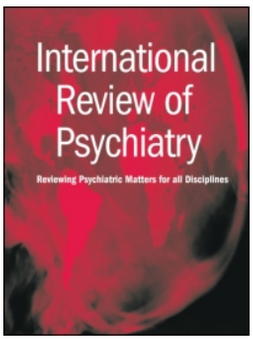

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REVIEW ARTICLE

Can neurophysiologic measures serve as biomarkers for the efficacy of repetitive transcranial magnetic stimulation treatment of major depressive disorder?

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ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for Major Depressive Disorder (MDD). There are clinical data that support the efficacy of many different approaches to rTMS treatment, and it remains unclear what combination of stimulation parameters is optimal to relieve depressive symptoms. Because of the costs and complexity of studies that would be necessary to explore and compare the large number of combinations of rTMS treatment parameters, it would be useful to establish reliable surrogate biomarkers of treatment efficacy that could be used to compare different approaches to treatment. This study reviews the evidence that neurophysiologic measures of cortical excitability could be used as biomarkers for screening different rTMS treatment paradigms. It examines evidence that: (1) changes in excitability are related to the mechanism of action of rTMS; (2) rTMS has consistent effects on measures of excitability that could constitute reliable biomarkers; and (3) changes in excitability are related to the outcomes of rTMS treatment of MDD. An increasing body of evidence indicates that these neurophysiologic measures have the potential to serve as reliable biomarkers for screening different approaches to rTMS treatment of MDD.

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Introduction

Repetitive transcranial magnetic stimulation (rTMS) has been proven to be an effective clinical treatment for a variety of physiological (Brunelin et al., 2007) and psychiatric disorders (Gao, et al., 2016). The primary clinical indication for rTMS is the treatment of Major Depressive Disorder (MDD), with evidence from multiple large randomized clinical trials (Perera et al., 2016). The treatment parameters most commonly in use for MDD in the US are 3000 pulses at a frequency of 10 Hz, administered at an intensity of 120% of the motor threshold (MT) to left dorsolateral prefrontal cortex (DLPFC) target (Grimm et al., 2008; Janicak & Dokucu, 2015; Padberg et al., 1999; Pellicciari, Cordone et al., 2013; Walter, Wolf, Spitzer, & Vasic, 2007). These are the parameters used in the pivotal trial that formed the basis for initial approval by the US Food and Drug Administration (Connolly, Helmer, Cristancho, Cristancho, & O'Reardon, 2012; O'Reardon, et al., 2007). These parameters lead to outcomes that are comparable to those obtained from medication treatment (Carpenter et al., 2012; Demitrack & Thase, 2009), with benefits that commonly are sustained for at least a year (Dunner et al., 2014).

There is considerable application of rTMS for treatment of MDD using stimulation parameters that are outside of the FDA's labelling. These include varying the frequency of stimulation (1 Hz, 5 Hz), using novel patterned stimulation such as intermittent or continuous theta burst (iTBS and cTBS, respectively), altering the intensity of stimulation (80–120% of MT), changing the number of pulses (500–5000 total pulses), as well as directing stimulation at different neuroanatomic targets (right DLPFC, dorsomedial prefrontal cortex, or DMPFC). There are clinical data that support the efficacy of many different approaches to the treatment of MDD (Blumberger et al., 2012; Dell'Osso et al., 2015; Downar & Daskalakis, 2013; Philip,

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Ridout, Albright, Sanchez, & Carpenter, 2016; Richieri et al., 2012), and it remains unclear what combination of stimulation parameters is optimal to relieve depressive symptoms. Because of the costs and complexity of studies that would be necessary to explore and compare the large number of combinations of rTMS treatment parameters, the number of comparative efficacy studies of different parameters remains very limited.

An alternate approach to comparing the efficacy of different rTMS parameters for treating depressive symptoms would be to examine biomarkers of treatment effect as surrogate end-point measures. This approach may be more feasible for rTMS than for other antidepressant treatment modalities. As with most treatments for MDD, the mechanism of action (MOA) of TMS remains incompletely understood. Studies of rTMS, however, have an advantage over studies of other treatment modalities in that the neuroanatomic site at which the beneficial effects of treatment are initiated (that is, the site of stimulation) can be identified with a high degree of precision. While the cascade of events associated with treatment efficacy beyond the site of stimulation is not fully elucidated, it may be possible to identify local physiologic effects of rTMS treatment that are strongly associated with treatment outcome and could be used as proxy measures for treatment efficacy.

The effects of rTMS on the stimulated cortex have been best characterized using neurophysiologic measures. The most immediate demonstrable effect of TMS applied to a cortical target is altered excitability of the stimulated region, manifested as changes in neuronal firing rates and amplitudes, as well as cerebral oscillatory activity (Aydin-Abidin, Moliadze, Eysel, & Funke, 2006; Fröhlich, 2015; Kozyrev, Eysel, & Jancke, 2014; Veniero, Vossen, Gross, & Thut, 2015). Because of the observed linkage between rTMS administration and changes in excitability, the effectiveness of a particular set of treatment parameters in inducing changes in excitability could potentially be used as a marker for screening different treatment paradigms. Those paradigms that show the greatest modulatory effect on cortical excitability may be those that show the greatest clinical efficacy for treatment of MDD.

We examine below the data indicating that measures of cortical excitability may be suitable as surrogate biomarkers for the efficacy of rTMS treatment. We review below the literature to address three broad questions:

1. What is the evidence that changes in excitability are related to the mechanism of action of rTMS?
2. What is the evidence that rTMS has consistent effects on measures of excitability that could constitute reliable biomarkers? and
3. What is the evidence that changes in excitability are related to the outcomes of rTMS treatment of MDD?

What is the evidence that changes in excitability are related to the mechanism of action of rTMS?

