TMS

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Introduction

Since its introduction in 1984, transcranial magnetic stimulation (TMS) has become firmly established as a useful diagnostic and investigative tool in clinical neurophysiology. TMS has also become increasingly popular as a probe in the exploration of normal human brain physiology and the correlates between brain activity and behavior (For review on TMS, see Pascual-Leone et al. 2002, Kobayashi and Pascual-Leone, 2003).

A growing number of studies suggest that TMS may have a place in the *treatment* of a range of neurologic conditions including Parkinson's disease (Pascual-Leone et al., 1994; Mallory and Stone, 1998, Málly et al., 2004), writer's cramp (Siebner et al., 1999), epilepsy (Tergau, 1999), or stroke recovery (Mansur et al., 2005).

However, such suggestions of therapeutic potential of TMS in neurologic disease are very preliminary and much experimental work is still needed to assess their practical significant if any.

Similarly, the use of TMS for the treatment of psychiatric disorders is relatively recent (Belmaker and Fleischmann, 1995), but an increasing number of studies provide extensive knowledge that enables clinicians to draw some conclusions in this open field.

Basic Principles

TMS uses the principle of inductance to get electrical energy across the scalp and skull without the pain of direct percutaneous electrical stimulation. It involves placing a small coil of wire on the scalp and passing a powerful and rapidly changing current pulse through it.

This produces a magnetic field, which passes relatively unimpeded through skin, scalp, and skull, and is tolerated extremely well by most subjects. This magnetic field induces a much weaker electrical current in the brain. The strength of the induced current is a function of the rate of change of the magnetic field.

In 1987, stimulators capable of generating pulses at up to 60 Hz were introduced, thus providing a technology that allows modulation of human cortical excitability non-invasively. More recently, stimulators capable of delivering repetitive TMS (rTMS) at rates of > or = 100 Hz have become available. Trains of focal rTMS of appropriate frequency, intensity, and duration can lead to a transient increases or decreases in excitability of the affected cortex (Maeda et al., 2000). The safety rTMS depends on an interaction of these and other stimulation parameters.

Terminology

Single-pulse TMS refers to single stimuli to a given brain region every 5 to 10 second. Repetitive stimulation can be slow or fast. Slow (or low frequency) rTMS refers to stimulation at a frequency of 1 Hz or less. Fast (or high frequency) rTMS refers to stimulation at rates above 1 Hz (Wassermann, 1998).

TMS and Depression

In patients with Major Depressive Disorders (MDD), rTMS applied to the appropriate regions and with appropriate stimulation parameters has shown antidepressant effects. TMS has now been approved as a treatment for depression in a wide variety of countries (European Union, Canada, Australia and New Zealand among others). Moreover, rTMS is also offered by an increasing number of physicians and clinics as an off-label application of an approved device in the US.

Following an initial surge of great enthusiasm for the potential of rTMS in the treatment of depression, later on, the heterogeneity in the design of the studies with discordant results triggered critics and skepticism.

Nevertheless, recent meta-analysis studies send an optimistic message about the state of the art on TMS as a therapeutic option in depression. There is currently widespread support for the antidepressant potential of rTMS, but the full extend of the clinical significance of the effects remains uncertain and there is a need for multi-center, well-controlled trials with sufficient number of patients.

Safety guidelines

Obviously, all studies should follow the current safety guidelines to minimize the risk for the subjects. Guidelines for the safe use of rTMS were first published in 1993 by Pascual-Leone et al., and were updated at the First International Workshop on the Safety of Transcranial Magnetic Stimulation held in June 1996 in Bethesda, Maryland (Wassermann, 1998).

At this workshop, a revised table for maximum single rTMS train duration depending on rTMS frequency and intensity for the safe application of rTMS was agreed upon. Repetitive TMS appears to be safe, if the proposed safety guidelines are followed. The International Federation for Clinical Neurophysiology has endorsed these safety recommendations (Hallett et al., 1999).

Remarkably, the same parameters of stimulation that exert and antidepressant effect in patients in normal subjects can result in increased subjective sadness and reduced happiness ratings (George et al., 1996; Pascual-Leone et al. 1996a; Martin et al., 1997).

Mechanisms of Action of TMS in Depression

Pathophysiology of depression

Repetitive TMS provides a mechanism to modulate activity in a distributed neural network. In the case of depression the prefrontal cortex provides a "window" to a distributed neural network that involves cortical and subcortical struictures. Resting cerebral metabolism and blood flow in the dorsolateral prefrontal cortex (particularly on the left) are decreased in PET studies (Strafella et al., 2003).

This suggests a decrease in neural activity that appears to be correlated with the severity of depression and is reversed with recovery from depression (Baxter et al., 1989), (Martinot et al., 1990), (Bench et al., 1995). These findings have been confirmed through electroencephalography studies that linked a decrease in left frontal regions (increased alpha power) to depression (Henriques et al., 1991), (Bruder et al., 1997), (Debener et al., 2000), (Davidson et al., 2002). An enhanced activity in the anterior cingulate cortex has also been related to depression (Drevets, 1999), (Videbech et al., 2002), (Drevets et al., 2002).

Long term depression/long term potentiation

A growing body of literature on animal experimentation describes the manipulation of the efficacy of synaptic transmission through repetitive electrical stimulation of the nervous system. These phenomena are named *long-term potentiation*, if there is an enhancement of synaptic efficiency, and *long-term depression* (LTD) if the former actually decays. For many years researchers have sought proof of the existence of analogous mechanisms in humans.

