Optimising repetitive transcranial magnetic stimulation for neural circuit repair following traumatic brain injury

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PERSPECTIVE

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While it is well-known that neuronal activity promotes plasticity and connectivity, the success of activity-based neural rehabilitation programs remains extremely limited in human clinical experience because they cannot adequately control neuronal excitability and activity within the injured brain in order to induce repair. However, it is possible to non-invasively modulate brain plasticity using brain stimulation techniques such as repetitive transcranial (rTMS) and transcranial direct current stimulation (tDCS) techniques, which show promise for repairing injured neural circuits (Henrich-Noack et al., 2013; Lefaucher et al., 2014). Yet we are far from having full control of these techniques to repair the brain following neurotrauma and need more fundamental research (Ellaway et al., 2014; Lefaucher et al., 2014). In this perspective we discuss the mechanisms by which rTMS may facilitate neurorehabilitation and propose experimental techniques with which magnetic stimulation may be investigated in order to optimise its treatment potential.

Since the year of its first application, interest in rTMS has increased exponentially and it is widely applied as a non-invasive method for brain stimulation in experimental and clinical settings (Pell et al., 2011; Di Lazzaro et al., 2013). During magnetic stimulation, an electric coil induces a magnetic field which passes through the skull to produce an electric field in the brain (Pell et al., 2011; Deng et al., 2013). As immediate effects of rTMS can be easily visualised in humans, *e.g.*, stimulation to the motor cortex results in muscle twitches, it is generally accepted that eddy currents induced in the cortex lead to action potential firing. As the magnetic field deteriorates only with distance from the central point of stimulation (Deng et al., 2013), the discrete stimulated brain regions are surrounded by adjacent cortical and sub-cortical tissue that also receive stimulation albeit at lower intensity (Rodger et al., 2012; Makowiecki et al., 2014), but whose contribution to the effects of rTMS remain ill-defined (Ellaway et al., 20214).

However, in the last few years, there has been mounting evidence that rTMS may not induce reliable and reproducible effects. The high variability within and between subjects, and often-contradictory outcomes of rTMS experiments in different laboratories, has made its use somewhat controversial. Thus in recent years, the viability of rTMS as a therapeutic tool has increasingly come under scrutiny (Di Lazzaro et al., 2013; Lefaucher et al., 2014). This lack of reproducibility reflects that rTMS has been used clinically for almost two decades without preceding fundamental animal and *in vitro* research to identify the cellular effects beyond inducing action potentials. Given that human experiments allow limited opportunity to investigate underlying cellular and molecular mechanisms, developing the stimulation tools to conduct rTMS experiments in animals and *in vitro* models is critical to allow an improved understanding of the primary actions of rTMS on neurons and neural circuits. This fundamental approach is necessary if we are to successfully manipulate brain stimulation in order to harness the excitability and plasticity that promote optimal recovery following injury.

What rTMS parameters may promote neural repair?: (1) *Activity dependent plasticity*–Although we know that rTMS induces action potentials in cortical neurons, the factors that determine whether a magnetic pulse will lead to an action potential remain poorly characterised. Key factors are magnetic field intensity (directly related to distance from stimulation device) and its focus (Deng et al., 2013). Computational modelling studies suggest that the likelihood of action potential firing may also depend on properties of the neuron (Pell et al., 2011), such as intrinsic excitability, morphology and orientation with respect to the magnetic field, yet these have never been directly investigated in real neurons. Moreover, the cerebral cortex is a complex heterogeneous tissue, thus rTMS may stimulate a combination of excitatory, inhibitory and neuromodulatory neurons that activate internal regulatory circuits (Pell et al., 2011). This, in turn, will confound interpretation of what any given stimulation paradigm is doing to neural activity, how this may be altered when that circuit is damaged (Ellaway et al., 2014) and thus whether such activation may facilitate repair.

Moreover, as magnetic stimulation induces action potentials, rTMS-induced activity will trigger long term potentiation (LTP) and long term depression (LTD)-like synaptic plasticity. Evidence for this comes indirectly from human studies with long lasting post-stimulation changes in cortical excitability (Pell et al., 2011), but also directly from *ex vivo* neonatal mouse brain slices in which rTMS induces LTP (Vlachos et al., 2012). Not surprisingly, the effects of magnetic stimulation frequency match those of electrical stimulation observed in classical electrophysiological experiments: low frequency inhibits, and high frequency excites neural circuits *via* the induction of LTD or LTP (Pell et al., 2011).

The frequency-specific aspect of long term rTMS outcomes is a major clinical advantage because treatments can be tailored to specific dysfunctions: low frequency stimulation has been successful in treating disorders associated with cortical hyper-excitability such as stroke and spinal cord injury, while high frequency stimulation is effective in treating depression (Pell et al., 2011). Human studies have hinted at improved cognitive function and faster reaction times but evidence is patchy and poorly reproducible (Pell et al., 2011). However, recent animal studies reveal that rTMS may have significant and lasting impact by reopening developmental critical periods and altering metaplasticity (Makowiecki et al., 2014; Mix et al., 2015). This is a more powerful outcome than a simple change in excitability because it has the potential to facilitate long term structural and functional change, effectively rewiring the brain.