Changes in cortical excitability have been postulated to be linked to the MOA of rTMS through induction of long-term potentiation (LTP), long-term depression (LTD), and resultant changes in neuroplasticity (Iezzi et al., 2011; Ogiue-Ikeda, Kawato, & Ueno, 2003; Suppa, Li Voti, Rocchi, Papazachariadis, & Berardelli, 2015). LTP and LTD represent mechanisms that are believed to underlie learning and memory at a cellular level in the hippocampus (Lüscher & Malenka, 2012). LTP- and LTD-like processes have been postulated to be responsible for learning and memory processes as well as changes in performance in humans (Pegado, Vankrunkelsven, Steyaert, Boets, & Op de Beeck, 2016), although it is not possible to demonstrate definitively the role of these processes in human subjects. Similarly, while it is tempting to speculate that the repetitive stimulation delivered during rTMS modulates the strength of synaptic connections and induces LTP- and LTD-like processes, a link between the MOA of rTMS and changes in neuroplasticity remains speculative (Chervyakov, Chernyavsky, Sinitsyn, & Piradov, 2015; Leuchter, Hunter, Krantz, & Cook, 2015). Facilitatory and inhibitory effects of rTMS are hypothesized to create LTP/LTD-like phenomena in circuits linked to the site of stimulation, and induce changes in cortical output which persist even after stimulation ends (Iezzi et al., 2011; Noh, 2016).

There are a number of different forms of LTP and LTD, and their roles in the nervous system vary depending on the synapses and circuits that are involved (Malenka & Bear, 2004). One particular form of LTP/LTD that is of interest is that mediated through N-Methyl-D-aspartate receptors (NMDAR), which is well established to play a role in changes in synaptic strengthening in the hippocampus and elsewhere in the nervous system (Hrabetova & Sacktor, 1997; Lüscher & Malenka, 2012). The role of NMDAR in LTP has been demonstrated through pharmacologic studies in which NMDAR antagonists have been shown to block LTP/LTD (Albensi, Alasti, & Mueller, 2000; Hrabetova & Sacktor, 1997; Mueller, Albensi, Ganong, Reynolds, & Jackson, 1991; Peng et al.,

2010). In order to test whether LTP/LTD-like effects may mediate rTMS effects on the brain, NDMAR antagonists have been administered in association with rTMS protocols to determine the effect of these pharmacologic agents on changes in cortical excitability, connectivity, and plasticity.

The literature suggests that NMDAR antagonists do suppress changes in excitability of rTMS, with five of the seven studies demonstrating significant effects of NMDAR blockade. Cortical excitability can be assessed by measuring the MT, as well as intracortical facilitation or inhibition (ICF and ICI, respectively). The MT measures membrane excitability and is defined as the stimulation intensity that consistently evokes an motor evoked potential (MEP) >50 microvolts (Rossini et al., 1994). ICF and ICI are paired-pulse TMS paradigms that involve the delivery of a subthreshold conditioning stimulus prior to a suprathreshold test stimulus, leading to MEP facilitation or inhibition, depending upon the timing of the pairing (Kujirai, Sato, Rothwell, & Cohen, 1993; Nakamura, Kitagawa, Kawaguchi, & Tsuji, 1997).

Ketamine is particularly useful as a non-competitive NMDAR antagonist (Höffken et al., 2013), with a large literature about its effect in modulating the after effects on cortical excitability of rTMS (Ciampi de Andrade, Mhalla, Adam, Texeira, & Bouhassira, 2014; Di Lazzaro et al., 2003; Labedi, Benali, Mix, Neubacher, & Funke, 2014) and more recent data supporting its potential efficacy as a treatment for major depressive disorder (Fond et al., 2014). Di Lazzaro et al. (2003) reported that increasing doses of ketamine produced a progressive reduction in the MT as well as an increase in the amplitude of EMG responses evoked by magnetic stimulation. In contrast to responses evoked by magnetic stimulation, responses evoked by electric stimulation were not modified by ketamine. The authors concluded that the distinction between the effects of magnetic and electric stimulation indicated that sub-anaesthetic doses of ketamine enhanced recruitment of excitatory cortical networks in the motor cortex. Höffken et al. (2013) demonstrated that sub-anaesthetic doses of racemic ketamine did not have any after-effects on human cortical excitability of rTMS, and it was not until the highest amount (50 ng/ml) was administered that ICI was reduced and ICF was enhanced significantly. In contrast, Labedi et al. (2014) found that high doses of ketamine in rodents completely inhibited the molecular after-effects of iTBS mediated by NMDA receptors. Ciampi de Andrade et al. (2014) demonstrated that, whereas ketamine did significantly lower the analgesic effects of 10 Hz rTMS in both M1 and the DLPFC, these effects were not associated with changes in measures of cortical excitability including MT, MEP, ICI, and ICF. Although there is variability in the results from these studies, each demonstrated a significant change in neurophysiologic response to rTMS following ketamine administration, supporting the importance of NMDAR in the mechanism of action of TMS.

Schwenkreis et al. (1999) administered the NMDAR antagonist memantine before a paired pulse TMS paradigm. The presence of memantine led to enhanced ICI and reduced ICF compared to placebo. Reis et al. (2006) administered amantadine, a drug with varied actions including NMDAR antagonism, effects on monoaminergic and cholinergic transmission, and potassium channels, before administering rTMS. They reported a significant dose-dependent reduction of ICF and a significant increase of late ICI, but not short ICI, when compared to placebo. Moreover, amantadine had no significant effects on MT, MEP recruitment curves, cortical silent period (CSP), or peripheral excitability.