Huang and Rothwell (2004) have recently safely reproduced a phenomenon that behaves like LTP in humans exposed to rTMS. Further investigations (Huang et al., 2005) drew impressive results applying "theta burst" paradigms to motor areas. The authors tested 3 stimuli at 50 Hz repeated every 200 ms. A short intermittent protocol such as two-second trains with an inter-stimulus interval of 10 s for a total of 190 s (total of 600 pulses) triggers rapid facilitation of synaptic transmission.

Nevertheless, when a long-lasting uninterrupted train is given for 40 seconds (total of 600 pulses), an initial facilitatory effect is eventually converted into an inhibitory effect.

Similarly it has been hypothesized that the depressant effect of rTMS on human cortical excitability is related to LTD. A "priming train" (brief pre-treatment in the range of 5-6 Hz) increases the ability of 1 Hz rTMS to trigger a decrease in synaptic efficacy (Christie and Abraham, 1992).

Therefore, previous neural activity modulates the following plastic changes. Abraham and Bear named this phenomenon metaplasticity (Abraham and Bear, 1996), (Abraham and Tate, 1997).

Iyer et al. (2003) proposed a sham-controlled study in which 6 Hz rTMS priming of 1 Hz rTMS on the motor cortex increased cortical suppression compared to sham. These data have clinical implications for rTMS applications designed to enhance cortical responsiveness (Parkinson's disease or depression) and also for safety of high frequency rTMS studies.

However, it is important to realize that even if the physiologic observations to date are consistent with LTP and LTD effects of rTMS, it remains unproven whether the modulatory effects of rTMS in humans are truly exerted at the level of synaptic transmission or at the level of network modulation.

Mechanisms of action of TMS on mood regulation

Some interesting effects related to the physiology of mood have been observed using TMS:

- Several investigators have reported a delay of the onset of rapid eye sleep (REM) in normal subjects (Cohrs et al., 1998). Sleep disturbances play a crucial role in depression and mood disturbances and the modification of sleep may in fact secondarily exert antidepressant effects.
- Several reports have assessed the effect of long-term rTMS with SPECT (Zheng, 2000) and PET (Speer et al., 2000), (Kimbrell et al., 1999). Despite the variability in the applied TMS protocols, the findings suggest that it is possible to increase prefrontal metabolism or blood flow.
- Elevation of plasma thyroid-stimulating hormone (TSH) in healthy males in a placebo controlled trial (Cohrs et al., 2000); and elevation of TSH and mood in depressed patients (Szuba et al., 2001) have been described. A link between endocrinologic and mood regulatory mechanisms may account for antidepressant effects.
- rTMS has also been shown to normalize the response to dexamethasone in depression (Pridmore, 1999; Reid and Pridmore, 1999).
- The inhibitory effect of low frequency rTMS seems to mediate the delivery of g-aminobutyric acid (GABA) (Ziemann et al., 1996) (Werhahn et al., 1999) and elevation of dopamine release in the caudate nucleus has been reported following fast rTMS to the prefrontal cortex (Strafella et al., 2003). Shifts in neurotransmitters may account for the antidepressant effects.

Animal studies

It seems clear that increasing the clinical significance of TMS as a therapeutic application in depression, and other neuropsychiatric conditions, will require a more in depth understanding of the mechanisms of action of TMS. This will likely require animal studies.

Some technical difficulties limit the use of TMS in animals. The coil to head ratio, for example, has not been properly considered in the past and this will critically influence the magnitude of the induce current density in the brain.

Other concerns are the different distance from coil to brain between animals and humans, the need to adjust the current and the effects of anesthesia (often needed in animals) when associated with TMS (e.g., Ghaly et al., 1990). In addition to this, human and animal behaviors are not easily comparable (Belmaker and Grisaru, 1998).

The first studies in animal models showed that rTMS or electrical stimulation can enhance forebrain serotonin output (Juckel et al., 1999) and modulate 5-HT receptor function (Ben-Schachar et al., 1999; Kole et al., 1999). Also rTMS has produced behavioral (like shortening the immobility time in the forced swimming test) and biochemical (like a depression of responsiveness of the noradrenaline-stimulated cyclic AMP generating system) changes similar to that produced by electro convulsive therapy (ECT) (Zyss et al., 1997).

Finally, rTMS, like ECT and antidepressant drugs, can regulate gene expression and may have an impact on neuronal viability and synaptic plasticity (Lisanby and Belmaker, 2000; Levkovitz et al., 2001).

Evidence of Therapeutic Efficacy of TMS in Depression

First open studies in depression

Evidence of an antidepressant action for rapid rTMS comes from a number of open studies (Figiel et al., 1998; Lyndon, 2001). There have been case reports of recoveries by individuals (Avery et al., 1999). In addition to this, TMS can possibly induce mania as do some antidepressant drugs (Dolberg et al., 2001).

The first studies, with small sample and opened design, suggested that low frequency stimulation on the vertex could have antidepressant effects (Hoflich et al., 1993; Grisaru et al., 1994; Kolbinger et al., 1995).

George et al. (1995) reported the use of rapid rTMS on the left dorso-lateral prefrontal cortex to treat depression in humans. This was an open uncontrolled study using a figure of eight shaped coil. Subsequent studies have varied the intensity and the number of days of treatment. They treated six patients and the depression scores for the group improved significantly. Two patients showed robust improvement, two showed slight improvement and two showed no improvement.

