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Safety of rTMS to non-motor cortical areas in healthy participants and patients

Katsuyuki Machii, Daniel Cohen, Ciro Ramos-Estebanez, Alvaro Pascual-Leone *

Center for Noninvasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, KS-452, Boston, MA 02215, USA

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Abstract

Objective: rTMS is increasingly being used for stimulation to non-motor areas, but available safety guidelines are derived from experience with motor cortex rTMS. We reviewed the literature and our own data to assess the safety of rTMS to non-motor areas.

Methods: We reviewed for adverse effects all articles published from January 1998 to December 2003 that applied rTMS to non-motor areas, and analyzed data from our own studies from January 1997 to December 2003.

Results: Adverse effects were infrequent and generally mild. Headache was the most common, occurring in 23% of the subjects and more frequent with frontal rTMS. More serious adverse effects were rare and consisted of two seizures and four instances of psychotic symptoms induced by rTMS to the dorsolateral prefrontal cortex in patients with depression.

Conclusions: Overall, as currently applied rTMS to non-motor areas appears to be safe with few, generally mild adverse effects. In future studies, we recommend systematic reporting of adverse effects and careful documentation of machine type, coils used, and actual intensity as a function of maximum stimulator output. Phosphene threshold might be used to index stimulation intensity when rTMS is applied to the visual cortex, and research should be directed to identifying other indexes of intensity for TMS to other non-motor areas.

Significance: rTMS under the present guidelines is safe with minimal adverse effects, when applied to non-motor areas.

Keywords: rTMS; Non-motor areas; Safety; Adverse effect

1. Introduction

Repetitive Transcranial Magnetic Stimulation (rTMS) has become a promising therapeutic tool for a variety of neurological and psychiatric diseases (Wassermann and Lisanby, 2001), as well as a powerful addition to the armamentarium of cognitive neuroscientists (Robertson et al., 2003). This is resulting in a rapid expansion of the number of laboratories utilizing rTMS for research and clinical purposes, and increasingly rTMS is being applied to non-motor areas. However, rTMS carries increased risks when compared to single-pulse TMS, and current safety guidelines (Wassermann, 1998) are based on the determination of rTMS intensity as percentage of motor threshold (MT) despite a lack of correlation between the effects of TMS on motor cortex and non-motor areas (Robertson et al., 2003; Stewart et al., 2001a). In the present study, we summarize the safety data from a review of the published literature and our own experimental experience with rTMS to non-motor areas in order to provide up-to-date information and recommendations for expanded safety guidelines.

2. Methods

2.1. Literature review

Using PubMed we identified 173 papers applying rTMS to non-motor areas published from January 1998 to December 2003 (see Appendix). The search criteria relied

* Correspondence author. Tel.: +1 617 667 0203; fax: +1 617 975 5322.
E-mail address: apleone@bidmc.harvard.edu (A. Pascual-Leone).

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on the following key words: 'rTMS' or 'repetitive TMS', and 'frontal', 'parietal', 'occipital', 'temporal' or 'cerebellum'. We reviewed all 173 papers and noted the incidence of reported adverse effects and the stimulation parameters. When not explicitly stated in the manuscript, we tried to obtain the relevant information from personal communication with the authors. Intensity of stimulation was recorded as a percentage of MT, phosphene threshold (PT), or maximal stimulator output.

2.2. Center for non-invasive brain stimulation at BIDMC

We analyzed the data from all studies at our laboratory from January 1997 to December 2003 employing rTMS to non-motor cortical regions in healthy participants. We identified 249 subjects in whom, in addition to recording rTMS parameters, we had detailed information on adverse effects since all had completed a side-effect questionnaire before and after rTMS. The questionnaire contained rating scales for the presence and severity of headache, neck pain, hearing changes, impaired cognition, trouble concentrating, and acute mood changes. Furthermore, the experimenter documented Mini Mental State Exam scores (Folstein et al., 1975) before and after rTMS. All studies had been conducted with a Magstim Super-Rapid Magnetic Stimulator (Magstim Corporation, United Kingdom) and commercially available 8-shaped coils with each wing measuring 7 cm in diameter. Stimulation intensity was calculated as percentage of maximal stimulator output as well as percentage of MT.

In addition, we analyzed data on 249 patients with major unipolar depression who underwent daily sessions of rTMS to the dorsolateral prefrontal cortex (DLPFC) for 10 days. These patients participated in institutional review board approved studies between 1997 and 2003, all of which were parallel group, random assignment, sham-controlled double-blind trials. In the various studies, rTMS could be high-frequency (10 or 20 Hz) or low-frequency (1 Hz) rTMS to the left or right DLPFC. To be eligible for these studies, patients had to be outpatients diagnosed with unipolar major depressive disorder by a board-certified psychiatrist in accordance with DSM-IV criteria, without psychotic features or other co-morbid Axis 1 disorders. In addition, patients had to be right-handed (Oldfield Questionnaire), aged 21–80 years, and naive to TMS. Following informed consent, patients underwent a 14-day washout of all psychotropic medications (antidepressants, anxiolytics, mood stabilizers, sedatives, barbiturates, etc.). The reinstatement of psychotropic medications was not permitted until completion of the protocol. However, in one of the studies, PRN lorazepam (up to 2 mg/d) was permitted for insomnia or agitation during the first week of medication washout, but not thereafter. MT was determined on the first day of the study following the medication washout. For all patients across the various studies, intensity of stimulation was set at 110% of MT for induction of motor evoked potentials in the fully relaxed right abductor pollicis brevis muscle. Stimulation settings for the left or right DLPFC high-frequency rTMS were: (a) 20 trains per session, pulse frequency of 10 Hz, train duration of 8 s and inter-train interval of 52 s; or (b) 40 trains per session, pulse frequency of 20 Hz, train duration of 2 s and inter-train interval of 28 s. Stimulation settings for the left or right DLPFC low-frequency rTMS consisted of a single train of stimuli delivered at 1 Hz frequency for 26.7 min. Consequently, all patients received 1600 pulses per session in less than 30 min of time.