Memantine was administered by Huang, Chen, Rothwell, and Wen (2007), who showed that it blocked the increases in excitability associated with iTBS as well as the decreased excitability seen with cTBS, while having no effect on MT. The results of Teo, Swayne, and Rothwell (2007) also serve as further evidence of the NMDAR-dependent after-effects of iTBS. These investigators administered D-cycloserine, and reported that, in the presence of this partial NMDAR agonist, iTBS effects switched from facilitatory to inhibitory. This reversal of modulatory effect demonstrates pharmacological modulation of the effects of rTMS.

There are, however, some apparent inconsistencies in the reported effects of NMDAR antagonists. Kaelin-Lang et al. (2002) found that the increased MEP amplitudes in response to rTMS were blocked by the GABA(A) receptor agonist lorazepam, but not by the NMDAR antagonist dextromethorphan. Reis et al. (2002) reported that topiramate, which has broad activity as a sodium-channel blocker, a GABA(A)-receptor agonist, and a NMDAR antagonist, elicited a significant increase of ICI compared to placebo. Although these findings support the implication of a glutamatergic mechanism for changes in the cortical excitability in response to rTMS, they also suggest that these effects may be due to other neurotransmitter receptor-mediated signalling or ion channel activity other than those mediated via NMDAR.

There also is evidence that monoamine neurotransmitters also play a role in modulating cortical

excitability. LTP and LTD-like effects can be induced with TMS using the Paired Associate Stimulation (PAS) paradigm (Ziemann et al., 2006). With a short inter-stimulus interval (e.g. 10 ms ISI), LTD-like diminution of the resulting MEP is seen; with longer ISIs (e.g. 25 ms), LTP-like facilitation of the MEP is observed. Using this paradigm, the modulatory effects of monoamine neurotransmission on cortical plasticity processes have been reported, most commonly using dopaminergic agents. PAS effects (facilitatory and/or inhibitory) are modified with non-linear, generally inverted-U shaped dose–response functions, with either L-DOPA (Thirugnanasambandam, Grundey, Paulus, & Nitsche, 2011), the selective D2-receptor agonist bromocriptine (Fresnoza et al., 2014), or the D2/D3-receptor agonist ropinirole (Monte-Silva, et al., 2009). Single-doses of either haloperidol or the alpha-1 adrenergic antagonist prazosin abolish facilitatory PAS effects (Korchounov & Ziemann, 2011), whereas the co-administration of L-DOPA rescues the inhibitory PAS effect that is abolished by the D2-receptor antagonist sulpiride, suggesting the role of D1-receptors in LTD-like processes (Nitsche et al., 2009). The L-DOPA enhancement of MEP facilitation induced with theta burst stimulation (TBS) is abolished in 6-hydroxydopamine-lesioned rats, suggesting the importance of DA for TBS-induced plasticity as well (Hsieh et al., 2015). Interestingly, the enhancement of TMS-induced MEPs with practice is also subject to monoaminergic modulation, as both methylphenidate and cabergoline enhance practice-dependent plasticity, whereas haloperidol and prazosin attenuate this effect (Meintzschel & Ziemann, 2006). The serotonergic system has been addressed in a single PAS study, which found citalopram to abolish inhibitory PAS effects and enhance facilitatory PAS effects (Batsikadze, Paulus, Kuo, & Nitsche, 2013) (Table 1).

What is the evidence that rTMS has consistent effects on measures of excitability that could constitute reliable biomarkers?

rTMS effects on excitability in primary motor cortex

rTMS effects on excitability have most extensively been studied in the primary motor cortex (M1), largely because the MEP can be reliably measured and interpreted as an output of activity from that brain region. A large literature supports M1 MEP amplitude as a putative indicator of cortical excitability and possible neuroplasticity, comparing amplitudes before, immediately after, and at later times after stimulation to determine if changes in cortical excitability persisted (Huang, Rothwell, Edwards, & Chen, 2008). While functional magnetic resonance imaging (fMRI) studies of the effects of rTMS on functionality connectivity are another possible indicator of changes in cortical plasticity (Bilek et al., 2013), EEG-TMS measurements primarily have been used to characterize the effects of rTMS on stimulated neuronal circuits (Casarotto et al., 2010) and provided evidence for a link between induced excitability and LTP/LTD-like events (Noh, 2016).

Both basic and clinical research literature indicates that rTMS can have either facilitatory or inhibitory effects on neuronal firing, depending upon the stimulation parameters. In a review of the effects of different stimulation parameters on excitability, Fitzgerald, Fountain, and Daskalakis (2006) reviewed the effects of stimulation in M1 on amplitude of MEP. Although there was some variation among studies, most studies have concluded that low-frequency rTMS ($\leq$1 Hz) led to a reduction in cortical excitability. Thirteen studies reported a decrease in MEP amplitude after low-frequency stimulation; of the six studies that did not report a decrease in cortical excitability, five utilized low stimulation intensities (between 85–90% of resting MT) so that they might not have had a significant effect on excitability. Conversely, high-frequency rTMS (defined as 5 Hz or greater) elicited persistent excitation in the motor cortex, with nearly all of the studies reporting a significant increase in MEP amplitude following rTMS.

Subsequent studies of low frequency rTMS have been largely consistent with the findings from Fitzgerald et al.'s (2006) review, indicating a significant decrease in MEP amplitude after treatment with 1 Hz rTMS (Casula et al., 2014; Di Lazzaro et al., 2008; Fischer & Orth, 2011; Nojima, Katayama, & Iramina, 2013; Sale, Rogasch, & Nordstrom, 2016; Sommer, Norden et al., 2013). Variation in the duration and intensity of inhibitory stimulation has yielded differing degrees of effectiveness in inhibition. Decreased MEP amplitude was shown in treatments, with as few as 900 (Di Lazzaro et al., 2008; Sommer, Norden et al., 2013) and as many as 1800 pulses delivered (Casula et al., 2014; Fischer & Orth, 2011). Nojima et al. (2013) reported that administration of a larger number of pulses elicited greater decreases in MEP amplitude, seen at a range of intensities from 85–115% MT. Increased intensity of stimulation, however, was not associated with greater inhibition. rTMS stimulation at 85% MT led to a greater decrease in MEP amplitude compared with stimulation at 100%

Table 1. Summary of the effects of administration of different pharmacologic agents on cortical excitability during TMS.

