modelled, the calcium level was driven to higher levels and the protocol again favoured inhibition. This last result, the effect of previous activity, is an example of *metaplasticity*. However, the model did not test other notable TBS results, for example the switch in plasticity direction for cTBS (from LTD to LTP) and iTBS (from LTP to LTD) when a 600 pulse protocol was extended to 1200 pulses (Gamboa et al., 2010) (although see (Hsu et al., 2011) for a report of MEP facilitation following 1200 pulses of iTBS). Moreover, the model ignored many physiological effects such as the detailed dynamics of calcium concentration, instead generalized effects were described using a few phenomenological and arbitrarily estimated parameters.

Wilson et al (2014) considered a spatially uniform neural field model including excitatory and inhibitory populations of cortical cells including STDP to model TBS and paired pulse paradigms. Spatial uniformity means that, in the neural field wave equation describing spatiotemporal propagation of activity across a population, the spatial (but not temporal) derivatives are zero, meaning that activity can change with time but not position. This is not quite a neural mass model, which would further assume that spatial propagation of activity across a population is instantaneous. This spatially uniform activity case of a neural field model better describes the temporal changes in activity that underlie plasticity mechanisms than a neural mass model. However, it does not model spatial detail that is unnecessary given the wide area of cortex that a TMS pulse stimulates. The model drew parameters from biological measurement where possible, minimizing arbitrary decisions about parameter values. The change in excitatory to excitatory synaptic weight was modeled following various protocols. The increase of excitability after canonical iTBS was recovered; likewise the reduction in excitability following cTBS. Furthermore, a paired-pulse paradigm was also modeled, with results indicating a decrease in MEP after short interstimulus intervals (<20 ms), which changed to an increased MEP when ISI was increased, peaking at about 40 ms, returning to approximately no change after very long ISIs (>160 ms). While this described the shape of a typical paired-pulse result, the exact timings were not reproduced exactly, with MEP facilitation typically peaking experimentally at around 10-15 ms for subthreshold conditioning intensities.

Fung and Robinson (2013) used a spatially uniform neural field model, with spatially uniform activity, to describe PAS and frequency dependence of simple rTMS protocols. They used the the *NFTsim* neural field model (Sanz-Leon et al., 2017) with a single excitatory population, assuming uniform spatial activity and using a model of calcium dependent plasticity. In (Fung and Robinson 2013) changes in synaptic coupling between excitatory populations were used to estimate the TMS-induced change in cortical excitability, measured experimentally as MEPs. Results for one-second pulse trains of simple repetitive TMS are summarized in Fig. 2A for one-second pulse trains. Low frequencies (<8 Hz) resulted in little change in synaptic weight, higher frequencies (8-14 Hz) resulted in LTD, while yet higher frequencies (>14 Hz) gave very strong LTP. Human rTMS studies generally show LTD-like effects at 1 Hz and LTP-like effects above 5 Hz, following many repeated pulse trains. The model has qualitatively reproduced the general pattern of LTD at low and LTP at high frequencies, however the frequency ranges do not exactly match experimental data (Fitzgerald et al., 2006). Using stimulation paradigms that more closely resemble those used in human experiments (e.g., 5 Hz stimulation with 5 s on and 25 s off over 1500 pulses), including a metaplasticity scheme (Fung and Robinson, 2014), or more refined collaboration between modeling and experimentation may improve quantitative precision. PAS was also modeled; the plasticity at different interstimulus intervals (ISI) was calculated for a single population of excitatory cells. This model predicted depression for ISI between approximately -20 to 0 ms (NB: negative times mean that the TMS pulse occurred before the nerve stimulus arrived), potentiation for ISI between approximately 0 and 10 ms, and a second small depressive window for longer ISI, from about 10 to 30 ms, roughly in agreement with human PAS experiments (Wolters et al., 2003). The predictions are shown in Fig. 2C.

