Tactile Stimulation Interventions: Influence of stimulation parameters on sensorimotor behavior and neurophysiological correlates in healthy and clinical samples

Franca H. Parianen Lesemann[1,2], Eva-Maria Reuter[2], Ben Godde[2]

[1]University of Utrecht, Graduate School of Life Sciences, Utrecht, the Netherlands

[2]Jacobs Center of Lifelong Learning, Jacobs University Bremen, Bremen Germany

Abstract

The pure exposure to extensive tactile stimulation has been revealed to enhance sensorimotor functioning, without the requirement of attention or training. The induced effects, including increased tactile acuity and manual dexterity are assumed to rely on the induction of plasticity in the somatosensory cortex. They have repeatedly been observed in basic as well as clinical research. However, found results vary greatly in respect to the strength and direction of the induced effects on the behavioral and on the brain level. Multiple evidences show that differences in the stimulation protocols (e.g. one vs. multiple stimulation sessions) and parameters (e.g., duration, frequency, amplitude) might contribute to this variability of effects. Nevertheless, stimulation protocols have not yet been systematically compared. Identifying favorable parameters for tactile stimulation interventions is especially important because of its possible application as a convenient treatment option for patients suffering from sensory loss, maladaptive plasticity or certain forms of motor impairment. This review aims to compare the effects of different tactile stimulation protocols and to evaluate possible implications for tactile stimulation in research and application purposes. In order to do so, we reviewed the current research on tactile stimulation in the healthy population, with a focus on the effectiveness of the applied parameters regarding psychophysiological measures. Herewith we will discuss the association of stimulation-induced changes on the behavioral level with alterations in neural representations and response characteristics. Afterwards, we will specify practical applications of tactile stimulation in the healthy and clinical population and evaluate, whether the paradigms of our review apply to these contexts as well. The outlook is thereby to identify ways of optimizing stimulation protocols for research and application purposes, to induce a long lasting improvement of sensorimotor performance.

Keywords: repetitive Tactile Stimulation, hebbian learning, stimulation parameters, sensory perception, motor performance

Introduction- What is repetitive tactile stimulation and where is it applied?

In the 1970 and 1980ies numerous findings made it evident that the somatosensory cortex is highly plastic even in adults (Buonomano & Merzenich, 1998; Merzenich et al., 1984). It has been revealed that this adult plasticity is dependent on sensory experience and spatiotemporal stimulus statistics. This was found through active manipulation of stimulus perception in animals (Allard, Clark, Jenkins, & Merzenich, 1991; Armstrong-James, Diamond, & Ebner, 1994; Clark, Allard, Jenkins, & Merzenich, 1988; Jenkins, Merzenich, Ochs, Allard, & Guic-Robles, 1990), but also through research in humans whose regular tactile input differs from that of the general population, e.g. blind Braille readers (Sterr et al., 1998). In both, animals and humans, the differences in sensory input were accompanied by changes in the organization of somatosensory cortical representations. Hebbian type synaptic mechanisms play a major role in this reorganization (e.g. Beste & Dinse, 2013; Dinse & Boehmer, 2002). Determined by the temporal order of pre- and postsynaptic activation, this might cause either long-term potentiation (LTP) or depression (LTD) of the synapse. That is to say, it could strengthen the cell’s synaptic connections or diminish them, respectively, depending on the stimulation protocol applied. These changes in synaptic efficacy can lead to long-term changes in the organization of neuronal circuits. They are considered a base of plasticity and learning. Whereas LTP and LTD have mainly been investigated in hippocampal slices, different types of stimulation interventions were developed to test if similar mechanisms apply to cortical plasticity in vivo. Intracortical microstimulation (Spengler & Dinse, 1994) was used to stimulate large cortical neuron populations directly without involving subcortical and peripheral structures. Inspired by whisker pairing experiments in mice (Armstrong-James et al., 1994), Godde et al. (1996; 2000) introduced a paradigm of peripheral associative tactile stimulation. The paradigm was characterized by extensive (several hours) simultaneous repetitive tactile stimulation (rTS) of separated receptive fields on the skin. This form of stimulation was driven by two ideas. Firstly, extensive stimulation of separated locations on the skin results in hebbian-like synchronous coactivation of respective neural afferents. Secondly, this stimulation intervention can induce brain plasticity in terms of neural response characteristics and cortical topography. Indeed, in humans, the induced cortical changes were associated with changes in tactile perceptual abilities comparable to those occurring after application of active perceptual learning paradigms. Since then, many studies that used different variants of tactile stimulation interventions, revealed supportive evidence that induced cortical changes rely on hebbian like processes (Beste & Dinse, 2013; Ragert, Kalisch, Bliem, Franzkowiak, & Dinse, 2008). Furthermore it could be shown that, as for the induction of LTD and LTP, the temporal pattern and frequency of tactile stimulation protocols were decisive for the found effects in terms of neural excitability, cortical topography, as well as tactile performance (Beste & Dinse, 2013; Dinse et al., 1996; Kalisch, Tegenthoff, & Dinse, 2007). Also the duration of the induced effects was similar for the effects induced by cellular stimulation and those induced by tactile stimulation (Kalisch et al., 2007). At last, pharmaceutical research showed that drugs supporting LTP induction, can boost the behavioral and neurophysiological effects of rTS (Dinse, Ragert, Pleger, Schwenkreis, & Tegenthoff, 2003), while drugs blocking NMDA receptors involved in LTP induction prevented stimulation effects (Dinse et al., 2003). RTS protocols provide an elegant and efficient means to mimic the effect of extensive and long-term tactile experience in a very short time. Indeed, stimulation was shown to induce similar behavioral effects as yearlong tactile training, which lasted for several hours (Ragert, Schmidt, Altenmüller, & Dinse, 2004). In accordance, rTS can be used to study a wide range of perceptual and neurophysiological changes (Table 2). As the changes are actively induced by the researchers and little cooperation by the participant is needed, rTS enables to manipulate and control for more influencing factors than other forms of training. It thus allows for a systematic investigation on perceptual learning processes (Fraser et al., 2002), and also for practical applications. For example, rTS might help to increase tactile abilities in individuals with a high need for these, such as artists and fine mechanics (Ragert et al., 2004; Reuter, Voelcker-Rehage, Solveig, & Godde, unpublished), or with sensory impairments due to age (Dinse et al., 2006; Kalisch, Tegenthoff, & Dinse, 2008; Kalisch, Tegenthoff, & Dinse, 2010; Voelcker-Rehage & Godde, 2010) or stroke (K. Johansson, Lindgren, Widner, Wiklund, & Johansson, 1993; Sullivan & Hedman, 2008).

In a clinical setting, rTS was applied to reverse harmful patterns of perception, as they occur exemplarily in patients with phantom limb pain (Flor, Denke, Schaefer, & Grüsser, 2001). Thereby rTS helped to reorganize the cortical representations of the affected limbs. Also other forms of maladaptive plasticity, such as interhemispheric misbalance and certain forms of spasticity, have been shown to decrease after rTS (Dewald, Given, & Rymer, 1996; Levin & Hui-Chan, 1992; e.g. Pascual-Leone, Amedi, Fregni, & Merabet, 2005). At last, rTS was shown to also affect the motor cortex, which enables applications such as treating paralysis and motor impairment (Conforto, Cohen, dos Santos, Scaff, & Marie, 2007; Conforto et al., 2010; e.g. Kalisch et al., 2008). In addition to its non-invasive nature, rTS has the advantage of being relatively easy and convenient to apply. This allows for self-administered and home based application as well as the treatment of severely impaired patients. RTS might thus serve as a regenerative treatment opportunity for patients with brain lesions and other forms of neuronal loss or degeneration (Feys et al., 2004; e.g. K. Johansson et al., 1993; Peurala, Pitkänen, Sivenius, & Tarkka, 2002). Importantly, the results of rTS based treatment vary, as do the results of basic research. Thereby, part of this variability might rely on stimulation parameters, including exemplarily the time and amount of administration (e.g. Hummel & Cohen, 2005; Kalisch et al., 2010). Thus, for both, clinicians and basic researchers it is of particular importance to determine which stimulation protocols are most effective. While the multitude of studies on rTS have led to some general agreement about the nature of stimulation effects (e.g. Beste & Dinse, 2013; Seitz & Watanabe, 2005), there is no review yet that systematically compares the effectiveness of these different protocols regarding the size of the effect and its longevity. Furthermore, the question whether these implications on parameter choice from basic research also apply to practical applications of rTS remains open. This review aims to draw a comparison between different rTS paradigms in humans and their effects on the neural and behavioral level. We will then deal with the question, whether the same criteria of effectiveness also apply when rTS is applied to treat sensory loss, maladaptive plasticity or motor impairment. At last, we will propose some general guidelines for effective rTS protocols in research or application contexts.