Study	Drug name	Drug description	Protocol	effects
Schwenkreis et al. (1999)	Memantine	NMDA receptor antagonist	ppTMS	Intracortical inhibition enhanced, intracortical facilitation reduced
Huang et al., (2007)	Memantine	NMDA receptor antagonist	iTBS	Blocked changes in excitability associated with iTBS and cTBS, no effect on MT
Kaelin-Lang et al. (2002)	Dextromethorphan	Uncompetitive NMDA receptor antagonist	rTMS	No effect on TMS after-effect
	Lorazepam	GABA(A) receptor agonist	rTMS	Blocked excitatory after-effects of TMS on MEP amplitude
Reis et al. (2006)	Amantadine	Weak NMDA receptor antagonist, increases dopamine release	rTMS, ppTMS	Increased ICI, decreased ICF, no effect on MEP amplitude
Teo et al. (2007)	d-Cycloserine	Competitive NMDA receptor antagonist at high doses	iTBS	Modulates iTBS after-effects from excitatory to inhibitory
Reis et al. (2002)	Topiramate	GABA(A) receptor agonist, non-NMDA glutamate receptor antagonist	rTMS, ppTMS	Dose dependent increase of ICI in response to TMS, no effect on RMT or CSP
Höffken et al. (2013)	Ketamine	Non-competitive NMDA receptor antagonist	ppTMS	Only at highest doses: ICI significantly reduced, ICF tended to be enhanced
Ciampi de Andrade et al. (2014)	Ketamine	Non-competitive NMDA receptor antagonist	10 Hz rTMS	Decreased the analgesic effects of rTMS, no effect on ICI, ICF, MEP, or RMT
Di Lazzaro et al. (2003)	Ketamine	Non-competitive NMDA receptor antagonist	rTMS	Dose dependent reduction in RMT and AM, increased EMG amplitudes
Labedi et al. (2014)	Ketamine	Non-competitive NMDA receptor antagonist	iTBS (Rodent)	Dose dependent reduction of iTBS after-effects of gene expression
Thirugnanasambandam et al. (2011)	L-DOPA	Dopamine precursor	PAS	Modified PAS effects in a non-linear, generally inverted-U shaped dose-dependent function
Fresnoza et al. (2014)	Bromocriptine	Selective D2-receptor agonist	PAS	Modified PAS effects in a non-linear, generally inverted-U shaped dose-dependent function
Monte-Silva et al. (2009)	Ropinirole	D2/D3-receptor agonist	PAS	Modified PAS effects in a non-linear, generally inverted-U shaped dose-dependent function
Korchounov and Ziemann (2011)	Haloperidol	D2 Receptor antagonist	PAS	Abolished facilitatory PAS effects
	Prazosin	Alpha-1 adrenergic antagonist	PAS	Abolished facilitatory PAS effects
Nitsche et al. (2009)	L-DOPA	Dopamine precursor	PAS	'Rescues' sulpiride abolished inhibitory PAS effect
Batsikadze et al. (2013)	Citalopram	Selective serotonin reuptake inhibitor	PAS	Abolished inhibitory PAS effects and enhanced facilitatory PAS effects

and 115% MT. Sale et al. (2016) administered low-frequency rTMS at three different frequencies (0.05, 0.2, and 1 Hz). Their data indicated that the lowest frequencies of stimulation elicited the lowest change in MEP amplitude, such that 0.05 Hz stimulation corresponded with the weakest MEP amplitude fluctuations, and 1 Hz corresponded with the strongest. Overall, this literature indicates that rTMS administered at 1 Hz elicits decreases in excitability when administered to the primary motor cortex.

Research on high-frequency rTMS has been largely consistent in showing that stimulation frequencies greater than or equal to 5 Hz increase excitability of the M1 cortex. Nine studies have shown increased MEP amplitude in healthy subjects following rTMS administered at 5 Hz (Cosentino et al., 2014; Gilio et al., 2007; Lorenzano et al., 2006; Matsunaga et al., 2005; Park, Kim, Chang, Kwon, & Shin, 2014; Sczesny-Kaiser, Tegenthoff, & Schwenkreis, 2009; Sommer, Rummel et al., 2013; Trebbastoni et al., 2016; Yin et al., 2015). Exploration of different stimulation parameters has elucidated the role of duration and intensity of excitatory effects. Significant increases in MEP amplitude were observed in the range from 60 (Cosentino et al., 2014) to 1250 pulses (Sczesny-Kaiser et al., 2009), although one study (Trebbastoni et al., 2016) found no change in MEP amplitude until after 70 pulses were administered. The effect of

changes in stimulation intensity have been similarly consistent. Increases in MEP amplitude were seen, with intensities ranging from 90% MT (Park et al., 2014; Sczesny-Kaiser et al., 2009; Sommer, Rummel et al., 2013; Yin et al., 2015) to 120% MT (Cosentino et al., 2014; Trebbastoni et al., 2016). These changes in MEP amplitude have been shown to persist for roughly 30 min (Yin et al., 2015). The effects seen in healthy controls, however, may differ from those in clinical populations. No change in MEP amplitude was observed in response to 5 Hz rTMS stimulation in patients with Huntington's Disease (Lorenzano et al., 2006) or Alzheimer's Disease (Trebbastoni et al., 2016), and, in patients with chronic migraine, a decrease in MEP amplitude following 5 Hz stimulation was observed (Cosentino et al., 2014).

