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Non-invasive induction of plasticity in the human cortex: Uses and limitations.

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Abstract

The last couple of decades have seen the development of a number of non-invasive brain stimulation (NIBS) techniques that are capable of inducing short-lasting plasticity in the human cortex. Importantly, the induction of lasting plastic changes can, under some conditions, reversibly modify behaviour and interact with learning. These techniques have provided novel opportunities to study human cortical plasticity and examine the role of cortical regions in behaviour. In this review we briefly summarise current NIBS techniques, outline approaches to characterise and quantify cortical plastic change, and describe mechanisms that are implicated in the induced plastic changes. We then outline the areas in which these techniques might be useful, namely, investigating the mechanisms of human cortical plasticity, the characterisation of influences on plasticity, and the investigation of the role of cortical regions in behaviour. Finally, we conclude by highlighting some current limitations of the techniques and suggest that further development of the current NIBS paradigms and more focussed targeting should further enhance the utility of these powerful non-invasive techniques for the investigation of the cortical plasticity and pathophysiology.

Keywords: plasticity; non-invasive brain stimulation; transcranial magnetic stimulation; transcranial direct current stimulation, paired associative stimulation; learning.

The last couple of decades have seen the development of a number of non-invasive brain stimulation (NIBS) techniques that are capable of inducing short-lasting plasticity in the human cortex. As a result, many groups have investigated the potential of NIBS protocols to induce functionally-relevant plasticity.

There are three basic forms of NIBS. Firstly, there is repetitive transcranial magnetic stimulation (rTMS), which involves the application of trains of transcranial magnetic stimuli at various frequencies to targeted cortical regions. If the stimuli are of sufficient intensity, then intracortical axons are stimulated and there is resultant synaptic activation. When trains of stimuli are applied in appropriate temporal patterns enduring changes in cortical excitability are induced, which are indicative of modifications in synaptic efficacy, i.e. plasticity. The nature of the plasticity induced by rTMS protocols in the target cortical region is dependent upon a complex interaction between the stimulation frequency, intensity, and train duration. In conventional paradigms, trains of stimuli are applied at regular intervals. In general, low frequency rTMS protocols (< 1 Hz) decrease cortical excitability and high frequency rTMS protocols (>5 Hz) increase cortical excitability (Di Lazzaro et al., 2011; Ridding & Rothwell, 2007). With conventional paradigms, it is usually necessary to employ quite high stimulus intensities (above motor threshold) and high numbers of stimuli to induce changes in cortical excitability that outlast the stimulation period. Typically, these conventional paradigms are applied over periods of many minutes.

More recently "patterned" stimulation protocols have been developed, which involve the application of high frequency (30-50Hz) bursts at theta frequency (theta-burst

stimulation; TBS). These protocols are based on the well-described theta-burst paradigms that are used to induce long-term potentiation (LTP) in animal models (Hess, Aizenman, & Donoghue, 1996; Huemmeke, Eysel, & Mittmann, 2002; Larson & Lynch, 1986; Vickery, Morris, & Bindman, 1997). The effects induced with these techniques are dependent upon the temporal pattern of the applied bursts and can bi-directionally modulate cortical excitability. Continuous TBS (cTBS), involving the continuous application of bursts (3 stimuli at 50 Hz every 200 ms) for 20-40 seconds, can induce a lasting reduction in cortical excitability (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). In contrast, intermittent TBS (iTBS), which involves the application of bursts for 2 seconds every 10 seconds for a total duration of 190 seconds, can increase cortical excitability (Huang et al., 2005). TBS paradigms have several advantages over conventional rTMS protocols; they are applied in a much shorter period of time, require lower stimulus intensities, and result in longer lasting effects (Di Lazzaro et al., 2011).

A second NIBS technique involves the repeated application of a peripheral nerve stimulus paired with an appropriately timed TMS pulse (to a target region of the cortex), a technique termed paired associative stimulation (PAS) (Stefan, Kunesch, Cohen, Benecke, & Classen, 2000). Approximately 100-200 pairs of stimuli, delivered over 15-30 minutes, can bi-directionally modulate excitability. The induced changes in excitability are critically dependent on the interval between the peripheral and central (TMS) stimuli; increases in cortical excitability can be induced when the interval between the peripheral and cortical stimuli is ~25 ms (PAS_{25}; arrival of the afferent volley in the cortex at approximately the same time that the TMS is applied) and decreases in excitability can be induced when the interval is ~10 ms (PAS_{10};

afferent volley arriving before the cortical stimulus is applied) (Stefan, Kunesch, Benecke, Cohen, & Classen, 2002; Stefan et al., 2000; Wolters et al., 2003). More recently, PAS-like protocols have been used to modulate connectivity within cortico-cortical pathways (Arai et al., 2011; Buch, Johnen, Nelissen, O'Shea, & Rushworth, 2011; Groppa et al., 2012). While only a few studies to date have used 'cortical PAS', they suggest that cortical PAS can induce changes in synaptic strength in the stimulated pathways.

