

# A Review of Combined TMS-EEG Studies to Characterize Lasting Effects of Repetitive TMS and Assess Their Usefulness in Cognitive and Clinical Neuroscience

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**Abstract** Transcranial magnetic stimulation (TMS) has developed into a powerful tool for studying human brain physiology and brain–behavior relations. When applied in sessions of repeated stimulation, TMS can lead to changes in neuronal activity/excitability that outlast the stimulation itself. Such aftereffects are at the heart of the offline TMS protocols in cognitive neuroscience and neurotherapeutics. However, whether these aftereffects are of applied interest critically depends on their magnitude and duration, which should fall within an experimentally or clinically useful range without increasing risks and adverse effects. In this short review, we survey combined TMS-EEG studies to characterize the TMS-aftereffects as revealed by EEG to contribute to the characterization of the most effective and promising repetitive TMS-parameters. With one session of conventional repetitive TMS (of fixed pulse frequency), aftereffects were consistently comparable in magnitude to EEG-changes reported after learning or with fatigue, and were short-lived (<70 min). The few studies using recently developed protocols (such as theta burst stimulation) suggest comparable effect-size but longer effect-durations. Based on the reviewed data, it is expected that TMS-efficacy can be further promoted by repeating TMS-sessions, by using

EEG-gated TMS to tailor TMS to current neuronal state, or by other, non-conventional TMS-protocols. Newly emerging developments in offline TMS research for cognitive neuroscience and neurotherapeutics are outlined.

**Keywords** Transcranial magnetic stimulation · Electroencephalography · Aftereffects · Repetitive TMS · Safety

## Introduction

Transcranial magnetic stimulation (TMS) is increasingly used for noninvasive stimulation of the human brain in healthy participants and patients to study brain–behavior relations, the pathophysiology of diseases, and the potential of neuromodulation for rehabilitation and therapy (e.g. Walsh and Cowey 2000; Kobayashi and Pascual-Leone 2003; Rossi and Rossini 2004; Ridding and Rothwell 2007; Fregni and Pascual-Leone 2007; Hallett 2007). TMS can be applied as one stimulus at a time (single pulse), as trains of stimuli delivered at a fixed frequency (conventional repetitive TMS, usually in the range of 1–20 Hz), or in more complex trains combining different frequencies, such as for example 50 Hz pulse-trains repeated at a rate of 5 Hz, termed theta burst stimulation (TBS) (Huang et al. 2005). In repeated paired associative stimulation (PAS) (Classen et al. 2004), repetitive median nerve stimulation at very low frequencies (e.g. 0.1 Hz) is combined with concurrent contralateral post-rolandic TMS. Provided safety guidelines are met (Wassermann 1998; Rossi et al. 2009), TMS is considered safe in humans as shown through comprehensive surveys of potential adverse effects and

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complications (Chen et al. 1997; Wassermann 1998; Machii et al. 2006; Bae et al. 2007; Rossi et al. 2009).

An important aspect of TMS is that the effects of each single pulse or single-train can summate with repeated application, leading to effects outlasting a stimulation session (Robertson et al. 2003; Rossi and Rossini 2004; Ridding and Rothwell 2007; Hallett 2007). This has been termed the offline repetitive TMS (rTMS) approach, which is used to transiently modulate brain function in healthy participants beyond TMS to probe for the implication of the stimulated area (or network) in perception and cognition (e.g. Robertson et al. 2003), or with the aim of modifying brain activity over longer time-scales in patients with specific neurological disorders for therapeutic intent (e.g. Kobayashi and Pascual-Leone 2003; Rossi and Rossini 2004; Fregni and Pascual-Leone 2007; Hallett 2007). However, while many studies have used these protocols with the above-mentioned aims, little is known on the magnitude and duration of the induced changes broken down according to the parameter space of offline rTMS-protocols. Because TMS can transiently induce as well as interfere with electrical brain activity (reviews in Komssi and Kähkönen 2006; Miniussi and Thut 2009; Taylor et al. 2008), surveying combined TMS-EEG studies for TMS-induced aftereffects can provide useful information here. In particular, EEG-activity is likely to be a more sensitive measure for evaluating TMS-impact on brain function than behavioral effects, given that on several instances robust TMS-aftereffects in EEG-activity have been reported without a behavioral correlate, when both EEG and behavior have been co-examined (e.g. Rossi et al. 2000; Hansenne et al. 2004; Holler et al. 2006; Ortu et al. 2009). In analogy, TMS-aftereffects in electromyographic (EMG) measures of motor cortex excitability have been observed in the absence of apparent changes in amplitude or velocity of voluntary movements (e.g. Muellbacher et al. 2000). While it is sensible to base the design of TMS experiments on observable behavioral manifestations, it is therefore also of interest to interrogate potentially more sensitive physiological changes to assess the impact of TMS.

This review focuses on TMS-aftereffects on EEG-activity in repeated TMS designs. In surveying combined TMS-EEG research, we shall address the following questions: (1) Which rTMS parameters evoke the most reliable aftereffects in terms of magnitude and direction of changes in EEG/evoked potentials (EPs)? Is the effect-size in the order of physiological changes, such as those observed after learning or fatigue, or does it markedly exceed the normal range? (2) Which rTMS parameters do evoke the most long-lasting effect? The results are discussed in terms of future developments for boosting the efficacy and utility of rTMS protocols.

## Methods

### Literature Review

Using Pubmed and the references from relevant articles, we identified more than 100 TMS-EEG studies in >1000 participants that have been published over the last 20 years (Jan 1989–May 2009). Inclusion criterion for review was quantification of aftereffects in EEG activity/Evoked Potentials (EPs) after rTMS delivery.

We reviewed all reports and noted (i) article references, (ii) total number of participants and population (i.e. healthy or patients), (iii) TMS parameters (including number of trains, train-duration, intertrain interval, stimulation site and intensity, number of applied pulses), (iv) EEG-measures, (v) timing of EEG-recordings relative to TMS (before, during or after), (vi) presence or absence of aftereffects (and their nature), (vii) aftereffect size (percent change relative to pre-TMS or sham control) and (viii) duration of aftereffects on EEG (when assessed). See Table 2.

### Review-Sample

The reviewed study sample ( $n = 51$  experiments in  $\sim 650$  participants with the majority being healthy volunteers) represents approximately 40% of all TMS-EEG studies identified during the reviewed period.