Stimulation at frequencies of 10 Hz or greater were reviewed by Fitzgerald et al. (2006). The general consensus of the literature is that administering 10 Hz frequency rTMS to the primary motor cortex leads to an increase in cortical excitability, as evidenced by significant increases in MEP amplitudes (Arai et al., 2007; Chang et al., 2010; Jung, Shin, Jeong, & Shin, 2008; Khedr, Rothwell, Ahmed, Shawky, & Farouk, 2007; Kim et al., 2015; Simis et al., 2013; Vasant, Michou, Mistry, Rothwell, & Hamdy, 2015). Larger increases in MEP amplitude usually have been reported with increases in the duration of stimulation from 50 (Vasant et al., 2015) to 1000 pulses (Arai et al., 2007; Kim et al., 2015), although the relationship with duration may be more complex. Vasant et al. (2015) compared three different conditions (50, 250, and 500 pulses) and found that 250 pulses was associated with the largest increase in MEP amplitudes, followed by 50 pulses, but that 500 pulses did not elicit a significant change in MEP amplitude. Other studies have elicited increased cortical excitation using 750 (Khedr et al., 2007) or 1000 pulses (Arai et al., 2007; Kim et al., 2015), calling into question why MEP amplitudes would be significantly affected by using 250 pulses or fewer and 750 pulses or greater, but not at 500 pulses. Significant increases in MEP amplitude in response to 10 Hz stimulation have been reported, with stimulation intensities ranging from 80% (Jung et al., 2008) to 100% MT (Kim et al., 2015; Simis et al., 2013). These changes in MEP amplitude have been reported to persist from 30 (Khedr et al., 2007; Vasant et al., 2015) to 120 min after the end of stimulation (Jung et al., 2008).

In addition to the total duration of stimulation, other studies have examined the effects of burst duration and pulse waveform (Arai et al., 2007; Jung et al., 2008). Jung et al. (2008) administered 1000 pulses of 10 Hz rTMS at 80% in one of two conditions, 1.5 s and 5 s burst duration. Subjects in the 1.5 s condition demonstrated enhanced MEP amplitudes, while subjects in the 5 s condition demonstrated decreased MEP amplitudes. This finding suggests that the length of the pulse train of uninterrupted rTMS may play a critical role in determining whether high-frequency stimulation produces a persistent decrease or increase in cortical excitability. Arai et al. (2007) demonstrated that the stimulation waveform also can affect whether stimulation is facilitatory or inhibitory. These investigators reported that subjects who received monophasic waveform rTMS exhibited a greater change in MEP amplitudes for a longer period of time than those who received biphasic rTMS. They hypothesized that monophasic pulses selectively activated a population of neurons with the same orientation relative to the stimulating magnet, such that effects of monophasic stimulation summated and persisted more consistently than biphasic pulses that activated neurons with different orientations at a slightly later time point.

Excitability studies of the motor cortex suggest that, while higher frequency stimulation may be facilitatory, there may be an upper frequency limit to the effect. Several studies of motor cortex stimulation performed at frequencies greater than or equal to 20 Hz have shown no significant effect on MEP amplitude (Khedr, Etraby, Hemeda, Nasef, & Razek, 2010; Malcolm & Paxton, 2015; Vasant et al., 2015). However, Malcolm and Paxton (2015) did find a significant increase in ICF and decrease in ICI in response to 2000 pulses of 20 Hz rTMS at 90% RMT. Although 10 Hz stimulation has been reported to elicit a larger increase in MEP amplitude than 5 Hz (Vasant et al., 2015), there may be an upper limit at which the frequency becomes too high to elicit facilitation.

The effects of rTMS on excitability in the DLPFC

While a number of studies have assessed the effects of TMS on cortical excitability in the M1 cortex, much less work has examined the effects on excitability in DLPFC, the most common site of stimulation for the treatment of MDD. This constitutes a significant gap in the literature. While there is some correlation between the neurophysiologic reactivity of the motor cortex and DLPFC to TMS stimulation, there are significant differences in the properties of neuronal excitability between these two cortical regions (Kähkönen, Komssi, Wilenius, & Ilmoniemi, 2005; Kähkönen, Wilenius, Komssi, & Ilmoniemi, 2004). Differences in

latency, size, and spread of TMS evoked potentials (TEP) across cortical regions may reflect differences in metaplasticity between the motor and non-motor cortex, as well as the differences in the extent and pattern of cortico-subcortical and cortico-cortical connectivity (Chung, Rogasch, Hoy, & Fitzgerald, 2015; Nordmann, Azorina, Langguth, & Schecklmann, 2015). A major determinant of response differences among cortical regions is the cortico-thalamic 'module' to which a region belongs (Rosanova et al., 2009). For example, DLPFC has reciprocal innervations, primarily with the dorsomedial nucleus (DM) of the thalamus, and responds to TMS by production of gamma frequency (~21–50 Hz) activity, while the sensorimotor cortex has reciprocal innervations primarily with ventral and lateral nuclei and responds to stimulation with beta frequency (~13–20 Hz) activity (Berger, Minarik, Liuzzi, Hummel, & Sauseng, 2014; Rosanova et al., 2009).