Fung and Robinson (2014) developed their spatially uniform neural field modeling further with the inclusion of metaplasticity in a BCM scheme, with the aim of modeling the effects of TBS. A single excitatory population of cells was modeled and the plasticity response (calculated as the change in synaptic coupling between excitatory populations, Δs) for the canonical cTBS and iTBS protocols (Huang et al., 2005) was simulated. The model predicted the canonical LTD and LTP for cTBS and iTBS, respectively (Fig. 2B), but also a broader range of results. Of particular importance was the predicted dependence of the plasticity response on the number of pulses in the protocol. Either doubling or halving the number of pulses reversed the TBS outcome, with cTBS resulting in LTP and iTBS resulting in LTD, also consistent with experimental findings (Gamboa et al., 2010; Gentner et al., 2008). Furthermore, reducing TMS activation of the excitatory population also reversed the excitability change following both iTBS and cTBS. This pattern is consistent with the finding in humans that differences in activation of excitatory and interneuron populations by the TMS pulse (e.g., differences in MEP latency following stimulation with anterior-posterior current flow) are tightly correlated with the resulting TBS outcome (Hamada et al., 2013). However, this modeling work was limited to a single population of excitatory cells and applied only to TBS paradigms. (Wilson et al., 2016) extended the neural field model of (Fung and Robinson, 2014) to include both excitatory and inhibitory populations of cortical neurons, using realistic synaptic response times for both $GABA_A$ and $GABA_B$ receptors as in Fig. 1C, with CaDP and metaplasticity. The model reproduced the increase/decrease in excitability following canonical iTBS/cTBS and also made predictions of how excitability changes would depend on the parameters of the protocols, including theta-burst frequency and

the number of pulses within a burst. Similar predictions were also made using an STDP model rather than CaDP, suggesting that phenomenological STDP and physiological CaDP modeling approaches towards TMS-induced plasticity can be considered complementary. Taken together, these findings demonstrate that neural field models incorporating CaDP are capable of reproducing the main patterns of excitability change following three major TMS plasticity paradigms. These results agree with experimental evidence, suggesting that CaDP is a key mechanism of macroscale TMS-induced plasticity.

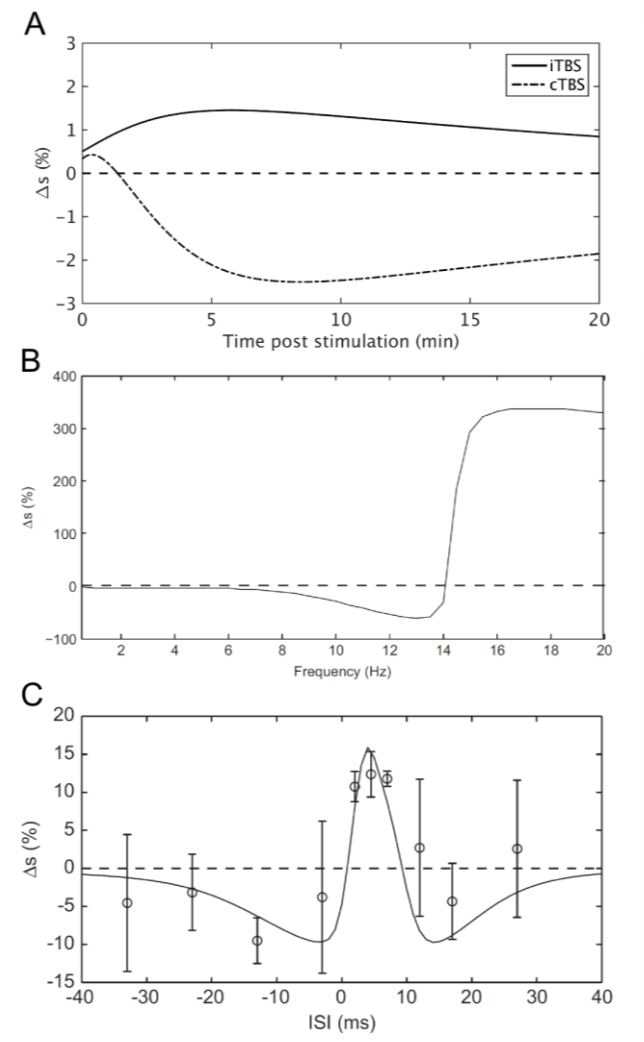

Figure 2: Plasticity effects of different TMS paradigms predicted by a single excitatory population CaDP model. A The effect of iTBS and cTBS on excitatory synaptic coupling (Δs). B The effect of rTMS frequency on change in synaptic coupling between excitatory populations. C The effect of interstimulus interval during PAS on the change in excitatory synaptic coupling (solid line). The circles and error bars represent changes in MEP amplitude from human participants (Wolters et al., 2003). A and C are taken from (Fung and Robinson, 2013) with permission.

