Safety of Theta Burst Transcranial Magnetic Stimulation: A Systematic Review of the Literature

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Abstract: Theta burst stimulation (TBS) protocols have recently emerged as a method to transiently alter cortical excitability in the human brain through repetitive transcranial magnetic stimulation. TBS involves applying short trains of stimuli at high frequency repeated at intervals of 200 milliseconds. Because repetitive transcranial magnetic stimulation is known to carry a risk of seizures, safety guidelines have been established. TBS has the theoretical potential of conferring an even higher risk of seizure than other repetitive transcranial magnetic stimulation protocols because it delivers high-frequency bursts. In light of the recent report of a seizure induced by TBS, the safety of this new protocol deserves consideration. We performed an English language literature search and reviewed all studies published from May 2004 to December 2009 in which TBS was applied. The adverse events were documented, and crude risk was calculated. The majority of adverse events attributed to TBS were mild and occurred in 5% of subjects. Based on this review, TBS seems to be a safe and efficacious technique. However, given its novelty, it should be applied with caution. Additionally, this review highlights the need for rigorous documentation of adverse events associated with TBS and intensity dosing studies to assess the seizure risk associated with various stimulation parameters (e.g., frequency, intensity, and location).

Key Words: Theta burst stimulation, Safety, Transcranial magnetic stimulation, Adverse events, Risks, Meta-analysis.

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Transcranial magnetic stimulation (TMS) can be used to experimentally manipulate brain activity and is capable of inducing long-term (in the order of minutes to days) changes in cortical excitability. TMS is based on the principles of electromagnetic induction, whereby a strong, rapidly fluctuating magnetic field pulse (produced by the TMS coil) generates electrical currents in underlying tissue (Kobayashi and Pascual-Leone, 2003; Wagner et al., 2007). When TMS is applied at appropriate intensity, the induced electrical current is sufficient to depolarize neurons and create action potentials (Pascual-Leone et al., 2002). In the case of single pulses of TMS, the effect is not thought to last long beyond the time of stimulation (Pascual-Leone et al., 2002). In contrast, when trains of multiple pulses of TMS are applied to the brain with a short interstimulus interval (1 Hz or greater), the net effects are longer-lasting changes in cortical excitability, which can be sustained well beyond the time of stimulation (Pascual-Leone et al., 1994).

TMS is considered quite safe if applied within current safety guidelines; however, TMS does pose some risk for adverse side effects (Rossi et al., 2009). The most serious acute risk is a seizure occurring at the time of treatment. Less serious but more frequent side effects of repetitive TMS (rTMS) include headache and neck pain. Based on reported incidences of such adverse events, safety guidelines have been established for rTMS protocols (Rossi et al., 2009). Updating prior guidelines (Wassermann, 1998), the Consensus Statement reached at the Sienna Meeting (Rossi et al., 2009) includes information about asynchronous trains, such as theta burst stimulation (TBS) paradigms. However, at the time of the Consensus meeting, there were still relatively few studies published that used TBS. The rapidly increasing number of studies and the absence of an actual safety study stress the importance of carefully reviewing the experience in the 5 years since the introduction of TBS.

TBS refers to a rTMS protocol where pulses are applied in bursts of three, delivered at a frequency of 50 Hz and an interburst interval of 200 milliseconds (5 Hz). These parameters were originally developed based on studies in both the rodent and human brain indicating that theta rhythms are associated with long-term potentiation (Hill, 1978; Klimesch et al., 1996; Larson et al., 1986; Staubli and Lynch, 1987). It was noted that when an animal explores a new environment, pyramidal cells in the hippocampus fire in short (approximately 30 milliseconds) bursts and at a frequency of approximately 5 to 7 Hz (Hill, 1978). Additionally, when a human is asked to do an implicit memory task, electroencephalogram (EEG) power in the theta (5–7 Hz) band is elevated (Klimesch et al., 1996). Rodent studies (both slice and *in vivo*) also reveal that when hippocampal CA1 pyramidal cells are stimulated with bursts in the theta frequency range, long-term potentiation (LTP) can be reliably elicited (Larson et al., 1986; Staubli and Lynch, 1987).