The gap in the literature for DLPFC may reflect the fact that, while MEP amplitude is a longstanding and well-accepted indicator of motor cortex facilitation or inhibition, there have not until more recently been similar well-validated measures for DLPFC. There are, however, neurophysiologic methods that are applicable to characterize excitability in DLPFC in response to TMS administration. These methods include changes in local and global mean field power (LMFP and GMFP, respectively) (Ilmoniemi et al., 1997; Schalk, 2015). LMFP can be used as a measure of excitability at the site of TMS stimulation in any local region of cortex, and GMFP is a measure of global excitability that has been used to study a number of non-invasive neuromodulation treatments (Casarotto et al., 2013; Chung et al., 2015; Huber et al., 2008; Lehmann & Skrandies, 1980; Pellicciari, Brignani, & Miniussi, 2013; Romero Lauro et al., 2014). After administration of a local stimulus, a focal change in excitability may come to elicit a global change; as a result, GMFP can be used to interpret LMFP and determine whether a local change in excitability remains focal, or becomes part of a global change in excitability. Esser et al. (2006) delivered 5 Hz rTMS at 90% MT to the motor cortex while recording EEG, which they used to calculate GMFP. This study showed significant enhancement of the amplitude of oscillatory response after rTMS at EEG electrodes located bilaterally over the premotor cortex. This measure also could be used to examine excitability in DLPFC.

TMS-evoked potentials (TEPs) represent another approach to assessing cortical excitability. They are average EEG responses at specific latencies following the TMS pulse. Short latency potentials (i.e. 30 ms) reflect excitatory activity, whereas longer latency potentials (i.e. 100 ms or greater) reflect cortical inhibition (Hill, Rogasch, Fitzgerald, & Hoy, 2016; Rogasch & Fitzgerald, 2013). Long-latency potentials have been the subject of the greatest research in this area. Paired-pulse experiments show that a second TMS pulse administered 50–150 ms after an initial pulse blunts the size of the second TEP compared to a single pulse alone (Valls-Sole, Pascual-Leone, Wassermann, & Hallett, 1992). This technique appears to be useful across cortical regions. Lioumis, Kicić, Savolainen, Mäkelä, and Kähkönen (2009) performed rTMS at 90%, 100%, and 110% MT to elicit N100 TMS-evoked potentials both in M1 and DLPFC. They reported that reproducible N100 measures could be elicited in both cortical areas, although amplitudes were on average 5-times larger in M1 than DLPFC using the same stimulation parameters (Casula et al., 2014; Lioumis et al., 2009). Recent results suggest that N100 responses may be similar across multiple cortical regions. Du, Choa, Summerfelt, Rowland, Chiappelli, Kochunov, et al. (2016) reported that the N100 response to rTMS was not significantly different in regions including the 'left prefrontal, left motor, left primary auditory cortices, the vertex and posterior cerebellum with stimulations performed using supra- and subthreshold intensities' (p. 69).

Another measure of cortical excitability is long-interval cortical inhibition (LICI), which refers to the temporary suppression of neuronal activity when a pair of suprathreshold TMS pulses are administered using an inter-stimulus interval between 50–200 ms., resulting in the inhibition of the TEP produced by the second pulse (Valls-Sole et al., 1992). Daskalakis et al. (2008) examined LICI in DLPFC following 100 rTMS pulses administered at 120% MT with an ISI of 100 ms. They reported significant suppression of TMS-evoked cortical activity in the DLPFC, which also was significantly correlated to a decrease in cortical evoked activity in the motor cortex in response to LICI TMS. Rogasch, Daskalakis, and Fitzgerald (2015) examined LICI and TEPs in DLPFC, as well as working memory performance, in healthy controls. LICI resulted in significant suppression of all TEP peaks, with a correlation between LICI and N100. Interestingly, LICI and N100 were differentially correlated with working memory performance, suggesting that LICI and N100 following represented complementary methods for assessing cortical inhibition in the DLPFC. The LICI paradigm also may yield similar

results across cortical areas. Fitzgerald et al. (2008) demonstrated significant cortical inhibition using an LICI TMS paradigm at 120% MT in the DLPFC, with a significant association between suppression of cortical activity in DLPFC and the primary motor cortex. The absence of a significant difference between the two regions suggests that the LICI paradigm is applicable both to DLPFC and M1.

Cortical excitability also can be assessed through examination of the structure, synchrony, and distribution of resting state oscillations across the frequency spectrum (Henry, Herrmann, & Obleser, 2014). TEPs can be conceived of not only stereotyped waveforms at different latencies following a stimulus, but also as evokved oscillations of different frequencies: for example, the N100 TEP represents an evoked alpha frequency rhythm of 10 Hz, and the P60 an evoked beta oscillation of 16.7 Hz. This is consistent with the view that both the N100 and alpha rhythms are detected in the cortex during inhibitory states, and the P60 and beta rhythms are detected in the cortex during excitatory conditions. As discussed above, each corticothalamic module produces a dominant rhythms following cessation of stimulation: alpha oscillations (8–12–Hz) in occipital, beta (13–20–Hz) in parietal, and beta/gamma (21–50 Hz) in frontal cortices (Rosanova et al., 2009). Thus, rather than alpha rhythms reflecting excitability across all cortical regions, each region appears to produce a different frequency of activity associated with changes in excitability (for example, beta oscillations are most indicative of parietal cortex excitability) (Samaha, Gosseries, & Postle, 2017). The duration, amplitude, and precise frequency of the evoked oscillations depend not only upon the specific location of stimulated cortex, but also upon whether the stimulation is single, paired, or a sustained train of repetitive TMS pulses (Chung et al., 2015), as well as for how long after the cessation of stimulation oscillations are examined. Relatively few studies have examined resting state oscillations as an indicator of cortical excitability.