5. Understanding interindividual variability and model-based optimization of stimulation parameters

One of the major factors limiting the practical use of TMS plasticity paradigms is the large interindividual variability in response. Modeling approaches, which allow experimental results to be interpreted in terms of inferred neurophysiological parameters, may be able to provide new insights into the reasons behind these broad interindividual responses to TMS and thereby help inform the design of future experiments.

As an example, the CaDP model of TBS with metaplasticity has been used to simulate synaptic strength over time following iTBS and cTBS protocols, as shown in Fig. 3. Results show that the change in synaptic strength following a protocol depends upon the duration of the protocol. This dependency arises in the model as a result of the interplay between calcium concentration, plasticity signaling, and metaplasticity, giving rise to an oscillatory behavior, with the direction of change in synaptic coupling dependent on the concentration at the end of stimulation (Fung and Robinson, 2014). The implication of this finding is that *both* iTBS and cTBS are capable of producing increases *and* decreases in cortical excitability depending on the length of stimulation. Furthermore, the phase of the calcium oscillation during stimulation is shifted by altering the level of TMS activation on the excitatory population (Fung and Robinson, 2014). As such, the number of pulses required for an increase/decrease in excitability following iTBS/cTBS may differ between individuals depending on how TMS interacts with excitatory cortical populations. This may be due to the differences in structure of brain convolutions or genetic differences in physiology between individuals, with the same applied field strength and pattern activating slightly different groups of neurons. These results suggest that differences in the response to TBS between individuals can be minimized by adequately adjusting either the number of pulses given, or the TMS intensity for the individual. It is possible that by identifying and understanding the elements of physiology that most affect TMS response, we may be able to build personalized models, and use these models to tailor clinical treatments.