3. Results

3.1. Literature review on safety of rTMS to non-motor cortical areas

3.1.1. TMS settings

The stimulation settings used in the reviewed papers are summarized in Table 1. In 150 studies, with a total of 2740 subjects, percentage of MT was used as index of TMS intensity. Of these studies, 80 (for a total of 1659 subjects) applied rTMS at 100% of MT or above (mean ± SD =

Table 1
Studies and subjects studied with rTMS to non-motor areas depending on criterium used to define rTMS intensity

Index of intensity			Total number of studies	Total number of subjects	Stimulation site (Number of studies) F	P	O	T	C
MT			150	2740	128	29	17	12	6
	100% or > 100% MT	(100–150% MT)	80	1659	74	20	9	4	2
	< 100% MT	(70–95% MT)	70	1081	54	9	8	8	4
PT		(80–120% PT)	7	160			7		
Output		(35–100% output)	16	192	9	4	6	4	2
Total			173	3092	137	33	30	16	8

F, frontal area; P, parietal area, O, occipital area; T, temporal area; C, cerebellum. MT, motor threshold; PT, phosphene threshold; output, % of maximal output of machine.

114.0±12.7% of MT; range 100–150% of MT), while 70 studies (with a total of 1081 subjects) applied rTMS with an intensity below MT (mean±SD=87.0±5.0%; range 70–95% of MT). Seven published studies with a total of 160 subjects (Antal et al., 2002; Bohotin et al., 2002; Brighina et al., 2002; Fumal et al., 2003; Niehaus et al., 2000; Théoret et al., 2002; Thut et al., 2003) applied rTMS to the occipital lobes and used PT rather than MT to set their stimulation intensity which ranged from 80 to 120% of PT. In 16 published studies with a total of 192 subjects, the authors used the percentage of maximum stimulator output to define the intensity of rTMS, which ranged from 35 to 100% of maximal machine output (Brandt et al., 1998; Campana et al., 2002; Conca et al., 2002; Franck et al., 2003; Feinsod et al., 1998; Gerschlager et al., 2002; Gironell et al., 2002; Ikeguchi et al., 2003; Juan and Walsh, 2003; Lavidor and Walsh, 2003; Liederman, 2003; Mottaghy et al., 1999; Menkes and Gruenthal, 2000; Shimamoto et al., 2001; Sparing et al., 2001; Stewart et al., 2001b). The most common stimulation site was the frontal area (79.1%). Other sites of stimulation were: parietal area (19%), occipital area (17.3%), temporal area (9.2%) and cerebellum (4.6%).

Table 2 (a) and (b) summarizes the index used to set the stimulation index depending on the characteristics of the subjects, separating high-frequency (>1 Hz) and low-frequency rTMS (≤1 Hz). Healthy participants and patients with depression account for the majority of subjects stimulated with high frequency rTMS to non-motor areas. Small numbers of other patient groups also received high frequency stimulation, including: epilepsy, migraine, Parkinson's Disease, schizophrenia, obsessive compulsive disorder, treatment seeking smokers, and others. In the

Table 2
Summary of reviewed rTMS studies depending on subject population, and index of rTMS intensities (1998–2003)

Subject	Index of intensity	Total number of studies	Total number of subjects
(a) High Frequency rTMS			
Healthy	100% or >100% MT	41	688
	<100% MT	20	278
	PT	2	33
	output	7	86
Depression	100% or >100% MT	23	489
	<100% MT	25	414
Epilepsy	100% or >100% MT	1	31
Migraine	PT	1	30
PD	100% or >100% MT	1	10
Schizophrenia	<100% MT	1	12
Blindness	100% or >100% MT	1	35
Phantom limb pain synd	100% or >100% MT	1	2
OCD	100% or >100% MT	1	12
Posttraumatic Stress Synd	<100% MT	1	6
Auditory Hallucination	<100% MT	1	1
Treatment-seeking smoker	<100% MT	1	14
(b) Low Frequency rTMS			
Healthy	100% or >100% MT	13	228
	<100% MT	21	249
	PT	5	84
	Output	4	45
Depression	100% or >100% MT	5	112
	<100% MT	4	48
	Output	2	18
Schizophrenia	100% or >100% MT	1	31
	<100% MT	2	12
	Output	2	11
PD	100% or >100% MT	1	10
	Output	2	21
Migraine	<100% MT	1	9
	PT	1	13
Chronic Tinnitus	100% or >100% MT	1	1
OCD	100% or >100% MT	1	10
Visuospatial Negelect	<100% MT	1	3
Posttraumatic Stress Synd	<100% MT	1	6
Primary Focal Dystonia	<100% MT	1	7
Tourette Synd	<100% MT	1	16
Essential Tremor	Output	1	10
Epilepsy, Cortical Dysplasia	Output	1	1

MT, motor threshold; PT, phosphene threshold; output, % of maximal intensity of machine; PD, Parkinson's disease; OCD, obsessive compulsive disorder.

patients with migraine, stimulation was to the occipital cortex using 100% PT as the stimulation intensity. Low frequency stimulation has been applied to similar patient groups. In addition, sub-motor threshold low frequency stimulation was used in patients with visuospatial neglect, primary focal dystonia, and Tourette's syndrome. Low frequency stimulation was also applied to 10 patients with essential tremor using 100% of maximum stimulator output as the intensity.

3.1.2. Reported adverse effects

Table 3 shows the number of studies according to whether adverse effects were detailed. We found 74 reports in which the authors reported the presence or absence of adverse effects related to rTMS. Forty-five papers reported adverse effects that occurred during or shortly after exposure to rTMS (see Table 4, separated by the index of stimulation intensity), whereas 16 studies explicitly stated the absence of any adverse effects during the experiments (Bäumer et al., 2003; Bestmann et al., 2002; Brandt et al., 1998; Evers et al., 2001; Feinsod et al., 1998; Franck et al., 2003; Gothe et al., 2002; Ikeguchi et al., 2003; Khedr et al., 2002; Müncahu et al., 2002; Nahas et al., 2003; Pecuch et al., 2000; Padberg et al., 2002; Siebner et al., 2001, 2003; Sparing et al., 2001). Thirteen papers reported that it was 'well tolerated' or 'no serious side effects' (Brighina et al., 2003a; Brighina et al., 2003b; Chen et al., 2003; Chouinard et al., 2003; Fierro et al., 2000, 2003; García-Toro et al., 2001; Herwig et al., 2003a; Nahas et al., 1999; Jing and Takigawa, 2002; Rosenberg et al., 2002; Shajahan et al., 2002; van Honk et al., 2003). In the remaining 99 papers, there were no details of adverse effects.