The remainder of the TMS-EEG studies (other 60%) consisted of single-pulse TMS experiments studying the TMS-evoked electrical activity and its spreading immediately after stimulation ( $<1$  s) in the absence of pulse-effect summation, or of rTMS experiments that inspected background EEG for TMS-induced epileptiform activity for safety evaluation (for a detailed review of this aspect see Rossi et al. 2009).

All reviewed studies either used TMS protocols with repeated pulse administration at fixed pulse repetition frequencies (conventional rTMS protocols) or the protocols of TBS (Huang et al. 2005) or PAS (Classen et al. 2004). Within the conventional protocols, only a discrete number of frequencies were tested (0.9–1 Hz:  $n = 17$ , 5 Hz:  $n = 6$ , 10 Hz:  $n = 8$ , 20 Hz:  $n = 4$ , 25 Hz:  $n = 1$ ) often in association with varying number of trains, train-duration, intertrain interval, and TMS-intensities across studies, leading to a large number of employed parameter-combinations (see tables). Three studies used very low frequencies of 0.6 Hz (Van Der Werf and Paus 2006) and 0.2 Hz (Urushihara et al. 2006; Hosono et al. 2008) and are discussed separately where of interest. To reduce this parameters space, we collapse for our analysis across low-frequency (0.9–1 Hz) versus high-frequency (5 Hz and above) protocols. This grouping seems reasonable also

because previous studies on motor cortex excitability have reported these two protocols to differ in terms of aftereffect-direction (suppression vs. facilitation) (e.g. reviewed in Hallett 2007). Note that no TMS-EEG study has looked at aftereffects of conventional TMS in the frequency-range between 1 and 5 Hz, where the reversal of effect-direction is to be expected. In regards to TBS and PAS, employed parameters were more uniform across studies.

Table 1 provides a summary of TMS parameters broken down by TMS-protocols (average and range over studies/experiments). The figures and Table 2 depict the results per individual study/experiment.

## Results

### TMS-Induced Aftereffects in EEG: Affected EEG/EP-Measures

Aftereffects were observed on a variety of measures including somatosensory, visual, cognitive and motor potentials as well as oscillatory activity (Table 2). In general, TMS affected a specific component of the potentials depending on site of stimulation, e.g. C1 after occipital pole stimulation (Schutter and van Honk 2003), distinct SEP-components after stimulation of sensory/motor cortices (e.g. Katayama and Rothwell 2007; Ishikawa et al. 2007; Restuccia et al. 2007), P300 after prefrontal stimulation (e.g. Evers et al. 2001; Hansenne et al. 2004; Jing et al. 2001a), or the negative slope of the motor readiness potential after M1-stimulation (Rossi et al. 2000; Ortu et al. 2009). With respect to oscillatory activity, rolandic alpha- and beta-oscillations were frequently affected after sensory or motor cortex stimulation, both regarding movement-related changes (e.g. Strens et al. 2002; Tamura et al. 2005) as well as background activity at rest (Fuggetta et al. 2008; Brignani et al. 2008) (see also Table 2). Overall, the topography of the aftereffects in dependence of stimulation site is consistent with the expected generators and functional roles of the affected EPs or oscillatory components.

### Direction and Size of TMS-Induced Aftereffects

The results in regards to effect-direction (sign thereof) are illustrated in Fig. 1b for each study that observed TMS effects. Figure 1c depicts the associated effect-size (percent change relative to pre-TMS or sham) when reported or quantifiable post hoc (multiplied by effect-direction). The figures point towards a systematic difference across protocols in regards to effect-direction. Note for example in Fig. 1b, c the predominantly negative effect-direction (aftereffect of suppressive or inhibitory nature) after

**Table 1** TMS parameters, aftereffect-size and aftereffect-duration broken down according to TMS protocols

Protocol	Total N subjects	Mean total N of pulse	Mean N of pulses per train	Mean train-duration	Mean N of trains	Mean intertrain interval	Mean intensity	Mean effect-size	Mean effect-duration (time until recovery)
Conventional Low-F: 0.9–1 Hz	N = 177	n = 882 (200–1500)	n = 882 (200–1500)	15 min (3.3–25 min)	n = 1	–	101%MT (80–130%MT)	31% (n = 11: 10–82%)	31 min (n = 8: 15–70 min)
Conventional High-F: 5–25 Hz	N = 251	n = 704 (24–2000)	n = 60 (20–300)	9 s (2–60 s)	n = 17 (1–100)	102 s (5–300 s)	96%MT (80–110%MT)	30% (n = 11: 10–60%)	28 min (n = 3: 25–30 min)
cTBS	N = 55	n = 600 (600–600)	n = 600 (600–600)	39 s (33–40 s)	n = 1	–	80%MT (80–80%MT)	35% (n = 5: 15–50%)	70 min (n = 3: 60–90 min)
iTBS	N = 35	n = 600 (600–600)	n = 30.3 (30–31)	2 s (2–2 s)	n = 19.5 (19–20)	8 s (8–8 s)	80%MT (80–80%MT)	17.5% (n = 2: 15–20%)	no data
PAS	N = 92	n = 150 (90–180)	–	–	–	–	128%MT (105–150%MT)	22.5% (n = 3: 10–50%)	40 min (n = 2: 20–60 min)

Values represent means or ranges (minimum–maximum)