Use of excitability measures to characterize the effects of novel patterned pulse rTMS paradigms

Further evidence for the usefulness of excitability measures to characterize the effect of different rTMS pulse parameters is provided by studies using novel patterned pulse paradigms. Theta-burst stimulation (TBS) is one such pulse paradigm that has garnered considerable attention as a new therapeutic modality. It holds some advantages over traditional rTMS in that it is able to induce similar strong and persistent after-effects on cortical excitability, but at a lower stimulation intensity and shorter protocol time (Cárdenas-Morales, Nowak, Kammer, Wolf, & Schönfeldt-Lecuona, 2010). The TBS paradigm was first introduced by Huang, Edwards, Rounis, Bhatia, and Rothwell (2005), who introduced two forms of TBS, excitatory intermittent theta-burst stimulation (iTBS) and inhibitory continuous theta burst stimulation (cTBS). In both iTBS and cTBS, a burst of three stimuli at 50 Hz is repeated every 200 ms (or 5 Hz, which is within the theta range of brain oscillations). However, in iTBS this pattern of triplet bursts is administered in 2-s trains every 10 s, whereas in cTBS a 40-s train of uninterrupted triplet pulse bursts are given.

The majority of the literature has shown that TBS is highly effective at eliciting changes in cortical excitability in the primary motor cortex (Cárdenas-Morales et al., 2010), and specifically that iTBS leads to a significant increase in MEP amplitude, and cTBS a significant decrease, for ∼30 min (Huang et al., 2005; Wischnewski & Schutter, 2015). In a comprehensive review from Wischnewski and Schutter (2015), 38 of the 43 iTBS protocols elicited a significant increase in MEP amplitude lasting from 15–50 min, and 51 of the 58 cTBS protocols elicited a significant decrease in MEP amplitude lasting from 5–60 min. These effects were all observed with protocols with stimulation intensities of either 70% resting MT or 80% active MT.

While the initial parameters utilized by Huang et al. (2005) produce consistent changes in excitability, different stimulation parameters yield significantly different results. Nettekoven et al. (2014) reported that iTBS performed at 70% MT for up to 1800 pulses (three blocks of 600 pulses) produced dose-dependent increases in excitability and connectivity. However, Gamboa, Antal, Moliadze, and Paulus (2010) demonstrated that increasing the stimulation from 1800 to 3600 pulses paradoxically yielded iTBS that produced inhibitory effects, and cTBS that was excitatory. The frequency at which TBS is administered also plays an important role in modulation of cortical excitability (Goldsworthy, Pitcher, & Ridding, 2012; Vernet et al., 2014). Modifying the traditional cTBS paradigm from 50 Hz triplets at 5 Hz to 30 Hz triplets at 6 Hz produced greater inhibition of longer duration (Goldsworthy et al., 2012; Vernet et al., 2014). Lastly, the after-effects of iTBS and 5 Hz rTMS on cortical excitability were compared by Di Lazzaro et al. (2011), whose data illustrated that iTBS elicits on average a significantly larger increase in MEP amplitude over 5 Hz rTMS.

Quadripulse Stimulation (QPS) is another novel patterned pulse paradigm in which a burst of four

Table 2. Summary of the effects of quadripulse stimulation (QPS) on cortical excitability.

Study	Intensity	ISI (ms)	Amount of pulses	Effects on MEP amplitude
Hamada et al. (2007)	90% AMT	5	720	No effects on MEP
	130% AMT	5	720	Increased MEP lasting 30 min
	90% AMT	5	1440	Increased MEP lasting 10 min
	130% AMT	5	1440	Decreased MEP lasting 75 min
Hamada et al. (2008)	90% AMT	1.5	1440	Increased MEP lasting 30 min
	90% AMT	5	1440	Increased MEP lasting 30 min
	90% AMT	10	1440	Slightly increased MEP lasting 30 min
	90% AMT	30	1440	Slightly decreased MEP lasting 20 min
	90% AMT	50	1440	Decreased MEP lasting 30 min
	90% AMT	100	1440	Decreased MEP lasting 30 min
	90% AMT	1250	1440	No effects on MEP
Watanabe et al. (2014)	90% AMT	5	1440	Increased MEP lasting 90 min
	90% AMT	50	1440	Decreased MEP
Simeoni et al. (2016)	90% AMT	5	1440	Increased MEP
	90% AMT	50	1440	Decreased MEP
Nakatani-Enomoto et al. (2012)	90% AMT	5	1440	Increased SEP
	90% AMT	50	1440	Decreased SEP

monophasic pulses are delivered at 50 Hz, separated by inter-stimulus intervals of 1.5–1250 ms, which is within the theta frequency range (Hamada, Hanajima, Terao, Arai, Furubayashi, Inomata-Terada, et al., 2007). QPS has been posited to induce longer-lasting cortical potentiation and inhibition in the motor cortex than TBS, with facilitation reported to last from 75–90 min (Enomoto et al., 2015; Hamada et al., 2007; Nakamura et al., 2011; Simeoni et al., 2016). The length of the inter-stimulus-interval (ISI) has been reported to significantly affect whether stimulation is inhibitory or excitatory, with an ISI of 1.5–5 ms being facilitatory and 30-100 ms inhibitory (Hamada et al., 2008; Simeoni et al., 2016; Watanabe et al., 2014). ISIs of 1.5 and 5 ms have been reported to elicit greater excitation than 10 ms, and 50 and 100 ms greater inhibition than 30 ms. However, when the ISI was increased to 1250 ms, no effect on excitability was reported (Hamada et al., 2007). Increasing both the intensity and the number of the pulses has been reported to increase the duration of the effect (Hamada et al., 2007). The general consensus of the current literature suggests that QPS is an effective and safe way to induce long-term-plasticity in the human motor cortex (Table 2).

What is the evidence that changes in excitability are related to the outcomes of rTMS treatment of MDD?