Headache was the most common complaint, as reported by 32 studies. Twenty-two of these studies reported headaches during high frequency rTMS, and 11 studies during low frequency rTMS. The occurrence of headache with high frequency rTMS ranged from 3.6 to 66.7% (mean ± SD = 23.6 ± 16.0%), and with low frequency rTMS it ranged from 6.3 to 60% (mean ± SD = 22.5 ± 15.6%). In addition, headaches induced by sham-stimulation were reported in several reports (Berman et al., 2000; Boutros et al., 2002; Herwig et al., 2003b; Hoffman et al., 2003; Höppner et al., 2003; Kimbrell et al., 2002; Koren et al., 2001; Manes et al., 2001; Rollnik et al., 2002). From personal communication with some of the authors, headache and neck pain were mentioned as the most common complaints, although these were not described in the manuscripts. In these cases, no serious adverse effects were reported, and the incidences of minor adverse effects are not known.

Table 3
The number of studies reporting adverse effects

Adverse effects reported	Number of studies		
Yes	74	No adverse effect	16
		No serious adverse effect or well-tolerated	13
		Details of adverse effects	45
No	99		
Total	173		

There is one report of nausea in two subjects from rTMS over the cerebellum at an intensity of 90% of MT with a frequency of 0.9 Hz for 15 min (Satow et al., 2002). A small number of reports described focal pain, discomfort, and other minor symptoms.

There are two reports of a seizure (Conca et al., 2000; Flitman et al., 1998) during rTMS, and two cases of seizure-like episodes or syncope occurring several hours after rTMS treatment (Figiel et al., 1998). In the case reported by Flitman et al. (1998), rTMS was applied to the left prefrontal area at an intensity of 120% of MT, frequency of 15 Hz, 750 ms train duration with inter-train intervals lasting 250 ms. Conca et al. (2000) applied rTMS to the left DLPFC at an intensity of 110% of MT, frequency of 20 Hz, 10 s train duration with inter-train intervals lasting at least 60 s. Figiel et al. (1998) reported that one depressed patient experienced a syncopal episode 6 h after rTMS treatment, and this was deemed unrelated to rTMS treatment. Another depressed patient reported left focal motor seizures 2 weeks after starting rTMS treatment. Prior to the start of the study, she denied a history of epilepsy but later admitted to preexisting left facial twitching. The spells continued despite therapeutic phenytoin levels, and the incidence of spells was highly correlated with attendance at church and funerals. Two episodes were eventually witnessed in a psychiatry clinic and diagnosed as pseudoseizures. In both of these cases, rTMS was applied to the left DLPFC at an intensity of 110% of MT and a frequency of 10 Hz in trains of 5 s duration with a 30 s inter-train interval.

There are three reported patients in whom rTMS to prefrontal cortex led to the induction of muscle twitches in the contralateral hand, and the possibility of spread of the TMS effects was raised (Pascual-Leone et al., 1994). Figiel et al. (1998) reported two depressed patients in whom they observed muscular contractions spread from a single hand muscle to more proximal muscles in the right upper extremity during rTMS applied to the left DLPFC at an intensity of 110% of MT and a frequency of 10 Hz in trains of 5 s duration and 30 s inter-train interval. Grunhaus et al. (2000) also reported the occurrence of motor evoked potentials 20 ms following each TMS pulse applied to the left DLPFC at an intensity of 90% of MT and a frequency of 10 Hz in trains of 2 s duration. In these cases, no seizures or afterdischarges were observed, and the patients completed participation in the studies, including rTMS sessions on subsequent days, without complications.

Finally, in patients with major, medication-resistant depression, there are three cases of induction of manic

Table 4
Reported adverse effects related to rTMS to non-motor areas since 1998

Source	rTMS						Number of Subjects	Adverse effect	Frequency (%)
	Index of Intensity (% of MT)	Frequency (Hz)	Total nuber of pulses	inter-train intervals	Duration	Stimulation site			
(a) MT as an index of intensity									
Cohrs et al. (1998)	120	20	160 trains 800 stimuli/session	8 s	0.25 s/train	rt prefrontal	13 healthy	headache	7.7% (1/13)
Figiel et al. (1998)	110	10	10 trains 500 stimuli/day 5 days	30 s	5 s/train	lt prefrontal	56 depressed	headache spread of muscular contractions left body dysesthesia syncopical episode psudoseizure (focal motor seizure?)	3.6% (2/56) 3.6% (2/56) 1.8% (1/56) 1.8% (1/56) 1.8% (1/56)
Flitman et al. (1998)	120	15	150 trains	250 ms	750 ms/train	rt prefrontal lt prefrontal rt parietal lt parietal	7 healthy	seizure	14.3% (1/7)
Garcia-Toro (1999)	90	20	30 trains	30 s	2 s/train	lt DLFPC	1 depressed (case report)	manic symptom	100% (1/1)
Klein et al. (1999)	110	1	2 trains 120 stimuli/day 10 days	3 min	1 min/train	rt prefrontal	16 schizo	facial muscle twitches headache worsening of preexisting akathesia worsening of preexisting obsessive compulsive symptom	17% (3/16) 11% (2/16) 11% (2/16) 11% (2/16)
Klein et al. (1999)	110	1	2 trains 120 stimuli/day 10 days	3 min	1 min/train	rt prefrontal	35 depressed	discomfort due to facial muscle twitches headache	14% (5/35) 9% (3/35)
Loo et al. (1999)	110	10	30 trains 1500 stimuli/day	30 s	5 s/train	lt DLPFC	18 depressed	headache increase of auditory threshold	16.'% (3/18) 5.6% (1/18)
Menkes et al. (1999)	100	0.5	5 20-dtimuli	1 min	40 s/train	rt prefrontal	6 healthy	headache	33.3% (2/6)
Padberg et al. (1999)	90	10	5 trains 250 stimuli/day	>30 s	5 s/train	lt DLPFC	6 depressed	focal pain headache	50% (3/6) 16.7% (1/6)
	90	0.3	10 trains 250 stimuli/day 5 days		84 s	lt DLPFC	6 depressed	focal pain headache	33.3% (2/6) 16.7% (1/6)
Triggs et al. (1999)	80	20	50 trains (=2000 stimuli)	28 s	2 s/train	lt prefrontal	10 depressed	scalp discomfort headache insomnia	50% (5/10) 30% (3/10) 10% (1/10)
Wassermann et al. (1999)	130	15			2 s/train	motor speech area	14 temporal lobe epilepsy	discomfort	28.6%(4/14)
Bermann et al. (2000)	80	20	20 trains 800 stimuli/day 10 days	58 s	2 s/train	lt DLPFC	10 depressed	headache	60% (6/10)