**Table 2** Quantified EEG changes after repeated TMS pulses

Authors	Subjects	TMS-parameters	EEG-measures	Timing of EEG	Aftereffects	Duration of aftereffects
Urushihara et al. (2006)	<i>N</i> = 9 healthy	0.2 Hz/21 min of monophasic M1,PM,SMA/85%rMT/250p	SEP-amplitude	Before and after TMS	Yes: ~55% facilitation after PM-stim	Not assessed
Hosono et al. (2008)	<i>N</i> = 13 healthy	0.2 Hz/20 min/mono- vs. biphasic PM,sham/85%rMT/250p	SEP-amplitude	Before and after TMS	Yes: ~30–40% facilitation for mono-but no effect for bi-phasic	At least 10 min but recovered after 30 min
Van Der Werf and Paus (2006)	<i>N</i> = 12 healthy	0.6 Hz/15 min M1,PM/90%rMT/540p	TMS-induced response	Before and after TMS	Yes: ~60% amplitude decrease, reduction in induced activity (theta)	At least 40 min not studied longer
Satow et al. (2003)	<i>N</i> = 8 healthy	0.9 Hz/16.6 min S1/90%rMT/900p	SEP-amplitude	Before and after rTMS	No	n.a.
Rollnik et al. (2004)	<i>N</i> = 11 healthy	0.9 Hz/15–20 × 60 s trains frontal/90%MT	Error-related negativity	After TMS	Yes: attenuation of ERN	At least 3 min not studied longer
Chen et al. (2003)	<i>N</i> = 8 healthy	0.9 Hz/15 min PM/90%aMT/818p	Movement-related power/coherence (task)	Before and after TMS	Yes: less task-related alpha/beta decrease coherence increase (alpha)	Up to 15 min recovered after 30 min
Enomoto et al. (2001)	<i>N</i> = 7 healthy	1 Hz/3.3 min PM, M1,S1/110%aMT/200p	SEP-amplitude	Before and after rTMS	Yes: ~40% suppression with M1 but not PM or S1	Up to 60 min recovered after 70 min
Restuccia et al. (2007)	<i>N</i> = 8 healthy	1 Hz/20 min S1/sham/80%MT/1200p	Early/late HF-SEPs	Before and after TMS	Yes: ~18/26% facilit./suppress. after S1 relative to sham	Up to 15 min recovered after 20 min
Bohotin et al. (2002)	<i>N</i> = 24 healthy	1 Hz/15 min occipital/100%PT/900p	VEP-amplitude & habituation	Before and after TMS	Yes: ~15% suppression in controls	Up to 15–30 min
Fumal et al. (2003)	<i>N</i> = 24 healthy	1 Hz/15 min occipital/100%PT/900p	VEP-amplitude & habituation	Before and after TMS	Yes: ~15% suppression	Up to 33 min recovery after 40 min
Schutter and van Honk (2003)	<i>N</i> = 8 healthy	1 Hz/20 min occipital/110%MT/1200p	VEP-amplitude	After TMS and sham	Yes: ~55% suppression	Not assessed
Thut et al. (2003)	<i>N</i> = 6 healthy	1 Hz/10 min Occipital/110%PT/600p	VEP-amplitude alpha-changes	Before and after TMS	Yes: ~40% suppression of desynchronization (alpha)	At least 8 min recovered after 20 min
Evers et al. (2001)	<i>N</i> = 14 healthy	1 Hz/2 min DLPFC/95%MT/120p	Visual P300	Before and after TMS	No	n.a.
Hansenne et al. (2004)	<i>N</i> = 17 healthy	1 Hz/10 and 15 min DLPFC/100%MT/600–900p	Auditory P300	Before and after TMS	Yes/No: latency increase after 15 min but not 10 min rTMS	Not assessed
Rossi et al. (2000)	<i>N</i> = 5 healthy	1 Hz/15 min M1/110%MT/900p	Readiness potential	After TMS and Sham	Yes: ~30% focal amplitude decrease	Not assessed
Strens et al. (2002)	<i>N</i> = 15 healthy	1 Hz/25 min M1/90%aMT/1500p	Spectral power coherence (rest and task)	Before and after TMS	Yes: ~15% focal increase in coherence (alpha)	Up to 25 min recovered after 30 min
Tamura et al. (2005)	<i>N</i> = 12 healthy	1 Hz/10 min M1/95%rMT/600p	Movement-related oscillations	Control and after TMS	Yes: ~10% decrease in synchronization (beta)	Not assessed

Table 2 continued

Authors	Subjects	TMS-parameters	EEG-measures	Timing of EEG	Aftereffects	Duration of aftereffects
Brignani et al. (2008)	<i>N</i> = 6 healthy	1 Hz/10 min M1/110%MT/600p	EEG power (rest)	During TMS	Yes: max 82% focal, cumulative increase in power (alpha)	Not assessed
Pastor et al. (2006)	<i>N</i> = 6 healthy	1 Hz/10 min Cerebellum/60% max/600p	Steady-state potentials	Before and after TMS	Yes: change in prefrontal oscillations (gamma)	At least 7.5 min not studied longer
Schutter et al. (2001)	<i>N</i> = 12 healthy	1 Hz/20 min DLPFC/130%MT/1200p	Spectral power (rest)	After TMS and sham	Yes: increase in prefrontal power (theta)	At least 1 h not studied longer
Ragert et al. (2004)	<i>N</i> = 13 healthy	5 Hz/5 × 5 × 10 s: 5 s ITI S1/90%MT/250p	Paired pulse SEP-inhibition	Before and after TMS	Yes: suppression of inhibition with ipsilateral S1	At least 1 h not studied longer
Holler et al. (2006)	<i>N</i> = 8 healthy	5 Hz/5 × 60 s train: 60 s ITI M1/90%MT/1500p	Anticipatory CNV	Before and after TMS/sham	Yes: focal amplitude increase	Not assessed
Oliviero et al. (2003)	<i>N</i> = 16 healthy	5 Hz/10 s single train M1/100%aMT/50p	Spectral power coherence (rest and task)	Before and after TMS	Yes: ~25% focal coherence decrease (alpha)	Immediately after TMS recovered after 25 min
Fuggetta et al. (2008)	<i>N</i> = 11 healthy	5 Hz/20 × 4 s trains: 30 s ITI M1/80–100%MT/400p	EEG power and coherence (rest)	During TMS	Yes: ~30–40% focal incr/decr in alpha and beta power/coherence	Not assessed
Huber et al. (2007)	<i>N</i> = 10 healthy	5 Hz/5 × 6 × 10 s train: 5 s ITI M1/90%rMT/1500p	Sleep EEG	After TMS and sham	Yes: ~40% local increase in slow wave activity	Up to 30 min of nREM recovered after 31 min
Esser et al. (2006)	<i>N</i> = 7 healthy	5 Hz/5 × 6 × 10 s train: 5 s ITI M1/90%rMT/1500p	TMS-induced response	Before and after rTMS	Yes: ~60% amplitude increase	At least 10 min not studied longer
Restuccia et al. (2007)	<i>N</i> = 8 healthy	10 Hz/12 × 10 s trains: 20 s ITI S1/sham/80%MT/1200p	Early/late HF-SEPs	Before and after TMS	Yes: ~-14% –facilit. after S1 relative to sham	At least 20 min
Bohotin et al. (2002)	<i>N</i> = 30 Migraine	10 Hz/18 × 5 s trains: 10 s ITI occipital/100%PT/900p	VEP-amplitude & habituation	Before and after TMS	Yes: ~15% facilitation in migraineurs	Up to 9–30 min
Jing et al. (2001b)	<i>N</i> = 15 healthy	10 Hz/2 × 3 s train: 5 min ITI DLPFC/100%MT/60p	Auditory P300	Before and after TMS	Yes: ~15–25% decrease in N100-amplitude, changes in P200/P300-latencies	Not assessed
Jing et al. (2001a)	<i>N</i> = 29 healthy	10 Hz/2 × 3 s train: 5 min ITI DLPFC/100%MT/60p	Auditory P300	Before and after TMS	Yes: latency-increase	Not assessed
Griškova et al. (2007)	<i>N</i> = 18 healthy	10 Hz/100 × 2 s train: 10 s ITI DLPFC/110%MT/2000p	Spectral power (rest)	Before and after TMS	Yes: ~400% increase in delta-power	At least 10 min, not studied longer
Okamura et al. (2001)	<i>N</i> = 32 healthy	10 Hz/2 × 3 s train: 300 s ITI Frontal/100%MT/60p	Spectral power (rest)	Before and after TMS	Yes: change in peak frequency and power (~10%, many frequencies)	At least 5 min not studied longer
Jing and Takigawa (2000)	<i>N</i> = 19 healthy	10 Hz/2 × 3 s train: 5 min ITI DLPFC/100%MT/60p	Coherence (rest)	Before and after TMS	Yes: max 32% focal directed coherence increase (alpha)	At least 5 min not studied longer
Klimesch et al. (2003)	<i>N</i> = 16 healthy	High frequency/IAF-20 Hz 1.2–4.8 s trains: >12 s ITI parietal,frontal/110%MT/24p	Band power and event-related desynchronization	Before and after TMS	Yes: ~40% increase of desynchronization (alpha)	Not assessed
Evers et al. (2001)	<i>N</i> = 14 healthy	20 Hz/3 × 5 s train: 1 min ITI DLPFC/95%MT/300p	Visual P300	Before and after TMS	Yes: latency-decrease	Not assessed