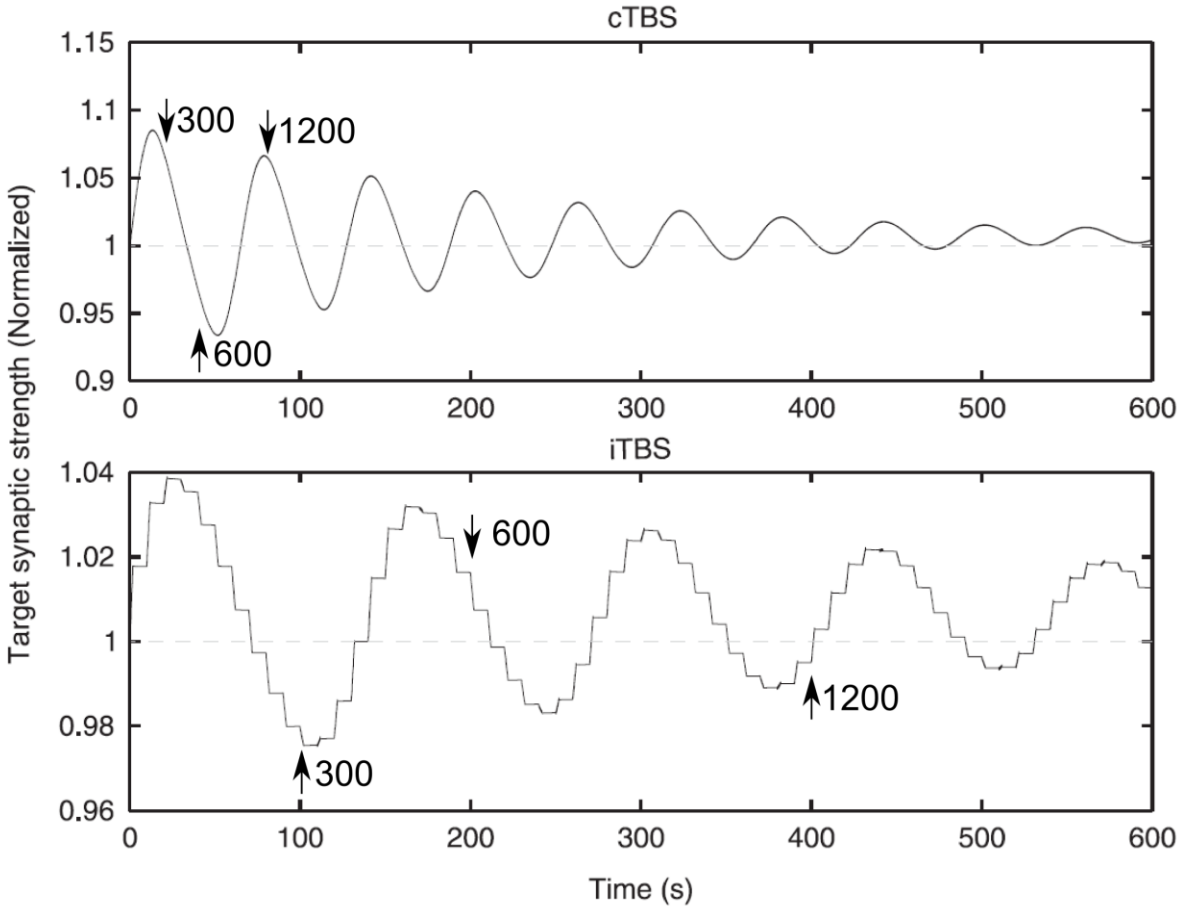

Figure 3. Predicted change in synaptic strength as a result of oscillations in calcium concentration during cTBS (top) and iTBS (bottom). Vertical axes indicate the synaptic strength attained (relative to the initial strength) if the stimulation protocol is ceased at the point in time indicated on the horizontal axis. Arrows indicate the change in excitability for different numbers of pulses. Following the standard 600 -pulse protocol, the canonical decrease/increase in excitability with cTBS/iTBS is predicted by the model. However, for 300 pulses and 1200 pulses, the model predicts a reversal of the above pattern. Figure taken from (Fung and Robinson, 2014) with permission.

Additionally, modeling can be used to explore the vast stimulation parameter space to inform optimization of TMS paradigms. A benefit of capturing the relevant physiological dynamics and interactions in a model is that alterations in parameters can be simulated numerically, without the need to perform costly experiments. This is of particular use for protocols like TBS, where the vast parameter space defining myriad combinations of stimulation timing and strength remains mostly unexplored, but can be simulated straightforwardly (Wilson et al., 2016, 2014).

Figure 4 shows the predicted change in MEP strength after 600 pulses of close-to-threshold cTBS (part A), and iTBS (2 s ‘ON’ time, 8 s ‘OFF’ time, part B) for a wide range of different interburst (theta) stimulation frequencies, intraburst (gamma) frequencies, and pulses-per-burst applied to the neuronal model of (Wilson et al., 2016) (Fig. 1A). The canonical cTBS and iTBS

protocols (Huang et al., 2005) are part of this set; they are shown by the crosses in Fig. 4. It is clear that an increase in intraburst stimulation frequency generally leads to an increase in potentiation. Likewise, higher numbers of pulses per burst favor LTP over LTD. The effect of interburst (theta) frequency is more subtle; for cTBS at lower theta frequencies increasing stimulation rate favors LTD over LTP, but at high theta frequencies and for iTBS the potentiation is not greatly dependent on stimulation rate.

The results demonstrate the ease with which constrained models of candidate neurophysiological mechanisms can generate predictions about the results of new experiments, in this case helping the experimenter to understand the impact of stimulation timing parameters for TBS. The impact of such predictions could be important for selecting optimal stimulation settings for addressing a given scientific question, or to obtaining the maximal treatment response; issues that cannot currently be addressed systematically from first principles. An important next step will involve testing these model predictions using human experiments.