Different stimulation protocols

RTS is based on the idea that effects depend on a sufficient amount of applied stimuli and the coactivation of neural afferents or cortical sites. However, rTS paradigms vary in respect to how they meet these requirements. They differ in their choice of stimulation frequency, duration, site and intensity.

A sufficient amount of stimulation can be reached by either applying bursts of tactile stimuli at a high frequency (in the following termed “burst stimulation”) or by stimulation with single pulses for a longer duration (“single pulse stimulation”). The applied frequencies vary a lot even within each of these two groups of stimulation paradigms. Whereas the first experiments reported by Godde et al. (1996, 2000) used a single pulse protocol with variable inter stimulus intervals and mean frequencies of 1 – 1.7 Hertz (Hz), more recently, stimulation frequency was drastically increased to about 20 Hz, allowing reduction of stimulation duration to less than half an hour. Here, burst stimuli, with inter-burst intervals of about 5 seconds were used (Freyer, Reinacher, Nolte, Dinse, & Ritter, 2012; Freyer, Becker, Dinse, & Ritter, 2013; Kalisch et al., 2007; Tossi, Stude, Schwenkreis, Tegenthoff, & Dinse, 2013).

A third group of studies applied even higher frequencies of stimulation at 50 Hz, for 30 minutes (Christova, Rafolt, Golaszewski, & Gallasch, 2011; Golaszewski et al., 2010; Kaelin-Lang et al., 2002).

Synchronicity of tactile afferents and neuronal representations is achieved by stimulation of an area of the tip of one finger, covering a large amount of separated and (partly) overlapping receptive fields (Godde et al., 1996; Godde, Ehrhardt, & Braun, 2003; Hodzic, Veit, Karim, Erb, & Godde, 2004; Pleger et al., 2001; Pleger et al., 2003), two- or more adjacent fingers (e.g. Dinse et al., 2006; Höffken et al., 2007; Kalisch et al., 2007; Kalisch et al., 2008; Pilz, Veit, Braun, & Godde, 2004), or rather stimulation of the whole hand simultaneously with a specific glove to maximize the effect of coactivation (Christova et al., 2011; Golaszewski et al., 1999; Golaszewski et al., 2004; Golaszewski et al., 2010; Golaszewski et al., 2012). Few studies also stimulated other body parts, such as the palm or foot (Christova, Rafolt, Mayr, Wilfling, & Gallasch, 2010; Christova et al., 2012; Peurala et al., 2002). A complete overview is given in Table 2. Irrespective of the stimulated body parts, the area of stimulation needs to be sufficiently large to make sure that afferents with separated receptive fields are stimulated synchronously. By comparison, rTS on only a single “point-like” location of the skin has been found to be insufficient to induce plastic changes (Pleger et al., 2003; Ragert et al., 2008).Besides tactile stimulation, direct transcutaneous electrical stimulation (TENS) of the median, peroneal, radial and/or the ulnar nerve, respectively, was applied, thus providing simultaneous activation of a broad population of the sensory afferents themselves with non-overlapping and (partly) overlapping receptive fields. Although this is not tactile stimulation in the proper sense, rationales behind and induced effects are similar. Thus we will include TENS in our review. Most TENS studies used stimulation durations of 2 hours applied at 10 Hz (Table 2). Electrical stimulation was first used to overcome technical limitations of mechanical stimulation, especially the limited intensity range (Kalisch et al., 2010). It was proposed that electrical and mechanical stimulation might activate different groups of nerve afferents, yet both are assumed to induce hebbian learning (Kalisch et al., 2010). For an overview of the most frequent stimulation protocols and the terms used in this review, please see Table 1.

In order to investigate underlying mechanisms and effects of variations in the temporal characteristics of rTS, some studies also combined rTS with other types of stimulation. Paired associative stimulation protocols, for instance, combine tactile with electrical stimuli (Torebjörk, 1974) or somatosensory with cortical stimulation, such as transcranial magnetic stimulation (TMS) (Rosenkranz & Rothwell, 2006; for a related reviwe see e.g. Stefan, Kunesch, Cohen, Benecke, & Classen, 2000) or transcranial direct current stimulation (tDCS) (e.g. Celnik, Paik, Vandermeeren, Dimyan, & Cohen, 2009).

Table 1. Most frequently used stimulation protocols, their prevailing parameters and the terms used to refer to them in this review.

Term	Body part	Frequency	ISI/ ITI	Intensity	Duration	Stimulation device
Single pulse stimulation	One or multiple fingers	1-1.7 Hz	100-3000 ms/ 8-1761 ms ISI	Suprasensory threshold	3 hours	mechanical
Finger burst stimulation	One or multiple fingers	20 Hz	5 ms ITI	Suprasensory threshold	20-30 min	Mechanical/ electrical
Whole hand stimulation	Whole hand	50 Hz	20 ms ISI	Suprasensory threshold	30 min	Electrical (mesh glove)
TENS	Median, nerve	10 Hz	1 s ITT	Supra/ subsensory threshold	2 h	Electrical

Note: TENS= transcutaneaous electrical nerve stimulation, ISI= Interstimulus Interval, ITI= Intertrain interval, h= hours, min= minutes, Hz= Hertz

All stimulation methods described above have in common that they affect tactile perception and processing on several levels. The effects are highly specific for the stimulated body part and hardly spread to other fingers or limbs. Most stimulation protocols differ in the quality and duration of the induced effects, but not in their general nature. However, some forms of rTS cause opposite effects on the neurophysiological as well as the behavioral level (see Table 2). Next to the large amount of behavioral studies, neurophysiological measures and imaging techniques were used to assess the exact mechanisms through which rTS influences cortical processing and behavioral performance. These measures were used to compare cortical excitability and organization before and after rTS. They included functional magnetic resonance imaging (fMRI) (Kalisch et al., 2008; Pilz et al., 2004; Pleger et al., 2003), electroencephalography (EEG) (Pleger et al., 2001), magnetoencephalography (MEG) (Braun et al., 2001; Godde et al., 2003) and TMS (Dinse et al., 2003). Also behavioral studies were used to assess the effect of rTS on sensory perception

*Table 2.*Stimulation protocols used to induce behavioral and/or neurophysiological changes on a sensory level.

Single Pulse Stimulation

No	Author	Body part	device	Frequency	ISI	Intensity	Duration	Specification	Sensory measures	Motor measures
1	Godde et al., 1996	2 digits	m	1Hz	ISI 100-3000 ms	sup	2/ 6 h		2PD	
2	Godde et al., 2000	D2	m	1 Hz vs. 1.7 Hz	ISI 100-3000 ms / 8 & 1761 ms	sup	6/ 2/ 0.5 h		2PD	
3	Pleger et al., 2001	D2	m	1 Hz	ISI 100-3000 ms	sup	3 h		2PD SSEPs	
4	Pleger et al., 2003	D2	m	1 Hz	ISI 100-3000 ms	sup	3 h		2PD fMRI (CoG, BOLD activity)	
5	Godde et al.,2003	D2	m	1.7 Hz	ISI 8 & 1761 ms	sup	3 h		2PD MEG (polar angle/ dipole amplitude)	
6	Hodzic, et al., 2004	D2	m	1.7 Hz	ISI 8 & 1761 ms	sup	3 h		GOT, FD fMRI (CoG, activated clusters)	
7	Pilz et al.,2004	D2-D4	m	1.7 Hz	ISI 8 & 1761 ms	sup	3 h	synchronous vs. asynchronous	Localization fMRI (CoG)	