The third NIBS technique is that of transcranial direct current stimulation (tDCS). tDCS involves the application of weak direct currents, delivered between two surface electrodes placed over the scalp (Michael A. Nitsche et al., 2008). The nature of the change induced with tDCS is determined by whether a depolarising or hyperpolarising stimulus is applied to the target cortical region. In general, increases in cortical excitability are induced with anodal tDCS and decreases in cortical excitability are induced with cathodal tDCS. Typically, tDCS involves the application of a constant stimulus of a set intensity (1-2 mA) for many minutes (10-20 mins). More recently, modifications of this technique have been developed that use alternating current stimulation or random noise stimulation. Transcranial alternating current stimulation (tACS) involves the application of oscillating electrical currents, typically using sinusoidal waveforms, and is thought to have the capacity to synchronise or desynchronise intrinsic cortical oscillations (Antal et al., 2008; Chaieb, Antal, & Paulus, 2011; Neuling, Rach, Wagner, Wolters, & Herrmann, 2012). While there has been little systematic investigation, the after-effects of tACS are likely to be dependent on the frequency, intensity, phase, and waveform of the stimulation (for review see Antal & Paulus, 2013). Transcranial random noise stimulation (tRNS)

involves the application of random frequency oscillating electrical currents (low frequency between 0.1-100 Hz and high frequency between 101-640 Hz)(Terney, Chaieb, Moliadze, Antal, & Paulus, 2008). tRNS can result in lasting increases in cortical excitability (Terney et al., 2008), however, the mechanisms underlying the changes in excitability are not well understood. In this review, we will focus the discussion on the literature of the better-characterised tDCS technique (for tACS and tRNS reviews, see Antal & Paulus, 2013; Herrmann, Rach, Neuling, & Struber, 2013).

How do we investigate NIBS-induced plasticity?

Most studies using NIBS techniques have targeted the primary motor cortex (M1). The primary reason for this is that a single, suprathreshold transcranial magnetic stimulus applied to M1 elicits a motor response that can be recorded in contralateral muscles (usually in the hand), known as the motor evoked potential (MEP). In contrast, stimulation of other cortical regions rarely results in a response that is as easily measured as the MEP. The MEP is the result of TMS activating motor cortical output cells and evoking a descending volley in the corticospinal tract. A single, suprathreshold stimulus to M1 evokes a complex descending corticospinal volley that is composed of a series of components know as direct (D) and indirect (I) waves. The D-wave is thought to reflect direct activation of the corticospinal output cells, while the later I-waves reflect transynaptic activation of the output cells. Therefore, the amplitude of the MEP provides an indication of the excitability within the corticospinal system and, as such, is influenced by changes in synaptic efficacy within the cortical network activated by the stimulus. The MEP elicited by single-pulse TMS

is routinely used to assess plastic changes induced in the motor cortex by NIBS techniques.

The investigation and characterisation of plasticity in non-motor areas is somewhat more challenging, but there are a number of options. Firstly, it is possible to induce phosphenes via stimulation of the occipital cortex. Although a subjective measure, the threshold for evoking phosphenes can be reliably measured and changes in the threshold for evoking phosphenes provides an indication of changes in the excitability (plasticity) of the visual cortex (Cowey & Walsh, 2000; Pascual-Leone & Walsh, 2001). Modulations in phosphene threshold have been observed following application of rTMS to the occipital cortex (likely V1/V2), and modulations in the direction of moving phosphenes evoked by TMS to the motion-selective area V5 have been observed following visual motion adaptation (Antal et al., 2002; Boroojerdi, Prager, Muellbacher, & Cohen, 2000; Cattaneo & Silvanto, 2008; Guzman-Lopez, Silvanto, & Seemungal, 2011; Ray, Meador, Epstein, Loring, & Day, 1998). Secondly, it is possible to investigate plasticity induction by quantifying changes in evoked potentials generated in the target cortical region. For example, Dinse and colleagues have shown that NIBS paradigms targeting the sensory cortex can modulate excitability within that region, which is evidenced by a change in somatosensory evoked potentials elicited by electrical nerve stimulation (Ragert, Becker, Tegenthoff, Pleger, & Dinse, 2004). Likewise, targeting the visual cortex can induce changes that are reflected by modulations of visual evoked potentials (Bohotin et al., 2002; Fumal et al., 2003).