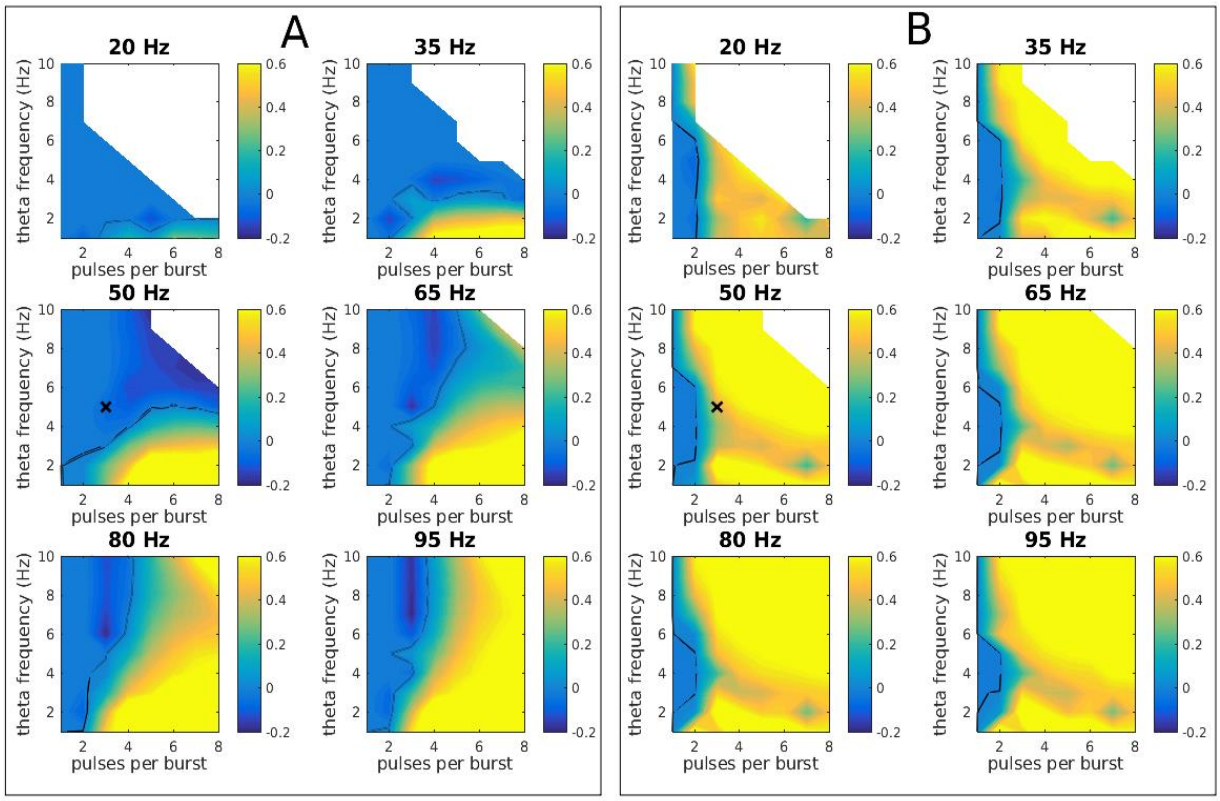

Figure 4: Estimated change in excitatory-excitatory synaptic strength (CaDP with BCM metaplasticity; coupled excitatory and inhibitory populations) for continuous bursting (A) and intermittent bursting (B) protocols. Parts (A) and (B) both show the relative change in synaptic coupling (0 = no change, positive values shown as green-yellow = LTP, negative values shown as blue = LTD) immediately after 600 pulses of close-to-threshold TBS versus three variables: 1. The interburst (theta) stimulating frequency (1 - 10 Hz, on the vertical axis); 2. The number of pulses in a burst (1 - 8, on the horizontal axis); and 3. The intraburst stimulation frequency (20 -

95 Hz, indicated above each set of axes). The solid black contours denote the boundary between LTD and LTP . The 'X' symbols in parts (A) and (B) denote respectively the cTBS and iTBS protocols of (Huang et al., 2005).

6. Challenges and Limitations

In the above we have demonstrated how physiologically-based models of neural populations, coupled with physiological theories of plasticity, can replicate experimental results and make useful and testable predictions. However, there are still many challenges pertaining to the formulation of these models, and to the interpretation of their results.

Neural field modeling of plasticity, as described here, draws from physiological principles at a *microscopic* level. Variables such as mean neuronal firing rate and postsynaptic calcium concentration describe microscopic effects. Yet TMS is performed at a *macroscopic* level, by applying a stimulus with a coil, and its effects are assessed at macroscale for example using MEPs. Modeling carries underlying assumptions regarding the mapping of macroscopic stimulation to microscopic processes and back to macroscopic observables such as MEPs and EEG. For example, the firing activity of a population of cortical excitatory cells can reasonably be used as a proxy for EEG, but this must be interpreted carefully, for example including attenuation effects due to the skull. Other variables have been used as a proxy for MEPs, but these implementations are less robust (Wilson et al., 2014). For example, models have used changes in synaptic weight, changes in the balance of excitation and inhibition, or average axonal firing activity to represent MEP changes. However, these quantities have only indirect links with changes in MEP.