No	Author	Body part	device	Frequency	ISI	Intensity	Duration	Specification	Sensory measures	Motor measures
8	Höffken et al., 2007	D2	m	1 HZ	ISI 100-3000 ms	sup	3h		2PD; PPR SEPs	
9	Kalisch et al.,2007	D2	m	1Hz	ISI 100-3000 ms	sup	3 h		TS, 2PD	
10	(Wilimzig, Ragert, & Dinse, 2012)	D2	m	1Hz	ISI 100-3000 ms	sup	3 h		perceptual decision making	
Pharmacological modulation										
11	Dinse et al., 2003a	D2	m	1 Hz	ISI 100-3000 ms	sup	3 h	gaba receptor agonist	2PD	
12	Dinse et al., 2003b	D2	m	1 Hz	ISI 100-3000 ms	sup	3 h	amphetamine and NMDA receptor blocker	2PD fMRI (distance, amplitude, angle dipole)	
13	Bliem et al., 2007	D2	m	1 Hz	ISI 100-3000 ms	sup	3 h	dopamine	2PD	
14	Bliem et al., 2008	D2	m	1 Hz	ISI 100-3000 ms	sup	3 h	cholinergic antagonist	2PD	
Combination with TMS										
15	Ragert et al. 2003	D2	m	1 Hz	ISI 100-3000 ms	sup	3h	Combined rTS, rTMS	2PD	

No	Author	Body part	device	Frequency	ISI	Intensity	Duration	Specification	Sensory measures	Motor measures
Specific groups										
16	Ragert et al., 2004	D2	m	1 Hz	ISI 100-3000 ms	sup	3h		2 PD	
17	Dinse et al. 2006	D1-D5	m	1 Hz	ISI 100-3000 ms	sup	3 h		2PD	
18	Kalisch et al., 2008	D1-D5	m	1 Hz	ISI 100-3000 ms	sup	3 h	Older participants	2PD, TT, localization haptic obj. rec.	Pegboard

Burst Stimulation

No	Author	Body part	device	Frequency	ISI	Intensity	Duration	Specification	Sensory measures	Motor measures
19	Ragert et al., 2008	D2	m	20 Hz	ITT 5s	Sup	20 min	Frequency varied to 1 Hz	2PD	
20	Kowalewski et al., 2012	D1&D2	e	20 Hz	ITT 5s	Sup	30 min		2PD, TT, PPT	Pegboard Test
21	Schlieper & Dinse, (2012)	D2	e	20 Hz	ITT 5s	Sen-pain	30 min		2PD	
22	Freyer et al., 2012	D2	e	20 Hz	ITT 5s	Sup	30 min		2PD EEG (resting state)	
23	Freyer et al., 2013	D2	e/m	20 Hz	ITT 5s	Sup	30 min		2PD	

No	Author	Body part	device	Frequency	ISI	Intensity	Duration	Specification	Sensory measures	Motor measures
Combination with TMS										
24	Tossi et al., 2013	D2	m	20 Hz	ITT 5s	Sup	20 min	TMS	2PD PPR	
Specific Groups										
25	Kalisch et al., 2010	D1-5	e	20 Hz	ITT 5s	Sup	30 min	age 66–79 years, repeated	2PD, habt. Obj. rec.	pegboard
26	Voelcker-Rehage & Godde, 2010	D1-2	m	18–24 Hz	ISI 100-3000 ms	Sup	30 min	66–78 years	2PD, frequency disc.	grip force mod.
Clinical Research										
27	(P. S. Smith, Dinse, Kalisch, Johnson, & Walker-Batson) 2009	D1-5	e	20 Hz	ITT 5s	pain	90 min	Repeated, stroke treatment	2PD, TT, habt. Obj. rec.	motor tapping, Pegboard Test

Other forms of finger stimulation

No	Author	Body part	device	Frequency	ISI	Intensity	Duration	Specification	Sensory measures	Motor measures
28	(Braun et al.),	D1&D5	m		ITT 10 min			Repeated,		MEG

No	Author	Body part	device	Frequency	ISI	Intensity	Duration	Specification	Sensory measures	Motor measures
	2001							task related		(amplitude, distance, polar angle dipole)
29	Schweizer et al., 2001	D1 and/ or D5	m	ca. 0.5 Hz	mean 2000ms	sen	60 min	repeated	localization	

Whole Hand Stimulation

No	Author	Body part	device	Frequency	ISI	Intensity	Duration	Specification	Sensory measures	Motor measures
30	Christova et al., 2012	palm & D1-5	m	25 Hz	Con	sup	20 min	repeated	fMRI (BOLD S1)	fMRI (BOLD M1)
31	Golaszewski et al. 1999	wh	e	50 Hz	19,4 ms	sub	20 min		fmri (BOLD S1,S2+ M1)	fmri (BOLD M1)
32	Golaszewski et al. 2004	wh	e	50 Hz	19,4 ms	Sub	30 min		fmri (BOLD S1,S2+ M1)	fmri (BOLD M1)
33	Golaszewski et al., 2010	wh	e	50 Hz	19,4 ms	Sup, sen	30 min			motor threshold (MT), TMS (MEPs, recruitment curve)
34	Golaszewski et al., 2011	wh	e	50 Hz, 2HZ	19,4 ms	Sup, sub, motor	30 min		TMS (MEPs, recruitment curve)	

No	Author	Body part	device	Frequency	ISI	Intensity	Duration	Specification	Sensory measures	Motor measures
35	Christova et al., 2011	wh	e	10 Hz/ 25 Hz	Con	sup	20 min		TMS (MEPs, recruitment curve)	

TENS

No	Author	Body part	device	Frequency	ISI	Intensity	Duration	Specification	Sensory measures	Motor measures
36	Mima et al., 2004	mn	e	90 Hz	ISI ca. 11 ms	sup	30 min	2PD, TT	TMS (MEP)	
37	Wu et al., 2005	mn	e	10 Hz	ITT 5s	Below motor	2 h	fMRI (BOLD, activated clusters S+M)		

Note: No.= Number assigned to the study (also used in figures) .device= form of stimulation (e=electrical, m=mechanical), TT= Tactile sensitivity threshold, 2PD, two-point discrimination threshold, intensity= intensity of stimulation (sup= sensory suprathreshold intensity, sub= sensory subthreshold intensity, motor= motor intensity, sen= at threshold of sensory perception, pain= at the pain threshold), ISI= Interstimulus Interval (ITI= Intertrain interval, D2= index finger, h= hours, min= minutes), body part= point of stimulation (wh= whole hand, mn= median nerve), FD= Frequency Discrimination, PPR= Paired pulse ratio, BOLD= Blood oxygen level dependent response, TMS= transcranial magnetic stimulation

rTS induced changes in somatosensory cortical representations

Topography. Rat experiments using extracellular microelectrode recordings showed that rTS leads to increased and more overlapping somatosensory cortical representations of the stimulated fingers (Godde et al., 1996). Similar effects were found in humans using fMRI. In two studies applying single pulse stimulation, the center of activation shifted by approximately 5 to 12 mm for the contralateral S1 and by 4.89 to 12.9 mm for the contralateral S2 (Hodzic et al., 2004; Pleger et al., 2003). This shift in center of gravity of activation indicates an asymmetric enlargement of the finger's representations in the direction of the thumb by a factor of 2 to 3. One of these single pulse studies reported a respective shift of the centers of gravity by 9.17 mm also in S2 of the ipsilateral sensory cortex (Pleger et al., 2003). The number of activated voxels was increased by 327 % in S1 and 87 % in S2, indicating enlarged cortical representations in both areas of the sensory cortex (Pleger et al., 2003). Electrical subthreshold burst stimulation of the whole hand increased the number of activated voxels by 33 % in the area of the sensory and motor cortex (Golaszewski et al., 2004), indicating a weaker effect after this kind of stimulation. Despite the lower strength of effect, this study also reported increased activation of the ipsilateral cortex. Wu, van Gelderen, and colleagues (2005) found the number of activated voxels in SI to be increased by approximately 50 % after low frequency TENS. Yet, in these studies it is difficult to estimate in how far the increase in voxel number reflected increased cortical representation or just a stronger blood-oxygen-level dependent (BOLD) signal. BOLD signal strength has been shown to increase by about 20 % after TENS as well as after 20 minutes of mechanical 25 Hz stimulation (Christova et al., 2012; Wu et al., 2005). A single pulse protocol reported a 100 % increase in signal strength (Pleger et al., 2003). Constant stimulation of the finger and palm at 25 Hz led to more localized changes in fMRI signal. In sum, stimulation in the low frequency range of 1-10 Hz seems to have relatively stronger effects as compared to burst stimulation with respect to topographical changes that are reflected through fMRI.