Mimicking such studies, rTMS protocols were originally developed in an effort to investigate plasticity mechanisms in the human brain. Given the complexity of the human cortex, it may be surprising that the same protocols that result in induction of LTP in single cells in the hippocampus would apply to TMS (which stimulates large numbers of cortical neurons nonspecifically). However, TBS protocols seem to lead to sustained changes in cortical activity lasting well beyond the duration of the TMS application, providing a putative index of underlying LTP and long-term depression processes that can be recorded *in vivo* from the human brain. TBS paradigms have also been applied in studies investigating cognitive functions and as novel treatment interventions for a variety of neurologic conditions.

Additionally, these effects seem to be dependent on *N*-methyl-D-aspartic (NMDA) receptors, suggesting that the after effects might be mediated by LTP-like synaptic plasticity (Huang et al., 2007). There are two commonly used patterns of TBS, continuous TBS (cTBS) and intermittent TBS (iTBS). In cTBS, bursts of 3 pulses at 50 Hz are applied at a frequency of 5 Hz for either 20

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seconds (100 bursts) or 40 seconds (200 bursts). In iTBS, 20 2-second periods (10 bursts) of TBS are applied at a rate of 0.1 Hz. In hand muscles, consistent with the findings in slice preparations, cTBS reduces motor-evoked potential amplitude (producing an long-term depression-like phenomena), whereas iTBS increases motor-evoked potentials (producing an LTP-like phenomena), in both cases for approximately 30 minutes after the end of the stimulation.

Since their introduction into the literature in 2005, these paradigms have been increasingly used. Although early on these paradigms seemed to be used in a select few laboratories, recent years have seen increasing use of these paradigms, evidenced by a total of 10 publications between 2004 and 2006 and more than 50 published reports between 2007 and 2009. Researchers who use TBS highlight that these paradigms use less pulses and shorter duration of stimulation than typical rTMS paradigms. One implication is that TBS may be safer than other frequently used rTMS trains. However, it cannot be ignored that TBS protocols use very high-frequency stimulation. It is currently unknown whether frequency, duration, or total number of pulses is a better predictor for risk of adverse events, including the risk of seizure. Current guidelines on safety of TMS (Rossi et al., 2009) do not include recommendations for the maximum duration or intensity of stimulation when applying patterned trains of stimulation such as TBS. Thus, we believe that in light of the growing number of studies using TBS and the lack of any safety studies, it is necessary to examine the risk profile associated with these types of paradigms. Accordingly, in this study, we present a comprehensive review of adverse events occurring after TBS that have been published in the literature.

METHODS

Literature Review

Using the PubMED database, we identified 64 English language publications (from May 2004 to December 2009) describing 64 theta burst TMS protocols. The PubMED search criteria used the following keywords: Theta Burst Stimulation TMS and Theta Burst Stimulation Transcranial Magnetic Stimulation. We reviewed all reports and noted any associated article references. The following criteria were also cataloged for each protocol: the total number of relevant subjects, demographic information about the subjects, TBS parameters (including stimulation intensity, type of TBS, number of trains, and stimulation site), and incidence of adverse events. When not explicitly stated in the article, we obtained the relevant information about adverse events by personal communication with the corresponding authors.

Statistical Analysis

The crude risks of seizures and other adverse events were computed separately. We limited our statistical analysis to crude per-person risk and crude risk per TBS session. Our rationale for doing so was based on the small number of reported adverse events, on the inconsistency in sample size (which ranged from 1 to 50 subjects per study), and on the diversity of the TBS protocols used (e.g., cTBS, iTBS, or other modified TBS protocols) between studies. Accordingly, we calculated crude risk averages weighted by sample size and by session number (total sessions per patient).