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Table 4 (*continued*)

Source	rTMS						Number of Subjects	Adverse effect	Frequency (%)
	Index of Intensity (% of MT)	Frequency (Hz)	Total nuber of pulses	inter-train intervals	Duration	Stimulation site			
	sham						10 depressed	headache	50% (5/10)
Conca et al. (2000)	110	20	10 trains	>45 s	5 s/train	lt DLPFC	1 depressed	pseudoabsence seizure	100% (1/1)
	110	1	1 train		300 s	rt DLPFC	(case report)		
	110	20	10 trains	>60 s	10 s/train	lt DLPFC			
Eschweiler et al. (2000)	90	10	20 trains 2000 stimuli/day 10 days	50 s	10 s/train	lt DLPFC	12 depressed	headache	25% (3/12)
Grunhaus et al. (2000)	90	10	20 trains 400/1200 stimuli/day 20 days	unknown	2/6 s	lt DLPFC	20 depressed	headache spread MEP discharge	25% (5/20 5% (1/20)
ong et al. (2000)	80	8	single train		5 s	F, FT, T, TP, P	8 healthy	temporal muscle contraction	unknown
Mosimann et al. (2000)	100	20	40 trains	28 s	2 s/train	lt prefrontal	25 healthy	headache	20% (5/25)
Rollnik et al. (2000)	80	20	20 trains 800 stimuli/session 10 sessions	unknown	2 s/train	lt DLPFC	12 schizo	headache	25% (3/12)
Alonso et al. (2001)	110	1	single train 1200 stimuli/session 18 sessions		20 min	rt prefrontal	10 OCD	headache	10% (1/10)
Dolberg et al. (2001)	90	10	20 trains 1200 stimuli/day 20 days	30 s	6 s/train	lt DLPFC	12 depressed	manic symptom (case report)	16.7% (2/12)
Garcia-Toro et al. (2001)	90	20	30 trains 1200 stimuli/day 10 days	20–40 s	2 s/train	lt DLPFC	11 depressed	headache	27.2%(3/11)
Gerschlager et al. (2001)	90	1	5 trsains 1500 stimuli	1 min	5 min/trasin	PF, PM, M, P	8 healthy	mild local disvcomfort	Unknown
Graf et al. (2001)	90	20	40 trains 1600 stimuli	28 s	2 s/train	lt DLPFC	8 healthy	pain in the region of the left trigeminal nerve	12.5% (1/8)
Koren et al. (2001)	120	1	2 trains 120 stimuli	3 min	1 min	rt prefrontal lt prefrontal	16 healthy 15 healthy	headache headache	37.5% (6/16) 60% (9/15)
	sham						15 healthy	headache	33.3% (5/15)
Manes et al. (2001)	80	20	20 trains 800 stimuli	1 min	2 s/train	lt DLPFC	10 depressed	local pain headache local discomfort	10% (1/10) 40% (4/10) 40% (4/10)
	sham						10 depressed	Local discomfort	40% (4/10)

								anxiety	10% (1/10)
Sachdev et al. (2001)	110	10	30 trains 1500 stimuli/day	25 s	5 s/train	lt DLPFC	12 OCD	headache	25% (3/12)
Stewart et al. (2001)	120–140	10	single train 10 stimuli/session	30 s	1 s/train	posterior lateral to motor cortex	11 healthy	discomfort due to activation of facial nerve	27.3% (3/11)
Boutros et al. (2002)	80	20	20 trains 800 stimuli	58 s	2 s/train	lt prefrontal	12 depressed	headache	66.7% (8/12)
								transient scalp tenderness	25% (3/12)
								hearing problem	8.3% (1/12)
								transient concentration difficulties	41.7% (5/12)
								diarrhea	8.3% (1/12)
	sham						9 depressed	headache	55.6% (5/9)
								transient scalp tenderness	11.1% (1/9)
Conca et al. (2002)	110	10	10 trains	60 s	10 s/train	lt DLPFC	12 depressed	headache	19.1% (7/36)
	110	1	1 train		300 s	rt DLPFC			
	110	10	1 train	6 s	10 s/train	lt DLPFC	12 depressed		
	110	1	1 train	6 s	30 s/train				
	110	10	13 trains	?	10 s/train	lt DLPFC	12 depressed		
Dragasevic et al. (2002)	110	0.5	5 trains (=100 stimuli)	60 s	40 s/train	rt & lt prefrontal	10 depressed with PD	burning sensation	40% (4/10)
								headache	30% (3/10)
Janicak et al. (2002)	110	10	20 trains 1000 stimuli/session	20, 30 s	5 s/train	lt DLPFC	15 depressed	facial twitching	40%(6/15)
								erythema	40%(6/15)
								mild pain and discomfort	40%(6/15)
								feeling of warmth	20% (3/15)
								tapping sensation	13.3% (2/15)
								headache	6.7%(1/15)
Kimbrell et al. (2002)	80	1	single train 1800 stimuli		30 min	lt prefrontal	14 healthy	local discomfort	unknown
	sham								
Müncahu et al. (2002)	80	1	single train 1200 stimuli		20 min	premotor	16 Tourette syndrome	headache	6.3% (1/16)
								excessive tiredness	12.5% (2/16)
Rollnik et al. (2002)	90	0.9	single train 270 stimuli			rt DLPFC	25 healthy 13 healthy	headache	13.2% (5/38)
	sham								
Satow et al. (2002)	90	0.9	single train 900 stimuli			C	8 healthy	nausea	25% (2/8)
Zwanzger et al. (2002)	100	10	15 trains 1500 stimuli/day	30 s	10 s/train	lt DLPFC	1 depressed (case report)	dellusion	100% (1/1)
Eichhammer et al. (2003)	90	20	20 trains	42.5 s	2.5 s/train	lt DLPFC	14 treatment-seeking smoker	headache	14.2% (2/14)

