

A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression



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Abstract

There is growing interest worldwide in rTMS as a clinical treatment for depression. Apart from efficacy, its safety as a clinical treatment must be considered before its widespread use can be advocated. All published, sham-controlled rTMS depression trials were reviewed for reported side-effects and outcomes of formal neuropsychological testing. In addition, all reports of seizures occurring with rTMS were reviewed. Other safety concerns (effects on hearing; headache, pain, induced currents in electrical circuits, histotoxicity, electromagnetic field exposure, psychiatric complications, safety in pregnancy) are discussed. Common side-effects were of a minor nature, e.g. headache. There was a low incidence of accidental seizures and induced hypomania, both of which were associated with identified risk factors for which subjects should be screened. Long-term effects of repeated rTMS sessions are as yet unknown. When given within recommended guidelines, the overall safety profile of rTMS is good, and supports its further development as a clinical treatment.

Received 26 November 2006; Reviewed 10 January 2007; Revised 23 January 2007; Accepted 10 February 2007

Key words: Clinical trials, depression, safety, transcranial magnetic stimulation, treatment.

Introduction

There is considerable interest worldwide in the use of subconvulsive repetitive transcranial magnetic stimulation (rTMS) for the treatment of depression. rTMS has excited the interest of clinicians and is highly acceptable to patients (Walter et al., 2001), because of its ability to stimulate focal areas of brain cortex non-invasively. Unlike electroconvulsive therapy (ECT), it does not involve a general anaesthetic or seizure. Numerous sham-controlled trials and several meta-analyses support its efficacy in treating depression (reviewed in Loo and Mitchell, 2005). Recently, the largest rTMS sham-controlled trial to date involving over 300 pharmacotherapy refractory depressed subjects reported positive results (O'Reardon et al., *In Press*). In some countries, e.g. Canada, rTMS has already been approved for the clinical treatment of depression. Elsewhere, debate on its adoption into

clinical practice beyond the research realm has been ongoing for some years (e.g. Sachdev, 2003).

In this context, it is timely to review the safety of rTMS as a treatment for depression and to consider necessary safety precautions in any clinical facility giving rTMS. This review focuses on seizure risk, the main adverse effect of concern; evidence from sham-controlled clinical trials on neuropsychological effects of a treatment course; and commonly reported side-effects, other potential side-effects and theoretical concerns.

Risk of seizure

Accidental seizures are the most serious adverse events reported with TMS to date. Seizures have resulted from both single-pulse TMS (sTMS), usually at high stimulus intensities, and high-frequency rTMS.

Seizures in subjects with neurological disorders

Subjects with pre-existing neurological disorders (e.g. epilepsy, stroke) have a greater risk of seizures with sTMS or rTMS (Dhuna et al., 1991; Homberg and Netz,

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1989; Hufnagel and Elger, 1991; Kandler, 1990; Schrader et al., 2004). However, the incidence of TMS-induced seizures is low and it is relatively difficult to provoke seizures with TMS even in epileptic subjects (Dhuna et al., 1991; Jennum and Winkel, 1994; Tassinari et al., 1990). In fact, EEG changes suggesting that epileptic activity was suppressed after rTMS have been reported (Jennum et al., 1994).

Of concern are reports of delayed seizures after TMS in epileptic subjects, occurring several minutes after TMS had ceased (e.g. Hufnagel and Elger, 1991). Cases of spontaneous seizures occurring days to weeks after TMS in the absence of any prior history of seizures have also been reported in those with pre-existing neurological disorders. Homberg and Netz (1989) reported a first seizure during sTMS and another occurring spontaneously 4 wk later in a subject who had had a cerebrovascular accident 6 months previously, resulting in a large ischaemic scar. Kandler (1990) reported that two subjects with multiple sclerosis had spontaneous seizures 3 and 4 wk after receiving sTMS. From these case reports, the contribution of rTMS to subsequent seizures to rTMS cannot be confirmed or discounted with any certainty. However, the possibility that TMS can induce a seizure disorder where there is a pre-existing neurological disorder cannot be discounted. (See discussion on 'kindling' below.)

Seizures in depressed and healthy subjects

To date there have been 12 case reports of seizures occurring during TMS in subjects who are healthy, depressed or have a disorder not known to increase seizure risk (tinnitus, chronic pain) TMS (see Table 1). Most of these have occurred during rTMS. Among the seven non-depressed subjects who had a seizure, two (cases 1 and 12, Table 1) were during rTMS at stimulation parameters exceeding subsequently suggested safety guidelines (Wassermann, 1998). The others, though, were provoked by rTMS at parameters within, if near the upper limit of, these guidelines. In two of these cases (cases 2 and 3, Table 1), the interval between rTMS trains was short and this may have been a contributing factor. However, the remaining three subjects (cases 4, 5 and 8, Table 1) with no neurological disorder had seizures with rTMS at parameters generally considered to be safe and within the range of stimulation commonly used in depression treatment trials. A contributory factor in one subject may have been the concurrent use of fluoxetine, which may increase seizure risk (Pisani et al., 2002). Of relevance also is that these seizures occurred with stimulation of

the motor cortex, thought to be the cortical area with the lowest seizure threshold (Gottesfeld et al., 1944), and the risk of seizure induction may be lesser with the prefrontal cortical stimulation typically used in depression treatment trials.

The first documented seizure in a depressed subject occurred in the depression treatment study by Pascual-Leone et al. (1996) (case 6, Table 1). Details of this case are given in Wassermann (1998). The rTMS involved was at parameters exceeding subsequent recommended guidelines (Wassermann, 1998). Furthermore, this subject had received identical rTMS in previous sessions without mishap but had taken medications likely to lower seizure threshold (amitriptyline, haloperidol) (Pisani et al., 2002) the day prior to the rTMS-induced seizure.