RESULTS

The subject demographic characteristics and TBS parameters are summarized in Table 1. The data represent 67 studies with a combined total subject number of 1,040 people and involving a total number of sessions exceeding 4,500. Of the 1,001 subjects, 776 were healthy control participants, while 225 were clinical patients with a variety of diagnoses including autism spectrum disorders (n = 27), chronic pain (n = 6), stroke (n = 42), tinnitus (n = 67), Parkinson disease (n = 37), dystonia (n = 14), amyotrophic lateral sclerosis (n = 20), fragile X (n = 2), and multiple sclerosis (n = 10). Regarding location of stimulation, 632 subjects received stimulation to primary motor cortex (M1), 235 to prefrontal cortex [including premotor/supplementary motor area (150), dorsal lateral prefrontal cortex (97), and frontal eye fields (20)], 98 to primary sensory cortex, 56 to other parietal loci, 67 to temporal cortex (including 46 to primary auditory cortex, 20 to inferior temporal cortex, and 1 to temporal-parietal junction), 102 to occipital cortex, and 44 to the cerebellum. Of note, multiple studies used more than one site of stimulation in separate sessions. The average age of the participant in these studies was 34 years, but they ranged in age from 18 to 74 years. Adverse events or lack there of were reported (or obtained from personal communication from the corresponding author) for all studies. Of the subjects in the 67 protocols (n = 1,001, 776 healthy controls), the reported adverse events were (1) seizure in one healthy control subject during cTBS, (2) mild headache in 24 subjects (20 healthy controls, 2 patients with tinnitus, and 2 patients with Parkinson disease), (3) nonspecific discomfort in five patients with tinnitus, (4) mild discomfort due to cutaneous sensation and neck muscle contraction in five healthy control subjects, (5) worsening tinnitus in three tinnitus patients, (6) nausea in one patient with Parkinson disease, (7) light headedness or vagal responses in 11 healthy control subjects, and (8) unilateral eye pain and lacrimation in one healthy control subject (which ceased on cessation of the treatment session). These findings are summarized in Fig. 1.

The one incident of seizure induced by TBS was described by Oberman and Pascual-Leone (2009) and occurred in a 33-year-old healthy man with no risk factors for epilepsy. The seizure occurred after approximately 50 trains (10 seconds) of TBS to the primary motor cortex at an intensity of 100% of resting motor threshold (MT). Given this one incident of a seizure, the resulting crude risk per subject of seizure as a result of TBS is estimated as 0.1%, whereas the crude risk per subject of mild adverse events (encompassing the remainder of the reported events) is 5% overall and 4.8% for healthy controls. As many studies involve multiple sessions of TBS, we also calculated the crude risk of seizure per session of TBS as approximately 0.02%, and 1.1% for mild adverse events.

DISCUSSION

On the basis of our meta-analysis of the published literature, we find that both the reported symptoms and general risk of adverse events during TBS is comparable with or less than other high frequency rTMS protocols [see the study by Rossi et al. (2009) for a review]. Seizure, the most severe reported adverse event, has only occurred once in more than 4,500 sessions resulting in a crude risk of 0.02%, whereas the overall crude risk of any adverse event is estimated as 1.1%. This is comparable with other high-frequency rTMS protocols where seizures have occurred in less than 0.1% of patients. The most common reported adverse event during TBS is also the most common in other rTMS protocols, transient headache and neck pain. This adverse event has been reported in up to 40% of patients undergoing high-frequency rTMS (Rossi et al., 2009) and was experienced by less than 3% of the subjects receiving TBS.

Only crude risk estimates are reported due to three specific limitations of the literature to date: first, no study has followed up with participants in the subsequent hours or days after TBS, and thus, only immediate effects can be estimated. Additionally, there are no standardized methods for obtaining information regarding adverse events, thus it is unclear whether values would be larger if participants were asked explicitly whether they are experiencing specific symptoms and if participants were followed up several hours later or the following day. Second, although the majority of

TABLE 1. Studies Included in the Review of the Literature, Representing Published Manuscripts from 2005 to 2010 Using Theta Burst Transcranial Magnetic Stimulation Paradigms