(2) *Are action potentials necessary for rTMS effects?*–Because human rTMS studies most commonly measure muscle responses to magnetic fields applied at intensities close to those required to activate the motor cortex, the effects of rTMS are generally assumed to be due to induction of action potentials in neurons. However, there is a significant body of work showing that low intensity magnetic fields, several orders of magnitude lower than the common rTMS protocols, are also effective at inducing neural modulation. In humans, low intensity rTMS (LI-rTMS) modulates cortical excitability, induces analgesia and alleviates depression (Di Lazzaro et al., 2013). In mice, LI-rTMS induces structural changes in

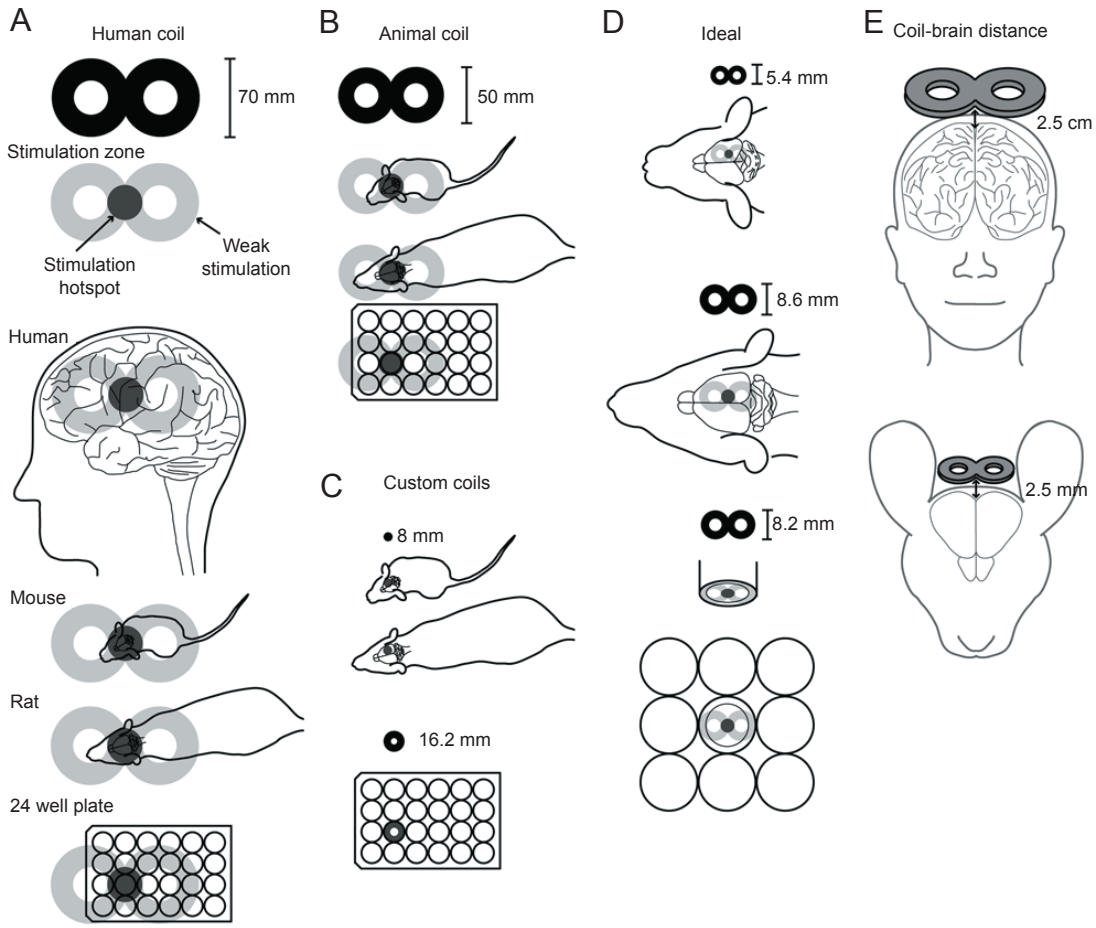

Figure 1 Summary of available and desired coils to deliver magnetic fields to animals and *in vitro* that are equivalent to those applied in human repetitive transcranial magnetic stimulation (rTMS).
For all panels, coils are shown in black and the approximate location of the induced current is in grey. For simplicity, the direction of current flow is not shown. A typical human "figure of eight" coil (A) showing in dark grey the hotspot of maximal "focal" stimulation normally used to elicit motor evoked potentials (MEPs). When applied to the human head, the hotspot is positioned over the target brain region, but the rest of the brain also receives stimulation, albeit at lower intensity. However, when this human coil is applied in animals or *in vitro*, the hotspot is no longer focal relative to the target, but rather stimulates the entire head/culture, with the induced current no longer being contained within the target (*e.g.*, Vlachos et al., 2012). This reduces the efficiency of magnetic induction and changes the properties of the induced current. In some studies, a small figure of eight coil is used, (B) which improves focality to one hemisphere in rats, but has similar disadvantages relative to efficiency of induction. To address this problem, custom-made round coils have been used to deliver focal stimulation in rodents and in culture (Rodger et al., 2012; Makowiecki et al., 2014; Grehl et al., 2015) (C). Although these deliver low intensity magnetic fields, the induced current is fully contained within the brain, increasing efficiency of induction. The coils are small enough to stimulate one hemisphere in both mice and rats, and a single culture well. In panel D, we propose "ideal" small "figure of eight" coils which would provide focal stimulation in animals and in culture, while maintaining a similar coil to target ratio as that used in humans. Although a limitation of small coils is that they cannot deliver high intensity magnetic fields without significant heat generation, the small coil to brain distance in rodents and in culture means that it may not be necessary to deliver a magnetic field of the same magnitude required in humans in order to stimulate smaller targets at the same intensity (E).

