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Reviews

Efficacy and Time Course of Theta Burst Stimulation in Healthy Humans

Miles Wischnewski*, Dennis J.L.G. Schutter

Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, the Netherlands

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ABSTRACT

Background: In the past decade research has shown that continuous (cTBS) and intermittent theta burst stimulation (iTBS) alter neuronal excitability levels in the primary motor cortex.
Objective: Quantitatively review the magnitude and time course on cortical excitability of cTBS and iTBS.
Methods: Sixty-four TBS studies published between January 2005 and October 2014 were retrieved from the scientific search engine *PubMED* and included for analyses. The main inclusion criteria involved stimulation of the primary motor cortex in healthy volunteers with no motor practice prior to intervention and motor evoked potentials as primary outcome measure.
Results: ITBS applied for 190 s significantly increases cortical excitability up to 60 min with a mean maximum potentiation of 35.54 ± 3.32%. CTBS applied for 40 s decreases cortical excitability up to 50 min with a mean maximum depression of −22.81 ± 2.86%, while cTBS applied for 20 s decreases cortical excitability (mean maximum −27.84 ± 4.15%) for 20 min.
Conclusion: The present findings offer normative insights into the magnitude and time course of TBS-induced changes in cortical excitability levels.

Introduction

Over the past two decades researcher have developed numerous transcranial magnetic stimulation (TMS) paradigms to modulate cortical excitability levels. These paradigms include low (1 Hz) and high frequency (≥5 Hz) repetitive TMS (rTMS), paired associative stimulation (PAS) and theta burst stimulation (TBS) [1–7]. In particular, TBS has gained much interest, which is arguably due to its efficacy and the short stimulation period [4]. Rooted in basic research for the induction of long-term potentiation (LTP) and long-term depression (LTD) in animal brains, TBS applied to the primary motor cortex (M1) has shown to induce frequency-dependent potentiation and depression of cortical excitability [4,8,9]. The continuous TBS (cTBS) protocol involves triplets of pulses with a frequency of 50 Hz delivered every 0.2 s (5 Hz), which depresses cortical excitability levels [4,10]. Even though some studies show successful depression of cortical excitability levels after 300 pulses ($cTBS_{300}$) for 20 s [4,11,12], the majority of studies uses 600 pulses during 40 s of stimulation ($cTBS_{600}$) [4,10]. Intermittent TBS (iTBS) involves series of 10 bursts of 50 Hz triplets delivered every 0.2 s (5 Hz) separated by 8 s non-stimulation intervals. Commonly, iTBS consists of 600 pulses delivered over a 190 s period and is able to increase cortical excitability levels in the M1 ($iTBS_{600}$) [4,13]. Whereas initial studies examined effects of TBS applied to the M1, TBS is nowadays also applied over non-motor cortical regions [14–21].

Although the existing literature suggests that TBS applied to the motor cortex is effective, there is to our knowledge no systematic study that has quantified its magnitude and time course of TBS-related effects on cortical excitability. To this end, the present quantitative review aimed to give a normative overview of TBS administered in healthy volunteers to provide a normative estimate of motor cortical plasticity of the human cerebrum.

Material and methods

Articles for the present analyses were retrieved from the scientific search engine *PubMed* in a period between January 2005 and October 2014. *Theta burst stimulation* in title or abstract was used as search criterion, which yielded 327 initial

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* Corresponding author. Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Montessorilaan 3, Suite B.01.21, 6525 HR Nijmegen, the Netherlands. Tel.: +31 24 361 2604.
E-mail address: m.wischnewski@donders.ru.nl (M. Wischnewski).

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Table 1
Overview of TBS experiments that have been used for analysis in the present article.