More recent open studies (Schiffer et al., 2002), (Mosiman et al., 2003), (Mottaghy et al., 2002), (Dragasevic, 2002), (Schüle et al., 2003), (Zwanzger et al., 2003), (Brasil-Neto et al., 2003) provide further evidence about TMS's effect on depression.

These results were encouraging. However, given the open study design, there may have been placebo responses. Nevertheless, most patients in these studies suffered long-standing medication-resistant depression, and thus may have been less likely to exhibit a placebo response.

Controlled studies in depression

Pascual-Leone et al., (1996b) published the first blind placebo controlled study of fast rTMS in 17 depressed patients. Eleven patients experienced an initially pronounced improvement that faded over the following two weeks. This was a complex trial in which patients underwent multiple cross-overs to different parameters of stimulation. The study design could have obscured the results by introducing a carry-over effect in some subjects even though the authors tried to allow for sufficient wash-out time.

Furthermore, the complex design and the need for multiple cross-overs resulted in a selection of patients, who despite suffering psychotic depression, where stable enough to complete the five month-long project. Despite these limitations, this study provided the first evidence from a controlled trial supporting the antidepressant potential of rTMS.

Several other subsequent controlled studies have been performed (e.g., George et al., 1997, Padberg et al., 1999, and George et al., 2000). Most of these studies have found a statistical (though not always clinically) significant antidepressant effect of rTMS. However, the patient populations and particularly the stimulation parameters used have been quite variable and hence comparison across studies is difficult.

There is a study that couldn't show any improvement with rTMS in treatment-resistant depressed patients. Loo et al. (1999) reported an improvement in the sham stimulation (placebo) group equivalent to that in the real rTMS group. Hence, this was really a failed trial. Lisanby et al. (2001) shed some light into these results showing that the sham stimulation used by Loo et al., may have been active.

More recent studies have continued to show an active place for rTMS as an antidepressant (Berman et al., 2000), (Eschweiler et al., 2000), (George et al., 2000), (Garcia-Toro et al., 2001), (Janicack et al., 2002), (Fitzgerald et al., 2003), (Hoppner et al., 2003), (Herwig et al., 2003), (O'Connor et al., 2003), (Loo et al., 2003), (Grunhaus et al., 2003), (Nahas et al., 2003), (Kauffmann et al., 2004), (Haussmann et al., 2004), (Mosiman et al., 2004), (Jorge et al., 2004), (Koerselman et al., 2004).

Metaanlyses of TMS in depression

A series of recent meta-analyses provide further evidence about the effects of rTMS on depression. *McNamara et al.* (2001) studied the effect of five published randomized controlled trials in which rTMS was applied as treatment for depression. All

the analyzed controlled trials but Loo's (1999), already addressed in this review, showed statistically significant benefit of rTMS. The difference between rate of improvement in the treated group and that in the control group was 43% (95% CI 25% to 61%).

Holtzheimer et al. (2001) included twelve studies that had a control arm with sham stimulation and were assessed with Hamilton's Depression Rating Scale. rTMS showed a statistically significant greater effect than sham stimulation. Nevertheless, the studies did not have a clinically relevant effect. These results could be explained by the limited number of stimuli received per session and the low number of sessions in which TMS was applied in the considered studies.

Burt et al. (2002) published ameta-analysis including a wide variety of controlled studies. It draws interesting results as it acknowledges the statistical significance of rTMS as an antidepressant. Nevertheless, TMS fails to reach clinical significance in this metaanalysis.   Different effect sizes reflect the heterogeneity of the trials in the field by the time this study was published.

Kozel and George (2002) analyzed ten studies in which high frequency rTMS was applied to the left prefrontal cortex. It reports a clinically relevant effect size of 0.53 in a total sample of 230 patients. However, this study also highlights the many limitations of individual studies in the field till that moment.

Another relevant metaanalysis *(Martin et al., 2003)* includes those studies with acceptable randomization and blinding that report all the initially randomized patients regardless of whether they completed the study or not (thus allowing an intention to treat analysis). MDD and bipolar trials (in depressed phase) were included.

Thirteen studies were analyzed that applied left-sided high-frequency rTMS with sham stimulation control. There is a pooled effect of rTMS on the Hamilton Rating Scale for Depression scores when compared to sham. This effect was present after two weeks of treatment (standardized mean difference=-0.35; 95% CI −0.66 to −0.04). However, the analysis failed to be significant at the two-week follow up.

Thus, these results show an effect of rTMS in a 2-week window that support the idea of a required maintenance treatment after this period. Interestingly, the subjective measure of the Beck Depression Inventory did not corroborate the former findings.

In conclusion

If safety precautions are followed, rTMS is safe when applied for a 1 to 4 week period. The variety of designs and treatment parameters diminishes the relevance of meta-analyses conducted to date. Nevertheless, this fact should not be confused with a lack of effect of rTMS in depression, but as the sign for the critical need for multi-centered controlled double blind randomized studies involving a large number of patients.

TMS and ECT

Electroconvulsive therapy (ECT) is a well-known treatment for depression, especially for the medication-resistant forms and those with psychotic symptoms. ECT is highly effective; nevertheless, ECT needs anesthesia and muscle relaxation. Furthermore, it is associated with memory impairment. (See also Dr Shashi Kant Jha's article on ECT.)