Study	No. Subjects (Subjects per Session)	TMS Parameters (Trains, Type of TBS, MT)	Adverse Events
Stimulation over primary motor cortex (M1)			
Oberman et al., under review	25 ASD and 25 HC (1–2 SPS)	200 trains of cTBS over M1 at RMT and at 80% RMT, 200 trains of iTBS at RMT	None
Oberman et al., 2010	2 HC, 2 ASD, and 2 FX (2–4 SPS)	200 trains of cTBS over M1 at 80% AMT, 200 trains of iTBS over M1 at 80% AMT	None
Oberman and Pascual-Leone, 2009	1 HC (1 SPS)	50 trains of cTBS over M1 at RMT	1 seizure
Mori et al., 2010	10 MS (10 SPS)	200 trains of iTBS over M1 at 80% AMT	None
Di Lazzaro et al., 2009	10 ALS (60 SPS)	200 trains of cTBS over M1 at 80% AMT	None
Di Lazzaro et al., 2010	17 stroke (1 SPS)	200 trains of iTBS over M1 at 80% AMT	None
Swayne et al., 2009	10 HC (2 SPS)	200 trains of iTBS over M1 at 80% AMT	None
Ragert et al., 2009	17 HC (1 SPS)	200 trains of iTBS over M1 at 80% AMT	2 headache
Todd et al., 2009	28 HC (3–5 SPS)	200 trains of cTBS over M1 at 80% AMT, 200 trains of iTBS over M1 at 80% AMT	None
Csifcsak et al., 2009	10 HC (1 SPS)	200 trains of cTBS over M1 at 80% AMT	None
Stagg et al., 2009	16 HC (1 SPS)	200 trains of cTBS over M1 at 80% AMT	None
McAllister et al., 2009	9 HC (2 SPS)	200 trains of cTBS over M1 at 70% AMT, 200 iTBS over M1 at 70% AMT	None
Cheeran et al., 2008	36 HC (1 SPS)	100 trains of cTBS over M1 at 80% AMT, 200 trains of iTBS over M1 at 80% AMT	None
Iezzi et al., 2008	10 HC (4–7 SPS)	100 trains of cTBS over M1 at 80% AMT, 200 trains of iTBS over M1 at 80% AMT	None
Suppa et al., 2008	18 HC (2–13 SPS)	200 trains of cTBS over M1 at 80% AMT, 200 trains of iTBS over M1 at 80% AMT	None
Di Lazzaro et al., 2008b	28 HC and 2 chronic pain (1 SPS)	200 trains of iTBS over M1 at 80% AMT	None
Zafar et al., 2008	9 HC (8 SPS)	200 trains of cTBS over M1 at 80% AMT, 200 trains of iTBS at 80% AMT	None
Di Lazzaro et al. 2008a	12 stroke (2 SPS)	200 trains of cTBS over M1 at 80% AMT, 200 trains of iTBS at 80% AMT	None
Rothkegel et al., 2009	22 PD (2 SPS)	200 trains of cTBS over M1 at 80% AMT, 200 trains of iTBS at 80% AMT	2 headache 1 nausea
Agostino et al., 2008	17 HC (2 SPS)	200 trains of iTBS over M1 at 80% AMT	None
Poreisz et al., 2008b	13 HC (1 SPS)	200 trains of cTBS over M1 at 80% AMT	None
Huang et al., 2008	14 HC (1–6 SPS)	100 trains of cTBS over M1 at 80% AMT, 200 trains of iTBS at 80% AMT	None
Andoh et al., 2008	14 HC (1 SPS)	200 trains of iTBS over M1 at 90% AMT	None
Huang et al., 2007	6 HC (4 SPS)	100 trains of cTBS over M1 at 80% AMT, 200 trains of iTBS over M1 at 80% AMT	None
Mistry et al., 2007	9 HC (1 SPS)	200 trains of cTBS over M1 at 80% AMT	None
Talelli et al., 2007	6 stroke (4 SPS)	200 trains of cTBS over M1 at 80% AMT, 200 trains of iTBS at 80% AMT	None
Talelli et al., 2007	18 HC (3 SPS)	100 trains of cTBS over M1 at 80% AMT, 200 trains of iTBS at 80% AMT	None
Voss et al., 2007	16 HC (2 SPS)	100 trains of cTBS over M1 at 80% AMT, 200 trains of iTBS at 80% AMT	None
Teo et al., 2007	6 HC (2 SPS)	200 trains of iTBS over M1 at 80% AMT	None
Edwards et al., 2006	14 dystonia and 16 HC (1 SPS)	100 trains of cTBS over M1 at 80% AMT	None
Martin et al., 2006	8 HC (3–6 SPS)	200 trains of cTBS over M1 at approximately 120% AMT	None

(*Continued*)