Study [reference]	Sample size (male/female)	Age mean ± SD	TBS protocol	Target muscle	TBS intensity	Effect on MEP size (duration)
Huang et al., 2005 [4]	N = 9		$cTBS_{300}$	FDI	80% AMT	↓ (~20 min)
	N = 9	33.6 ± 7.8[a]	$cTBS_{600}$			↓ (~60 min)
	N = 9		$iTBS_{600}$			↑ (~15 min)
Edwards et al., 2006 [22]	N = 10 (7/3)	43	$cTBS_{300}$	FDI	80% AMT	↓ (~20 min)
Martin et al., 2006 [23]	N = 8	30.6 ± 8.2	$cTBS_{600}$	FDI	80% AMT	↓ (≥30 min)
Ishikawa et al., 2007 [17]	N = 12 (10/2)	42.3 ± 6.9	$cTBS_{600}$	FDI	80% AMT	↓ (~40 min)
Talelli et al., 2007 [24]	N = 10	29.6 ± 3.9[a]	$cTBS_{300}$	FDI	80% AMT	↓ (~15 min)
	N = 6		$iTBS_{600}$			↑ (~20 min)
Gentner et al., 2008 [25]	N = 16	26.6 ± 7.4[a]	$cTBS_{300}$	APB	70% RMT	↑ (≥25 min)
	N = 9		$cTBS_{600}$			↓ (~15 min)
Huang et al., 2008 [11]	N = 9 (6/3)	31 ± 8	$cTBS_{300}$	FDI	80% AMT	↓ (~20 min)
	N = 7 (5/2)	32 ± 6	$iTBS_{600}$			↑ (~20 min)
Iezzi et al., 2008 [26]	N = 10 (6/4)	35 ± 3	$cTBS_{300}$	FDI	80% AMT	↓ (≥30 min)
	N = 10 (6/4)	35 ± 3	$iTBS_{600}$			↑ (≥30 min)
Murakami et al., 2008 [27]	N = 6	27.1 ± 4.8[a]	$cTBS_{600}$	FDI	80% AMT	↓ (≥35 min)
	N = 6		$iTBS_{600}$			↑ (~15 min)
Stefan et al., 2008 [12]	N = 7	25.7 ± 5.6[a]	$cTBS_{300}$	APB	70% RMT	↓
	N = 10		$cTBS_{600}$			↓ (≥35 min)
Suppa et al., 2008 [13]	N = 15	31 ± 5[a]	$cTBS_{600}$	FDI	80% AMT	↓ (~15 min)
	N = 15		$iTBS_{600}$			↑ (≥30 min)
Zafar et al., 2008 [28]	N = 9 (4/5)	21.3	$cTBS_{600}$	ADM	80% AMT	↓
	N = 9 (4/5)	21.3	$iTBS_{600}$			↑
Huang et al., 2009 [29]	N = 8 (3/5)	35 ± 14	$cTBS_{300}$	FDI	80% AMT	↓ (~25 min)
Ortu et al., 2009 [30]	N = 7 (7/0)	29.6 ± 4.2	$cTBS_{600}$	OP	80% AMT	↓ (≥30 min)
Todd et al., 2009 [31]	N = 28 (12/16)[b]	25.6 ± 8.6[b]	$cTBS_{600}$ (3×)	FDI	80% AMT	↓
	N = 8 (4/4)	27 ± 10	$iTBS_{600}$			↑
Gamboa et al., 2010 [32]	N = 14 (7/7)	Between 21 and 27	$cTBS_{600}$	FDI	80% AMT	↓ (~50 min)
	N = 14 (7/7)	Between 21 and 27	$iTBS_{600}$			↑ (~50 min)
Huang et al., 2010 [33]	N = 15 (7/8)[b]	30.5 ± 3.6[b]	$cTBS_{300}$ (2×)	FDI	80% AMT	↓ (~20 min)
	N = 16 (4/12)[b]	32.7 ± 7.1[b]	$iTBS_{600}$ (2×)			↑ (≥20 min)
Iezzi et al., 2010 [34]	N = 11 (9/2)	30 ± 5.2	$cTBS_{600}$	FDI	80% AMT	↓
Oberman et al., 2010 [35]	N = 5 (2/3)	38.6 ± 13.8	$cTBS_{600}$	FDI	80% AMT	↓ (~30 min)
	N = 5 (2/3)	38.6 ± 13.8	$iTBS_{600}$			↑ (~30 min)
Orth et al., 2010 [36]	N = 14 (5/9)	42.4	$cTBS_{300}$	FDI	80% AMT	↓ (~20 min)
Di Lazzaro et al., 2011 [37]	N = 10	26.6 ± 4.1	$cTBS_{600}$	FDI	80% AMT	↓ (<30 min)
	N = 10	26.6 ± 4.1	$iTBS_{600}$			↑ (<30 min)
Doeltgen et al., 2011 [38]	N = 16 (8/8)	25.2 ± 3.5	$cTBS_{300}$	FDI	70% RMT	↑ (≥30 min)