Conca et al. (2000) reported a unique case of an apparent complex partial seizure involving the frontal lobe in a depressed subject receiving high-frequency rTMS to the left dorsolateral prefrontal cortex. Again, stimulation parameters were beyond the recommendations of safety guidelines and the same subject had previously received rTMS uneventfully when stimulus parameters were within recommended guidelines. Other risk factors in this case are a history of prior seizure in response to medication (maprotiline), and a change of medication (commencement of venlafaxine) in the days prior to rTMS.

In Prikryl and Kucerova (2005) seizure induction in a depressed subject appears to have arisen from a combination of stimulation parameters exceeding recommended guidelines and the effect of sleep deprivation, as the subject had received five uneventful treatment sessions prior to seizing during the sixth session after two sleepless nights. On the other hand, the possibility of a 'kindling' effect with rTMS cannot be excluded.

Of concern are recent reports of seizures in two subjects during sTMS (Thayaril et al., 2005) and 1 Hz rTMS (Nowak et al., 2006), i.e. forms of TMS not previously known to generate seizures in the absence of epilepsy or neurological disorder. Some features of the 'seizure' described in the latter case were atypical and it has been suggested that a faint rather than genuine seizure activity occurred (Epstein, In Press). However, the report by Thayaril et al. (2005) is worrying as it occurred with minimal TMS (a small number of single pulses at moderate intensity, with long interstimulus intervals) in the presence of few subject risk factors [history of a single childhood seizure in subject's brother; modest dose (50 mg/d) of chlorpromazine]. The subject was hypomanic at the time. It has been suggested that manic patients may

Table 1. Accidental seizures occurring with TMS in subjects without neurological disorders

Case no.	Publication and study description	Subjects	Medications	Seizure type	TMS stimulation parameters
1	Pascual-Leone et al., 1993 Safety of rTMS in normals	Female, healthy, 35	Nil	Generalized	Motor cortex. 208%, 10 Hz, 3 trains \times 10 s, ITI=5 min
2	Wasserman et al., 1996 rTMS and language processing	Female, healthy, 27	Nil reported	Generalized	L prefrontal cortex. 105%, 15 Hz, 3 trains \times 0.75 s, ITI=0.25 s
3	Wasserman et al., 1996 rTMS and ITI safety	Female, healthy, 39	Nil reported	Generalized	L motor cortex. 110%, 25 Hz, 4 trains \times 0.8 s, ITI=1 s
4	Wasserman, 1998 NINDS	Female, healthy, 26	Nil reported	Generalized	Motor cortex. 120%, 15 Hz, ? trains \times 2.5 s, ITI=120 s
5	Mercuri B	Male, healthy	Nil reported	Partial motor	Motor cortex. 130%, 3 Hz, 1 train \times 7 s, ITI='long'
6	Pascual-Leone (1991) rTMS depression treatment trial	Female, psychotic depression	Amitriptyline Haloperidol	Generalized	Prefrontal cortex. 90%, 10 Hz, 20 trains \times 10 s, ITI=60 s
7	Conca et al., 2000 Antidepressant augmentation therapy with rTMS	Female, mixed depressive-anxiety, 36	Trazodone Venlafaxine Lorazepam Thyroxin	'Pseudoabsence' Frontal lobe complex partial seizure	L dorsolateral prefrontal cortex. 110%, 20 Hz, 3 trains \times 10 s, ITI \geq 60 s
8	Bernabeu et al., 2004 Effects of traumatic brain injury on cortical excitability as measured by TMS	Female, healthy, 28	Fluoxetine	Focal motor/ secondarily generalized seizure	Motor cortex. 110%, 20 Hz, 1 train \times 2 s
9	Prikryl and Kucerova, 2005 rTMS depression treatment trial	Male, depression, 45	Nil reported	Generalized tonic-clonic	L dorsolateral prefrontal cortex. 110%, 15 Hz, 6 trains \times 10 s, ITI=30 s
10	Tharayil et al., 2005 Pilot study of motor threshold estimation	Male, bipolar hypomanic, 35	Lithium carbonate Chlorpromazine	Generalized tonic-clonic	Motor cortex. 60% MSO, 5 single pulses over 3 min, then 58% MSO, 2 single pulses 60 s apart
11	Nowak et al., 2006 rTMS tinnitus treatment trial	Male, tinnitus, 27	Nil	Right versive seizure (aura, LOC, eyes rotated upwards, tonic extension of limbs)	L primary auditory cortex. 90%, 1 Hz, 580 pulses over 570 s
12	Rosa et al., 2006 rTMS chronic pain trial	Female, chronic pain, 24	?Analgesics	Generalized tonic-clonic	L motor cortex. 100%, 10 Hz, 25 trains \times 10s, ITI=20 s

%, Percent of subject's resting motor threshold unless otherwise specified; ITI, inter-train interval; L, left; LOC, loss of consciousness; MSO, maximum stimulator output; NINDS, National Institute of Neurological Disorders and Stroke.

have a lower seizure threshold, at least compared to depressed patients receiving ECT (Mukherjee et al., 1994). No seizures have been reported in manic subjects receiving rTMS treatment (Grisaru et al., 1998; Kaptan et al., 2003). Chlorpromazine has been

reported to have relatively high seizurogenic potential compared to other antipsychotic agents (Pisani et al., 2002).

While the exact incidence of rTMS-induced seizures in depressed subjects is unknown (as the denominator,

i.e. total number of depressed subjects treated with rTMS worldwide, is uncertain), it is low and likely to be comparable to the estimated incidence of spontaneous seizures with antidepressant therapy (0.1–0.6%, Pisani et al., 2002), with the advantage that seizures usually occur during rTMS stimulation and are hence more readily managed.

Theoretical concerns – kindling

Apart from the immediate precipitation of seizures, there are also concerns that rTMS may have lasting effects on seizure threshold. This is akin to the phenomenon of ‘kindling’, i.e. where repeated sub-convulsive electrical cortical stimuli eventually result in seizure activity (Goddard et al., 1969). ‘Kindling’ has been demonstrated so far only in animals (Sato et al., 1990) and not in humans despite the use of similar stimulation parameters (Engel, 1987).