These features derive from the fact that the skull is highly resistant to the passage of electricity (Lorimer et al., 1949), which therefore cannot be accurately focused from electrodes placed outside (Hayes, 1950). Probably for this reason a generalized convulsion is associated with and possibly required for therapeutic effect.

The electrical currents resulting from TMS can be applied focally, without inducing a generalized convulsion because electromagnetism allows a reliable bridge across the skull. Zyss et al. (1997) published preliminary data comparing the behavioral and biochemical effects of electroconvulsive stimulation and TMS in rats, suggesting that both might involve similar mechanisms of action. As a matter of fact, Pridmore et al. (1998) tested a combination of ECT plus TMS, suggesting a possible summing effect.

Antidepressant effects of TMS and ECT

Several studies comparing the antidepressant effects of TMS and ECT (Grunhaus et al., 2000), (Pridmore et al., 2000), (Janicack et al., 2002) have shown similar remission rates (56% versus 46% for ECT and rTMS respectively).

Grunhaus et al. (2000) reported a study in which patients with major depression were off medications. They were allocated to ECT or 20 TMS sessions. When data was stratified by the presence or absence of psychotic features, ECT proved to be much more efficacious when psychotic data was present.

Nevertheless, among those patients with no psychotic features TMS and ECT were equal. In a subsequent study, Grunhaus et al. (2003) found no significant difference in Hamilton Depression Scores decrease between rTMS and ECT patients. Additionally, Kozel et al. (2004) have shown that rTMS presents a favorable cost effectiveness profile compared to ECT and in both, acute and maintenance settings.

Finally, Grunhaus's group (Grunhaus et al., 2000), (Grunhaus et al., 2003) and Janicack's (2002)assessed the effect of rTMS in patients off-medications and provide additional evidence to Berman's initial report (Berman, 2000) on rTMS as a stand-alone therapy in some cases.

Significantly less side-effects

Importantly, from a cost-benefit ration, rTMS is associated with significantly less side-effects than ECT. Therefore, in patients who have not responded to medications (or cannot tolerate them) and who are stable enough to delay acute hospitalization and ECT treatment for a couple of weeks, a trial of rTMS seems indicated.

MDD Maintenance

Acute benefit of rTMS on depressive symptoms seems to be limited in time. Duration of the effects in most patients is limited to about 4 months until a new relapse. Therefore, strategies to maintain the antidepressant efficacy of rTMS are needed.

Dannon and Grunhaus (2003) reported on a patient with drug-resistant depression who received TMS treatment for over three years. The first full course triggered a full recovery. The second and third courses generated a limited improvement that even so kept building up into completely asymptomatic periods after rTMS.

This group had already reported similarly good results (Dannon et al., 2002) with regards to the ability of TMS to produce beneficial effects in the case of a relapse after a previous successful treatment.

Greater sensitivity?

The authors hypothesize that the modulation TMS exerts on the brain may induce a greater sensitivity to previously not too successful medications. Moreover, they suggest that this effect may last for up to a year after TMS.

The role of antidepressants on a maintenance phase after TMS has been analyzed by Schüle et al. (2003). They studied the effect of 10 to 13 sessions of rTMS with 10 Hz at 100% motor threshold intensity to the dorsolateral prefrontal cortex followed by the introduction of mirtazapine.

TMS by itself or its subsequent combination with mirtazapine resulted in a 77% overall response rate measured by Hamilton Depression Scale Scores performances. Thus, the authors concluded that TMS should be followed by immediate antidepressant pharmacotherapy or further TMS treatment to prevent from a relapsing episode.

Moreover the putative priming effect that TMS could have on subsequent pharmacotherapy might be related to the action mechanisms both rTMS and antidepressants have shown so far.

Mirtazapine

For instance, mirtazapine increases cell firing at the synaptic cleft and also inhibits alpha2-adrenergic heteroreceptors at the 5HT nerve terminals (de Boer and Ruigt, 1995). As previously mentioned, TMS animal studies have shown to modulate 5-

HT receptor function (Ben-Schachar et al., 1999; Kole et al., 1999).

Mirtazapine is also an acute inhibitor of cortisol and ACTH secretion in humans (Laakman et al., 1999). (Schüle, et al., 2002). rTMS induces a reduction in arginine vasopressin release at the paraventricular nucleous in rats (Keck et al., 2000), anda significantly attenuated stress-induced elevation of plasma corticotrophin and corticosterone in rats (Keck et al., 2001), (Post and Keck, 2001).

This attenuation of the hypothalamic-pituitary-adrenocortical axis hyperactivity could favor clinical responsiveness to subsequent pharmacological treatment. Thus, it maybe the case that mirtazapine and rTMS have a synergistic effect on mood. Furthermore, the implications of this study can be taken a step further through performing rTMS while patients are already on antidepressants.

Presumably, this multi-prong approach could draw even better results with regard to the initial efficacy of the treatment and to its ability to prevent relapses.

Relapse rates equal

Importantly, relapse rates after TMS or ECT are equal, around 30% in both cases (Dannon et al., 2002); or even higher for those patients undergoing ECT (Wijkstra et al., 2000). Kozel et al. (2004) compared ECT and rTMS in both, acute and maintenance settings, in terms of cost effectiveness. rTMS seemed to provide a financial advantage in both situations. Thus, it might be worth exploring rTMS maintenance even for those patients who require an initial ECT course.