More recently, a number of groups have reported that it is possible to record electroencephalographic (EEG) responses evoked by single TMS pulses, which have been termed TMS-evoked potentials (TEPs). TEPs provide quantifiable markers of the cerebral neurophysiological state (Carlo Miniussi & Thut, 2010; Rogasch & Fitzgerald, 2013) and, in a similar fashion to MEPs, are influenced by TMS intensity (Kahkonen, Wilenius, Komssi, & Ilmoniemi, 2004; Komssi, Kahkonen, & Ilmoniemi, 2004) and coil orientation (Bonato, Miniussi, & Rossini, 2006). While the amplitude of TEPs is greatest in the stimulated cortical area, it is possible to measure TEPs at cortical sites distant to the site of stimulation, potentially providing a useful measure of connectivity (Ilmoniemi et al., 1997; Kahkonen, Komssi, Wilenius, & Ilmoniemi, 2005; Komssi et al., 2002; Komssi et al., 2004). Initial studies have characterised both early (5 – 30 ms) and later potentials (45 – 300 ms) comprising several positive and negative potentials (Bonato et al., 2006; Casarotto et al., 2010; Esser et al., 2006; Komssi et al., 2004; Lioumis, Kicic, Savolainen, Makeka, & Kahkoen, 2009; Veniero, Maioli, & Miniussi, 2010). Subsequently, a handful of studies have provided evidence of TEP modulation both during and following application of plasticity-inducing NIBS protocols (Esser et al., 2006; Hamidi, Slagter, Tononi, & Postle, 2010; Huber et al., 2008; Veniero et al., 2010), suggesting that TEPs will likely prove valuable for investigating induced plastic changes within non-motor areas.

Finally, it is possible to gain insights into the effects of NIBS on function in both motor and non-motor brain regions by combining NIBS with functional imaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and near infrared spectroscopy (NIRS). For example, Siebner and colleagues (2003) used PET to show that 1 Hz rTMS delivered to the premotor cortex

reduces regional cerebral blood flow (rCBF) in premotor and primary motor cortices bilaterally as well as influencing rCBF in more remote areas including the putamen and cerebellum. This is an important finding as it provides evidence that focal application of NIBS protocols can have widespread effects within the brain (Siebner et al., 2003). Using fMRI, Tegenthoff et al. (2005) showed that 5 Hz rTMS delivered to the hand area of the primary somatosensory cortex led to an enlargement of the index finger representation. Further, the magnitude of change in this representation was positively correlated with improvements in index finger tactile discrimination. This finding provides further evidence that the changes induced by NIBS techniques have behavioural significance. More recently, Stagg and colleagues (Stagg, Bachtiar, & Johansen-Berg, 2011) used magnetic resonance spectroscopy to investigate the effects of anodal tDCS delivered to M1 and demonstrated a reduction in γ–aminobutyric acid (GABA) concentration following stimulation. Furthermore, the degree of GABA modulation following anodal tDCS was positively correlated with both measures of short-term motor learning and fMRI blood-oxygen level-dependent signal change in M1 associated with motor-learning. This work provides further evidence for the important relationship between the GABA modulation and motor learning, and, indeed, extends this to show a relationship between the capacity for GABA modulation and motor learning. Several recent reviews have focused on the use of NIBS combined with neuroimaging techniques and the reader is directed to these for further information (Dayan, Censor, Buch, Sandrini, & Cohen, 2013; Reithler, Peters, & Sack, 2011; Saiote, Turi, Paulus, & Antal, 2013; Siebner et al., 2009; Venkatakrishnan & Sandrini, 2012).

Mechanisms of NIBS induced plasticity

While necessarily indirect, there is good and mounting evidence that the lasting changes in cortical excitability induced by current NIBS protocols are due to stimulation-induced neuronal activation and the resultant activity dependent changes in synaptic efficacy (Cooke & Bliss, 2006). Indeed, NIBS-induced changes have a number of features that are consistent with the involvement of mechanisms similar to the activity-dependent long-term potentiation/long-term depression (LTP/LTD) that is well described in animal models (Bliss & Gardner-Medwin, 1973; Dudek & Bear, 1993). Both conventional and patterned rTMS protocols induce changes in cortical excitability that outlast the stimulation period and are reversible (Berardelli et al., 1998; Chen et al., 1997; Huang et al., 2005). Furthermore, the nature of the changes induced by both conventional and patterned rTMS protocols is determined by the temporal pattern of stimulation (Berardelli et al., 1998; Chen et al., 1997; Huang et al., 2005; Maeda, Keenan, Tormos, Topka, & Pascual, 2000). Pharmacological manipulations provide further information about the mechanisms underlying rTMS-induced plasticity. For example, NMDA receptor antagonists block both the inhibitory and facilitatory effects of rTMS protocols, providing further evidence that these induced excitability effects reflect NMDA receptor–mediated LTP/LTD-like mechanisms in glutamatergic circuits (Huang, Chen, Rothwell, & Wen, 2007).