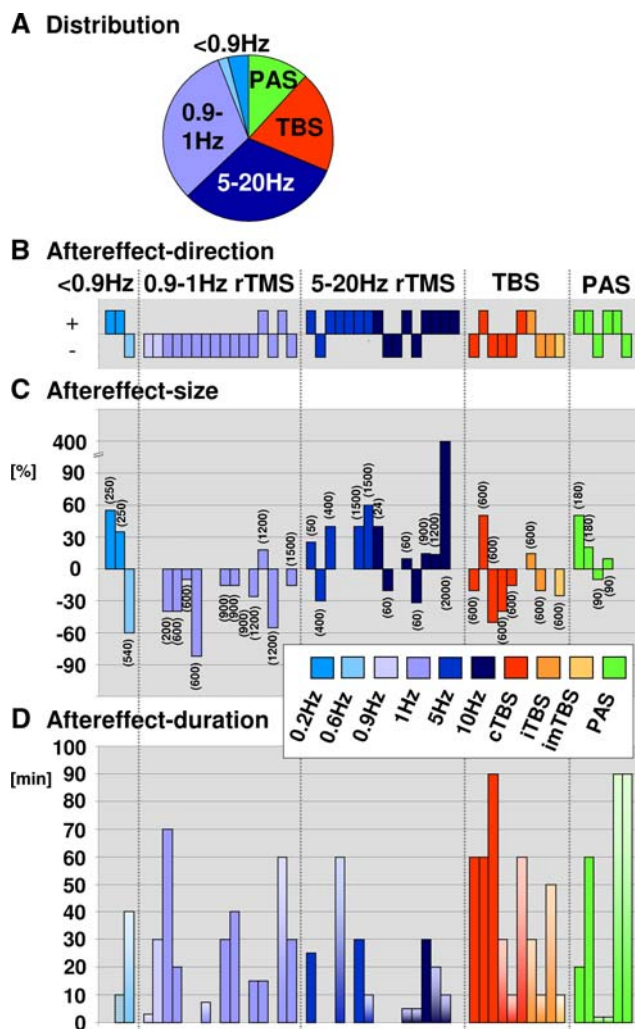
Table 2 continued

Authors	Subjects	TMS-parameters	EEG-measures	Timing of EEG	Aftereffects	Duration of aftereffects
Graf et al. (2001)	N = 8 healthy	20 Hz/40 × 2 s train: 28 s ITI DLPFC/90%MT/1600p	Sleep EEG	Before and after TMS	Yes: minor reduction in sleep stage 1	Not assessed
Cohrs et al. (1998)	N = 13 healthy	20 Hz/160 × 0.25 s: 8 s ITI DLPFC/120%rMT/800p	Sleep EEG	After TMS and sham	Yes: delay in REM-latency prolonged nREM-REM cycle	Not assessed
Schutter et al. (2003)	N = 5 healthy	25 Hz/80 × 10 s train: 5 s ITI Cerebellum/80%MT/2000p	Spectral power (rest)	Before and after TMS	Yes: change in prefrontal asymmetry (gamma)	At least 15 min not studied longer
Ishikawa et al. (2007)	N = 12 healthy	cThetaBS/40 s M1,S1/80%aMT/600p	SEP-amplitude	Before and after TMS	Yes: ~20% suppression with S1 vs. ~50% facilitation with M1	Up to 53 min recovered after 60 min
Sağlam et al. (2008)	N = 8 healthy	cThetaBS/40 s M1,S1/80%aMT/600p	EEG-EMG-coherence	Before and after TMS	Yes: ~50% suppression with M1 but not S1	Up to 30–60 min recovered after 90 min
Schindler et al. (2008)	N = 4 healthy	cThetaBS/33 s right FEF/80%rMT/600p	Spectral analysis (rest)	Before and after TMS	Yes: ~enhanced synchronization in stimulated hemisphere	At least 60 min not studied longer
Ortu et al. (2009)	N = 7 healthy	cThetaBS/40 s M1,PM/80%aMT/600p	Readiness potential	Before and after TMS	Yes: ~30–50% suppression with left M1 but not right M1 nor PM	At least 30 min not studied longer
Grossheinrich et al. (2009)	N = 12 healthy	cThetaBS/40 s DLPFC,mPFC/80%rMT/600p imThetaBS as sham	Spectral analysis (rest)	Before and after TMS	No	n.a.
Poreisz et al. (2008)	N = 12 healthy	iThetaBS/20 × 2 s: 8 s ITI imThetaBS as sham	Spectral analysis	Before and after TMS	Yes: alpha-power enhancement after DLPFC	Up to 50 min not studied longer
		cThetaBS/40 s S1,Sham/80%aMT/600p	Laser-evoked potential	Before and after TMS	Yes: ~15% suppression of N2	Up to 8–10 min not studied longer
		iThetaBS/20 × 2 s: 8 s ITI S1,Sham/80%aMT/600p	Laser-evoked potential	Before and after TMS	Yes: ~20% suppression of N2	Up to 8–10 min not studied longer
		imThetaBS/8 × 5 s: 10 s ITI S1,Sham/80%aMT/600p	Laser-evoked potential	Before and after TMS	Yes: ~25% suppression of N2	Up to 8–10 min not studied longer
Katayama and Rothwell (2007)	N = 11 healthy	iThetaBS/19 × 2 s: 8 s ITI M1,S1/80%aMT/600p	SEP-amplitude	Before and after TMS	Yes: ~10–20% facilitation with S1 but not M1	Up to 30 min not studied longer
Tsuji and Rothwell (2002)	N = 9 healthy	PAS, 30 min M1/105%rMT/180p	SEP-amplitude	Before and after TMS	Yes: ~40–60% facilitation	Up to 10 min recovered after 20 min
Wolters et al. (2005)	N = 64 healthy	PAS, 30 min M1,S1/150%rMT/180p	SEP-amplitude	Before and after TMS	Yes: ~15–20% facilitation with S1 but not M1	Up to 30 min recovered after 60 min
Huber et al. (2008)	N = 19 healthy	PAS, 22.5 min M1/130%rMT/90p	TMS-induced response	Before and after TMS	Yes: ~10% facilitation or 10% inhibition depending on ISI	At least 2 min not studied longer
			Slow wave activity (sleep)	After TMS	Yes: correlation with change in TMS-induced response	At least 90 min not studied longer