Parameters that Predict a Clinically Significant Response to rTMS

The range of effectiveness observed in the published reports is strikingly wide. There are some factors that were not taken in consideration in the first studies, but seem to play a relevant role on response rates.

Psychotic features

As mentioned previously, the occurrence of psychotic features seems to be associated to a greater response to ECT (Grunhaus et al., 2000). Nevertheless, these results should not discourage researchers about conducting long course rTMS trials in psychotic depression.

Length of current depressive episode

Holtzheimer et al. (2004) noted a significant negative correlation between length of the current depressive episode and response to rTMS. Distinctively, those patients with a current episode of 4 yrs or less showed a 56% reduction in mean HAM-D whereas those with a current episode longer than 10 yrs showed only a 7% decrease.

Older patients

Some studies (Figiel et al., 1998), (Janicack et al., 2002) have observed that older patients responded less effectively to rTMS. The aging brain presents with a greater degree of cortical atrophy and the enlargement of the sulci may play a role. A greater amount of cerebrospinal fluid collections probably diminishes the focality of the treatment in this patient population.

Previous response to rTMS

Preliminary evidence indicates that a previous response to rTMS increases the response rate for new treatments when relapses occur (Dannon et al., 2000). Conversely, two studies run on patients that failed to respond to TMS reported that ECT is less likely to be effective (Eschweiler et al., 2000). (Dannon and Grunhaus, 2001). However, a non-response to rTMS reflects on a poorer behaviour on ECT requires further consideration (Holtzheimer et al., 2004).

Cortical excitability changes

Cortical excitability changes have been addressed by Maeda et al., (2000a; 2000b; 2002) in both healthy and depressed subjects. TMS paired-pulse studies measure intracortical inhibition or facilitation. Hence, they allow having a reliable correlate of the modulatory effect of TMS in the cortex.

Therefore, if TMS is applied with the same parameters that the clinical treatment is going to be provided, and before and after doing so, the amplitude of motor evoked potentials is measured, the clinician will have an accurate idea of whether and how TMS modulates the patient's cortex. Thus, low frequency stimulation will diminish the amplitude of the motor evoked potentials, whereas high frequency TMS will exert the opposite effect.

Imaging studies

Imaging studies with SPECT (Teneback, et al., 1999) and PET (Kimbrell et al., 1999) can also provide evidence about those patients that may be better responders to TMS. It seems that the baseline activity in the inferior frontal lobe is higher in patients that tend to respond to rTMS (Teneback et al., 1999).

Conversely, hypometabolism in both temporal lobes, the cerebellum, and the anterior cingulate and occipital areas was associated with a better response to 20 Hz rTMS. The opposite was true for a greater improvement after 1 HZ rTMS.

Length of treatment

The length of the treatment, this is the number of sessions provided, is extremely heterogeneous in literature. Several reports (Pridmore et al., 2000), (Grunhaus et al., 2000), (Janicack et al., 2002), (Grunhaus et al., 2003), (Fitzgerald et al., 2003) highlight the relevance of rTMS long treatment courses.

Explicitly, Pridmore et al. (2000) determined a trend towards improvement in patients with medication-resistant depression after an rTMS course lasting for more than 15 sessions. Therefore, with the exception of Schüle's report on rTMS plus subsequent mirtazapine (2003) most papers in which > or = 10 sessions were provided (Grunhaus 2000), (Pridmore et al., 2000), (Janicack et al., 2002), (Grunhaus et al., 2003), (Fitzgerald et al., 2003) show stronger results with regard to remission than those limited to two weeks (George, 1997), (Garcia-Toro, 2001), (Garcia-Toro et al., 2001b), (Berman, 2000), (George, 2000).

Schüle's results maybe explained by synergistic mechanisms in the way mirtazapine and rTMS act. In summary, the rationale for these results maybe a possible cumulative effect of rTMS over time. Conversely, it could be also argued that the effect builds up depending upon the length of the therapeutic intervention. Nonetheless, the delayed clinical outcome as a result of antidepressant medications or ECT disputes this theory.

High intensity TMS

Studies applying high intensity TMS, around 100% to 110% of the motor threshold, (George, 2000), (Pridmore et al., 2000), (Janicack et al., 2002), (Brasil-Neto et al., 2003), (Zwanzger et al., 2003), (Nahas et al., 2003), (Kauffmann et al., 2004), (Hausmann et al., 2004), (Jorge et al., 2004), (Holtzheimer et al., 2004), (Boechat-Barros and Brasil-Neto, 2004) seem to report better results than those employing 80% to 90% of the motor threshold intensity (George, 1997), (Garcia-Toro, 2001), (Garcia-Toro et al., 2001b), (Berman, 2000), (Grunhaus, 2000), (Loo et al., 2003), (O'Connor et al., 2003).

Two recent studies showed good results with low intensity stimulation, but most importantly associated to high frequency (20 Hz) rTMS (Hoppner et al., 2003), (Koerselman et al., 2004).