Many of the underlying microscopic physiological mechanisms and parameters in the model are still not well understood. In part, this is due to the difficulty in performing invasive measurements during stimulation. This can lead to poorly constrained parameters and therefore to poorly defined results. However, we note that there are methods by which parameters can be constrained. A good model must be able to reproduce established experimental results using parameters which are biologically plausible. This sets limits on some parameters that may not otherwise be easily measurable. For example, the metaplasticity modeling of (Fung and Robinson, 2014; Wilson et al., 2016) includes several characteristic timescales, for example for protein cascades; these are somewhat arbitrary but have been assigned based on known experimental results. A similar argument is made in (Huang et al., 2011) for allocating the timescale of calcium decay. Invasive animal models may help to provide biologically plausible parameter limits for microscopic variables which are not measurable in humans.

Another difficulty is modeling the interaction between the TMS pulse and the cortical neural populations. The dynamics of a neuron will depend on the details of the transmembrane currents induced by the field. It is often assumed that the gradient of electric field along an axon is the most important factor for determining whether a neuron will be stimulated; however, recent experimental work suggests that it is the field intensity and not direction that matters (Bungert et al., 2016). Additionally, the time-course of stimulation also plays a role, with longer

pulses decreasing motor threshold in paired-pulse TMS (Shirota et al., 2016). The exact processes that occur to cause these effects remain debatable. As such, it is difficult to estimate how best to model the TMS/neural interaction (see section 7).

A pressing limitation is that none of the models discussed in this paper have accurately described known experimental results across all TMS paradigms. Models have tended to concentrate on just one or two paradigms. For example, comprehensive modeling of either repetitive paired pulse or quadripulse TMS has not been performed, and model explanations of traditional rTMS paradigms to not align well with experimental findings. A good model should be able to make predictions of changes in many experimental parameters, not only MEP changes. Most importantly, the predictive power of these models has yet to be tested. These models should be used to make predictions across a range of paradigms and these predictions then tested experimentally. Such an approach requires large amounts of data from a broad range of TMS paradigms. The availability of open TMS data sets would be of particular use for constraining and testing models. However, the practice of making data sets openly available is not common practice in the field of TMS at the current time.

7. Generalizing TMS outcomes across modalities and cortical regions, and other future directions

Neural population models incorporating excitatory and inhibitory cortical populations have successfully described TMS plasticity effects observed in human motor cortex, using synaptic coupling strength as an analog for MEP amplitude. However, MEP formation is complicated, reflecting polysynaptic connections between cortical, corticospinal, and motor neurons (Ziemann et al., 2015). Indeed, changes in synaptic properties at the spinal level may contribute to MEP changes following rTMS (Perez et al., 2005; Quartarone et al., 2005). Future models should include spinal and motor neuron populations to more accurately capture the effect of TMS on the corticospinal system. Encouragingly, neural population models can also capture other TMS phenomena, such as short-interval cortical inhibition and intracortical facilitation following paired pulse paradigms (Wilson et al., 2014). More detailed models considering many discrete neurons in multiple layers are also able to capture these paired-pulse phenomena (Esser et al., 2005; Rusu et al., 2014), but at the cost of an increase in model complexity.

If a model of a neural system is a good approximation to the true biology, then it should be able to describe multiple phenomena with the same biophysically constrained parameters. Values for model parameters can be found either from experiments that measure them directly or by finding appropriate ranges that reproduce known effects. A good model must be able to generate predictions beyond the data used to constrain it. Neural population models, such as those described in this work, are capable of reproducing not just experimental results of TMS, but also a wide range of experimental phenomena, including oscillatory and evoked EEG activity (Rennie et al., 2002; Robinson et al., 2001), and slower hemodynamic oscillations measured with functional MRI (Steyn-Ross et al., 2009); these results can be used to further constrain model parameters.