Doeltgen et al., 2011 [39]	N = 14 (4/10)	24.5 ± 3.1	$cTBS_{600}$	FDI	80% AMT	↓ (~20 min)
	N = 14 (4/10)	24.5 ± 3.1	$iTBS_{600}$			↑ (≥30 min)
Freitas et al., 2011 [40] [c]	N = 36	Between 19 and 81	$cTBS_{600}$	FDI	80% AMT	↓
Gamboa et al., 2011 [41]	N = 12 (6/6)	24.6 ± 1.97	$cTBS_{600}$	FDI	80% AMT	↓ (~50 min)
	N = 10 (7/3)	24.7 ± 1.39	$iTBS_{600}$			↑ (~50 min)
Iezzi et al., 2011 [42]	N = 10 (6/4)	32 ± 5.0	$cTBS_{600}$	FDI	80% AMT	↓ (≥30 min)
	N = 10 (6/4)	32 ± 5.0	$iTBS_{600}$			↑ (≥30 min)
Suppa et al., 2011 [43]	N = 14 (11/3)	60 ± 11.3	$iTBS_{600}$	FDI	80% AMT	↑ (≥30 min)
Suppa et al., 2011 [44]	N = 12 (7/5)	30 ± 4.9	$cTBS_{600}$	FDI	80% AMT	↓ (≥30 min)
	N = 12 (7/5)	30 ± 4.9	$iTBS_{600}$			↑ (≥30 min)
Conte et al., 2012 [45]	N = 15	~68[d]	$cTBS_{600}$	FDI	80% AMT	↓ (≥30 min)
	N = 15	~68[d]	$iTBS_{600}$			↑ (≥30 min)
Doeltgen et al., 2012 [46]	N = 17 (7/10)	23.1 ± 5.1	$cTBS_{600}$	FDI	80% AMT	↓ (~45 min)
Goldsworthy et al., 2012 [47]	N = 12 (5/7)	26.3 ± 2.3	$cTBS_{600}$	FDI	80% AMT	–
Goldsworthy et al., 2012 [48]	N = 12 (6/6)	23.7 ± 8.1	$cTBS_{600}$	FDI	80% AMT	↓ (~5 min)
Kishore et al., 2012 [49]	N = 10	~53.5[d]	$cTBS_{600}$	FDI	80% AMT	↓ (~20 min)
	N = 10	~51.4[d]	$iTBS_{600}$			↑ (~20 min)
Kishore et al., 2012 [50]	N = 10	n/a	$cTBS_{600}$	FDI	80% AMT	↓ (≥20 min)
	N = 10	n/a	$iTBS_{600}$			↑ (≥20 min)
Koch et al., 2012 [51]	N = 14	n/a	$cTBS_{600}$	FDI	80% AMT	↓ (≥30 min)
	N = 14	n/a	$iTBS_{600}$			↑ (≥30 min)
Murakami et al., 2012 [52]	N = 9 (7/2)	29.2 ± 6.9	$cTBS_{600}$	FDI	80% AMT	–
	N = 9 (7/2)	29.2 ± 6.9	$iTBS_{600}$			–
Oberman et al., 2012 [53] [c]	N = 35 (30/5)	38.1 ± 12.4	$cTBS_{600}$	FDI	80% AMT	↓ (~30 min)
	N = 24 (21/3)	42.0 ± 11.1	$iTBS_{600}$			↑ (~30 min)
Player et al., 2012 [54]	N = 16 (9/7)	n/a	$iTBS_{600}$	FDI	80% AMT	–
Riek et al., 2012 [55]	N = 8	n/a	$cTBS_{300}$	FDI	80% AMT	↓ (~30 min)
Wu et al., 2012 [56]	N = 11	~27.6[d]	$iTBS_{600}$	FDI	80% AMT	↑ (≥10 min)
Zamir et al., 2012 [57]	N = 10 (4/6)	63.1 ± 8.8	$iTBS_{600}$	FDI	80% AMT	↑ (≥60 min)
Belvisi et al., 2013 [58]	N = 14 (11/3)	41.9 ± 11.4	$iTBS_{600}$	FDI	80% AMT	↑ (≥30 min)
Cardenas-Morales et al., 2013 [59]	N = 12 (7/5)	39 ± 11	$iTBS_{600}$	APB	70% RMT	↑ (~15 min)
Hamada et al., 2013 [60]	N = 52	30.3 ± 7.4	$cTBS_{600}$	FDI	80% AMT	–
	N = 52		$iTBS_{600}$			–
Mori et al., 2013 [61]	N = 13 (8/5)	35.5 ± 9.2	$cTBS_{600}$	FDI	80% AMT	↓ (≥15 min)
	N = 13 (8/5)	35.5 ± 9.2	$iTBS_{600}$			↑ (≥15 min)
Munneke et al., 2013 [62]	N = 10 (10/0)	49.0 ± 3.6	$cTBS_{600}$	APB	70% RMT	↓