Number of rTMS pulses

The number of rTMS pulses per session is also important. Studies in which 1200 to 1600 pulses were delivered in each session (Garcia-Toro, 2001), (Garcia-Toro et al., 2001b), (George, 2000), (Pridmore et al., 2000), (Grunhaus et al., 2003), (Herwig, et al., 2003), (Nahas et al., 2003), (Kauffmann et al., 2004), (Jorge et al., 2004), (Holtzheimer et al., 2004) were more successful in either terms of remission rates or net mood response than those applying 800 to 1000 pulses a day (George, 1997), (Berman, 2000), (Janicack et al., 2002).
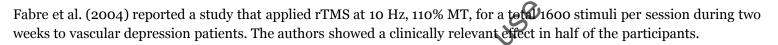
Vascular Depression

Depressive disorders and cerebrovascular disease have been recently assessed in the literature (Rao, 2000; Ramasubbu, 2000). Although not quite defined yet, some clinical features have been proposed to classify vascular depression (Steffens and Krishman, 1998), (Rigaud et al., 2002).

These patients usually present with cognitive impairment that does not reach the criteria for dementia and a first depressive event late in life (>60 years). White matter lesions are also associated with a history of late life depression (de Groot et al., 2000), and predict a poor response to treatment (Taragano et al., 2001).

Furthermore, subcortical white matter lesions seem to be related to a higher rate of delirium due to antidepressants and ECT (Soares and Mann, 1998). The distribution of leukoaraiosis in subcortical areas is also associated with a distinct neuropsychological profile.

Hence, periventricular white matter lesions are linked to a delayed recall after distraction, while basal ganglia hyperintensities relate with decreased verbal fluency, and pontine reticular formation affection translates into impaired psychomotor performance (Simpson et al., 1997). Most patients with late depression suffer from anticholinergic side effects due to regular antidepressant therapy and may benefit from rTMS.

Effect in half of the participants

Fabre et al. (2004) reported a study that applied rTMS at 10 Hz, 110% MT, for a total 1600 stimuli per session during two weeks to vascular depression patients. The authors showed a clinically relevant effect in half of the participants.

Another sham controlled randomized parallel double blind study (Jorge et al., 2004) assessed the effect of rTMS on post-stroke depression. The patients were off-medications and the parameters applied were 10 Hz, at 110% MT, 1000 stimuli per session during 10 sessions. rTMS was associated with significant response and remission rates that were independent for age or white matter lesions.

However, only patients with right hemisphere strokes or deep subcortical lesions were included in the study, which precluded the authors from far reaching conclusions. Overall, the authors conclude that despite of the fact that this type of depression is highly refractory to other therapeutic options, it is reasonable to think that a longer period of rTMS (three or four weeks) can draw better clinical results.

Nonetheless, further studies assessing the volume and location of the stroke should be conducted in order to elucidate the role of TMS in this condition.

Depression in Parkinson's Disease

Dragasevic et al. (2002) first conducted a study on TMS and depression in patients with Parkinson's disease. It was an open study, thus the results were preliminary as far as the authors could not rule out a placebo effect. Nevertheless, 10 parkinsonian patients (8 with bilateral Parkinson's disease) with dysthymia (n=6) or depression (n=4) received 0.5 Hz, the intensity was 110% of the motor threshold, 100 stimuli per hemisphere, bilaterally at the prefrontal cortex for 10 days.

TMS was applied bilaterally because there is a diminished bilateral metabolism at the caudate, orbital frontal and inferior prefrontal cortex in depressed parkinsonian subjects compared to those with normal mood (Mayberg et al., 1990). The antidepressant effect remarkably lasted for 20 days after the last session.

Effect on depression

Fregni et al. (2004) studied the efficacy of TMS in depression in the context of Parkinson's disease. A group of 42 patients received 15 Hz plus placebo or fluoxetine (20 mg/day) plus sham during 10 days. Both groups showed the same response with regard to mood. As a matter of fact, TMS showed an effect on depression for eight weeks after the end of the protocol.

Additionally, TMS did not show any motor side effects attributed to fluoxetine, but an actual improvement. Thus, TMS

might be considered as a valid therapy for depression in patients with Parkinson's disease and may in fact provide dual benefit for the motor and mood disturbances. However, further controlled studies with a placebo arm (sham or sham plus antidepressants) are desirable.

TMS and Cognition

Possible long-term deleterious effects of TMS on cognition have been a concern since the beginning of its application as both a research and a clinical tool.

Healthy volunteers are frequently exposed to single pulse or repetitive TMS during experiments in neuroscience. Attention, memory, executive functions and motor processing have been examined in several studies to ensure that no deleterious effect on cognition can be attributed to TMS (Bridgers and Delaney, 1989), (Hufnagel et al., 1993), (Jahanshahi et al., 1997), (Pascual-Leone et al., 1993). Moreover, improvements in cognitive and motor performance have been reported (Siebner et al., 1999b), (Mottaghy, et al., 1999).

With regard to patients with depression, the evidence collected in healthy subjects does not suffice to establish safety, as there is a state-dependent cognitive impairment associated with depression (Austin et al., 2001). Since most protocols of rTMS in depression apply stimulation to the left or right prefrontal cortex, researchers usually employ batteries focused on frontal lobe function to assess cognitive impact.

The application of rTMS as a maintenance therapy for depression demands a thorough evaluation of its long term effects. Several studies lacked either a control group, or power due to a small sample size. Martis et al. (2003) assessed the effect of more aggressive rTMS parameters 10 Hz, 110% MT in severely depressed (unipolar and bipolar) treatment-resistant individuals for one to four weeks. There was a significant improvement in working memory-executive function, objective memory, and fine motor speed over the rTMS period independent of mood enhancement.