TABLE 1. (*Continued*)

Study	No. Subjects (Subjects per Session)	TMS Parameters (Trains, Type of TBS, MT)	Adverse Events
Di Lazzaro et al., 2006	10 ALS (10–60 SPS)	200 trains of cTBS over M1 at 80% AMT	None
Di Lazzaro et al., 2005	4 chronic pain (1 SPS)	100 trains of cTBS over M1 at 80% AMT	None
Huang et al., 2005	9 HC (54–154 SPS)	10, 25, 200 trains of cTBS, iTBS, and imTBS over M1 at 80% AMT	None
Huang and Rothwell, 2004[a]	15 HC (unknown SPS)	1 train of modified cTBS (5 or 15 pulses at 50 Hz) over M1 at 50%, 70%, or 80% AMT	None
Stimulation over prefrontal cortical sites			
Koch et al., 2007	21 HC (2 SPS)	100 trains of cTBS over premotor cortex at 80% AMT, 100 trains of iTBS over premotor cortex at 80% AMT	None
Schindler et al., 2008[a]	4 HC (1 SPS)	200 trains of modified cTBS (3 pulses at 30 Hz with 100 milliseconds ITI) over FEF at 80% RMT	None
Hubl et al., 2008[a]	7 HC (1 SPS)	200 trains of modified cTBS (3 pulses at 30 Hz with 100 milliseconds ITI) over FEF at 80% RMT	None
Stimulation over parietal cortex			
Poreisz et al., 2008a	19 HC (3 SPS)	200 trains of cTBS, iTBS, and imTBS over S1 at 80% AMT	None
Katayama and Rothwell, 2007	11 HC (1 SPS)	200 trains of iTBS over S1 at 80% AMT	None
Nyfeller et al., 2009[a]	7 stroke (2–6 SPS)	267 trains of modified cTBS (3 pulses at 30 Hz with 100 milliseconds ITI) over inferior parietal sulcus at 100% RMT	None
Cazzoli et al., 2009[a]	10 HC (4 SPS)	267 trains of modified cTBS (3 pulses at 30 Hz with 100 milliseconds ITI) over posterior parietal cortex at 100% RMT	None
Nyffeler et al., 2008[a]	22 HC (1 SPS)	267 trains of modified cTBS (3 pulses at 30 Hz with 100 milliseconds ITI) over posterior parietal cortex or vertex at 90% RMT	None
Stimulation over temporal cortex			
Poreisz et al., 2009	20 tinnitus (3 SPS)	200 trains of cTBS over inferior temporal cortex at 80% AMT and 80% RMT	2 headache 3 worsening tinnitus 5 nonspecific Discomfort
Soekadar et al., 2009	1 tinnitus (20 SPS)	200 trains of cTBS over temporal parietal junction at 80% AMT	None
De Ridder, 2007[a]	46 tinnitus (1 SPS)	200 trains of modified cTBS (3–5 pulses, ? Hz, 200 milliseconds ITI) over auditory cortex at 90% RMT	None
Stimulation over occipital cortex			
Franca et al., 2006	12 HC (1–2 SPS)	200 trains of cTBS over occipital cortex at 80% phosphene threshold, 200 trains of iTBS over occipital cortex at 80% phosphene threshold	5 cutaneous sensation/ neck muscle contraction
Silvanto et al., 2007[a]	6 HC (1 SPS)	25 trains of modified cTBS (8 pulses at 40 Hz with a 1,800 milliseconds ITI) over occipital cortex at 60% machine output	None
Stimulation over cerebellum			
Koch et al., 2009	15 PD (2–22 SPS)	200 trains of cTBS over lateral cerebellum at 80% AMT	None
Koch et al., 2008	20 HC (1–7 SPS)	200 trains of cTBS over lateral cerebellum and neck at 80% AMT and 90% RMT, 200 trains of iTBS over lateral cerebellum at 80% AMT	3 mild headache

(*Continued*)

TABLE 1. (*Continued*)