Relevant to this area are studies of the effects of rTMS on the motor cortex. For example, Pascual-Leone and colleagues’ work on rTMS to the motor cortex in healthy subjects (Pascual-Leone et al., 1994) found that single trains of 20 stimuli at high frequency and intensity (20 Hz, 150% motor threshold) resulted in a lowering of threshold, i.e. a motor-evoked response could then be elicited by a lower level of TMS stimulation to the motor cortex. This effect lasted 3–4 min and was not cumulative when trains were repeated 1 min apart. At least some of this effect is thought to result from increased excitability at the cortical level rather than in peripheral motor pathways (Pascual-Leone et al., 1994). However, it is uncertain whether the reduction in motor cortex threshold also implies a reduction in seizure threshold (see below). Lasting changes in cortical excitability have also been demonstrated after rTMS to the auditory cortex in animals (Wang et al., 1996).

As noted above, it is possible that TMS was responsible for the later development of ‘spontaneous’ seizures in a few subjects with pre-existing neuropathology. It is reassuring that there have been no reports of this among the thousands of healthy and depressed subjects who have received sTMS or rTMS. There have also been no reports of any subject developing epilepsy or repeated spontaneous seizures after TMS. All TMS-induced seizures to date have been transient and self-limiting, without long-term sequelae. Several studies have failed to find significant changes in EEG after rTMS stimulation to the motor cortex in healthy subjects (Pascual-Leone et al., 1993; Wassermann et al., 1996) and after multiple treatment sessions to the prefrontal cortex in depressed subjects

(Loo et al., 2001), suggesting that no lasting, significant changes, at least in epileptiform activity, have occurred.

Summary and recommendations

The majority of subjects in whom seizures have been induced by sTMS or rTMS have had a pre-existing neurological disorder and potential subjects should be carefully screened for seizure risk, for example using the Transcranial Magnetic Stimulation Adult Safety Screen by Keel et al. (2000). However, seizures have also occurred in mood-disordered and healthy subjects with no risk factors for seizure. The majority of these resulted from rTMS at relatively intense stimulation parameters and guidelines specifying ‘safe’ limits incurring minimal seizure risk have been published (Wassermann, 1998). The low incidence of seizures among participants in depression treatment trials probably reflects the widespread adoption of these stimulation limits. Care should also be taken that the interval between rTMS trains is not too brief as this was almost certainly a contributory factor in two of the cases reported above. The Wassermann (1998) guidelines do not specify minimum inter-train intervals but other researchers have published recommendations on this (Chen et al., 1997).

Concurrent medication has been implicated as a risk factor in some of the seizures reported above and some have suggested that certain medications, e.g. tricyclic antidepressants and neuroleptics, should be contraindicated in those receiving rTMS (Wassermann, 1998). On the other hand, hundreds of depressed patients, many on concurrent medications, have received rTMS in clinical trials, with only three reported seizures. In two of the cases above (subjects 6 and 7, Table 1), psychotropic medication was changed during the TMS course in the days preceding the seizure, i.e. rTMS was continued at the same absolute intensity in the presence of a probably altered seizure threshold.

The effect of medications on seizure risk may be partially adjusted for by the common practice of empirically establishing each subject’s motor cortical threshold at the outset (i.e. with the subject on medications which will remain stable throughout the TMS course) and setting the stimulus intensity for the treatment course relative to that. It follows that if medications are altered during the TMS course, the motor threshold should be remeasured and the stimulus intensity adjusted accordingly. This is based on the premise that medications which alter seizure threshold should also alter motor cortical threshold.

Empirical studies of the effects on motor threshold of various medications known to alter seizure threshold, e.g. lorazepam (Ziemann et al., 1996), haloperidol (Ziemann et al., 1997), anticonvulsants (sulthiame, Siniatchkin et al., 2006; cabamazepine, gapapentin, topiramate, Inghilleri et al., 2004; Turazzini et al., 2004; levetiracetam, Reis et al., 2004) yield mixed support for this premise, with some studies showing no change in motor thresholds, while others found increases in motor threshold in the presence of anticonvulsant medication. Inconsistencies between these studies may be due to differences in the doses of medication used. Until more convenient methods are available for adjusting TMS stimulus intensity when medications likely to affect seizure threshold are used, the above approach is recommended.

Alterations in other factors related to seizure risk should also be monitored closely during a course of rTMS treatment. One subject above received rTMS uneventfully until he had two sleepless nights. Our TMS laboratory routinely issues written guidelines to subjects receiving a course of rTMS, advising that alcohol and caffeine intake should not be altered (and should be within reasonable limits), medications should be unchanged, and subjects should inform us if there is any change in the above, if they have had a sleepless night, or developed any intercurrent medical illness.

From experience reported to date, despite the above precautions, seizures will still occur, albeit infrequently. Thus, it is recommended that centres in which TMS is given should be equipped with appropriate facilities and trained staff to manage an unexpected seizure (International Society for Transcranial Stimulation Consensus Statement on TMS, Belmaker et al., 2003).

Studies of neuropsychological function after a course of rTMS

The potential for rTMS to disrupt neuropsychological functioning during the actual stimulation is well recognized, with reports of its use as an investigative probe, essentially producing a temporary functional lesion to enable the localization of cortical areas involved in a particular task (Pascual-Leone et al., 2000). However, the safety of rTMS as a treatment is mainly concerned with the presence of any lasting effects after rTMS, rather than during stimulation.