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Table 4 (*continued*)

Source	rTMS						Number of Subjects	Adverse effect	Frequency (%)
	Index of Intensity (% of MT)	Frequency (Hz)	Total nuber of pulses	inter-train intervals	Duration	Stimulation site			
			1000 stimuliu/day						
Grunhaus et al. (2003)	90	10	20 trains (=1200 stimuli)	30 s	6 s/train	lt DLPFC	20 depressed	headache	15% (3/20)
								sleep disturbance	10% (2/20)
Herwig et al. (2003)	110	15	100 trains (=3000 stimuli)	4 s	2 s/train	lt or rt DLPFC	25 depressed (13 real, 12 sham)	headache	12% (3/25)
	sham								
Hoffman et al. (2003)	90	1	480 stimuli		8 min for 1st day	T	12 schizo	headache	33.3% (4/12)
			720 stimuli		12 min for 2nd day			lightheadeadness	25% (3/12)
			960 stimuli		16 min for next 7 days			concentration difficulties	16.7% (2/12)
			(single train)					increased AH	8.3% (1/12)
								racing thoughts	8.3% (1/12)
	sham		480 stimuli		8 min for 1st day	T	12 schizo	headache	8.3% (1/12)
			720 stimuli		12 min for 2nd day			lightheadeadness	8.3% (1/12)
			960 stimuli		16 min for next 7 days			concentration difficulties	16.7% (2/12)
			(single train)					memory difficulties	8.3% (1/12)
								increased AH	16.7% (2/12)
								shoulder pain	8.3% (1/12)
	90	1	480 stimuli		8 min for 1st day	T	9 schizo	headache	22.2% (2/9)
			720 stimuli		12 min for 2nd day			lightheadeadness	11.1% (1/9)
			960 stimuli		16 min for next 7 days			concentration difficulties	11.1% (1/9)
			(single train)					memory difficulties	11.1% (1/9)
								increased AH	22.2% (2/9)
								visual hallucination	11.1% (1/9)
Hoppner et al. (2003)	90	20	20 trains	60 s	2 s/train	lt DLPFC	10 depressed	headache	10% (1/10)
	110	1	2 trains	3 min	60 s/train	rt DLPFC	10 depressed	no	
	sham						10 depressed	no	
Loo et al. (2003)	90	15	24 trains 1800 stimuli/day 3 weeks	25 s	5 s/train	bil DLPFC	9 depressed	pain	55.6% (5/9)
								headache	33.3% (3/9)
								felling more enotional or anxious	33.3% (3/9)
								sudden tearfulness	11.1% (1/9)
Michael et al. (2003)	80	20	20 trains (=800 stimuli)	58 s	2 s/train	lt DLPFC	7 healthy	headache	28.6% (2/7)
								unusually disrupted sleep	14.3% (1/7)
Rami et al. (2003)	90	5	single train 50 stimuli	30 s	10 s/train	rt or lt DLPFC, C	16 healthy	headache	6.3% (1/16)
	110	1	single train 10 stimuli	30 s	10 s/train	lt DLPFC			

(b) PT as the index of intensity									
Niehaus et al. (2000)	80–120	5	1500 stimuli	5 s	10 s	O	11 healthy	headache, neckache	9% (1/11)
		10	1500–2000 stimuli	10 s	5 s				
		20	1200, 3800 stimuli	30 s	2 s				
Antal et al. (2002)	100	1	600 stimuli		10 min	O	15 healthy	headache	2%
Bohotin et al. (2002)	100	1	single train		15 min	O	24 healthy, 30 migraine	neckache	20%
		10	18 trains 900 stimuli	10 s	5 s				
Brighnia et al. (2002)	100	1	900 stimuli		15 min	O	15 healthy 13 migraine	headache, neckache, drowsiness	20–25%
Fumal et al. (2003)	100	1, 10			15 min, 5 s	O	24 healthy	neckache	20%
Theoret et al. (2002)	100	4	20 stimuli		5 s/train	O, F, P	12 healthy	headache	unknown
Thut et al. (2003)	110	1	600 stimuli		10 min	O	6 healthy	headache	unknown
(c) maximal output of machine as the index of intensity									
*Feinsod et al. (1998)	45 (1/2.2T)	1	2 trains	3 min	60 s	F	24 depressed, 10 schizo	?	
			120 stimuli/day 10 days						
*Brandt et al. (1998)	45–65	20	single train 10 stimuli		0.5 s	F, P	10 healthy	No	
Mottaghy et al. (1999)	55	20	single trains 60 stimuli		2 s	F, T	15 healthy	headache neckache	26.7% (4/15) 20% (3/15)
Menkes et al. (2000)	80 (max is 2.2T)	0.5	100 stimuli/day 4 weeks		200 s	P	1 epilepsy (case report)	No	
Shimamoto et al. (2001)	77.8	0.2	30 stimuli		150 s	F	9 PD	?	
*Sparing et al. (2001)	55	1	40 stimuli		40 s	F, T	16 healthy	No	
	35, 45, 55	20	40 stimuli		2 s				
Stewart et al. (2001)	75	10	single train 6 stimuli		600 ms	T	8 healthy	unknown	
Campana et al. (2002)	60	10	single train 5 stimuli		500 ms	O	12 healthy	neckache	unknown
Conca et al. (2002)	80	0.25	single train 38 stimuli/day 10 days		152 s	F	4 depressed	No	
Gerschlager et al. (2002)	40	1	single train 500 stimuli		500 s	C	15 healthy	headache	6.7% (1/15)
*Gironell et al. (2002)	100% of output	1	30 trains	30 s	10 s/train	C	10 essential tremor	headache	10% (1/10)
								photopsia	10% (1/10)
*Franck et al. (2003)	90	1	10 sessions		810–1000 s	T-P	1 schizo	contraction of masticator muscles	100% (1/1)

Table 4 (*continued*)

Source	rTMS						Number of Subjects	Adverse effect	Frequency (%)
	Index of Intensity (% of MT)	Frequency (Hz)	Total nuber of pulses	inter-train intervals	Duration	Stimulation site			
*Ikeguchi et al. (2003)	70	0.2	120 stimuli		total 9519 s		(case report)		
Juan et al. (2003)	65	10	single train 5 stimuli		10 min 500 ms	F, O O	12 PD 20 healthy	No ?	
Lavidor et al. (2003)	65	8	single train 4 stimuli		500 ms	O	8 healthy	No	
Liederman et al. (2003)	70	1	3 blocks 450 stimuli/block 1350 stimuli		7.5 min	O	16 healthy	headache	unknown