There is evidence that PAS-induced excitability changes are also due to modulations in synaptic strength brought about via LTP- and LTD-like processes (Stefan et al., 2002; Wolters et al., 2003; Ziemann, Iliac, Pauli, Meintzschel, & Ruge, 2004). PAS protocols are of particular interest because they demonstrate some of the characteristics of spike timing–dependent plasticity, wherein the order and precise temporal interval between presynaptic and postsynaptic spikes determine the direction

and magnitude of LTP-like or LTD-like synaptic changes (Stefan et al., 2000; Wolters et al., 2003). Pharmacological studies have provided good evidence that PAS-induced changes are NMDA-dependent; dextromethorphan, an NMDA receptor antagonist, blocks PAS-induced facilitation of MEP amplitudes (Stefan et al., 2002; Wolters et al., 2003).

The initial effects of tDCS are thought to be due to induced changes in neuronal membrane excitability and not by direct activation of neurones (Creutzfeldt, Fromm, & Kapp, 1962; Michael A. Nitsche et al., 2008; Purpura & McMurtry, 1965). However, studies in animals and humans have shown that the lasting effects of tDCS on cortical excitability are abolished by NMDA receptor antagonists (Fritsch et al., 2010; M. A. Nitsche et al., 2003; M. A. Nitsche et al., 2004). Therefore, it is likely that tDCS modulates membrane excitability which, in the presence of spontaneous or behaviourally related synaptic activity, can result in LTP-like and LTD-like changes in synaptic strength (Michael A. Nitsche et al., 2008). Furthermore, recent work in mouse M1 slices showed that both the deletion of the BDNF gene and the application of a BDNF scavenger abolish DCS-induced potentiation, providing some evidence that activity-dependent BDNF secretion may have a modulatory influence on DCS-induced plasticity (Fritsch et al., 2010).

How can NIBS plasticity induction paradigms be useful?

As described above, NIBS protocols induce short-lasting synaptic plasticity (reflected by changes in cortical excitability) that is mediated by LTP/LTD-like processes. Given that LTP and LTD have a critical role in many forms of learning and memory (for review see Feldman, 2009), NIBS techniques provide opportunities to gain novel

insights into the role of the cortex in these behaviours. Indeed, NIBS approaches have proven useful in several interrelated areas including (1) investigation of the mechanisms of human cortical plasticity, (2) assessment of neuroplastic capacity, and (3) the investigation of the role of cortical regions in behaviour.

1. Probing mechanisms of human cortical plasticity with NIBS

NIBS techniques can provide novel insights into the mechanisms of plasticity in humans. For example, a number of studies have employed NIBS in conjunction with pharmacological manipulation to investigate the mechanisms of human plasticity. It has been shown that the response to both cTBS (inhibitory), iTBS (facilitatory) and PAS are blocked by NMDA receptor antagonists (Huang et al., 2007; Stefan et al., 2002). These results provide evidence that the inhibitory and facilitatory effects of PAS and TBS involve NMDA receptor–mediated glutamatergic function and, additionally, that NMDA receptor dependent LTP/LTD-like processes operate in the human motor cortex. However, it should be noted that while the effects of the various PAS and TBS protocols appear to involve similar mechanisms, there may be some important differences. For example, the dopamine receptor antagonist sulpiride blocks the effect of the inhibitory PAS_{10} protocol but has no effect on the effects of the excitatory PAS_{25} protocol (M. A. Nitsche et al., 2009). In contrast, sulpiride blocks both the inhibitory effect of cTBS and the facilitatory effect of iTBS (Monte-Silva et al., 2011).

A second example of how NIBS techniques can provide mechanistic insights into human plasticity involves the investigation of metaplasticity. Metaplasticity describes the processes by which the history of synaptic activity influences the plastic response

to further activity or stimulation (Abraham & Bear, 1996; Artola, Brocher, & Singer, 1990) and is important for maintaining synaptic weights in a useful functional range. It is well established from animal studies that metaplastic control mechanisms operate in many brain regions (Abraham & Bear, 1996; Artola et al., 1990; Cohen, Raymond, & Abraham, 1998). NIBS has been used in a number of studies to provide indirect evidence that metaplastic control mechanisms operate in the human cortex. These studies have shown that synaptic activity in a target cortical region can modulate the response to the subsequent application of a NIBS paradigm. The "priming" synaptic activity can be due to either behaviour or experimentally evoked. For example, the cortical activity associated with a voluntary contraction modifies the response to NIBS subsequently applied to the motor cortex. Gentner and colleagues (2008) investigated the effect of prior voluntary contraction on NIBS-induced neuroplasticity using a short TBS protocol. An increase in cortical excitability was evident when TBS was applied without a prior voluntary contraction. However, when subjects performed a simple voluntary contraction of the target muscle (5 minutes duration), application of the same TBS protocol was associated with a decrease in cortical excitability. Iezzi et al (2008) examined the effect of a more complex, phasic, motor task on the response to NIBS. When applied without prior movement, cTBS and iTBS protocols induced a decrease and increase in excitability respectively. In contrast, when TBS was preceded by a period of phasic movement (voluntary index finger abduction/adduction), the effects of TBS were reversed. As an alternative approach to study cortical metaplasticity with NIBS, the "priming" synaptic activity can be evoked experimentally by NIBS. For example, we demonstrated that the response to inhibitory cTBS was enhanced when applied following the application of a facilitatory iTBS protocol (Todd, Flavel, & Ridding, 2009). Together, these studies