Studies ordered according to protocols and EEG-measure

*TMS-parameters:* iThetaBS: intermittent Theta Burst Stimulation; cThetaBS: continuous Theta Burst Stimulation, PAS: repeated paired associative stimulation; ITI: inter-train interval; aMT: active motor threshold; rMT: resting motor threshold; PT: phosphene threshold; p: pulses; IAF: individual alpha frequency; *Stimulation sites:* DLPFC: dorsolateral prefrontal cortex, PM: premotor; *EEG-measures:* SEP: somatosensory evoked potential; HF-SEP: high-frequency SEPs





**Fig. 1** Quantification of TMS-aftereffects in EEG/EPs. **a** Distribution of protocols. **b** Aftereffect-direction per study with TMS-effects. Each bar represents one experiment/study. A negative sign (–1) indexes the presence of a suppressive effect on post-TMS relative to pre-TMS or sham EEG/EPs, while a positive sign (+1) indexes facilitative effects. **c** Aftereffect-size (percent change in amplitude relative to pre-TMS or sham) per study reporting effect-size or from which effect-size could be calculated a posteriori ( $n = 37$ ). Data are grouped according to TMS protocols (conventional TMS, TBS, PAS) and ordered according to increasing number of applied pulses (see brackets) within 5 subgroups of rTMS (0.2–0.6 Hz, 0.9–1 Hz, 5–20 Hz, TBS, PAS). **d** Duration of aftereffects across studies having recorded effects until recovery ( $n = 17$ , uniformly colored bars) or having reported timing information but terminated EEG recordings before its normalization ( $n = 21$ , fading color bars)

conventional low-frequency TMS (0.9–1 Hz) and the more frequent positive effect-directions (facilitative effects) after conventional high-frequency TMS (5–20 Hz). In contrast to effect-direction, there was a high variability in effect-size across studies (ranging from  $\sim 10$ –400%, absolute values, Fig. 1c), with however some tendency towards stronger effect-size with increasing number of pulses

(indicated in brackets in Fig. 1c). This is further detailed next for conventional and TBS/PAS protocols separately.

**Conventional Repetitive Protocols:** All but three studies reported significant aftereffects in EEG, either on amplitude (spectral power, EP-components) or latencies (EP-components, sleep stages). The three null-results were observed with low frequency stimulation (0.9, 1 Hz and 1 Hz) and can be accounted for by short stimulation duration in one case (1 Hz for 2 min, Evers et al. 2001). The other two studies with null results (Satow et al. 2003; Hansenne et al. 2004) however do not differ in design (0.9–1 Hz for 10–16.6 min) from studies with significant EEG-changes. Overall, this may suggest that the induction of aftereffects is slightly less likely with low ( $\sim 1$  Hz) than high TMS-frequencies ( $>5$  Hz) when using parameters within the safety-margins. Notable is the report of after-effects in the two studies using very low frequencies of 0.2 Hz (250 pulses, 20 min stimulation) that can be explained by the use of repeated monophasic pulses (Urushihara et al. 2006; Hosono et al. 2008), shown to be more effective than the biphasic pulse form in repetitive designs (Hosono et al. 2008).

When aftereffects were present (both amplitude and latency effects considered), there were systematic differences between low-frequency (0.9 or 1 Hz) and high-frequency protocols (5–25 Hz) in terms of aftereffect direction. Facilitation prevailed over suppression after high-frequency TMS ( $n = 12$  vs.  $n = 4$ ), and suppression prevailed over facilitation after low-frequency TMS ( $n = 14$  vs.  $n = 2$ , Fig. 1b and Table 2). This distribution is significantly different from chance (according to a Chi-square test,  $P = 0.0004$ ; all effects per experiment counted; alpha-band increase/decrease taken as sign for suppression/facilitation). Again, the studies by Urushihara et al. (2006) and Hosono et al. (2008) are noteworthy in that 0.2 Hz-stimulation with monophasic pulses evoked facilitative aftereffects, i.e. an enhancement of EP-amplitude rather than suppression.

In those studies in which percentage change from pre-TMS values or a sham control was reported or could be calculated a posteriori based on the reported data, average size of the absolute TMS-aftereffect on EEG-activity/EPs was in the order of 30% change (only amplitude—but no latency—data considered, see Table 1 and Fig. 1c). Yet, while differences in effect-directions were observed across protocols (see above), there was no such difference in terms of effect-size between low (mean = 31%, range: 10–82%;  $n = 11$  studies) and high-frequency TMS (mean = 30%, range: 10–60%;  $n = 11$  studies), when the only outlier (400% change; Griskova et al. 2007) was discarded.