DLPFC, dorsolateral prefrntal cortex; MEP, motor evoked potential; OCD, obsessive–compulsive disorder; schizo, schizophrenia; MT, motor threshold; AH, auditory hallucinations; N, normal subjects; M, migraine; O, occipital; F, frontal; P, parietal. All adverse effects were personaly reported by the authors of each study to us. PD, Parkinson's disease; schizo, Schizophrenia; MT, motor threshold; aMT, active motor threshold; F, frontal; P, parietal; T, temporal; T-P, temporoparietal; O, occipital; C, cerebellum; ?, no information about adverse effect; unknown, not sure actual adverse effect or numbers. All adverse effects were reported in all of the papers listed in Table 4(a). *Side effects were reported in the paper. Adverse effects not marked with * were personaly reported by the authors of each study to us.

symptoms (Dolberg et al., 2001; García-Toro, 1999) and a case of severe delusions (Zwanzger et al., 2002) during a course of repeated, daily rTMS sessions. García-Toro (1999) applied rTMS to the left DLPFC at an intensity of 90% of MT and a frequency of 20 Hz in trains of 2 s duration and 30 s inter-train intervals. In the two cases reported by Dolberg et al. (2001), rTMS was applied to the left DLPFC at an intensity of 90% of MT and a frequency of 10 Hz, in trains of 6 s duration, and 30 s inter-train intervals. In the case with delusions (Zwanzger et al., 2002), rTMS was delivered over the left DLPFC at 100% of MT and a frequency of 10 Hz, in trains of 10 s duration and 30 s inter-train interval.

3.2. Center for Non-invasive brain stimulation at BIDMC

3.2.1. Adverse effect of rTMS to non-motor cortical areas in healthy participants

Table 5(a) summarizes the adverse effects in the study of 249 rTMS sessions on healthy participants at our laboratory with stimulation to non-motor cortical regions. It should be noted that a minority of participants underwent multiple rTMS sessions in separate protocols, so that the actual number of subjects represented by these data is not 249, but probably around 200. Headaches were the most common adverse effect, occurring in 22.9% of the TMS sessions overall. These were never severe and always responded promptly to acetaminophen when necessary. The incidence of headache was higher following low-frequency than after high-frequency rTMS to the DLPFC (34.1 versus 25%, respectively), and the incidence of headache was higher with frontal stimulation compared to other sites. Neck pain was the second most frequent adverse effect overall (12.4% of subjects), and it was especially common when rTMS was applied to the cerebellum (42.1%) and occipital area (27.8%). One subject complained of transient cognitive difficulties, but the examining neurologist found no objective signs of cognitive impairment on an extended mental status exam. There were no seizures induced by rTMS in any of our participants.

The average MT in our subjects was $57.3 \pm 13.4\%$ (mean $\pm$ SD %) of maximal machine output. The average PT (determined in 21 subjects) was $65.1 \pm 18.2\%$ (mean $\pm$ SD %) of maximal machine output.

3.2.2. Adverse effect of rTMS to non-motor cortical areas in patients with major depression

Table 5(b) summarizes the adverse effects in the study of 249 patients with major depressive disorder at our laboratory. The mean HDRS score at baseline was 31.1 ± 7.1 and the mean Beck Depression Inventory score was 29.7 ± 8.6. Patients participated in different study protocols. Left DLPFC stimulation was applied to 198 patients at a frequency of 1 Hz ($n = 11$ patients), 10 Hz ($n = 171$), or 20 Hz ($n = 16$). Right DLPFC stimulation was applied to 51 patients at 1 Hz ($n = 32$ patients) or 20 Hz ($n = 19$). All

patients underwent at least 10 daily sessions of rTMS over 2 weeks (Monday to Friday on 2 consecutive weeks).

Headaches were the most common adverse effect, occurring in 13.3% of the cases overall. Neck pain was the second most frequent adverse effect, occurring in 6.0% of the patients overall. There were no seizures induced by rTMS in any of our patients. Two patients with a prior history of tinnitus complained of an exacerbation of the tinnitus following rTMS. The frequency of headache and neck pain seemed to vary depending on the stimulation parameters (Table 5 (b)). Low frequency rTMS was more frequently associated with headache (44.2% of the time) than high-frequency rTMS (6.8%). Importantly, differential effects of rTMS on depressive symptoms cannot account for this difference in headache frequency. Antidepressant effects of rTMS (as indexed by a decrease in the HDRS score) were demonstrated for low-frequency rTMS to the right, but not the left DLPFC. However, the incidence of headache was equally high for right and left low-frequency rTMS. Furthermore, antidepressant effects seem to be similar in overall magnitude for low-frequency rTMS to the right DLPFC and high-frequency rTMS to the left DLPFC, but incidence of headache was much higher with the former than the latter. Similar findings can be noted for the incidence of neck pain.

4. Discussion

The present review of the literature and the experience at our own laboratory demonstrates that rTMS applied to non-motor areas according to the present rTMS safety guidelines (Wassermann, 1998) is associated with relatively minor adverse effects.

4.1. TMS settings

Most published studies have applied rTMS to non-motor areas based upon MT determination in agreement with current recommendations (Wassermann, 1998). However, it cannot be assumed that MT is a reliable surrogate of cortical excitability for non-motor areas (Robertson et al., 2003). Indeed, there is data to suggest that no correlation exists between the effects of TMS over motor and those induced over non-motor areas (Stewart et al., 2001a). Therefore, for stimulation of non-motor cortical regions, relating the stimulation intensity to other markers of TMS intensity seems worth considering. For example, stimulation of the visual cortex may induce phosphenes, and PT may be used as a reliable measure of visual cortical excitability (Afra et al., 1998; Aurora et al., 1998; Boroojerdi et al., 2002; Stewart et al., 2001a). In fact, PT is usually higher than MT in individual subjects (Stewart et al., 2001a). Therefore, rTMS studies in which stimulation intensity is based on PT may apply higher stimulation intensities than those in which rTMS intensity is referred to MT. From our review, the majority of authors did not describe the actual intensity of stimulation as a percentage of maximal stimulator output. It would be perhaps useful if they did so in order to eventually be able to compare experiences across studies. Therefore, we encourage careful documentation of the machine used, type of coil, and the intensity expressed as percent of stimulator output so that eventually a metanalysis might be able to generate site-specific guidelines for rTMS to non-motor areas. Calculations based on charge density may allow standardization of intensity across various commercially available magnetic stimulators, coil types, and pulse shape characteristics in order to determine absolute intensity parameters that can be applied to non-motor areas. In the meantime, the available data suggests that use of phosphene threshold for visual cortex and motor threshold for other non-motor areas is safe with minimal serious adverse effects.