demonstrate that the history of synaptic activity, in this case synaptic activity generated during a voluntary movement or a NIBS protocol, affects the subsequent LTP/LTD induction by NIBS and provide non-invasive evidence of human metaplastic control mechanisms.

2. Assessment of the capacity for plasticity

NIBS techniques can provide an indication of the capacity for plastic change of a target cortical region. The ability to predict the capacity for plasticity will likely prove useful in rehabilitation settings. Firstly, NIBS can characterise the influence of many intrinsic and extrinsic factors on human plasticity. For example, recent studies have employed NIBS techniques to characterise genetic influences on cortical plasticity. The influence of only a few genes has been investigated and, at present, the best characterised is the gene encoding brain derived neurotrophic factor (BDNF). BDNF is released in an activity-dependant manner and has a significant role in promoting changes in synaptic efficacy (Bramham, 2008; Lu, 2003). A single nucleotide polymorphism in the BDNF gene, which is evident in a substantial percentage of the population, leads to an amino acid substitution (valine to methionine) at codon 66 (val66met). Kleim and colleagues (2006) showed a reduction in the neuroplastic response typically observed following a simple motor learning task in those subjects with, compared to those without, the val66met polymorphism. Subsequently, Cheeran and colleagues (2008) examined the association between the val66met polymorphism of the BDNF gene and neuroplastic responses to several NIBS paradigms. A reduced neuroplastic response to TBS was observed in subjects with the val66met polymorphism. This group also showed an altered neuroplastic response to PAS_{25} in participants with this polymorphism; while there was a similar degree of LTP-like

facilitation following PAS when recorded in the target muscle, there was less spread of facilitation to adjacent muscles in those with the val66met polymorphism suggesting a more topographically restricted neuroplastic response.

More recently, Antal and colleagues (2010) examined the influence of the BDNF gene polymorphism on both rTMS- and tDCS-induced plasticity in the motor cortex. In val66met carriers, there was a reduced response to the facilitatory rTMS protocol (iTBS) compared to those without the polymorphism. In contrast, the response to facilitatory anodal tDCS was greater in val66met carriers. These findings support the notion that BDNF affects plasticity induction in humans. However, the effects are complex and likely to be influenced by the plasticity mechanisms being investigated.

Cheeran and colleagues (2008) examined the influence of the BDNF gene polymorphism on metaplastic processes within the motor cortex. In their study, metaplasticity was examined by applying cathodal tDCS prior to subthreshold 1 Hz rTMS, a protocol first used by Siebner and colleagues (2004). Subthreshold 1 Hz rTMS applied in isolation did not induce significant modulations in cortical excitability, however, when preceded by cathodal TDCS (which induced LTD-like depression of excitability), 1 Hz rTMS resulted in an increase in excitability that was significantly less in the val66met carriers compared to those without this polymorphism. Together, these findings provide good evidence to support the notion that BDNF is involved in mediating experience-dependent plasticity of human motor cortex. These investigations not only inform our understanding of genetic influences on cortical plasticity but are also likely to be useful in understanding the response to

NIBS in therapeutic situations, as well as patient responses to more conventional paradigms.

NIBS techniques are also providing new insights into the role of disordered plasticity in a variety of diseases and impairments. For example, a recent study examined plasticity in participants with focal hand dystonia by using several NIBS paradigms (Belvisi et al., 2013). These authors reported that participants with focal hand dystonia had a significantly greater plastic response to both PAS_{25} and PAS_{10} than controls. However, in contrast to the PAS results, dystonia patients had a reduced response to iTBS. These results make two important contributions to our understanding of disordered plasticity in focal hand dystonia. Specifically, that dystonia is characterised by (1) enhanced heterotopic spike timing dependent plasticity (PAS), which the authors suggest might be due to alterations in processing of sensory inputs, and (2), reduced homotopic LTP-like plasticity (iTBS) in M1 which may reflect abnormalities in intrinsic M1 circuitry (Belvisi et al., 2013).