*Theta Burst (TBS) and Repeated Paired Associative Stimulation (PAS)*: Only a few studies to date have explored EEG aftereffects with these protocols (TBS: Katayama and Rothwell 2007; Ishikawa et al. 2007; Sağlam et al. 2008; Schindler et al. 2008; Poreisz et al. 2008; Ortu et al. 2009; Grossheinrich et al. 2009; PAS: Tsuji and Rothwell 2002; Wolters et al. 2005; Huber et al. 2008). In these studies, both TBS and PAS were associated with significant aftereffects of effect-sizes comparable to those found following conventional rTMS (cTBS: mean = 35%, range: 15–50%,  $n = 6$  studies; iTBS: mean = 17.5%, range: 15–20%,  $n = 3$  studies; PAS: mean = 22.5%, range: 10–50%,  $n = 3$  studies; see also Table 1) and provoked either facilitation or suppression (see also Fig. 1b, c).

#### Duration of TMS-Induced Aftereffects

Duration of EEG aftereffects on EEG-activity/EPs has been explored in a total of 38 experiments, 17 of which recorded EEG/EPs until recovery (Fig. 1d, uniformly colored bars), and with the remainder of the studies ( $n = 21$ ) providing timing information but terminating the recording prior to full EEG normalization (Fig. 1d, fading color bars). The figure is suggestive of no consistent differences in aftereffect-duration across conventional protocols (Fig. 1d, blue bars), but somewhat longer aftereffect duration for TBS and PAS (Fig. 1d, red and green bars), as detailed below.

*Conventional Repetitive Protocols*: Absolute durations until recovery ranged from 15 to 70 min post-TMS. These aftereffect-durations did not differ between low frequency and high-frequency protocols (i.e. 0.9–1 Hz vs. 5–25 Hz rTMS: mean = 31 min vs. 28 min, range: 15–70 min vs. 25–30 min) (see Table 1 for range of employed parameters). No study so far suggests effect duration >70 min (see Fig. 1d).

*Theta Burst (TBS) and Repeated Paired Associative Stimulation (PAS)*: Of the 16 experiments using these protocols, 5 have estimated time of aftereffects until recovery (TBS: mean = 70 min, range: 60–90 min:  $n = 3$ ; PAS: mean = 40 min, range: 20–60 min:  $n = 2$ ). The duration of aftereffects seems overall higher than with conventional rTMS. Some of the studies that did not record until recovery have found aftereffects to persist at 90 min (see Fig. 1d, fading color bars), but this is based on a small number of studies and has to be investigated in more detail in the future.

Note that as compared to conventional protocols, TBS studies used similar number of pulses but considerably shorter duration and lower intensity of stimulation (Table 1) to equate risk (Katayama and Rothwell 2007; Ishikawa et al. 2007).

#### Prediction of Aftereffect-Size by TMS-Parameters

While there was no evidence for aftereffect-size to differ across protocols (see above), aftereffect-size correlated with several TMS-parameters.

*Conventional High-Frequency TMS (5–20 Hz)*: Aftereffect-size depended on number of pulses applied. The effect-size significantly increased with increasing number of pulses (Pearson correlation coefficient:  $r = 6.7$ ,  $P = 0.017$ ,  $n = 12$ ), a correlation that remained significant even when the two extremes in terms of number of pulses ( $n = 24$  pulses: Klimesch et al. 2003,  $n = 2000$  pulses: Griskova et al. 2007) were excluded ( $r = 6.3$ ,  $P = 0.049$ ,  $n = 10$ , see Fig. 2a). For high-frequency TMS, effect-size did also significantly increase with number of trains ( $r = 9.3$ ,  $P < 0.0001$  for  $n = 12$ / $r = 5.87$ ,  $P = 0.075$  for  $n = 10$  without Klimesch et al. 2003 and Griskova et al. 2007, results not illustrated), but did not show a significant relationship with any of the other TMS-parameters assessed (including TMS-intensity).

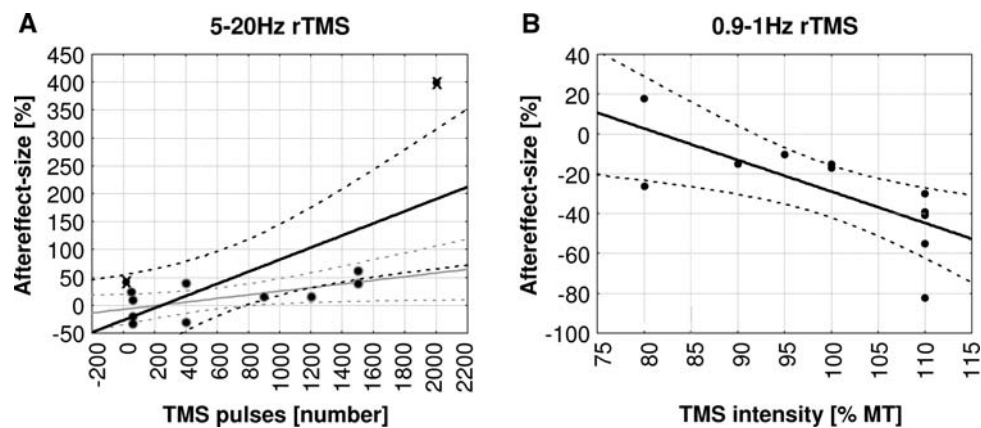
*Conventional Low-Frequency TMS (0.9–1 Hz)*: There was a significant negative relationship between aftereffect-size and TMS-intensity ( $r = -0.72$ ,  $P = 0.013$ ,  $n = 11$ ) indicating stronger suppressive effects with higher intensities (see Fig. 2b), but with no other TMS-parameter. Note that the dissociation of effect-size to correlate with number of pulses in high-frequency and with TMS-intensity in low-frequency applications might partially be explained by unequal variability of these two parameters across protocols. Number of pulses employed across studies was more variable for high- than low-frequency applications (standard deviation: 709 vs. 327;  $n = 12$  vs.  $n = 11$ ). Conversely, intensities employed were more variable for low- than high-frequency TMS (standard deviation: 11 vs. 8;  $n = 12$  vs.  $n = 11$ ).

No correlations between effect-size and TMS-parameters were computed for TBS and PAS due to lack of variance (see Table 1) and we did not find a correlation between effect-duration (time until recovery) and any of the TMS parameters.