TMS plasticity paradigms are often administered outside the motor system in cognitive and clinical applications where MEP measures are not possible and neuroimaging methods, such as EEG and fMRI, are increasingly used to assess how TMS alters brain function in these non-motor regions (Sale et al., 2015; Thut and Pascual-Leone, 2010). Several studies have applied biophysical models to gain a deeper mechanistic understanding on the impact of TMS on neural activity recorded by these methods (Hartwigsen et al., 2015). For example, Hartwigsen and colleagues assessed cortical activity and connectivity during a pseudoword reading task before and after cTBS to left inferior frontal gyrus (Hartwigsen et al., 2013). Conventional fMRI analyses revealed that hemodynamic activity was reduced at the site of stimulation following cTBS, but increased in the contralateral hemisphere. To assess whether these changes in activity reflected a reduction in interhemispheric inhibition from the left-to-right cortex, or an adaptive increase in right-to-left hemisphere connectivity, the authors applied dynamic causal modelling. This framework compares experimental data against outputs generated from biophysical models with differing biologically plausible structures (e.g. connections between neural populations) using Bayesian inversion (Friston et al., 2003). The 'winning' model (i.e. the most likely model from those assessed) suggested that connectivity was increased from the right-to-left frontal hemisphere, but not from left-to-right, providing support for a rapid adaptive increase in inter-hemispheric connectivity from the non-stimulated hemisphere following cTBS (Hartwigsen et al., 2013). Such modelling approaches provide deeper insight into the neural adaptations that occur following TMS plasticity protocols. An important future direction will be to include plasticity mechanisms within such models to estimate how TMS can impact hemodynamic activity and task performance.

Before one can model the effects of an induced electric field on neural populations in detail, the induced field distribution itself must be calculated. The electric field induced in the brain by a TMS pulse can readily be modeled with finite element models with varying degrees of complexity (Hartwigsen et al., 2015; Neggers et al., 2015), from simple geometries (Tang et al., 2016) through to folded human brain geometries extracted from MRI (Opitz et al., 2013; Thielscher et al., 2011). In simple geometries, analytical calculations may be sufficient (Pashut et al., 2014). How this field interacts with neurons, white matter tracts and brain regions to cause macroscale stimulation is not yet fully known. This is of critical importance for modeling and interpreting TMS effects.

Likely biophysical mechanisms of how electromagnetic fields interact with cortical structures have been reviewed by Neggers et al. (2015) and Hartwigsen et al. (2015). It is known that the orientation of the induced current with respect to the cortical sheet is important for stimulation, with induced currents perpendicular to the sulcal wall resulting in largest responses. This is likely because electric fields are enhanced in this geometry due to the abrupt boundary between the highly conductive cerebrospinal fluid in the sulcus and the less conductive gray matter. Strong electric fields can change excitability at cell bodies or along axons due to polarization of membranes. These areas of strong local activation can connect to other areas through white matter tracts, which can be identified using diffusion MRI. Compartmental models of neural geometries (Pashut et al., 2011; Rahman et al., 2013) and tracts (De Geeter et al., 2012) at various scales have been used to predict the effect of an electric field on axons in the tracts,

and thus stimulation of areas remote to the immediate source of TMS. Given that the outcome of TMS plasticity protocols is dependent on the neural populations stimulated by the pulse (Hamada et al., 2013), an important future direction will be combining electromagnetic models with plasticity models to determine optimal pulse parameters (e.g. electric field duration and direction) for targeting specific neural populations. Once optimal pulse parameters have been identified, these parameters can be directly assessed using new generation TMS machines capable of controlling TMS pulse properties (Hannah et al., 2016). A summary of how different models can link together into a coherent scheme is given in Figure 5.