congenitally abnormal brain circuits, resulting in improved behaviour (Rodger et al., 2012; Makowiecki et al., 2014). *In vitro* experiments have shown that such stimulation (LI-rMS) does not trigger action potentials, but nonetheless increases intracellular calcium within individual neurons, providing the basis for synaptic plasticity and metaplasticity processes to occur (Grehl et al., 2015). This finding raises some key questions about the mechanisms underlying rTMS:

• *Magnetic field or electric field?* There is evidence of magneto-reception in all vertebrate classes (Wiltschko and Wiltschko, 1995), yet in our focus on induced electric field and neuronal depolarisation, we forget that the magnetic field itself may exert a direct effect on cells.

• *Neurons are not the only targets.* Given that action potential firing may not be a pre-requisite for some aspects of rTMS effectiveness (Grehl et al., 2015), other cells within the brain such as glial cells, vascular endothelial cells, immune cells etc should be considered potential targets of rTMS.

What next? How to optimise rTMS for neural repair: Although our current knowledge provides tantalising information about the power of magnetic stimulation to modulate brain function, improve dysfunction and potentially repair an injured brain, the appropriate stimulation parameters remain unknown. The current major challenge is how to identify them. It is known in human research that stimulation devices can deliver slightly differing waveforms under the same settings, resulting in diverging cortical

effects over-and-above inter-subject variability (Pell et al., 2011). Unfortunately the effects of magnetic stimulation are based on the combination of several parameters, the impact of which can only be assessed by systematically acquiring data under highly controlled and standardized experimental conditions. This is the strength of animal and *in vitro* models, which allow manipulation not only of the external environment, but also of the genetic and pharmacological environment within the brain. However, the stimulation tools we possess at the moment are tailored for the human brain and we need to develop devices to extend our investigations to a wide range of stimulation parameters on a wide range of targets (**Figure 1**).

(1) *Coil design*–Although rodent models have revealed key molecular changes following rTMS (Pell et al., 2011; Vlachos et al., 2012; Grehl et al., 2015), most studies use coils that are larger than the rodent brain, such as small commercially available figure-of-eight or round coils of at least 50 mm outer diameter. Whilst the use of such coils allows for stimulation at the high intensities used in humans (1–2 T), they lack 2 crucial facets: equivalent spatial resolution which confounds correlation of its outcomes to humans; and similar stimulation fields which are determined by the coil-to-target size ratio (Deng et al., 2013). Therefore, animal researchers are increasingly beginning to design small coils tailored to their experimental requirements. However, with decreasing coil size, it is challenging to maintain high stimulation intensities, due to thermal and mechanical stress. Strategies to overcome these problems address the trade-off between stimulus focality and intensity: addition of inbuilt cooling devices in commercial coils, complex coil shapes to improve focus (Deng et al., 2013) or use of low intensity stimulation (Rodger et al., 2012; Makowiecki et al., 2014; Grehl et al., 2015). However, an "ideal" animal coil that accurately reproduces the physical properties of human rTMS in an animal brain has yet to be built (**Figure 1**). Thus, while a wide range of repetitive magnetic stimulation paradigms can be evaluated experimentally, if we are to understand the type of electric fields induced in human subjects during rTMS, there is an urgent need to develop small coils that deliver focal magnetic stimulation at high intensity in animal models and in culture dishes.

(2) *Control of stimulation parameters*–In addition to developing appropriate coils, it will be necessary to construct stimulation devices that can deliver the full range of rTMS parameters, controlling frequency, rhythm, number of pulses, intensity, waveform, field orientation, total length of stimulation, etc (Pell et al., 2011). These constraints are necessary to define the induced electrical field, which is what acts upon the neuronal tissue. Therefore the current convention of using rTMS intensities of "X % of motor threshold" or "Y % maximal output of the machine" does not permit valid comparison between studies because the induced electric field remains unknown.

Conclusion: rTMS presents a unique opportunity to modulate brain excitability and plasticity in a precisely controlled manner yet its role for neurorehabilitation remains poorly understood. We propose that rTMS is taken from the bedside back to the bench: the use of appropriate delivery devices in animal and *in vitro* models is crucial to provide a practical and theoretical framework to direct how rTMS can be applied following neurotrauma to promote regeneration and rehabilitation of neural circuits.

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