A number of studies have tested neuropsychological functioning in depressed subjects before and after a treatment course of left prefrontal rTMS. Most studies report improvements in cognitive test results over

time [e.g. Avery et al., 1999, 2005; Fitzgerald et al., 2003, 2006; George et al., 2000; Holtzheimer et al., 2004; Höppner et al., 2003; Jorge et al., 2004; Little et al., 2000; Loo et al., 2001, 2003a, In Press; McDonald et al., 2006; Mosimann et al., 2004; Padberg et al., 1999; Speer et al., 2001; see Table 2 (a fuller version is available online)]. However, it is important to note that in sham-controlled trials very few neuropsychological results are significantly different between active and sham treatment groups (see Table 2), suggesting that factors other than TMS (e.g. practice effects) may account for the improvements measured. Thus, only the results of sham-controlled depression trials are reviewed in this section. Table 2 summarizes formally measured neuropsychological outcomes and general side-effects reported in these trials.

Several studies have suggested that prefrontal rTMS may improve cognitive functioning. Avery et al. (1999) reported that subjects who had received ten sessions of active rTMS performed better than those in the sham treatment group across the whole neuropsychological battery. However, the number of subjects involved was small, no formal statistical comparisons were done, and the difference may have arisen from greater mood improvement in the active group. Padberg et al. (1999) found that verbal memory performance improved after 10 Hz rTMS but not 0.3 Hz or sham rTMS. This is despite the fact that greatest mood improvement occurred in the 0.3 Hz group [19% decrease in mean Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) score, cf. 6% decrease for the 10 Hz group, 6% increase for sham group], suggesting that high-frequency prefrontal rTMS may enhance memory, although the numbers involved are too small for any conclusion.

Fitzgerald et al. (2003) also reported that the active but not sham treatment group in their study improved on a range of neuropsychological measures (attention, frontal functioning, verbal memory, retrograde memory). However, the significance of this difference is unknown as no between-group statistical comparisons were reported.

There have also been isolated reports of worse performance after active than sham rTMS. George et al. (2000) found a significant difference in Mini-Mental State Examination (MMSE; Folstein et al., 1975) scores between the active treatment group which improved by 1.4%, compared with the sham group which improved by 12.5%. The sham group had lower MMSE scores pre-TMS and arguably more potential to benefit from practice effects, although a difference due to TMS cannot be ruled out. Loo et al. (2003a) found that the sham group improved and the active group

Table 2. Summary of neuropsychological assessments and side-effects reported in sham-controlled studies of rTMS for the treatment of depression [a more detailed version of this paper is available on the Journal's website (<http://journals.cambridge.org>)]

Publications	Neuropsychological assessments – tests (before TMS and end of course unless otherwise specified)	Neuropsychological assessment analysis and results
Pascual-Leone et al., 1996	No formal neuropsychological assessments	n.a.
George et al., 1997	No formal neuropsychological assessments	n.a.
Avery et al., 1999	GOAT (pre & post each session), WAIS-R Digit Span & Digit Symbol subtests, RAVLT, COWAT, TMT A & B, Stroop Colour Word Test	No formal analysis GOAT = 99/100 all subjects on all occasions Active performed better than sham on all tests except RAVLT trial V
Klein et al., 1999	No formal neuropsychological assessments	n.a.
Padberg et al., 1999	Verbal learning, RT (simple, choice and paradoxical choice)	ANOVA RT: Group × time interaction n.s. Verbal learning: group × time interaction ($p = 0.006$). 10 Hz: improvement ($p = 0.032$) 0.3 Hz: n.s. Sham: trend for worsening ($p = 0.09$)
Berman et al., 2000	No formal neuropsychological assessments	n.a.
Eschweiler et al., 2000	Formal neuropsychological assessments at baseline only as predictor of response	n.a.
George et al., 2000	MMSE	ANOVA Group × time interaction ($p = 0.02$): active improved more than sham, but lower scores at baseline in sham than active ANOVA (main effects only)
Little et al., 2000	Battery A: baseline and end of week 1, BSRT, Memory cards from Colorado Neuropsychiatric Battery, meta-memory task Battery B: baseline & end week 2, Memory cards from Colorado Neuropsychiatric Battery, category & letter fluency, BSRT, CPT	
Garcia-Toro et al., 2001	No formal neuropsychological assessments	n.a.
Lisanby et al., 2001	No formal neuropsychological assessments	n.a.
Loo et al., 2001a	MMSE, Digit Span, VPAL & TOL (CANTAB versions), COWAT, RAVLT, RT (simple and complex), AMI abbreviated Pre/post single session: Orientation, RT (simple and complex), finger tapping speed, stand-walk test	ANOVA Group × time interaction n.s. MMSE, COWAT-letter, RT, AMI: improvement over time $p \leq 0.05$ (NSAC) ANOVA Group × time interaction n.s. Finger tapping (right): trend for improvement over time $p < 0.05$ (NSAC)
Manes et al., 2001	MMSE	ANOVA Group × time interaction n.s.
Dolberg et al., 2002	MMSE	No formal analysis. Mean scores: Active improved by 1.1 Sham worsened by 0.2
Speer et al., 2001	BSRT, Memory cards from Colorado Neuropsychiatric Battery, letter & category fluency, CTP	Paired <i>t</i> tests, correlation with mood scores
Padberg et al., 2002	No formal neuropsychological assessments	n.a.

Table 2 (cont.)