Study	No. Subjects (Subjects per Session)	TMS Parameters (Trains, Type of TBS, MT)	Adverse Events
Stimulation over multiple cortical sites			
Galea et al., 2010	30 HC (1 SPS)	200 trains of cTBS over DLPFC or occipital cortex at 80% AMT	1 unilateral eye pain and lacrimation
Ortu et al., 2009	7 HC (3 SPS)	200 trains of cTBS over premotor and M1 at 80% AMT	None
Huang et al., 2009	11 HC (1–4 SPS)	100 trains of cTBS over premotor and M1 at 80% AMT	None
Catmur et al., 2009	8 HC (2 SPS)	100 trains of cTBS over premotor and posterior parietal cortex at 80% AMT	None
Wilkinson et al., 2010	32 HC (1 SPS)	200 trains of cTBS over M1, DLPFC, or supplementary motor area at 80% AMT	None
Saglam et al., 2008	10 HC (1–3 SPS)	200 trains of cTBS over M1 and S1 at 80% AMT	None
Stefan et al., 2008	18 HC (2–8 SPS)	100–200 trains of cTBS over M1, premotor, and medial occipital cortex at 70% RMT	None
Grossheinrich et al., 2009	25 HC (1–2 SPS)	200 trains of cTBS over M1 and DLPFC at 80% AMT, 200 trains of iTBS over M1 and DLPFC at 80% AMT	3 presyncopal/vasovagal events (2 during cTBS, 1 during iTBS) 8 lightheadedness (4 during cTBS, 4 during iTBS) 15 headache (7 during cTBS and 8 during iTBS)
Schabrun et al., 2008	15 HC (2 SPS)	200 trains of cTBS over M1 and S1 at 80% AMT	None
Gentner et al., 2008	36 HC (unknown)	100–200 trains of cTBS over M1, premotor and medial occipital cortex at 70% RMT	None
Ragert et al., 2008	23 HC (1 SPS)	200 trains of iTBS over S1 or M1 at 80% AMT	None
Ishikawa et al., 2007	12 HC (2–4 SPS)	200 trains of cTBS over M1, S1 at 80% AMT	None
Mochizuki et al., 2005	9 HC (2 SPS)	100 trains of cTBS over Premotor cortex and parietal cortex at 80% AMT and 90% AMT, respectively	None
Ko et al., 2008	10 HC (3 SPS)	3 sets of 100 trains of cTBS over DLPFC and cerebellum vermis at 80% AMT	None
Mochizuki et al., 2007[a]	8 HC (12 SPS)	100 trains of iTBS [34–36 s ITI (instead of 8)] over premotor cortex, M1, S1	None
Nyffeler et al., 2006a[a]	6 HC (1–3 SPS)	200 trains of cTBS (3 pulses/30 Hz/100 milliseconds ITI) over FEF and vertex at 80% RMT	None
Nyffeler et al., 2006b[a]	3 HC (2 SPS)	200 trains of cTBS (3 pulses/30 Hz/100 milliseconds ITI) over FEF and vertex at 80% AMT	None

[a]Modified TBS parameters were used.

HC, healthy control subjects; ASD, autism spectrum disorders; PD, Parkinson disease; ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis; FX, fragile X syndrome; SPS, sessions per subject; cTBS, continuous theta burst stimulation; iTBS, intermittent theta burst stimulation; AMT, active motor threshold; RMT, resting motor threshold; M1, primary motor cortex; S1, primary sensory cortex; FEF, frontal eye fields; DLPFC, dorsolateral prefrontal cortex.

protocols use the standard parameters (3 pulses at 50 Hz with a 200 milliseconds interstimulus interval at 80% of active MT), the site of stimulation varies across studies as do the populations. Adverse events are seen in stimulation across the cortex and in both clinical patients and healthy control participants. With clinical patients, medication may have contributed to the reported adverse events; however, it should be noted that the majority of adverse events were experienced by healthy control participants.

Additionally, a subset of experimental protocols (11/67) applied modified TBS parameters, which may or may not have the same risk profile. This heterogeneity in the literature may account for the presence of adverse events during some studies but not others. Finally, it is also possible that adverse events have occurred but were not noted either because they did not seem serious, were not specifically probed, or because they occurred after the subject left the laboratory.