We have recently used NIBS to investigate the influence of preterm birth on plasticity (Pitcher et al., 2012). Preterm birth is associated with poorly understood impairments in cognitive and motor skills that last at least into adolescence and probably throughout life (Chyi, Lee, Hintz, Gould, & Sutcliffe, 2008; Lindstrom, Winbladh, Haglund, & Hjern, 2007; Morse, Zheng, Tang, & Roth, 2009). We used a cTBS protocol that induces an LTD-like plastic response to assess motor cortical plasticity in a group of adolescents born preterm (between 26 and 36 weeks gestational age). Preterm birth was associated with a reduced cTBS neuroplastic response and we suggested that this impairment in plasticity might provide the physiological

underpinnings of the cognitive and motor deficits seen in children born preterm. Interestingly, we were also able to show that a component of the reduced plasticity was associated with changes in cortisol levels. This is interesting, as we have previously demonstrated that cortisol can modulate cortical plasticity (Sale, Ridding, & Nordstrom, 2008), and it is well known that preterm birth is associated with alterations in the HPA axis (Sullivan, Hawes, Winchester, & Miller, 2008). This study, again, provides evidence that NIBS techniques are useful tools for probing the pathophysiology of conditions associated with functional and behavioural deficits.

NIBS techniques have also provided evidence that cognitive engagement can have influence on plasticity in cortical motor areas. For example, Stefan and colleagues (2004) showed that the capacity for motor cortical plasticity, induced by paired-associative stimulation, is reduced under conditions of high cognitive demand such as completing arithmetic puzzles. Similarly, Antal and colleagues (2007) showed a reduced capacity for motor cortical plasticity induced by anodal tDCS during intelligence testing. More recently, Kamke and colleagues (2012) examined, specifically, the effect of attention on plasticity-induction. This group shows that plasticity induced by paired-associative stimulation was reduced during performance of a visual detection task with high attentional demands compared to performance of the same task with low attentional demands. Together, these studies show that cognitive demands, and more specifically, attentional demands, can substantially affect plasticity induction in cortical areas not intrinsically involved with task performance.

3. The role of cortical regions in behaviour

As described above, NIBS paradigms can bi-directionally modify synaptic efficacy within the cortical networks being targeted. In effect, this modifies the synaptic population available for engagement during behaviour. NIBS has been used to influence brain function in both online (i.e. during task performance) and off-line paradigms (i.e. prior to task performance) to investigate the role of particular cortical regions in behaviour. In this review, we will concentrate on the off-line paradigms that rely on short-term neuroplastic mechanisms and point the reader interested in on-line approaches to a recent review (C. Miniussi et al., 2008).

Motor cortex. Huang and colleagues (2005) demonstrated that an inhibitory (LTD-like) TBS paradigm targeted to the motor cortex could increase response times on a simple reaction time task involving the contralateral hand. This result provides evidence that the motor cortex has a critical role in this basic motor behaviour. Jung and Ziemann (2009) applied PAS immediately prior to motor training on a simple ballistic task and demonstrated that induced changes in motor cortical excitability modulated task performance (acceleration). Interestingly, performance improvements were greater for PAS_{10} (LTD-like) than PAS_{25} (LTP-like), suggesting that, in certain conditions, homeostatic interactions exist between induced plasticity and behavioural measures.

As well as effects on basic motor performance and the acquisition of motor skills, NIBS techniques have provided evidence that the motor cortex plays an important role in the early consolidation of practice effects. Muellbacher and colleagues (2002) showed that low-frequency rTMS (1 Hz), applied to M1 immediately after motor training on a ballistic thumb abduction task, impaired retention of performance

improvement gained during motor training. The disruptive effect of low-frequency rTMS was specific to performance improvements and did not influence the ability to learn during a subsequent period of motor training. Further, this group showed that that rTMS applied 6 hours after the initial motor training did not disrupt performance gains, leading the authors to suggest that rTMS to M1 disrupted early consolidation of motor learning (Muellbacher et al., 2002).

Premotor cortex: NIBS protocols have been used to study the role of the premotor cortex in complex motor behaviours. For example, cTBS applied over the left or right premotor cortex significantly increases reaction time in both hands in a forced-choice reaction time task (Mochizuki, Franca, Huang, & Rothwell, 2005). Stinear and colleagues (2009) studied the effects of a NIBS paradigm on an even more complex sequential reaction time task, which involved participants entering a four-digit sequence from memory, using specific keys as quickly and accurately as possible. Following application of a facilitatory (LTP-like) TBS paradigm to the left dorsal premotor cortex, response time was significantly reduced when performing the task with the contralateral hand. These findings provide evidence for the role of premotor cortex in complex motor behaviour and further, suggest that premotor cortex might prove a useful target for rehabilitation protocols incorporating NIBS.

Sensory cortex. NIBS paradigms targeting the primary sensory cortex (S1) have been shown to modulate tactile acuity. Specifically, impairments in tactile acuity in the hand have been demonstrated following the application of an inhibitory low frequency rTMS paradigm to the contralateral S1 (Knecht, Ellger, Breitenstein, Ringelstein, & Henningsen, 2003). In addition, significant improvements in tactile

acuity have been demonstrated when a facilitatory, high frequency rTMS paradigm was applied to S1 (Ragert et al., 2004). Importantly, improvements in tactile acuity achieved via behavioural training paradigms can be enhanced when used in conjunction with high frequency rTMS (Ragert et al., 2003).