Publications	Neuropsychological assessments – tests (before TMS and end of course unless otherwise specified)	Neuropsychological assessment analysis and results
Fitzgerald et al., 2003	TOL, AMI, PSMS, WAIS-R: Block Design, Digit Span, VPAL recall and recognition subscale, COWAT	Paired <i>t</i> tests, correlations (correction for multiple comparisons) with MADRS and BDI scores No significant deterioration in any group on any test. Active (10 Hz &/or 1 Hz): improved on VPAL ($p < 0.001$), COWAT ($p < 0.001$), digit span forwards ($p = 0.003$), PSMS ($p = 0.02$), AMI ($p = 0.05$) Correlation n.s. for any test and changes in mood scores
Höppner et al., 2003	d2-test – widely used test in German-speaking countries of psycho-motor speed and concentration	<i>t</i> tests No difference between groups. KL score (concentration): improved (20 Hz, $p = 0.001$; 1 Hz, $p = 0.005$; sham, $p = 0.002$) GZ-F score (concentration attention strain): improved (1 Hz, $p = 0.001$; sham, $p = 0.023$)
Loo et al., 2003a	MMSE, RAVLT, VPAL (CANTAB version), TOL (CANTAB version), COWAT	ANOVA TOL: group \times time interaction $p = 0.043$ (NSAC): active worsened and sham improved COWAT, VPAL: improved over time $p < 0.05$ (NSAC); RAVLT (retention): worse over time, $p < 0.05$ (NSAC)
	Pre/post single session: EPAT, shape recognition	ANOVA
Nahas et al., 2003	No formal neuropsychological assessments	Group \times time interaction n.s.
Hansen et al., 2004	No formal neuropsychological assessments	n.a.
Hausmann et al., 2004a	No formal neuropsychological assessments	n.a.
Holtzheimer et al., 2004	RAVLT, Digit Symbol Test, Digit Span, Stroop Test	ANCOVA (duration of episode & total treatment trials as covariates) RAVLT trial 7 (recall): group \times time interaction ($p < 0.05$): active improved more than sham
Jorge et al., 2004	MMSE, Stroop Test, TMT A/B, COWAT, RAVLT, BVRT, BNT, Token Test, Sentence Repetition Subtest of MAE, Block Design subtest (WAIS-III), Line Bisection Test	Mann–Whitney <i>U</i> test No significant difference between sham and active
Kauffmann et al., 2004	No formal neuropsychological assessments	n.a.
Koerselman et al., 2004	No formal neuropsychological assessments	n.a.
Mosimann et al., 2004	MMSE, VLT, Stroop Test, TMT A/B, word fluency test	ANOVA Group \times time interaction n.s. Word fluency: improvement over time ($p = 0.01$)
Avery et al., 2005	RAVLT, Digit Span, Digit Symbol Test, TMT A/B, MMSE, COWAT, Stroop Test, GOAT	Random effects repeated-measures analyses Group \times time interaction n.s.

[continues overleaf]

Table 2 (cont.)

Publications	Neuropsychological assessments – tests (before TMS and end of course unless otherwise specified)	Neuropsychological assessment analysis and results
Christyakov et al., 2005	No formal neuropsychological assessments	n.a.
Miniussi et al., 2005	No formal neuropsychological assessments	n.a.
Rossini et al., 2005a	No formal neuropsychological assessments	n.a.
Rossini et al., 2005b	No formal neuropsychological assessments	n.a.
Rumi et al., 2005	No formal neuropsychological assessments	n.a.
Su et al., 2005	No formal neuropsychological assessments	n.a.
Fitzgerald et al., 2006	HVLT, COWAT, WAIS Digit Span, Brief Visuospatial Memory Test – Revised, Visuospatial Digit Span	Paired <i>t</i> tests, then ANOVA when differences were seen Digit Span backwards: group × time interaction ($p=0.07$), improved in active group only but not correlated with change in MADRS score ($p < 0.05$)
Januel et al., 2006	Grober & Buschke's Test, Stroop Test, TMT, auditory & visual attention span (WAIS-R), Cardebat's fluency, COWAT, Visuospatial reasoning: Khos (WAIS-R)	ANOVA Group × time interaction n.s.
Garcia-Toro et al., 2006	No formal neuropsychological assessments	n.a.
McDonald et al., 2006	RBANS, BVMT-R, COWAT	ANOVA Group × time interaction n.s. RBANS immediate memory and COWAT-letter: improvement over time $p < 0.05$ RBANS language index and COWAT category: worsening over time $p \leq 0.05$
Loo et al., In Press	RAVLT, TMT A & B, Digit Span forwards & backwards, COWAT	ANOVA TMT A: group × time interaction ($p=0.003$), sham improved and active worsened RAVLT immediate and delayed recall: worsening over time ($p \leq 0.005$) TMT B: improvement over time ($p=0.007$)

AMI, Autobiographical Memory Schedule; BDI, Beck Depression Inventory; BNT, Boston Naming Test; BSRT, Buschke Selective Reminding Test; BVRT, Benton Visual Retention Test; BVMT-R, Brief Visuospatial Memory Test – Revised; COWAT, Controlled Oral Word Association Test; CPT, Continuous Performance Task; EPAT, Expanded Paired Associate Test; GOAT, Galveston Orientation and Amnesia Test; HDRS, Hamilton Depression Rating Scale; HVLT, Hopkins Verbal Learning Test; ITI, inter-train interval; MADRS, Montgomery–Asberg Depression Rating Scale (Montgomery and Asberg, 1979); MAE, Multilingual Aphasia Examination; MARS, Motor Agitation and Retardation Scale; MDTL, Mirror Drawing Task Left hand (left-handedly tracing outline of a 5-point star via a mirror); MDTR, Mirror-Drawing Task Right hand (right-handedly tracing outline of a 5-point star via a mirror); MMSE, Mini Mental State Examination; n.a., not available; n.s., non-significant; NSAC, non-significant after correction for multiple comparisons; PSMS, Personal Semantic Memory Schedule; RAVLT, Rey Auditory Verbal Learning Task; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RT, reaction time; SAFTEE, Systematic Assessment for Treatment Emergent Effects; TOL, Tower of London; TMT, Trail Making Test; VLT, Verbal Learning Task; VPAL, Visual Paired Associates Learning; WAIS-R, Wechsler Adult Intelligence Scale – Revised; WAIS-III, Wechsler Adult Intelligence Scale–III.

^a Equal numbers in each group unless otherwise specified.

^b L = left; R = right; DLPFC = dorsolateral prefrontal cortex. 1 week = 5 sessions on consecutive weekdays unless otherwise stated.