Many researchers have used intensities below MT or frequencies less than 1 Hz in their studies, although the current safety guidelines do not include these settings. It is commonly believed that rTMS intensity below MT or frequency less than 1 Hz carries less risk of seizure. Nevertheless, Dolberg et al. (2001) and García-Toro (1999) and Grunhause et al. (2000) have reported manic symptoms or the spread MEP discharges caused by stimulation below MT. In addition to these cases, Satow et al. (2002) reported the occurrence of nausea caused by rTMS stimulation over the cerebellum at an intensity below MT and frequency less than 1 Hz. Therefore, participants must be carefully monitored during rTMS stimulation even when stimulation intensity is low.

4.2. Adverse effects

The extensive review of the literature draws strikingly scarce figures on adverse effects. This could be due to a lack of any adverse effects, or perhaps authors frequently fail to report them. The findings at our laboratory suggest that there are indeed adverse effects that go unreported due to their relatively minor nature. As a matter of fact, only 16 studies explicitly mention a lack of any adverse effects. Moreover, 13 studies reported that it was ‘well-tolerated’ or ‘no serious side effects’. In response to our personal communication, authors acknowledged the occurrence of mild headaches or neck pain during or after rTMS stimulation, even though they did not described these adverse effects in their manuscripts. Thus, only the most significant, serious, unexpected adverse events seem to be regularly reported. In addition, there is generally no systematic follow-up for the emergence of potential late effects, particularly for participants that may be repeatedly exposed to rTMS over a period of years.

The most common adverse effects of rTMS are headache and neck pain. These are generally mild, but may affect, depending on stimulation settings and site of stimulation, more than 40% of the subjects. From our own data,

Table 5
Adverse effects of rTMS to non-motor cortical areas at the Harvard Center for Non-invasive Brain Stimulation

Stimulation site	N	Headache	(%)	Neck pain	(%)	Seizure	(%)	Tinnitus	(%)	Cognition Impaired	(%)	Acute Mood Change	(%)	Others	(%)
(a) Healthy participants															
High-frequency rTMS in our laboratory															
Lt DLPFC	18	5	27.8	2	11.1			2	11.1	1	5.6				
Rt DLPFC	18	4	22.2	3	16.7			1	5.6						
Total	36	9	25	5	13.9			3	8.3	1	2.8				
Low-frequency rTMS in our laboratory															
Lt DLPFC	50	17	34												
Rt DLPFC	38	13	34.2												
Lt Parietal	22	4	18.2	2	9.1					1	4.5				
Rt Parietal	30	3	10	1	3.3										
Occipital	54	7	13	15	27.8										
Cerebellum	19	4	21.1	8	42.1										
Total	213	48	22.5	26	12.2					1	0.5				
(b) Patients with depression															
High-frequency rTMS in our laboratory															
Lt DLPFC	187	9	4.8	5	2.7			2	1.1			1	0.5		
Rt DLPFC	19	5	26.3	2	10.5										
Total	206	14	6.8	7	3.4			2	1.0			1	0.5		
Low-frequency rTMS in our laboratory															
Lt DLPFC	11	5	45.454545	2	18.181818										
Rt DLPFC	32	14	43.75	6	18.75										
Total	43	19	44.2	8	18.6										

low-frequency rTMS to the prefrontal area may be associated with a higher incidence of headache and neck pain than high-frequency rTMS to the prefrontal area. Low-frequency rTMS tends to be done with longer trains than high-frequency rTMS. Neck pain and headache are likely to be at least partly the consequence of the duration of the TMS session, the need to hold the head is a relatively immobilized, forced posture, and additional mechanical factors associated with contact of the coil on the scalp. If scientifically acceptable, breaking up low-frequency rTMS sessions in shorter blocks of stimulation and allowing a break approximately every 5 min of stimulation, may prevent this adverse effect. In our experience, migraine headache induced by rTMS was quite rare. In fact, rTMS to left DLPFC has been shown to reduce pain due to migraine (Brighina et al., 2004). Headache has also been induced by sham-stimulation (Berman et al., 2000; Boutros et al., 2002; Herwig et al., 2003b; Hoffman et al., 2003; Höppner et al., 2003; Kimbrell et al., 2002; Koren et al., 2001; Manes et al., 2001; Rollnik et al., 2002). Thus, it is difficult to establish a direct relationship between headache and rTMS in some cases.

There are only two cases reporting nausea as a complication of rTMS, and in both cases stimulation was applied to the cerebellum (Satow et al., 2002). The authors suggested that the direct effect of stimulation of the posterior fossa triggered the symptoms, although the exact mechanism remains unclear. These two subjects underwent multiple sessions of rTMS to other brain areas without this complication, suggesting this may be a site-specific adverse effect. Subjects should be made aware of this potential side-effect.

Tinnitus, mood alterations, and mild, transient cognitive complaints are quite rare. In fact, cognition seems to improve due to rTMS stimulation to DLPFC in depressed patients independently from mood enhancement (Hausmann et al., 2004; O'Connor et al., 2003). There is insufficient evidence to suggest a relationship between the frequency of any reported adverse effects and the stimulation intensity, session duration, or number of pulses received within a session.

More serious adverse effects induced by rTMS to non-motor cortex since publication of the current safety guidelines (Wassermann, 1998) include seizures (Conca et al., 2000; Flitman et al., 1998), pseudoseizures (Figiel et al., 1998), syncope (Figiel et al., 1998), and induction of psychotic symptoms (Dolberg et al., 2001; García-Toro, 1999; Zwanzger et al., 2002).