None of the studies investigating changes in the BOLD signal *strength* could find differences in the activation of S2 (Christova et al., 2012; Golaszewski et al., 2004; Wu et al., 2005), which is in contrast to the findings on localization of activation peaks and activated clusters (Hodzic et al., 2004; Pleger et al., 2003). It was proposed that the lack of effect in studies treating BOLD signal changes relates to the fact that S2 is less somatotopically organized and that there is more overlap between representations of different body sites. This lack of clear organization might lead to a strong variation of activation patterns between subjects and clear results are harder to obtain (Pleger et al., 2003).

MEG, and EEG studies confirmed a representational shift in primary somatosensory cortex. Early somatosensory signal components shifted laterally and increaseed in strength after stimulation (Godde et al., 2003; Pleger et al., 2001). Single pulse stimulation induced a lateral dipole shift of 9.13 mm and a polar angle shift of 2.82 - 3.8 degrees (Pleger et al., 2001). Dipole strengths increased by 33 % in one single pulse study (Pleger et al., 2001). The other could not replicate this effect (Godde et al., 2003). By comparison, after burst stimulation the polar angle changed by 3.61 degrees and dipole strength increased by 36.94 %, indicating a comparable change as after single pulse stimulation (Dinse et al., 2003). The increase of cortical representations probably decreased the distance between them. If two limbs are stimulated simultaneously, their representations approximate and start to overlap. If they are stimulated asynchronously, these representations move apart. For instance, after synchronous single pulse stimulation of index middle and ring finger, the mean Euclidean distance between their representations decreased to 2.05 mm. By comparison, in the control group, these representations were apart by 3.42 mm (Pilz et al., 2004). An experiment by Braun and colleagues (2001) showed that this change in dipole can be task related. If rTS was applied during writing, participant's cortical representations showed lesser reorganization if the measurement was conducted during writing too, as opposed to the cortical representations reflected after measurement during resting (Braun et al., 2001). The authors suggested that different variations of cortical maps coexist in the cortex. Accordingly, extensive task training results in the development of a task specific version of the cortical map. During renewed performance of the trained tasks, the specific maps are reactivated (Braun et al., 2001).

Cortical excitability. A couple of studies used EEG or MEG to investigate effects of rTS on cortical excitability in terms of somatosensory evoked potentials in the somatosensory components of the signal (Höffken et al., 2007; Tossi et al., 2013) Special attention was paid to the paired pulse ratio. This ratio of the amplitudes of somatosensory evoked potentials, evoked by two pulses applied in very short intervals, reflects adaption to the first stimulus. For peripheral nerve stimulation intracortical facilitation (ICF) usually occurs at interstimulus intervals between 5 and 20 ms whereas intracortical inhibition (ICI) is steepest at intervals of 40-60 ms (Lesser, Gurd, & Klem, 1984). Burst stimulation influenced the relation between the first and second pulses without affecting the cortical reaction to the first one (Tossi et al., 2013). This suggests that rTS indeed influences ICF and ICI and not the general sensitivity to the stimuli. Thereby, effects on paired pulse ratio were stronger for single pulse stimulation (35 %) (Höffken et al., 2007) than burst stimulation (17 %) (Tossi et al., 2013).

Coherence in specific frequency bands. In addition to topographical changes, rTS influences connectivity of the sensory cortex, through interactions of sensory, motor and association cortices (Freyer et al., 2012). Evidence for this stems from EEG resting state measurements, which supported an increased connectivity of these areas after stimulation (Freyer et al., 2012).In order to estimate the connectivity, EEG coherence was measured during the resting state. This measure measures in how far the neuronal dynamics in different regions correlate. Through analysis of coherency it was found that after stimulation, distant sensory and motor regions show a stronger correlation of the mu rhythm, which is sensitive to sensorimotor processing. This indicates increased oscillatory coupling in these regions. The authors suggest that tactile stimulation might have changed the feed-back loops between the involved areas. However, there is no clear understanding of the involved processes yet (Freyer et al., 2012).

rTS induced changes on tactile performance. The influence of tactile stimulation on perception has been shown in more than 20 studies (Figure 1). Thereby it has been investigated, how accurately participants perceive and differentiate varying tactile stimuli before and after stimulation. For instance, studies measured participants’ ability to differentiate spatial and temporal characteristics of a stimulus (Table 2). A frequently assessed measure to determine spatial acuity of stimulus perception is the two-point discrimination threshold (2PD), which describes the minimal distance between two stimuli applied to the skin that is necessary for them to be perceived as separate (Table 2). Besides, spatial acuity can be tested through the Grating Orientation Task (Hodzic et al., 2004; Reuter et al., unpublished; Van Boven, Hamilton, Kauffman, Keenan, & Pascual–Leone, 2000). Another aspect of tactile perception is localization, that is the ability to determine, to what location on the limb or finger a very light stimulus is applied. Especially concerning neighboring digits, participants often confound this location, which is referred to as mislocalization.

Regarding tactile spatial acuity, the strength of effects differs regarding the type of stimulation. After 20 minutes of burst stimulation, a decrease of the 2PD threshold between 5 % (Schlieper & Dinse, 2012; Tossi et al., 2013) and 16 % (Ragert et al., 2008) was found. Slightly stronger effects were found for most single pulse studies, reporting improvements between 13 and 28.8 % (Figure 1). It is unlikely that high baseline thresholds, i.e. low performance in these studies (Godde et al., 1996; Godde et al., 2003; Höffken et al., 2007; Pleger et al., 2003) were the basis for stronger effects because another study with baseline threshold similar to those found in the studies mentioned above only reported a 13 % improvement (Pleger et al., 2001). Yet, differences in the participant's age group might affect the results. Correspondingly, single pulse stimulation seems to influence 2PD somewhat stronger than burst stimulation (Figure 1). However, if more than one finger is stimulated synchronously, the strength of effects increases especially for burst stimulation, rendering it more effective. While single pulse stimulation of multiple fingers results in a 15-20 % decrease of 2PD (Höffken et al., 2007; Kalisch et al., 2007), An even bigger improvement of up to 26 % was found after burst stimulation of two fingers (Kowalewski, Kattenstroth, Kalisch, & Dinse, 2012). We did not find a general difference between the strength of effects induced by either electrical or mechanical stimulation. The changes in tactile acuity were rather similar after electrical stimulation as compared to mechanical stimulation (for an overview, see Figure 1/ Table 2). Also one study that explicitly compared both means of stimulation only found marginal differences in tactile acuity change (Freyer et al., 2013).

Only one study systematically compared different stimulation intensities, namely stimulation just above sensory perception threshold, at pain threshold, and at intensity between sensory and pain threshold (suprasensory). Here, stimulation just above the sensory threshold was not able to induce significant changes of 2PD threshold (2.29 %). However, the overall effects in this study were rather weak. RTS at pain threshold (7.76 %) was slightly more effective than that at suprasensory threshold (5.36 %). Yet, significant differences between the induced effects could only be found between stimulation just above the sensory threshold and at pain threshold. At last, some variations of stimulation also led to decreased tactile acuity. Namely, asynchronous stimulation increased 2PD threshold (Kalisch et al., 2007). Also applying continuous 1 Hz stimulation for 20 minutes (Kalisch et al., 2007) or TENS at 90 Hz for 30 minutes (Mima et al., 2004) deteriorated performance.