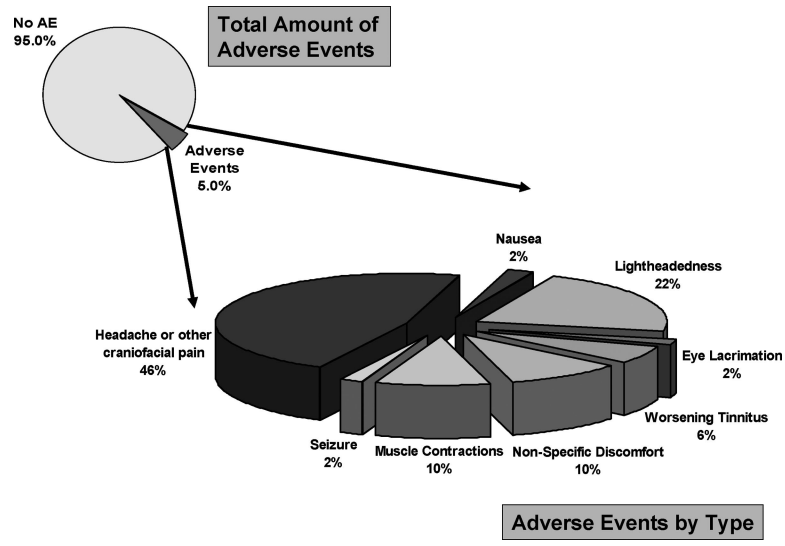

FIGURE 1. Percentage of adverse events reported during or immediately after theta burst stimulation.

As the majority of this data were collected in a relatively small number of laboratories, it is unclear whether the findings will generalize across laboratories and clinics. Given the increasing interest in neuromodulatory protocols for clinical purposes and the growing number of laboratories using TBS, our finding that the risk profile is comparable with that of other rTMS paradigms is promising. However, it is still recommended that researchers proceed with caution as the full range of safe parameters has not been explored. Furthermore, training of investigators and technicians is particularly important for the application of relatively novel paradigms, such as TBS. During application of cTBS or iTBS, precautions (including appropriate physician supervision and emergency medical care access) should be undertaken, even in subjects with no predisposing factors for seizures.

The one individual who experienced a seizure during TBS was stimulated at an intensity of 100% resting MT. As such, stimulating at or above 100% resting MT should only be performed with great caution, and lower intensity stimulation is preferred on current evidence. An additional consideration is that several factors could theoretically increase the risk of inadvertently stimulating at a higher than desired intensity including interindividual variability in MT (Wassermann, 2002), potential diurnal fluctuations in intraindividual MT, the propensity to overestimate MT with conventional "observational" techniques (Rossi et al., 2009), and the presence of other factors that could theoretically affect cortical excitability such as caffeine consumption, sleep deprivation, or other environmental influences. As TMS intensity positively correlates with induction of neural activity and net excitation, stimulating too high above threshold with high-frequency protocols leads to potentially greater risk for seizure (Rossi et al., 2009). In the case of the reported seizure, stimulus intensity was based on the MT established 1 hour before the stimulation. We recommend that whenever possible, TBS stimulation intensity should be adjusted according to MT established directly before application of TBS and through the use of conventional surface electromyography definition, rather than observation. When TBS is applied outside of the motor cortex, one may also use the TMS-evoked EEG response as an indication of cortical reactivity [see the review by Kahkonen et al. (2005)]. It is also recommended that subjects be observed for a period of time after TBS as there may be interindividual variability in response to TBS that may last well beyond the experimental session. Finally, adverse events should be specifically probed and documented after each application of TBS, such that a larger safety study may be conducted in the future.

CONCLUSION

TBS is an increasingly common method of administering rTMS. Among the advantages of TBS over more conventional rTMS is its ability to induce alterations in long-term depression and LTP as a way of studying neuroplasticity in humans (Huang et al., 2007). In addition, TBS can be administered over a shorter time interval than traditional forms of rTMS and may arguably be more efficacious (Huang et al., 2007). Still, given the high frequency bursts used, the safety of this technique merits exploration. In this study, we provide preliminary evidence that the safety profile associated with TBS (including that associated with seizure induction) is comparable with that of other rTMS modalities. The authors recommend that future experiments proceed with caution and systematically document adverse events until more formal safety guidelines have been established.

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