#### Discussion

We find the electroencephalographic aftereffects of rTMS to be robust with a mean effect-size of 30–35% change from baseline or sham and a mean duration of 35 min, in addition of being absent in only a very small number of studies. Furthermore, we find the aftereffect direction (suppression vs. facilitation) to depend on the protocol employed. Conventional low-frequency (1 Hz) and high-frequency TMS (5 Hz or above) differed in terms of their suppressive versus facilitative impact on brain activity, in





**Fig. 2** Linear correlations between aftereffect-size [%] and rTMS-parameters. **a** Aftereffect-size as a function of total number of TMS pulses applied in high-frequency protocols (5–20 Hz rTMS). Regression lines and 95% confidence intervals are shown for analyses

line with studies on rTMS-induced changes in human corticospinal motor excitability (e.g. Pascual-Leone et al. 1994; Maeda et al. 2000; Hallett 2007) as well as findings in animal models (Valero-Cabre et al. 2007). Finally, we did not find any evidence for aftereffect-size or aftereffect-duration to differ between the currently used TMS protocols (conventional rTMS, TBS, PAS). However, aftereffect-size did depend on the number of pulses, trains and intensities applied.

#### Aftereffect of a Single TMS-Session on EEG/EPs: Comparison with Other Measures

The observed aftereffect-size in the EEG/EPs after rolandic TMS for instance is in the range of physiological changes observed with motor learning, sustained movements, or muscle fatigue. The TMS-induced, 10–60% changes in SEP-amplitude (Enomoto et al. 2001; Tsuji and Rothwell 2002; Wolters et al. 2005; Katayama and Rothwell 2007; Ishikawa et al. 2007; Restuccia et al. 2007; Table 2) are equivalent to a 35–46% change in SEP-amplitude reported with motor skill acquisition (Nelson et al. 2001). Likewise, the TMS-induced, 10–82% changes in alpha/beta-activity (power/coherence) (Strens et al. 2002; Oliviero et al. 2003; Tamura et al. 2005; Fuggetta et al. 2008; Brignani et al. 2008; Table 2) compare in order of magnitude to changes in alpha/beta-oscillations as a consequence of sustained finger movements (10–40%: Erbil and Ungan 2007) and muscle fatigue (30–35%: Liu et al. 2005). Similarly, the TMS-induced, 30% change in the readiness-potential (RP) (Rossi et al. 2000; Table 2) is comparable to the 100% RP-change due to fatigue (Johnston et al. 2001; Schillings et al. 2006).

The observed aftereffect-duration in the EEG/EPs is furthermore comparable with the TMS-induced aftereffects

including all data points (black lines) and excluding outliers (grey lines, outliers marked by crosses, see also text). **b** Aftereffect-size as a function of TMS intensity applied in low-frequency protocols (0.9–1 Hz)

on corticospinal motor excitability measured via EMG (e.g. Gerschlagler et al. 2001; Münchau et al. 2002; Peinemann et al. 2004). It also matches in order of magnitude the time-course of apparent TMS-induced behavioral changes that have been assessed in studies on cognition (mostly using 1 Hz protocols), and shown to last approximately as long as the duration of the stimulation itself (Robertson et al. 2003). Based on this rule-of-thumb, we can estimate the behavioral aftereffects in the 1 Hz-TMS papers we reviewed (and for which time until recovery was assessed,  $n = 7$ ) to have lasted about 15.5 min (= mean duration of stimulation, see Table 2). This compares to a measured 31 min of EEG-changes.

Overall, the outcome of currently employed repetitive TMS protocols seems thus to lie within the range of physiologic changes (learning, fatigue) and not to outlast the duration of an experiment ( $\sim 1$  h). Within certain limitations (see paragraph below), this contributes to further characterize the safety of repetitive TMS (Rossi et al. 2009), in particular for experiments with healthy volunteers in whom short-lived effects are desirable. However, the effect-duration in the order of a couple of minutes also limits a more versatile use of rTMS in neurotherapeutics. In the following, we will discuss the most promising ways to further prolong effect-duration when desirable, such as in clinical applications. We will also discuss very recent developments that focus on potential short-lived frequency entrainment by a single train, which is of interest for research on brain oscillations.

#### Estimation of rTMS-Aftereffects by EEG/EPs: Possible Limitations

As a cautionary note, we would like to mention that the estimation of effect-direction and effect-size via EEG can

be confounded by several factors. Instances of enhanced EEG/EP-amplitude might not necessarily be the reflection of primarily facilitative aftereffects of the TMS-train, but could reflect a (secondary) mechanism compensating for initial inhibition. Conversely, a reduction of EEG/EP-amplitude could reflect secondary, potentially protective mechanisms against initial facilitation. Indeed, there are some reports of mixed facilitative and suppressive effects within the same experiment (but on different EEG/EP-measures) that have been explained by mechanisms of compensation (e.g. see Thut et al. 2003; Restuccia et al. 2007). Such physiological reactions of the brain to rTMS, possibly masking behavioral effects, might partially explain why EEG can detect changes when behavioral measures fail, as evidenced previously (Rossi et al. 2000; Hansenne et al. 2004; Holler et al. 2006; Ortu et al. 2009). However, it is conceivable that not only behavioral but also EEG changes might be masked by compensatory mechanisms, so that the range of changes detectable by EPs or EEG might be somewhat self-limiting, with EPs and oscillatory activity only disappearing in case of a discrete lesion. Such mechanisms of compensation might then lead to an effect-underestimation also by EEG. The likelihood of this to happen seems however smaller with EEG than with behavioral measures. In addition, the converse argument is also tenable. That is, it is conceivable that the EEG-measured aftereffects following TMS not only reflect the consequence of the direct TMS impact but also capture the rapid adaptation and compensatory responses by non-stimulated brain regions, which would lead to a multiplication rather than self-limitation of effects.

#### TMS-Efficacy: The Effect of Repeating rTMS Sessions

It is important to point out that there are no studies that have measured the duration of TMS-induced EEG-aftereffects following multiple repetitive TMS sessions over consecutive days. It is likely that the magnitude and duration of the EEG aftereffects will change in systematic ways over repeated sessions. Because the impact of rTMS can outlast the TMS-session (consisting of one long train in 1 Hz applications, or of consecutive short trains in high-frequency protocols, see Table 1), it is conceivable that a single TMS sessions, which may initially modify brain physiology without inducing clinically apparent signs, can be expanded into a therapeutically effective protocol through session-repetition at another day. In the same way as single-pulses or single-trains mutually interact when repeated within a session, lasting neurophysiologic effects may condition effects across TMS sessions. Indeed, Maeda et al. (2000) found that the effects of a repetitive TMS session on corticospinal excitability were greater when applied 24 h after an initial session, despite the initial

effect having washed-out by then. Thus, despite the absence of any behavioral or clinical signs, there appeared to be a neurophysiologic trace of the first rTMS session that conditioned the impact of the second session as long as a day later. Such lasting effects and the resulting differential impact of consecutive sessions could have profound relevance for therapeutic applications, where daily sessions of rTMS are applied for 5 and up to 20 consecutive days (Fregni and Pascual-Leone 2007).