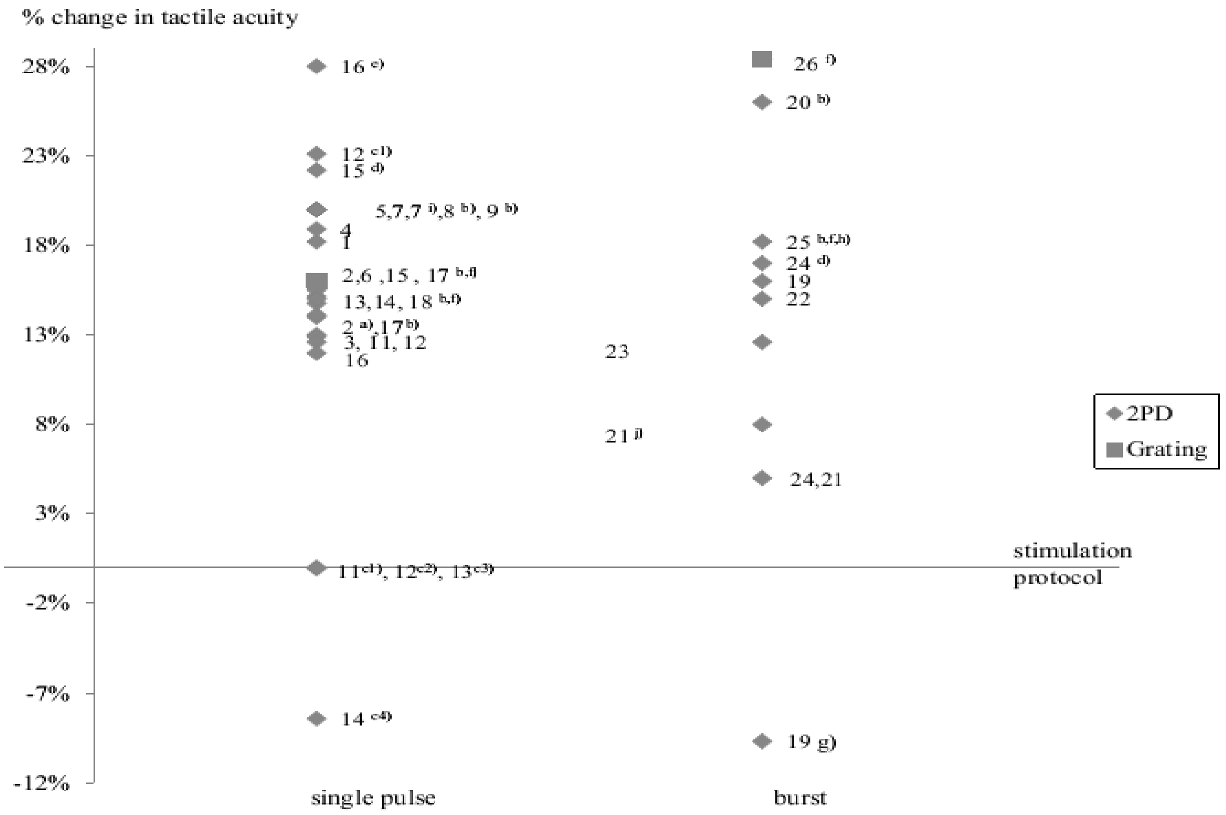

Figure 1. Tactile acuity change after different stimulation protocols. 2PD= two-point discrimination threshold, Grating= Grating Orientation Task a) 6 hours stimulation; b) multiple fingers; c) pharmacological; c1) gabaergic antagonist; c2) amphetamine; c3) dopamine; c4) cholinergic antagonist; d) combination with TMS; e) individuals with frequent tactile input; f) older participants; g) low frequency; h) repeated stimulation; i) asynchronous; j) pain threshold intensity; Numbers refer to the numbers assigned to each study in Table 2

In contrast to the general agreement on an effect of tactile stimulation on spatial acuity the findings on absolute thresholds for tactile perception, i.e. tactile sensitivity, are more controversial. Most studies rejected an influence of stimulation on absolute tactile sensitivity in the healthy population (Bliem, Tegenthoff, & Dinse, 2008; Dinse et al., 2003; e.g. Kalisch et al., 2007). However, after 30 minutes of 90 Hz TENS, the tactile sensitivity was decreased (Mima et al., 2004). Furthermore, one study reported increases in tactile sensitivity of 10.25 mN after 15 minutes of radial nerve stimulation. Notably, those changes only occurred in a group stimulated at 110 Hz with a pulse duration of 50 µs. Changing the frequency to 4 Hz and/or the pulse duration to 200 µs resulted in a stagnation of thresholds (Walsh et al., 1998). Accordingly, this effect might occur only after a very specific choice of parameters.

Concerning localization, the effects of rTS are highly dependent on the choice of stimulated fingers as well as the synchronicity of the stimulation. After *synchronous* single pulse stimulation of index and middle or middle and ring finger mislocalization between these fingers increased by approximately 37.5 %. On the contrary, *asynchronous* stimulation led to improved localization performance of approximately 22% (Pilz et al., 2004). Stimulating all fingers of one hand synchronously resulted in mislocalization also on more distant fingers (Kalisch et al., 2007). After stimulation of all fingers, participants were 50 % more likely to mislocalize a stimulus to the 3rd neighbor of the actually stimulated finger. Mechanical stimulation of the thumb and little finger at the very low frequency of 0.5 Hz for a period of 20 days led to a 37.5 % increase of mislocalization to the closest neighboring digit, but a 50 % decrease to the further digits (Schweizer, Braun, Fromm, Wilms, & Birbaumer, 2001). Even though, this study failed to show an effect of synchronous stimulation on localization, it indicates that repetitive stimulation over several days can induce changes even if applied at very low frequency. However, despite the longer duration of stimulation, the strength of effects was rather similar to that induced by one single session of stimulation. This supports the assumption that there are certain limits to the induced effects.

Thus, stimulation of all fingers seems to induce stronger cortical reorganization than that of 3 fingers, indicating an increase of effects in accordance with enlarged stimulation site.

Concerning temporal acuity, the findings differ for rTS induced effects. One study found increased temporal acuity after single pulse stimulation in a task in which participants had to differentiate frequencies between 29 and 39 Hz from a reference frequency (30 Hz) (Hodzic et al., 2004). However, another study using a reference frequency of 21 Hz found a positive effect of burst stimulation on temporal acuity in older adults (Voelcker-Rehage & Godde, 2010). Another burst stimulation study, assessing the ability to differentiate vibrating stimuli between 120 and 180 Hz, found an absence of effects in middle-aged adults, including fine mechanics, but a positive effect in older and younger adults (Reuter et al., unpublished). Furthermore, repeated 50 Hz stimulation in amputees increased temporal acuity (Mulvey et al., 2012). It seems possible that the effects of single pulse stimulation and burst stimulation differ with regard to temporal acuity, with single pulse stimulation inducing a negative and high frequency stimulation inducing a positive effect.

As with regard to mislocalization, as well as 2PD, prolonging stimulation from 2 to more hours could not improve tactile performance any further in either burst or single pulse stimulation (Freyer et al., 2012; Freyer et al., 2013; Godde et al., 2000; Ragert et al., 2008).

To sum it up, the behavioral effects of rTS differ with regards to the assessed dimension of tactile perception. Generally, burst and single pulse stimulation seem to induce similar effects on discrimination performance. But the changes induced by burst stimulation last longer and are more strongly influenced by variations, such as 2 finger stimulation.

Relation to baseline performance

In addition to the effects of different stimulation parameters, also differences between the participants influence the outcome of stimulation. Especially baseline performance predicted participant’s improvement. It has been found to negatively correlate with the stimulation induced improvement (Dinse et al., 2006; Reuter et al., unpublished)(Dinse, 2006).

Ceiling effects probably play an important role in this relationship (Dinse, 2006). A very good performance in the first session might leave very little room for improvement. However, these ceiling effects do not seem to influence every group to the same extent. Changes in behavioral performance have been shown to be especially strong in participant-groups, who already have a high baseline level resulting from their regular tactile input, e.g. musicians (Ragert et al. 2004), or precision mechanics (Reuter et al., unpublished). In the musicians, 2PD was decreased by 28 % after rTS (Ragert et al., 2004). In fine mechanics performance in tactile spatial and temporal discrimination tasks improved by approximately 50 % (Reuter et al., unpublished).