No deleterious effects on memory

The well-known ECT side effects were compared to TMS in some studies (O'Connor et al., 2003). O'Connor et al., compared a three session per week unilateral ECT protocol (lasting for two to four weeks) with rTMS at 10Hz 90% of MT for two weeks (n= 28). Those patients allocated to the ECT arm had a greater positive impact on their mood.

Nevertheless, cognitive evaluations showed transient disruptive effects of ECT on various aspects of memory, and a permanent retrograde amnesia. TMS did not exert any deleterious effects on memory. Hausmann et al. (2004) designed a study in which patients on current antidepressant therapy were treated with 20 Hz on the left DLPC, or allocated to a left high frequency plus 1 Hz right DLPC stimulation, or sham.

Neither the aggressive parameters used, nor the add-on design seemed to have a negative impact on cognitive measures focused on motor skills, learning, memory, attention, and executive functions. Moreover, verbal memory mildly improved compared to sham independently of the antidepressant effect.

In summary, no cognitive side effects of rTMS have been detected in healthy nor in depressed patients. In fact, there may be a beneficial effect of rTMS on cognition that may be independent of the antidepressant efficacy and warrants further evaluation.

Bipolar Disorder

Clinicians and investigators have also considered the possibility of introducing TMS during the depressive phase in bipolar mood disorder (BMD). Nahas et al. (2003) designed a parallel sham controlled study in which 11 patients with a BMD were treated on the left dorsolateral prefrontal cortex with 5 Hz, 110 MT% for a total 1600 stimuli per session, during ten sessions.

This study failed to show any significant differences between both groups. However, the authors acknowledged certain relevant limitations. First, patients with both types I and II BMD were included. Second, although some mood stabilizers had been washed out (lamotrigine) some participants were on carbamazepine or valproate.

Mood stabilizers are a matter of concern with regard to their ability to offset the tuning effect TMS exerts on the brain. Third, the authors were shy on the frequency used (5 Hz) concerned about the possibility of inducing a manic phase. This factor may have also played a role in the lack of effect ascertained in these patients.

There is not enough evidence with regard to TMS as a maintenance treatment for patients with a BMD. Li et al. (2004) applied rTMS on a weekly basis during one year to those participants who presented a clinically relevant response to TMS (n=7) in the protocol previously disclosed (Nahas et al., 2003).

These patients received TMS with the same parameters applied in the previous study. Around 40% of them presented no relapses during the 12 month follow up period when rTMS was combined with previously ineffective medications. Thus, the authors suggested that TMS might be considered as an adjunctive therapeutic maintenance option for BMD. Clearly controlled trials are needed.

Mania

Grisaru et al. designed the first controlled trial of rTMS for the treatment of mania (1998b). This study compared right hemisphere stimulation with left hemisphere stimulation, but had no sham control group. Right prefrontal cortex stimulation produced a greater improvement than contralateral TMS. These results were concordant with Shaldivin's (2001) measures in an amphetamine hyperactivity rat model for mania.

Michael et al. (2004) tested the effect of rTMS over the right prefrontal cortex in nine bipolar type 1 inpatients in a manic phase for four weeks for a total of 16 sessions at 20 Hz, 800 stimuli per session and 80% MT (as suggested by Grisaru, 1998b). The results were comparable to those of Grisaru's study. It should be noted that 70% of the sample was on mood stabilizers, mainly valproate, which did not appear to interfere with the effect of TMS.

In this study a careful assessment of the clinical subtype of the manic episode (euphoric versus dysphoric/mixed) and of the underlying temperament was performed. Mixed states or temperamental intrusions (Akiskal, 1992a), (Akiskal, 1992b) into the manic episode did not seem to influence the outcome when TMS was applied.

Acute mania (Garcia-Toro, 1999) and hypomania (Nedjat and Folkerts, 1999) have been reported as a side effect of high frequency left prefrontal rTMS.

Obsessive Compulsive Disorder

As a means of treatment for Obsessive Compulsive Disorder (OCD), right prefrontal rTMS applications has been reported to have modest, site-dependent effects on compulsions, whereas no effects on obsessions (Greenberg et al., 1997).

Unfortunately, direct stimulation of the orbito-frontal cortex, an area consistently implicated in OCD, is not possible with this technique. These results have to be considered very preliminary and certainly more studies in other laboratories are needed to establish the clinical significance, if any, of TMS in the treatment of OCD.

Schizophrenia

Auditory verbal hallucinations are the cardinal symptom in schizophrenia. PET (Silbersweig et al., 1995), and fMRI studies (Shergill et al., 2000) have localized the left parieto-temporal junction as the source of activity correlated with the hallucinations in right-handed individuals. Between 50 to 70% of schizophrenic patients suffer from auditory hallucinations (Andreasen and Flaum, 1991). Most of these individuals respond successfully to medications. Nonetheless, 25 to 30% of these patients are refractory to antipsychotic medications.

Grisaru et al. (1994) first attempted to apply rTMS in schizophrenic patients, but reached inconclussive results with regard to mood and thought disorder in their chronic patients. Feinsod et al. (1998) observed a decrease in the degree of anxiety and restlessness, but no effect on core psychotic symptoms. Klein et al. (1999) reported a double-blinded sham-controlled trial that failed to show any significant beneficial effects of rTMS on auditory hallucinations or other positive symptoms.

Promising reports

However, Hoffman et al. (1999; 2000) conducted a study in which the left temporo-parietal cortex was stimulated with TMS in patients reporting persistent auditory hallucinations. This group published an improvement in psychotic symptoms that lasted for weeks in some individuals. D'Alfonso and collagues (2002) described a clinically significant effect in eight patients in an open trial.