In the case reported by Flitman et al. (1998) and (Wassermann et al., 1996), the authors suspected that the seizure induced by rTMS was due to the unusually short inter-train intervals (250 ms). The current safety guidelines lack specific directives regarding inter-train intervals. Nevertheless, it seems that longer intervals are required for higher intensities and frequencies (Wassermann, 1998). Chen et al. reported that 10 rTMS trains at 20 Hz for 1.6 s and a stimulus intensity of 110% of MT might be safe at the inter-train interval of 5 s, but inter-train intervals of 1 s or less were unsafe (Chen et al., 1997). Thus, when repeated trains of rTMS are used, short inter-train intervals might be particularly epileptogenic.

The patient reported by Conca et al. (2000) was severely depressed and had a prior history of a single maprotiline-induced seizure. The TMS-induced seizure was a partial complex event consisting of nausea immediately followed by loss of consciousness and mild facial automatism for 8 s, without post-ictal confusion or any memory for the event. EEG immediately afterward showed bifrontopolar paroxysmal delta during hyperventilation and SPECT scan two days later showed left DLPFC hypometabolism, suggesting that the seizure originated from the stimulated frontal lobe. The patient was on multiple medications and had undergone a 5-day course of daily bilateral rTMS (20 Hz to the left and 1 Hz to the right DLPFC) 5 days before the unilateral, left-sided 20 Hz rTMS session that triggered the seizure. There are no current safety guidelines for bilateral rTMS application, and although the seizure in this patient occurred during unilateral rTMS, the preceding course of bilateral rTMS may have played a role. Furthermore, the patient had a prior seizure induced by maprotiline, a potent norepinephrine re-uptake inhibitor, and the rTMS-induced seizure occurred while the patient was on various serotoninergic and noradrenergic medications. Thus, pharmacological factors may have played a critical role. Finally, a train duration of 10 s at 110% MT and a frequency of 20 Hz is longer than recommended in the current safety guides. Importantly, none of these two patients who experience seizures with rTMS had any further seizures or developed epilepsy.

Figiel et al. (1998) reported a depressed patient with pseudoseizures and another with one syncopal episode several hours after rTMS. Differentiation of seizures, pseudoseizures, and syncope can be challenging at times. Therefore, careful assessment of the subjects and conduct of rTMS in appropriately equipped laboratories staffed by personnel trained in the prompt recognition and treatment of spells are critical.

There are three reported cases with muscular contractions appearing during rTMS to prefrontal cortex, but without evolving into clinically detectable after-discharges or seizures (Figiel et al., 1998; Grunhaus et al., 2000). In all three reports, rTMS was being delivered to the left DLPFC at a frequency of 10 Hz. TMS pulses stimulate both cortico-cortical connections and corticofugal fibers. Thus, this may have represented intracortical spread of excitation and a potential marker of increasing excitability, breakdown of surround inhibition, and a sign of risk for induction of epileptic discharges (Pascual-Leone et al., 1993). However, other possibilities need to be considered. For example, the threshold in neighboring areas might be lowered by rTMS and locally stimulated phenomena from such neighboring sites might emerge. Furthermore, it is difficult to rule out movement of the hand-held TMS coil without the help

of a frameless stereotactic system, so that it is likely that in these instances stimulation may have targeted a variable, larger region of the cortex (Gugino et al., 2001). Finally, the observed twitches may have been produced by the wing of the figure 8 coil targeting the motor cortex during stimulation focused on the DLPFC. In any case, it is worth noting that such instances of apparent spread of stimulation effects have not been followed by seizures or other complications as initially suspected (Pascual-Leone et al., 1993).

With regard to acute psychiatric effects, four patients exposed to high-frequency rTMS for the treatment of medically refractory depression warrant discussion. Acute mania with rapid mood fluctuations was reported in three patients with bipolar depression following rTMS to the DLPFC (Dolberg et al., 2001; García-Toro, 1999). Zwanzger et al. (2002) reported the onset of persecutory delusions in a patient with medication-resistant depression during a course of rTMS. Manic symptoms and delusion may be related to the abnormal activity in frontal and parietal association cortices, since these networks are known to be crucial for higher-order cognitive function, such as perceptual discrimination and attention tasks (Blumenfeld and Taylor, 2003; Lumer et al., 1998). Psychiatric symptoms may also be precipitated by rTMS through the modulation of neurotransmitter systems. This is in line with a recent study in rats showing a marked increase of extracellular dopamine in the hippocampus after frontal lobe stimulation with 20 Hz (Keck et al., 2000). Human studies reveal a significant dopamine release at the caudate nucleus evoked by rTMS to the left DLPFC (Strafella et al., 2001). A similar dopamine-mediated mechanism may cause de novo occurrence of psychotic symptoms. In healthy subjects such adverse effects have not occurred, and patients with medication-resistant major or bipolar depression may be at an increased risk due to underlying neurochemical abnormalities. It is noteworthy that these patients were taking medications, while the ones studied at our laboratory had been washed out of antidepressant and psychotropic agents. However, the data are certainly insufficient to assess whether pharmacological treatment actually contributes to the risk of this adverse effect. Overall this is a rare complication of rTMS (incidence $<0.15\%$ of patients in the studies reviewed), and many patients with psychiatric diseases on medications have tolerated rTMS without any complications.

5. Conclusions

rTMS to non-motor areas in accordance with the current guidelines (Wassermann, 1998) appears to be very safe. After extensive review of the literature, only limited conclusions may be drawn since most authors fail to report adverse effects. We recommend that authors use more diligence in reporting the occurrence (or lack thereof) of any adverse effects. In addition, documentation of the machine type, coils used, and the actual stimulation intensity as a function of machine output may all make comparison of experience across studies more reliable. Experience at our laboratory suggests that mild headache and neck pain are by far the most common adverse effects, and that their incidence depends on the site of stimulation. Low-frequency rTMS may be more commonly associated with these adverse effects than high-frequency rTMS, probably because of the longer duration of the stimulation sessions and the resulting longer periods of immobilization of the subjects. Eventually, it might be desirable to develop safety guidelines based on the prediction of actual current density induced in each subject's brain or control stimulation settings by the on-line monitoring of rTMS on cortical excitability as indexed by EEG measures. For now, current safety guidelines based on MT seem applicable to non-motor areas, and PT may be used to calculate the intensity of occipital rTMS.

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Appendix A

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