Relation between behavioral and neurophysiological effects

Improved tactile acuity after rTS seems to correlate with cortical reorganization. Performance changes in 2PD were related to the changes of cortical representations in S1 (Höffken et al., 2007; Pleger et al., 2001). Studies that found a stronger degree of reorganization tend to also show higher behavioral results (Dinse et al., 2003; Godde et al., 2003; Pleger et al., 2001) and drugs that boosted behavioral performance also increased the shift of cortical representations (Ragert et al., 2003). However as depicted in Figure 2 the relation between behavioral and neurophysiological effects varies a lot and is not clearly proportional.

Regarding the excitability of the sensory cortex, the correlation with behavioral results is even less clear (Figure 2). While one study did find a correlation between changes in excitability and behavioral performance (Höffken et al., 2007), the other one rejected it (Höffken et al., 2007; Tossi et al., 2013). Furthermore, the administration of amphetamine increased behavioral effects and cortical representation without affecting the excitability of the sensory cortex, as reflected through the dipole intensity of the somatosensory evoked potentials (Dinse et al., 2003). However, applying tactile stimulation after TMS led to inhibition of the cortical excitability increase as well as stagnation of behavioral performance (Tossi et al., 2013), emphasizing a relation between the two. Possibly, cortical excitability is necessary to induce the cortical reorganization underlying improved tactile performance, but not sufficient to improve performance on its own.

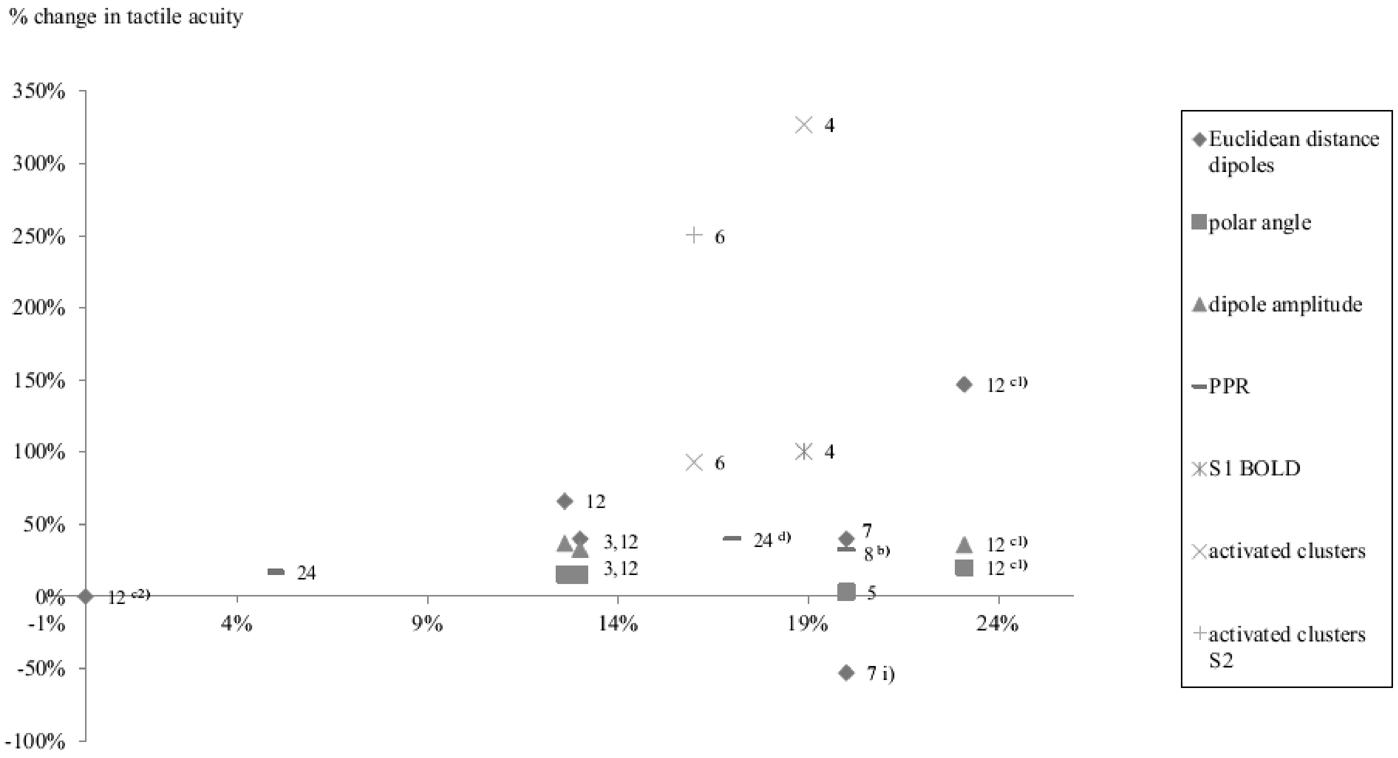

Figure 2. Strength of neurophysiological effect as related to changes in tactile acuity. PPR= paired Pulse Ratio; S1= sensoricortical area 1; b) multiple fingers c^1) gabaergic antagonist; c^2) amphetamine; d) combination with TMS; i) asynchronous; Numbers refer to the numbers assigned to each study in Table 2

There is no indication that topographical changes in S2 affect tactile acuity similarly to those in S1. In the studies that found changes in S2 activation, those were not correlated to discrimination performance (Pleger et al., 2003). Also for the ipsilateral cortex, no correlation between neurophysiological and behavioral measures was found, even though one study that found respective changes in the ipsilateral S2 also reached a very high improvement of discrimination threshold, possibly due to the low baseline performance (Pleger et al., 2003). Yet, a correlation between those measures was rejected (Hodzic et al., 2004; Pleger et al., 2003).

Also localization performance changes could be predicted by cortical reorganization (Pilz et al., 2004). This was explained by the overlap of cortical representations that was increased due to their growth after rTS. The more the cortical representations of two body parts overlap, the more difficult it is for a participant to differentiate to which limb a stimulus is applied. As a consequence, approximation of those cortical representations correlates with increased mislocalization (Pilz et al., 2004). In line with that, asynchronous stimulation that increases the distance between cortical representations also decreases mislocalization (Pilz et al., 2004). It has been proposed that larger cortical representations also result in increased effects as more neurons are activated by the stimulation (Ragert et al., 2004). This could possibly explain the stronger and longer lasting effects in seniors, as well as in people with extensive experience with tactile stimuli (Ragert et al., 2004; Reuter et al., unpublished). Both are known to have enlarged cortical representations (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995; Kalisch, Ragert, Schwenkreis, Dinse, & Tegenthoff, 2009). Furthermore, Ragert and colleagues (2004) proposed that this increased effect of tactile stimulation in experts might be due to differences in meta-plasticity in these individuals. Therefore, their repeated training renders them more sensible for the induction of plastic changes and breaches or elevates the limits of ceiling effects. This enables improvement even above regular participant's maximum capacity is reached.

Neurophysiological changes can also give some explanation for the restriction of the effect to certain body parts. Seemingly, the transfer of plastic changes relies on an overlap of receptive fields. Only if such an overlap is given between body parts, stimulation induced effects spread between them. The bigger the overlap is the more effective is the spread of these effects (Harrar, Spence, & Makin, 2013). As rTS can increase this overlap between cortical representations, repeated stimulation can enhance the spread of induced effects. For instance, TENS stimulation on a daily basis for 3 weeks was able to induce reorganization of the whole forearm as well as the hand motor cortex (Laufer & Elboim-Gabyzon, 2011; Meesen, Cuypers, Rothwell, Swinnen, & Levin, 2011).

A correlation between the longevity of changes and the degree of reorganization has been reported previously (Gilbert, 1993). Whereas short-term reorganization is paralleled by cortical changes of only about 2 mm, long-term changes can occur in a range of 1 cm (Gilbert, 1993). This might be related to the different situations in which long- and short-term plasticity occur in nature. Here, long-term plasticity is especially useful for the recovery of injuries, that is to say the persistent adaption to lasting changes in the cortex. Short-term plasticity serves the rapid adaption to a quickly changing environment (Gilbert, 1993).