Franck et al. (2003) treated a case of severe paranoid schizophrenia with refractory to antipsychotic medications auditory hallucinations that responded after 10 sessions with 1 Hz rTMS. The hallucinations were not completely suppressed, but the patient was able to keep distant from the voices. A double blind sham-controlled study (Hoffman et al., 2003) reported an improvement that lasted for 15 weeks in attentional salience and frequency of hallucinations with 1 Hz rTMS at 90% of the motor threshold and benefited half of the participants.

Poulet et al. (2005) run a study in which patients were allocated to five days (total of 10 sessions) with 1 Hz rTMS, 1000 stimuli per session applied to the left temporo-parietal cortex followed by a washout period of a week and five more sessions with sham stimulation at 90% motor threshold or vice versa.

All subjects were medication resistant but were receiving a constant regular dose of antipsychotic for the lat three months. Poulet's group reported the same magnitude of the effect Hoffman (2003) published, comprising 10 sessions in five days. However, some potential pitfalls must be considered in this study.

First, the washout period between treatment conditions was relatively short and a carry-over effect is difficult to exclude. Second, the coil placement, halfway between T3 and P3 according to international EEG 10 to 20 coordinates, could be questioned due to the individual variability in the location for language association cortex. Finally, language processing centers may not be as lateralized in schizophrenics as in the general population.

Thus, though some reports are promising, the avaialble trials are methodologically limited. Therefore, further trials are needed before the clinical significance of TMS in the treatment of refractory hallucinations can be determined.

Post-Traumatic Stress Disorder

Increased blood flow or metabolism in right limbic, paralimbic, and frontal cortical structures when recalling the traumatic event in patients with posttraumatic stress disorder (PTSD) (Shin et al., 1997; Rauch et al., 1996) have encouraged some studies with rTMS in patients with this disorder.

In one study, (Grisaru et al., 1998a) ten PTSD patients were given one session of slow TMS and found it to be effective in lowering the core symptoms of PTSD: avoidance (as measured by the Impact of Event Scale), anxiety, and somatization (as measured by the Symptom Check List-90). A general clinical improvement was found (as measured by the Clinical Global Impression scale).

However, the effect was rather short-lived and transient. McCann et al. (1998) reported two cases in which treatment in which there was an improvement in symptoms. However, a full follow-up trial reportedly failed to confirm the encouraging results of these initial two patients.

Limitations of the Current TMS Studies

Initial limitations in early TMS studies, such as the diverse shapes of the coil used, the number of trains per session and the duration of each train have been overcome by the definition of those parameters. Nonetheless, there are certainly some methodological pitfalls to be addressed in order to fully define the indications of TMS in neuropsychiatric conditions.

Suitable control stimulation

First, the choice of a suitable control or sham stimulation is difficult. It is possible that applying the sham condition by varying the orientation of the coil might not effectively blind the participants (McNamara, 2001) and available sham stimulation coils need improvement to provide a reliable blinding of the patients.

Sample sizes

Second the sample sizes are usually small in both, controlled and open studies, consequently preventing researchers from identifying subgroups of patients that could particularly benefit from rTMS (McNamara, 2001).

Heterogeneous

Third, the samples included in the studies are also heterogeneous in several aspects. Foremost, the conditions included in the experiments are diverse within a study and across studies (i.e. BMD types I and II, MDD, dysthymia). Additionally, most participants are usually on medications and sometimes a portion of the sample is not. Additionally, those patients on medications are usually receiving different treatments.

Blinded

Fourth, as pointed by Martin et al. (2002) it is more accurate to consider the trials as being single blinded and evaluated by blinded external assessors.Despite of the fact that blinding of the outcome assessment maybe more important than blinding administration (Day, 2000).There is a potential for a transfer of non-verbal information from the provider that would eventually reveal the nature of the treatment to the participant.

Antidepressant effect

Fifth, the duration of the antidepressant effect for acute MDD event has not yet been fully defined. Moreover, the design of maintenance treatments and the patients that would benefit the most from them have yet to be determined.

Clinical scales

Sixth, the clinical scales currently used to assess mood changes in the studies have some limitations. For instance, the Hamilton Rating Scale for Depression is based upon a semi-structured interview, which might be subject to an observation bias compared to other self-reported inventories as the Beck Depression Inventory (Hoptof et al., 1999).

Outcome definitions

Seventh, the outcome definitions vary across studies. Hence, it is difficult to establish comparisons among them. Diverse tests have been commonly used to quantify mood changes and as outcome measures. However, due to the difficulties interpreting psychometric scale results (Rosenberg, 2000) and the nature unstable and subjective of depression, more objective outcome measures should be pursued in future studies. Hospital readmissions, time to hospital discharge, time to adjunctive treatment, and time off work should be reported when assessing rTMS's efficacy.

Conclusions

TMS appears to have a definite roll in the treatment of depression in its various forms. Nevertheless there is a need to improve our knowledge on which are the optimal parameters and time frames for maintenance treatment. Furthermore, the duration of the benefits and the efficacy and safety of maintenance therapy are still largely unexplored.

In other psychiatric disorders TMS seems to be a promising therapeutic tool with a very encouraging side effect profile as compared to other techniques (i.e. ECT). Therefore, it seems reasonable to systematically study its mechanisms of action and potential clinical applications.

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