Parietal association cortex. In an elegant series of studies, Nyffeler and colleagues used NIBS to provide evidence for a role of the posterior parietal cortex (PPC) in visual exploration behaviour. First, this group showed that an inhibitory TBS paradigm applied to the right PPC significantly decreased cumulative fixation duration in the left-, and increased cumulative fixation duration in the right-half of the visual space for at least 30 minutes (Thomas Nyffeler et al., 2008). These results suggest that theta burst rTMS is a reliable method of inducing transient, neglect-like visual exploration behaviour. Subsequently, Nyffeler et al. (2009) showed that the neglect-like visual exploration behaviour observed following NIBS to the right PPC can be reversed by NIBS applied to the left PPC. This finding provides support for the hypothesis that an imbalance in interhemispheric interactions mediates visual neglect. Indeed, Nyffeler and colleagues went on to examine the use of NIBS for the treatment of visual neglect in stroke patients. They showed that two trains of an inhibitory TBS paradigm applied to the contralesional hemisphere significantly improves the number of perceived target stimuli in neglect-affected visual field for up to 8 hours (T. Nyffeler, Cazzoli, Hess, & Muri, 2009). In a clinically important follow-up, this group showed that increasing the number of TBS trains applied in a single session, to include eight trains of TBS applied to the contralesional PPC over two consecutive days, resulted in a significant improvement in spatial neglect symptoms that lasted for at least three weeks (D. Cazzoli et al., 2012).

In a proof-of-principle study, Sparing and colleagues (2009) showed that tDCS applied to the PPC influenced performance on a visual inspection task, with effects being dependent on the polarity of the tDCS and the hemisphere stimulated. In healthy adults, anodal tDCS led to an increase in detection of visual stimuli contralateral to the stimulation. Cathodal stimulation led to an increase and decrease in detection of visual stimuli when applied to the ipsi- and contralateral PPC respectively. In patients with left visuospatial neglect, both anodal tDCS to the ipsilesional PPC and cathodal tDCS to the contralesional PPC led to an improvement in neglect symptoms. This result is consistent with that of Nyffeler and colleagues (2008; 2006), showing that inhibitory TBS to the contralesional PPC improves symptoms of neglect. Furthermore, it suggests that facilitatory NIBS protocols applied to the ipsilesional PPC might also be effective in reducing neglect symptoms.

NIBS has also provided evidence for specific roles of the parietal cortices in attentional processing. For example, Romei and colleagues (2011) showed that rTMS of different frequencies applied to the right PPC differentially affected processing of visual stimuli at local and global levels. Specifically, beta frequency rTMS enhanced processing at the local level and theta frequency rTMS enhanced processing at the global level. Interestingly, rTMS applied to the left PPC did not affect processing at either the local or the global level. NIBS has also been used to investigate the role of the parietal cortex in salience processing. Bardi and colleagues (2013) applied tDCS with the anode placed over PPC of one hemisphere and cathode placed over PPC of the opposite hemisphere to examine hemispheric asymmetries in processing of low- and high-salient information. Processing of high-salient information was enhanced

during tDCS with the anode placed over the right hemisphere and the cathode placed over the left hemisphere, suggesting that the right parietal cortex is critically involved in the processing of high-salient information.

Prefrontal cortex. Nyffeler and colleagues (2006) demonstrated that an inhibitory (LTD-like), low frequency rTMS paradigm applied to the frontal eye field (in the prefrontal cortex) significantly increases saccadic eye movement latencies bilaterally. In subsequent studies, this group showed that the application of an inhibitory TBS paradigm also resulted in a significant increase in saccade latency, and that with repeated applications of TBS, the duration of the effect was disproportionately lengthened (T. Nyffeler, Wurtz, Luscher, et al., 2006).

The prefrontal cortex has also been targeted with NIBS in a number of studies examining cognitive performance. For example, Galea and colleagues (2010) reported that an inhibitory TBS paradigm, applied to the dorsolateral prefrontal cortex immediately after training on a sequence reaction time task, was associated with better task performance when participants were retested 8 hours later. The authors suggested that declarative and procedural consolidation processes appear to mutually interact, and that disruption of the dorso-lateral prefrontal cortex immediately after sequence learning degrades the consolidation of the sequence within the declarative memory system and thus facilitates consolidation within procedural memory systems. Further, Kinces et al. (2004) and Fregni et al. (2005) reported that a facilitatory tDCS protocol (anodal tDCS) improved performance on an implicit learning task and working memory tasks respectively, while an inhibitory tDCS protocol (cathodal tDCS) had no effect on performance on an implicit learning task. The results of these

studies suggest that anodal tDCS may offer some options for reducing age-related decline in cognitive function.