#### State-Dependency of TMS-Efficacy

A growing number of studies indicate that the effects of TMS depend on the state of neuronal activation in the targeted brain region at time of stimulation (for review see Silvanto and Pascual-Leone 2008). In human participants, single-pulse TMS has variable impact in evoking phosphene or peripheral muscle responses depending on the pre-TMS level of electrical activity over specific recording sites (Romei et al. 2008a, b; Sauseng et al. 2008; Lepage et al. 2008) or in evoking phosphene attributes depending on the nature of pre-TMS visual adaptation (Silvanto et al. 2007a). Likewise, the effect-size or effect-direction (facilitation versus suppression of excitability) of repetitive TMS can be shaped by prior passive viewing (adaptation) protocol (Silvanto et al. 2007b), or by pre-conditioning the cortex via an rTMS-prime (Iyer et al. 2003), direct current stimulation (Siebner et al. 2004; Lang et al. 2004) or antiepileptic medication (Fregni et al. 2006), i.e. both effect-size and -direction have been shown to depend on the pre-TMS neuronal activation state. In analogy, the response of visual neurons evoked by TMS in cats can be predicted by pre-TMS neuronal activity patterns (Pasley et al. 2009). A better understanding of the neurophysiologic basis of the state-dependency of rTMS-effects is thus likely to provide new ideas how to tailor rTMS-aftereffects in desired directions.

On the one hand, the state of activity in the targeted brain region might be altered by an initial rTMS session, conditioning the outcome of a subsequent session at another day as reviewed above. On the other hand, it is conceivable that individual EEG is carrying useful information for tailoring TMS-effects to fine-tune treatment benefits in patients, given that EEG can be used to infer momentary brain state across time and participants (e.g. Thut et al. 2006; Romei et al. 2008a, b; Sauseng et al. 2008). Future TMS-EEG studies are needed to address this point. The notion of EEG-gated TMS to maximize therapeutic efficacy is appealing. Indeed, it has been shown that the impact of TMS could be maximized when TMS application would be gated by the individually measured alpha or beta rhythm (e.g. Romei et al. 2008a, b; Sauseng et al. 2008; Lepage et al. 2008). Timing the TMS to the

underlying background EEG activity is likely to be critical also for the antiepileptic effects of TMS (see article by Rotenberg et al. in this issue). Therapeutic effects of TMS on depression, hallucinations, pain or stroke recovery might behave similarly.

#### Note on TMS-Efficacy Across Protocols

To date, only a small number of TMS-EEG studies using TBS and PAS are available. Although our review suggests there to be no major differences between conventional TMS and TBS/PAS, the latter two protocols hold more promise than conventional approaches for inducing longer lasting effects with clinical relevance. In fact, based on previous findings that behavioral changes to TBS can last up to 10 h (Nyffeler et al. 2006), longer lasting EEG-aftereffects are to be expected in future theta burst-EEG studies.

#### Interaction of rTMS-Frequency with Ongoing Background Activity

While the TMS-designs of the abovementioned studies with regular pulse and train repetitions do induce aftereffects >10 min on most measures of electrical brain activity (e.g. EP, sleep stages, oscillations), several recent studies have explored the potential of immediate (and likely shorter lasting) frequency entrainment at the rTMS-frequency (for a recent review, see Thut and Miniussi 2009). The question that is raised is whether a conventional, short TMS train (by virtue of its rhythmicity) will entrain background oscillations at the frequency of stimulation, if the train coincides with the neuronal frequency of the targeted brain area. This would contrast with the longer lasting (>10 min) aftereffects on brain oscillations by conventional rTMS reviewed above, which do not seem to be directly related to the stimulation frequency (and thus to be due to entrainment), because spreading to other frequency-bands (see e.g. changes in 10 Hz brain oscillations after 1 Hz-TMS; Brignani et al. 2008; Table 2). In other words, the longer lasting aftereffects seem to reflect changes in oscillatory properties of the stimulated neurons which are secondary to other, rTMS-induced neurophysiologic effects (as opposed to reflect entrainment of brain oscillations to the rhythmic TMS train).

While not much EEG information is available on the potential of rTMS to entrain rhythms, there is new evidence from behavioral studies that entrainment might indeed take place. Transcranial rhythmic stimulation has been shown to alter brain function in a frequency specific manner. For instance, performance in a task requiring visual imagery has been shown to be affected by prior parietal TMS at alpha frequency (10 Hz) (Klimesch et al. 2003). In addition, the restorative effect of sleep (Massimini et al. 2007) as well as

memory consolidation (Marshall et al. 2006) have been shown to be enhanced by nocturnal transcranial rhythmic stimulation at slow wave frequency (<4 Hz). Both effects are in line with these oscillations' suggested respective roles in visual and memory functions (e.g. Klimesch et al. 2003; Massimini et al. 2007, see also Thut and Miniussi 2009). Furthermore, because these effects of rhythmic transcranial stimulation were frequency specific, i.e. not observed with stimulation at other frequencies (Klimesch et al. 2003; Marshall et al. 2006), they are likely to be due to direct rather than secondary effects of the rhythmic trains. This is partially supported by recent findings of a trend for behavioral effects of parietal 10 Hz/alpha rTMS to depend on individual alpha frequency (IAF) (Hamidi et al. *in press*).

Future studies will have to show that the frequency-specific effects on behavior are also accompanied by an enhancement of oscillatory power in the EEG at the rTMS-frequency. If so, conventional short-train rTMS is likely to develop into a powerful tool for research on the functional role and anatomical origin of brain oscillations.

#### Concluding Remarks

Reviewing the literature on TMS-aftereffects in EEG, we found robust effects of 1 h duration or shorter with an effect-size in the range of a physiologic change (learning or fatigue), when current protocols and single sessions are used. The observed time-range and effect-size is suitable for studies in the healthy population, but limits the therapeutic utility of these protocols. Several factors are likely to help prolong these aftereffects when desired, such as repeating sessions over days, taking into consideration pre-TMS neuronal state, and the development of new, non-conventional protocols. Recent developments also suggest that single rTMS trains might entrain neuronal rhythms at stimulation frequency, which is of interest for the study of brain oscillations. Future combined TMS-EEG work is needed to explore and extend the utility of rTMS in both research and therapy.

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