^c rTMS started concurrently with new course of antidepressants.

worsened on the Tower of London test of problem solving and planning over the 3 wk of bilateral prefrontal rTMS ($p=0.043$). However, this was non-significant after correcting for the multiple comparisons done.

In Loo et al. (In Press) the active group worsened in the Trail Making A test while the sham group improved. However, a detrimental effect from rTMS seems unlikely in the presence of improved scores on the more complex Trail Making B test in same group over the same period.

A concern in interpreting the results of these studies is that mood change may have influenced results, e.g. that worsening in functioning caused by rTMS may have been offset by improvement in functioning secondary to mood improvement. It is reassuring that studies which examined for correlations between mood change and neuropsychological functioning did not find any significant relationship [Fitzgerald et al., 2003, 2006; Little et al., 2000; Loo et al., 2001 (open treatment phase); Speer et al., 2001].

Overall, given the number of comparisons involved as multiple neuropsychological tests were used within most studies, it is not surprising that isolated results have reached significance. In studies which corrected for the multiple comparisons done these results were no longer significant (Loo et al., 2001, 2003a). Studies so far have tested for functioning across a wide range of neuropsychological domains and results indicate that significant neuropsychological impairment from a course of rTMS is unlikely. The few studies that have tested for immediate effects (e.g. reaction time) after a single session of rTMS treatment also did not find any significant changes (Loo et al., 2001, 2003a).

Hearing

A click is produced by rapid mechanical deformation of the stimulating coil when current is discharged into it. The noise is deceptively mild, perhaps because brief sounds tend to be underestimated in intensity (Briel, 1980).

Initial reports of permanent increases in auditory threshold in rabbits exposed to sTMS at high stimulation intensities (Counter et al., 1990) raised safety concerns. Counter et al. (1990) documented large auditory threshold shifts of 60–70 decibels (dB) 3–4 wk after exposure to a session of 50 single TMS stimuli at 50–100% of maximum machine power. Higher power levels were associated with higher sound pressure levels (up to 157 dB measured at the eardrum) and greater hearing loss. The damage was evident across a wide range of acoustic frequencies. However, they

also demonstrated that plugging the ears prevented the hearing loss, i.e. that hearing was affected by the sound of the acoustic artefact of the coil and not directly by the magnetic fields. In a follow-up study (Counter, 1994), they also showed that the use of earplugs prevented hearing loss in rabbits exposed to the noise of TMS in the longer term, i.e. 1000 stimuli at 100% machine power over 12 months.

Counter and colleagues' work suggests that it is the intensity of the peak sound pressure level, rather than other factors, including overall duration of exposure, that determines the risk of hearing loss (Counter et al., 1993). However, experiments by Pascual-Leone and colleagues have suggested that the frequency of the stimuli may also be important. Although they found no transient or permanent impairment in hearing in human subjects after multiple sessions of sTMS (Pascual-Leone et al., 1992), three subjects exposed to high-frequency rTMS without earplugs were found to have a transient increase (<4 h) in auditory threshold (Pascual-Leone et al., 1993). Of the three, the two subjects who had normal hearing before the experiment had received the highest frequency stimulation of the experimental group, 20 Hz and 25 Hz. The authors suggest the frequency of stimuli may be important because of the timing of the acoustic reflex and because a period of increased susceptibility to hearing damage follows after initial exposure to a loud stimulus.

The risk with TMS may also depend on the type of machine and stimulating coil used. Different models of Cadwell machine were used for sTMS and rTMS in the above Pascual-Leone et al. studies. Starck et al. (1996) measured higher peak sound pressure levels with a Cadwell stimulator (132 dB) than with Dantec and Magstim stimulators (110 dB). Pascual-Leone et al. (1992) also measured different peak sound pressure levels and acoustic spectra for different coils used with the same machine.

Loo et al. (2001) assessed the auditory threshold before and after 30 sessions of rTMS given over 6 wk in a depression treatment trial. All subjects wore earplugs during stimulation. No significant mean changes were detected. Two subjects showed small bilateral increases in threshold at mid to high frequencies, which returned to previous levels when retested 1 month later.

The evidence above indicates that TMS can result in transient increases in auditory threshold if no precautions are taken, but that this is unlikely if earplugs are used. Thus the routine use of earplugs is recommended in all subjects receiving rTMS. As the noise of TMS is not substantially attenuated by distance,

operators and all other personnel in the TMS room should also wear earplugs during the delivery of stimulation.

Headache and pain

Mild headache responding readily to simple analgesia appears to be the most common side-effect reported in depression treatment trials (see Table 2). It may result from direct stimulation of superficial facial muscles or nerves, as TMS often causes an uncomfortable facial twitch, depending on coil positioning (C. K. Loo, personal observations) or possibly from changes in cerebral blood flow as a response to stimulation (Loo et al., 2003b). From sham-controlled studies which reported rates of side-effects, about 28% of subjects experienced headache and 39% experienced pain or discomfort during stimulation with active rTMS, compared with rates of 16% and 15% respectively after sham rTMS (see Table 2). The rates after sham rTMS are averaged from the minority of studies which reported side-effects after sham and are probably overestimates, reflecting a reporting bias. Side-effects after sham rTMS varied considerably between studies, depending on the type of sham used, e.g. occurring at a higher rate in studies which used an active coil at 30°–45° to the scalp (Table 2).

Stimulation at higher intensities and frequencies causes more pain, although subjects usually report lessening of the pain with subsequent treatment sessions, spaced daily (C. K. Loo, personal observations). From research on the use of rTMS to produce a virtual lesion to locate speech centres, Epstein et al. (1996) have suggested that the effectiveness of rTMS can be maintained while reducing associated pain by using stimulation of lower frequency and higher intensity. Others have trialled strategies such as local anaesthetic injections at the stimulation site, reported to be useful, at least in reducing pain during rTMS, although subsequent hypersensitivity occurred in some subjects (Borckardt et al., 2006). There have also been suggestions that prefrontal rTMS may itself increase pain tolerance (Graff-Guerrero et al., 2005).