Moreover, the effect of stimulation on cortical representations might also be influenced by the activation of neighboring representations. When the representation of a cortical area increases after stimulation, it recruits cells from other cortical representations which are less activated at that time. Exemplary, stimulation of the median nerve with subsequent thumb movement, led to a spread of the thumb's cortical representation towards those of the resting index and ring finger, which are all innervated by the median nerve. However, the cortical representations of the fingers that were not moved during the subsequent fMRI measurement did not increase (Wu et al., 2005). Possibly plasticity is induced to all fingers reacting to median nerve stimulation but the exact point of stimulation predicts, which of the so "primed" fingers recruits more neuronal resources and thus spreads it's representation (Wu et al., 2005). Accordingly, the occurrence of an effect might also rely on the use of the stimulated limb after stimulation and its activation in relation to neighboring cortical representations.

Duration of effects

Depending on the stimulation protocol, observed effects last from very shortly after simulation up to several days. Yet, most of the neurophysiological changes recover within 24 hours, including changes in dipole location (Pleger et al., 2001), center of gravity and increased amplitude of fMRI signal (Hodzic et al., 2004; Pleger et al., 2003), as well as paired pulse ratio (Höffken et al., 2007; Tossi et al., 2013). Studies investigating the reversibility of effects after a shorter time window found an even earlier recovery of fMRI signal changes within the range of 2 hours after whole hand burst stimulation (Golaszewski et al., 2004). The duration of fMRI signal changes induced by mechanical stimulation of the finger and palm were shorter lasting and recovered within 1 hour (Christova et al., 2012). Also median nerve stimulation induced changes for only 1 hour (Wu et al., 2005).

Most behavioral effects had a longer duration. Single pulse stimulation induced behavioral changes usually vanishing after 2 hours, with a full recovery after 8 hours (Godde et al., 2000). In opposition to that, burst stimulation could change behavioral performance up to 24 hours (Ragert et al., 2008). Accordingly, behavioral effects induced by burst stimulation seem to recover later.

Also stimulation of 2 or more fingers increased the persistence of the effects from 1 to several days (Kalisch et al., 2007; Pilz et al., 2004). Furthermore repeated stimulation over several days can be used to increase longevity (Godde et al., 2000). In one study, 6 hours of continuous stimulation did not improve the duration of performance changes as compared to 2 hours. However, if those 6 hours were not applied in 1 session, but distributed over 3 days, recovery was delayed to 24 hours and the effects were slightly stronger (Godde et al., 2000). One reason why the repeated application of stimulation on consecutive days is more effective, than applying the same amount of stimulation on one day, might be the importance of sleep in perceptual learning. Its consolidating role was also shown regarding other forms of sensory learning (Fahle, 2005). In summary, it seems the recovery of effects can be prolonged by stimulating more fingers or the whole hand as well as increasing the frequency but a mean to enhance performance permanently has not been found yet. Notably, to accomplish such an increase in duration, increasing the strength of effect might not be sufficient. For instance, the administration of amphetamine boosted performance stronger than whole hand stimulation, but the changes still vanished within 24 hours (Dinse et al., 2003).

Modulation of rTS induced neurophysiological and behavioral effects

To increase the strength of rTS induced effects, or to further investigate the underlying mechanisms, different variations of the protocol have been applied. Pharmacological modulations have supported the assumption that rTS might rely on LTP like processes. Namely, drugs supporting LTP induction can also increase the effects of rTS. For instance, the stronger neurophysiological and behavioural changes that rTS induced after amphetamine administration were explained through amphetamines LTP enhancing role. Amphetamine supports LTP through its influence on neurotransmitters such as dopamine, facilitates cortical reorganization and behavioral improvement induced by rTS (Dinse et al., 2003). Dinse and colleagues (2003) found that rTS under one dose of amphetamine (dosage not reported) led to an Euclidean distance between the N20 dipoles of somatosensory evoked potentials of 13.31 mm as compared to approximately 5.4 mm in the placebo condition without rTS (246 % increase) This was 166 % as much as for rTS alone (3.61 mm). In another study without drug administration, the dipole distance increased by approximately 1.5 mm only, after rTS (Pilz et al., 2004).Also the decrease in 2PD threshold after single pulse stimulation was doubled (23.1 % versus 12.6 %, respectively) as compared to the effect in the control group getting single-pulse stimulation alone (Dinse et al., 2003). Yet the shift of the dipole angles of about 4.33 degree did not significantly differ from the group that received only rTS stimulation (3.61 degree). Also dipole intensity did not significantly increase (Dinse et al., 2003), which is in line with the similar dipole intensity after burst and single pulse stimulation. No effects were found for the not stimulated left IF, indicating that amphetamine doesn’t affect tactile acuity per se, but only enhances rTS induced effects. The administration of memantine, a drug that blocks NDMA receptors, inhibited all amphetamine induced effects. This inhibiting effect of an NMDA receptor antagonist, supports the assumption that LTP induction through NMDA channels is involved in the induced behavioral and neurophysiological effects. Also other drugs that blocked the NMDA receptors involved in LTP induction, prevented stimulation effects (Dinse et al., 2003). For instance, cholinergic antagoinsts were shown to deteriorate tactile acuity by 8 %. Administration of Levodopa up to 250 mg did not influence tactile acuity, but 100 or 300 g of the dopamine inhibited any stimulation induced improvement, which was also explained through the influence of dopamine on NMDA receptors (Bliem et al., 2007).

As amphetamine, also TMS is considered a driver of brain plasticity (Hummel & Cohen, 2005) and thus to interact with rTS. If TMS was applied at the same time as single pulse stimulation, it increased the induced improvement of spatial acuity even further from around 15 %, to approximately 22 % (Ragert et al., 2003). RTS was hereby first applied singularly and 2 weeks later the applications was repeated in combination with TMS. Notably, there was an enormous difference between participants who showed strong improvement in the 1st session, where only rTS was applied, and those who showed a weak improvement in this rTS session. The latter showed a multiple of improvement (282.21 %) after combined rTS and TMS application, as compared to the improvement after rTS alone. Those who reacted well to single pulse stimulation responded less to the additional TMS application (Ragert et al., 2003). This indicates that there might be certain limits to the induction of excitability. In participants that experienced very strong changes through rTS, subsequent TMS had a weaker effect. One burst stimulation study that applied TMS *after* rTS confirmed limitations for the induction of plasticity through rTS and TMS. In this study, rTS as well as TMS induced an increase in cortical excitability as reflected by ICF, and an improvement of spatial acuity, as reflected by 2PD threshold (Tossi et al., 2013). However, if rTS was applied after TMS, this additional stimulation did not increase cortical excitability even further. Instead, excitability stagnated. This counterbalance of the two effects might indicate that they work homoestatically (Tossi et al., 2013). Thereby, the changes induced by TMS are generally stronger and build further up after the end of the stimulation. However, in this experiment also the effects found in the control group without TMS were much weaker then normally. Besides, there was no significant difference in the behavioral performance between the group receiving rTS after TMS and the group receiving only TMS. Modulation of rTS effects on tactile acuity by TMS seems to depend on rTS paradigms and timing of TMS. The opposing effects of subsequent TMS and rTS stimulation are in line with the assumption that there are certain limitations to the induction of plasticity. Several drivers of plasticity were shown to have an inhibitory rather than an excitatory effect on the cortex, if they are applied together with other excitatory stimulations (for a review see: Hummel & Cohen, 2005). It was therefore proposed that the brain balances plastic processes to prevent destabilization (Hummel & Cohen, 2005). Without this homeostatic plasticity, the risk for maladaptive plasticity might increase (Hummel & Cohen, 2005).

Another way to increase the effect of rTS is to integrate it in an active task such as frequency discrimination. Seitz and Dinse proposed in their review (2007) that not all sensory input results in learning. Instead, their model of perceptual learning includes a gating system that decides after which stimulus learning occurs. If a stimulus is reinforced or repeated, its chance to pass this gate to sensory learning is increased. Also paying attention to a certain stimulus enhances the probability that it results in learning. Thus, if participants pay attention to a stimulus, this stimulus is more likely to result in perceptual learning and respectively plastic processes (e.g. Flor et al., 2001; Liu, Poghosyan, Shibata, Khurshudyan, & Ioannides, 2005; Moseley, Zalucki, & Wiech, 2008; Recanzone, Merzenich, & Jenkins, 1992).