While the effects of TMS on a variety of measures of excitability have been extensively examined, the relationship of most of these measures to treatment outcome in MDD has not been reported. Treatment outcome has best been studied in relation to various measures of resting-state oscillatory activity, the structure, synchrony, and distribution of which represent an alternate measure of cortical excitability (Henry et al., 2014). As discussed above, few studies have examined resting state oscillations as an indicator of cortical excitability. Nevertheless, multiple studies indicate that these resting state oscillatory measures have great clinical utility and may constitute an intermediate phenotype for MDD: they are heritable measures of brain network organization (Smit, Stam, Posthuma, Boomsma, & de Geus, 2008) that are correlated with the presence of (Cook, Hunter, Korb, & Leuchter, 2014) and risk for MDD (de Geus, 2010). A series of studies have shown that changes in theta and alpha band synchrony during treatment with traditional antidepressant medications (Bares et al., 2007, 2008, 2010; Bares, Brunovsky et al., 2015; Baskaran, Milev, & McIntyre, 2012; Cook et al., 2002; Cook, Hunter, Abrams, Siegman, & Leuchter, 2009; Leuchter, Cook, Gilmer et al., 2009; Leuchter, Cook, Marangell et al., 2009) and possibly ketamine (Horacek et al., 2010) are strongly predictive of clinical response or remission.

A growing body of evidence indicates that resting-state measures of oscillatory synchrony such as power or cordance also may constitute reliable biomarkers of rTMS treatment efficacy. Bares, Brunovsky et al. (2015) examined prefrontal cordance in 25 subjects undergoing rTMS for treatment of MDD, and found decreases in theta band cordance, a measure of oscillatory synchrony, were significantly associated with treatment response. Pathak, Salami, Baillet, Li, and Butson (2016) used magnetoencephalography (MEG) to study oscillatory synchrony as well as functional connectivity in five MDD subjects treated with rTMS. They found that increases in gamma power as well as changes in delta and gamma band functional connectivity were significantly associated with treatment response. In one of the larger studies performed, Arns, Drinkenburg, Fitzgerald, and Kenemans (2012) studied

90 subjects treated with rTMS and psychotherapy prior to treatment with EEG and evoked potential measures. They reported that non-responders showed increased fronto-central theta EEG power, slower anterior individual alpha peak frequency, larger P300 amplitude, and decreased pre-frontal delta and beta cordance. The combination of these measures had significant accuracy in discriminating responders from non-responders to treatment. A second report (Arns, Cerquera, Gutiérrez, Hasselman, & Freund, 2014) applied three non-linear EEG measures (Lempel-Ziv Complexity or LZC, False Nearest Neighbours, and Largest Lyapunov Exponent) to recordings from these same subjects. They found that, in the alpha band (7–13 Hz), responders showed decreases in LZC, while non-responders showed increased LZC. Khodayari-Rostamabad, Reilly, Hasey, deBruin, and MacCrimmon (2011) used a mixture of factor analysis (MFA) to examine EEGs in 27 subjects treated with rTMS, and distinguished responders from non-responders with greater than 80% accuracy.

Some studies have utilized an entirely different approach to study the relationship between excitability and treatment outcome in depression. Canali et al. (2014) studied 21 depressed inpatients with bipolar disorder who were undergoing treatment with combined sleep deprivation and light therapy. They utilized TMS as a probe to measure excitability in DLPFC using GMFP and LMFP, and correlated these measures with clinical outcome. They found that excitability increased during the course of treatment, and that both higher baseline cortical excitability and greater increases during treatment were statistically significantly higher in patients that responded compared to those that did not respond. Pellicciari, Cordone et al. (2013) used yet a different approach and examined changes in alpha activity during REM sleep over DLPFC as a possible indicator of changes in cortical excitability during rTMS, following low frequency (1 Hz) over the right or high frequency (10 Hz) over the left hemisphere. In a sample of 10 subjects, they reported that reductions in alpha power were significantly correlated with clinical outcomes in those patients that responded to treatment.

The results of these studies illustrate significant effects of rTMS upon excitability in subjects with MDD, and indicate that EEG biomarkers may potentially be used as predictors of treatment response. While all of these results suggest the usefulness of neurophysiologic biomarkers, the use of naturalistic designs with differing lengths of treatment, different rTMS parameters among the studies, and different biomarkers across studies, make it difficult to assess the reliability of any specific biomarker for treatment outcome.

Conclusions

Studies of the neurophysiologic effects of rTMS indicate several important points. First, TMS has significant LTP- and LTD-like effects on cortical excitability, many of which are mediated through and/or modulated by NMDAR. Serotonergic and dopaminergic neurotransmission also play a modulatory role in the excitatory and inhibitory effects of TMS, consistent with the therapeutic effect of rTMS in depression. Second, the excitability effects of TMS in stimulated neuronal circuits are consistent and reproducible in groups of individuals, and can be used to characterize the effects of different stimulation parameters (Casarotto et al., 2010). Third, a growing number of studies support the paradigm of using measures of oscillatory synchrony, and other indicators of cortical excitability as biomarkers for treatment efficacy.

Taken as a whole, the evidence indicates that modulation of excitability plays a central mechanistic role, leading to clinical treatment response, and rTMS-induced changes in excitability in the cortex may constitute useful biomarkers for the effectiveness of novel magnetic stimulation parameters (Noh, 2016). rTMS induce LTP- and LTD-like effects that may be linked to the MOA for therapeutic benefit, although this linkage remains speculative. Such biomarkers may serve as useful surrogate end-points for large scale clinical trials of novel patterned pulse sequences and other changes to treatment parameters. While research indicates that several different neurophysiologic biomarkers may be useful, research reports have examined a number of different biomarkers and rTMS treatment parameters across studies, included limited numbers of subjects, and therefore have had limited replication of results. Future studies should emphasize use of a common suite of biomarkers that could be applied to a standard course of rTMS treatment, and firmly establish which biomarkers offer the greatest reliability.

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All other authors have nothing to disclose.

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