Induced currents in electrical circuits

During TMS, eddy currents will be induced in any conducting substances within the magnetic field. This poses the potential problems of heating or movement of metal substances (e.g. wires, electrodes) and malfunctioning of electrical devices. Pascual-Leone et al. (1990) reported heating of surface electrodes with TMS, with the risk of skin burns. This can be reduced

by cutting gaps in the electrodes to reduce electrical conduction (Roth et al., 1992).

Malfunctioning of deep brain stimulators has been demonstrated when TMS was given directly over the device (Kumar et al., 1999). It is recommended that extreme caution be taken before giving TMS to patients with any implanted electronic device (e.g. pacemaker, intracardiac lines, medication pump) and only if the likely benefit outweighs the risk (Wassermann, 1998). Intracranial metal implants are also of concern, as these may become heated or oscillate in the rapidly changing magnetic field, although there will be no net movement (in contrast to the effect of a static magnetic field).

Histotoxicity/structural brain changes

Animal experiments with repeated electrical stimulation of the brain have demonstrated histopathological damage after 7 h of stimulation at 50 Hz and various combinations of 'charge per phase' (charge transferred during each phase of stimulus waveform) and 'charge density' (charge per phase divided by surface area of the electrode) (McCreery et al., 1990). As noted above, calculations of the charge transferred during rTMS show this to be very small when compared with direct electrical stimulation.

Animal (rat) studies with rTMS support its relative safety. Most have failed to demonstrate any histopathological changes (e.g. Sgro et al., 1991). One study reported microvacuolar changes but these may have resulted from head jerking during the stimulation (Matsumiya et al., 1992). In an experiment reflecting the comparison between ECT and rTMS, Okada et al. (2002) found that a single 1-s convulsive electrical stimulus led to up-regulation of inflammatory mediators in rat brains, but that seven daily sessions of subconvulsive rTMS did not. The authors comment that this finding may have implications for neurodegenerative disorders.

However, there is reason for caution in extending findings from rat studies to human subjects. Concerns relate to the comparability of stimulating rat and human brains with the same TMS coils as matching of size between the coil and the object to be stimulated is critical to the level of magnetic stimulation effectively delivered. In fact, mathematical models suggest that rats in the studies above only received about one fifth of the expected stimulation intensity due to this factor (Weissman et al., 1992).

Evidence for the lack of histotoxicity in humans comes from a report by Gates et al. (1992) of two epileptic subjects who received rTMS to determine

laterality of speech function prior to undergoing temporal lobectomy. The excised tissue did not show any changes suggestive of damage from TMS.

In a MRI study, Nahas et al. (2000) reported no structural brain differences or volumetric changes in the prefrontal lobe in depressed subjects after 10 treatment sessions of high-frequency left prefrontal rTMS. In contrast, May et al. (2007) recently reported a significant volumetric increase in the grey matter of the temporal cortex as shown on MRI scans after 5 d of rTMS at parameters comparable to those used in treatment studies, in a sham-controlled study involving healthy subjects. Changes were noted bilaterally and also at distant brain sites (e.g. thalamus) and had resolved on scanning 3 months later. This is the first report of macroscopic cortical change after rTMS and this phenomenon should be tested and confirmed in further studies prior to its acceptance as a true finding. As noted by the authors, the significance of the change is uncertain, and may reflect neuronal alterations (e.g. in synaptic connections) or other processes (e.g. change in blood flow or interstitial fluid).

It is also important to note that there are inconsistent reports of changes in diffusion on MRI scanning (reflecting the movement of water molecules in brain tissue, an indicator of subtle tissue damage) at the site of stimulation after rTMS (Duning et al., 2004; Li et al., 2003). Thus, it is unclear if rTMS results in structural changes as demonstrated by brain imaging. Further studies are needed to clarify this issue, and the significance of any changes found, i.e. whether the changes represent therapeutic or detrimental processes.

Exposure to electromagnetic fields (EMF)

Long-term effects in subjects and experimenters of exposure to the strong pulsed EMF involved in TMS are as yet unknown. Concerns about EMF are related to the ongoing and unresolved debate regarding the carcinogenic effects of chronic exposure to radio-frequency EMF radiation associated with mobile phones, radio and television transmitters (Ahlbom et al., 2004; Westerman and Hocking, 2004).

However, it is unclear what relevance these findings bear to TMS exposure. TMS involves a magnetic pulse of about 250 μ s duration (Barker, 1991). If continuous, this would correspond to a frequency of 4 kHz, i.e. within the radiofrequency range (3 kHz to 300 GHz). However, TMS exposure parameters are very different, comprising relatively brief exposure to very high intensity, pulsed magnetic fields. Given a TMS pulse

duration of 250 μ s, a typical treatment course of rTMS as used in psychiatric disorders (e.g. 10 Hz, 20 \times 5 s trains, 20 sessions) yields about 5 s of total exposure time. A study administering up to 12 960 TMS pulses per day (\sim 3.24 s exposure time) to healthy subjects did not find any adverse effects during the study period (Anderson et al., 2006). It is unknown whether cumulative dose or the parameters of stimulation [e.g. intensity, frequency (Hz)] is the most important factor in terms of the risks of EMF exposure from TMS. Overall it is unclear if the high intensity, pulsed stimulation involved in TMS has the same biological implications as the chronic, low-intensity household and occupational exposure which has been mainly studied.

Given the above evidence, vigilance about the long-term effects of TMS for both patients and investigators is indicated, particularly for those with frequent exposure. It is judicious for TMS operators to position themselves within the room as far away from the stimulating coil as practical. As TMS technology originated in 1985 (Barker, 1991) with the development of rTMS and more widespread availability of TMS machines in the last decade, sufficient time may not have elapsed for the detection of delayed effects, particularly with respect to carcinogenesis, where cumulative effects over decades may be important. This is particularly relevant to subjects who receive repeated courses of rTMS over their lifetime, either for maintenance treatment or treatment of subsequent episodes of depression.