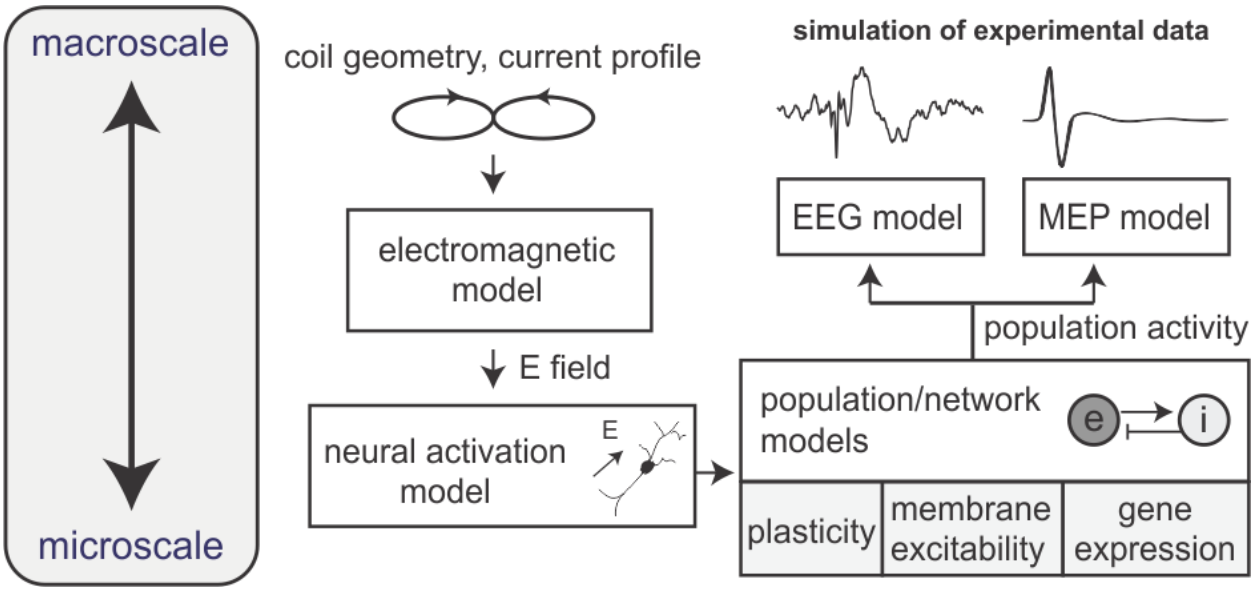

Figure 5. The stages of a comprehensive modeling architecture. Stimulation with a given coil and current profile induces an electric field, which can be determined with an electromagnetic model. This electric field then causes changes in neural activation and behavior at a network level. This network activity then induces changes in the network, through a variety of possible mechanisms, including plasticity, changes in membrane excitability and gene expression. Finally, the altered activity can be mapped with appropriate models to measurable quantities such as EEG and MEP.

Furthermore, while this work has discussed only plasticity, other mechanisms are likely to contribute to changes in neural activity following TMS. For instance, TMS-induced changes in membrane excitability (Pell et al., 2011) or the expression of biochemicals such as brain-derived neurotrophic factor (Gersner et al., 2011) could also influence plasticity and neural activity. Finally, this approach could be applied to other plasticity-inducing brain stimulation paradigms, such as transcranial direct current stimulation (Bestmann et al., 2015; Hämmerer et al., 2016). By incorporating these factors we aim to generate a powerful modeling framework in which brain stimulation can be systematically investigated and interpreted.

8. Summary

Understanding the mechanisms of TMS in humans is complicated by an interplay of different spatial and temporal scales. Neural plasticity and other possible drivers of TMS-induced effects occur at a microscopic scale, yet stimulation and measurement are made macroscopically. There is considerable variation in experimental results, since many of the key parameters, such as the initial cortical activity, are poorly controlled and differ between individuals. Moreover, the range of possible stimulating protocols is vast, but the range is mostly unexplored experimentally, with cTBS and iTBS protocols having dominated recent research. Mathematical modeling of the relevant physiology allows rapid evaluation of the effects of many paradigms and differing physiological states, and to explore the effects of microscopic changes on macroscopic outputs without the cost and time demands of experiment. We argue that the early modeling studies presented here hold great promise for providing a much needed theoretical framework with which to unify many diverse experimental findings and address many of the outstanding problems in the field.

Despite its transformative potential, TMS modeling is nascent. While the current models of TMS-induced plasticity have qualitatively captured several group-level findings following paradigms such as PAS and TBS, it remains to be seen whether these models can predict unobserved experimental findings, either at the group or individual level (e.g., the effect of changing the frequency of stimulation in TBS). An important next step is to design experiments that will directly test model predictions of unknown TMS parameters in order to assess the biophysical validity of these models. A goal for neural modeling is to design a general model capable of capturing a broad range of observed neural phenomena (e.g., neural oscillations, changes in brain states, event-related potentials). In order to test the generalizability of the plasticity models, future work will need to extend the current TMS plasticity models to incorporate spatial dynamics across cortical and subcortical regions. Continued development of models of TMS plasticity will enable closer integration between experimental and theoretical work to guide the field and unify diverse experimental findings in terms of underlying mechanisms.

Acknowledgments

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