Limitations with current NIBS approaches

As described above, NIBS techniques have been able to provide unique insights into cortical physiology, plasticity, and behaviour. However, there are a number of issues with current paradigms that are potentially limiting their exploitation. Firstly, the response to NIBS paradigms is highly variable (Hamada, Murase, Hasan, Balaratnam, & Rothwell, 2012; Ridding & Ziemann, 2010). A number of factors contributing to this variability have been identified. The influence of many intrinsic factors, such as brain structure and genetics, are relatively constant and contribute to between-subject variability but should contribute little to within-subject variability. In contrast, there are many other influences that vary, such as time of day of testing, attentional focus, and age (Ridding & Ziemann, 2010) which can contribute to both within- and between-subject variability. It is obviously important to control as many of these sources of variability as possible to minimise their confounding effects. Secondly, the time-course of the changes induced by current NIBS paradigms potentially limits their usefulness. The changes induced with conventional paradigms have been shown to last for ~30-60 minutes. While it is generally accepted that these short-lasting and labile changes are largely consistent with activity dependent LTP-like and LTD-like mechanisms, their limited life suggests that they only reflect the very earliest phase of activity-dependent plasticity. This, in itself, might help to explain why the induced changes are so variable and the effects on behaviour (in most instances) modest. Encouragingly, recent studies suggest that this limitation may be overcome, to some degree, by modifying the temporal patterns in which NIBS paradigms are applied.

Animal studies have shown that plasticity-inducing paradigms applied repeatedly, at short (10-15 min) intervals, induce more persistent and later phase activity-dependent plasticity than single applications (Abraham, 2003; Barnes, 1979; Bliss & Gardner-Medwin, 1973). Consistent with this, we have recently shown in humans that two inhibitory (cTBS) NIBS paradigms applied 10 minutes apart result in a plastic response that is less variable and longer lasting than that seen with a single application (Goldsworthy, Pitcher, & Ridding, 2012). As described above, there is evidence that such approaches can lead to significant and enduring behavioural effects (D. Cazzoli et al., 2012; T. Nyffeler et al., 2009; T. Nyffeler, Wurtz, Luscher, et al., 2006). These results suggest that applying NIBS paradigms in a spaced fashion may result in the induction of changes that are more consistent with behaviourally-significant later-phase plasticity.

Future directions

NIBS techniques have provided important insights into human cortical plasticity as well as preliminary evidence to suggest that these techniques can be used to modulate behaviour. However, several challenges must be overcome before these techniques can reach their full potential. Firstly, as described above, there are many sources of variability in the responses to NIBS protocols. A challenge for the field is to gain a better understanding of these factors and develop approaches that minimise this variability. Future studies should aim to develop NIBS protocols that induce more robust, longer-lasting plastic changes, and consider better targeting of these NIBS protocols. For example, simple measures such as controlling the time of day at which NIBS is applied might help in obtaining less variable outcomes (Sale, Ridding, & Nordstrom, 2007; Sale et al., 2008). Additionally, genetic profiling might enable

targeted application of NIBS protocols. Such an approach should lead to improvements in NIBS efficacy and might be especially useful when exploring the therapeutic potential of NIBS.

A further imperative is the development of better neurophysiological markers of plasticity. At present we are largely restricted to using changes in MEP amplitude as an index of plasticity and this is associated with two key limitations. Firstly, the MEP is only useful for providing a measure of plastic change when the motor cortex is being targeted and cannot be used when studying remote cortical regions. Further, the logic of using MEP threshold measure to establish NIBS intensity for targeting of non-motor areas is questionable. Secondly, the MEP is subject to a large degree of inter-trial variability that reduces its utility in certain situations. The development of approaches that utilise TMS evoked EEG potentials offers opportunities to address these issues.

Summary

In this review we have highlighted some novel opportunities provided by NIBS for studying human cortical plasticity and behaviour. We have outlined how NIBS approaches can be used to characterise the capacity of the cortex for plasticity to gain insights into behavioural impairments and also how NIBS can be useful for investigating the pathophysiology of neurological disorders. Further, we have described how NIBS induced changes in excitability can be used to investigate the role of cortical regions in behaviour. To date, most NIBS studies have focused on motor cortical areas, however, we have described a number of studies using NIBS techniques to investigate the physiology and pathophysiology of non-motor areas. It is

likely that we will see an increasing focus on non-motor areas once techniques (such as TMS-EEG) allowing investigation of induced change become more developed. While NIBS provides exciting opportunities for the investigation of human plasticity and its behavioural relevance, it is important to note that there are some limitations with current paradigms. Further development of paradigms and the targeting of their application should further enhance the utility of these powerful non-invasive techniques.

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