Psychiatric complications

Although much of the interest in therapeutic applications of TMS has focused on treating psychiatric disorders, in particular, depression, there have also been a few reports of unwanted psychiatric side-effects in depressed patients treated with rTMS.

Mania has been induced in three healthy subjects and five depressed subjects by high-frequency rTMS to the left dorsolateral prefrontal cortex. Nedjat and Folkerts (1999) reported hypomanic symptoms after only a single session of rTMS in three female subjects who did not have a prior history of mood disorder. In all, 50 healthy subjects had received rTMS, yielding a relatively high rate of manic complications. Stimulation parameters were comparable to those used in depression treatment studies and studies of mood changes in healthy subjects. It is possible that healthy subjects are more susceptible to manic changes with rTMS than depressed subjects.

Two subjects with unipolar depression have shown manic changes with rTMS treatment. George et al. (1995) reported mild hypomania in a patient with refractory recurrent unipolar depression. This female patient had responded well to previous shorter courses of rTMS, but became hypomanic after nine treatment sessions in the third course. The hypomanic symptoms resolved when rTMS was reduced to treatment every second day. Sakkas et al. (2003) reported on a 55-yr-old depressed male who became hypomanic for the first time after 3 wk of twice daily rTMS to the left dorsolateral prefrontal cortex and concomitant citalopram. Over the following week, medication was stopped, but rTMS continued. His symptoms deteriorated into mania and rTMS was also stopped. Five months later, a second course of 2 wk of twice-daily rTMS also resulted in hypomania. Thus, there may be some similarity with ECT, which may induce mania in depressed subjects, but is also effective in treating both depression and mania (Abrams, 2002). rTMS has also been shown to have therapeutic effects in mania, although this was after high-frequency rTMS to the right prefrontal cortex (Erfuth et al., 2000; Grisaru et al., 1998).

There are also six reports of mania induced by rTMS in patients with bipolar disorder (Dolberg et al., 2001; Garcia-Toro, 1999; Hausmann et al., 2004b; Huang et al., 2004; Sakkas et al., 2003). This is despite the use of concurrent mood-stabilizing medications during rTMS, suggesting that bipolar disorder patients need to be monitored closely for the emergence of mania even when prophylactic mood stabilizers are used.

Cohen et al. (2004) conducted a trial of right prefrontal rTMS for post-traumatic stress disorder, during which two patients developed a manic episode after the third session. One patient was randomized to 1 Hz rTMS and one to 10 Hz. It is also reported that another subject in this trial developed a 'mild rage attack, probably related to the stimulation'.

There is a single case report of high-frequency left prefrontal rTMS inducing persecutory delusions in a depressed, non-psychotic subject (Zwanzger et al., 2002). That the delusions were caused by rTMS is probable given the on-off-on nature of the symptoms in response to rTMS and antipsychotic treatment. The symptoms may have been mediated by TMS-induced dopamine release. There have been reports of dopamine release in response to prefrontal rTMS (Strafella et al., 2001).

In all the above cases, the psychiatric side-effects induced by TMS were transient, resolving with the cessation of TMS or rapidly responding to pharmaco-

logical treatment. Nevertheless, subjects receiving rTMS should be warned of the possible risk of developing psychiatric complications, in particular, mania or hypomania.

Pregnancy

The risk of TMS to the developing fetus is unknown, although a recent prospective study suggested that women in early pregnancy exposed to magnetic fields (unrelated to TMS) of ≥ 16 milligauss may be at increased risk of miscarriage (Li et al., 2002). Safety guidelines have suggested that pregnant women be routinely excluded from rTMS trials (Wassermann, 1998). Nahas et al. (1999) reported the uncomplicated inclusion of a depressed and anxious woman in her second trimester of pregnancy in a depression treatment trial. She received 14 daily treatments at 5 Hz and 100% motor threshold, with marked clinical improvement. Given the limited knowledge available in this area, caution should be exercised in giving rTMS to women of childbearing age and should only be given to pregnant women after careful consideration of relative potential risks and benefits. Likewise, a careful discussion of potential risks should be held with any pregnant staff who are TMS operators, although their risk is likely to be less than that of pregnant subjects, given that magnetic fields attenuate rapidly with distance (Barker, 1991).

Conclusion

rTMS as commonly used in the treatment of depression is a relatively safe procedure, but there are important risks of which patients should be warned. Apart from common side-effects such as headache and scalp pain, there is clear evidence that rTMS can also induce accidental seizures and hypomania. The incidence of these more major adverse effects is low, particularly where potential subjects are carefully screened for known risk factors and stimulation is given within recommended TMS parameter limits. Nevertheless, TMS should be given within a clinical setting where these adverse outcomes can be safely managed. Precautions should include the routine wearing of earplugs by both patients and TMS operators. Detrimental effects of repeated sessions of rTMS (as used in depression treatment) have not been evident over the last decade but longer term effects are as yet unknown and should be monitored. Likewise, our knowledge of the effects of rTMS on brain functioning and structure is still developing. Early studies failed to find any pathological

changes but the issue is under further examination with the availability of more sophisticated imaging methods. Overall, the safety profile of rTMS is good, and supports its further development as a clinical treatment.

Note

Supplementary information accompanies this paper on the Journal's website (<http://journals.cambridge.org>).

Acknowledgements

The authors thank Melissa Pigot and Aisha Karim for assistance in manuscript preparation. This work was supported by National Health and Medical Research Council (Australia) Program Grant no.: 2223208.

Statement of Interest

Dr Loo and Dr Mitchell were investigators in the Neuronetics trial of rTMS in depression, sponsored by the Neuronetics Company.

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