Possible Applications of rTS

Increasing sensory performance

One possible application of rTS is the recovery of sensory loss, or the reversal of sensory misperceptions. With regard to sensory loss, a positive effect of rTS was shown in seniors, as well as stroke patients. In stroke patients, whole hand or foot burst stimulation was shown to increase normality of somatosensory evoked potentials and upper limb sensation (Peurala et al., 2002).

In older participants, 2PD thresholds decreased by 15 % after single pulse stimulation, (Dinse et al., 2006; Kalisch et al., 2008) and by 28.4 % after burst stimulation (Voelcker-Rehage & Godde, 2010). If applied to all fingers bi-weekly, burst stimulation resulted in a 2PD threshold decrease between 15 and 23 % for all fingers that was still visible 2 weeks later (Kalisch et al., 2010). This supports a generally stronger effect of burst stimulation in seniors. The stronger effect of burst stimulation in the older population is contradictory to results in the middle aged populations, where burst stimulation seemed to influence tactile acuity rather less than single pulse stimulation. Kalisch et al. propose (2010) that electrical stimulation is more suitable to induce changes in older participants due to differences in the receptor distribution. Accordingly, mechanical stimulation activates more Merkel and Meissner cells, whose numbers decrease with age, whereas electrical stimulation (Sullivan & Hedman, 2008) activates large afferents from Golgi organs, or muscles and the skin that are equally distributed in the older and younger population. This variability in receptors cannot explain the higher effectiveness of burst stimulation, as only one of the two burst stimulation studies used electrical stimulation. However, it is possible that burst stimulation also affects different receptors than single pulse stimulation, which would explain the different effectiveness of the two stimulation protocols in populations of older age. In line with this, it has been proposed that high frequency stimulation (in the form of burst or continuous stimulation) can result in additional activation of muscle fibres (Sullivan & Hedman, 2008). Another difference between the effects observed in the middle age as compared to the older population, lies in the generally bigger size of effects. This stronger effect of rTS on tactile performance in older participants might be related to their lower baseline performance (see above). Also the recovery of changes is delayed in participants that respond very well to rTS. Changes of tactile acuity in older participants were shown to last at least 24 or 96 hours after single pulse stimulation (Dinse et al., 2006; Kalisch et al., 2008), and 1 week after burst stimulation (Kalisch et al., 2010).

Sensorimotor integration. In older participants, rTS also improved haptic object recognition that relies strongly on sensory perception. High frequency stimulation of all fingers reduced haptic object recognition time between 27 and 31 % during the 4 weeks of stimulation. Errors were reduced by 63 % after the first treatment week, respectively 70 % after week 4 (Kalisch et al., 2010). Both time and errors increased again after stimulation but significant changes could still be observed 2 weeks after the final session. Single pulse stimulation decreased the time needed to fulfil this task by approximately 20 % and the number of errors by approximately 40 %. Although the changes in time did not outlast 24 hours, errors were reduced for a minimum of 96 hours (Kalisch et al., 2008). Thus, burst stimulation improved haptic object recognition more than single pulse stimulation (also Figure 3). Probably due to the repeated stimulation in this study, the changes were also longer lasting.

Reversal of maladaptive plasticity

Treatment of painful misperceptions. Sensory misperceptions occur when the brain confounds incoming signals from the sensory systems. This can lead to the abovementioned mislocalization, but in extreme cases it can also result into painful sensations like phantom limb pain. The effectiveness of electrical stimulation to reduce pain was first shown in 1967 during 100 Hz afferent stimulation of patients with neuropathic pain (Wall & Sweet, 1967).

Several underlying mechanisms have been proposed for the reduction of pain after tactile stimulation. While it is probable that different forms of pain reduction base on distinct mechanisms, there is evidence that some forms of pain can be diminished through the help of hebbian plasticity through rTS. Exemplarily, in complex regional pain syndrome, painful sensations were related to shrinkage of cortical representations in S1 and increased 2PD threshold (Pleger et al., 2005). Recovery of pain was accompanied by a decrease in 2PD (Moseley et al., 2008; Pleger et al., 2005) and a normalization of cortical representations (Maihöfner, Handwerker, Neundörfer, & Birklein, 2004; Pleger et al., 2005)

Furthermore, Flor et al. (1995) reported that phantom limb pain might be related to cortical reorganization and can be treated with rTS as well. They found that the lips cortical representation had increased after amputation and innervated the cortical representation of the amputated limb, which correlated to the magnitude of phantom limb pain. One way to reverse this effect should be to re-establish the normal topography and size of the cortical representations neighboring the representation of the amputated limb. In a follow up study, Flor et al. (2001) therefore applied 10 session of 90 minutes stimulation at 50 Hz to the limb, during which participants had to discriminate the frequency and location of stimulation. This resulted in a decrease of pain magnitude. The decrease was correlated with reorganization of the cortical representations as well as improved sensory performance, which indicates that the mechanisms underlying this pain reduction are indeed similar to those applied in rTS. Further support for an involvement of hebbian learning processes was found by Huse et al. (2001), who applied asynchronous stimulation of 1-10 Hz to the lip and amputated limb for 2 weeks at 60 minutes a day. As, asynchronous stimulation usually increases the distance between cortical representations, it is possible that the lip and arms cortical representation were segregated through the stimulation. Indeed, the dipole amplitude of the lips cortical representation, increased as reflected through MEG. This increased amplitude was supposed to reflect an enlargement. The change in dipole amplitude correlated significantly with the decrease in pain magnitude (Huse et al., 2001). Also an improvement of sensory performance was found. Another study by Moseley and Wiech (2008) confirms that phantom limb pain can be diminished through tactile training and the respective cortical reorganization. The authors further report that the training affects pain and cortical reorganization more, if participants watch a reflection of their unaffected limb during the task (Moseley & Wiech, 2009). Changes recovered in less than 48 hours. In this study, pure tactile stimulation, without active training of the task, did not reduce pain. Notably, a very low stimulation frequency was used (approximately 0.066 Hz) for a rather short stimulation time of 24 minutes. Based on the results of basic research this choice of parameters does not seem to be sufficient to induce changes in tactile perception or cortical reorganization. That the stimulation was still successful if it was combined with active training of the task could be explained through the abovementioned supportive role of attention and training in learning. However, the low intensity of parameters poses the question, whether a more effective choice of stimulation parameters could not have increased the duration or strength of results.

There are further studies that found a positive effect of TENS on phantom limb pain (e.g. Mulvey et al., 2012), but to our knowledge, none of these studies assessed cortical reorganization or tactile performance. This makes it hard to judge whether they rely on the same hebbian mechanisms. Therefore, it is beyond the scope of this review to evaluate the effectiveness of the applied protocols. On the one hand, there are some similarities between the induced effects. Exemplarily, frequent TENS in patients with osteoarthritis enabled cumulative effects and long-term changes, indicating plastic processes (Cheing & Chan, 2009). On the other hand Kröling and Gottschild showed that the effect of TENS on the pressure pain threshold is not restricted to the stimulated body part, indicating cortico-spinal effects rather than reorganization of the affected body part (Kröling & Gottschild, 1999). Besides, burst stimulation did not significantly alter the pressure pain threshold (Kowalewski et al., 2012). Additionally, in certain forms of pain, TENS might not be a treatment option at all (for a review see exemplary: Sluka & Walsh, 2003).

Treatment of spastic cramps following maladaptive reorganization. Some patients suffering from maladaptive cortical plasticity, experience spastic cramps in the form of non-controlled actions of the muscles, as well as co-contraction of antagonist and agonist muscles (Tamura et al., 2009). Those forms of spasticity that base on maladaptive reorganization of cortical representations can be treated through hebbian learning. This is the case in patients that suffer from focal hand dystonia or writer's cramp, a form of spastic cramps, which occurs during motor tasks. There is evidence that these symptoms rely at least partly on an increased overlap between the cortical representations of the fingers, often due to frequent fast use of these fingers (Tamura et al., 2009). This fast use leads to simultaneous input to the fingers, which results in an integration and stronger overlap of the fingers' cortical representations. As a consequence, separate movement of the fingers is complicated by the common cortical activation. This phenomenon can in part be overcome by asynchronous rTS, which is known to separate receptive fields and cortical representations (Schabrun, Stinear, Byblow, & Ridding, 2009).

Effects of rTS on the motor level.

Next to its positive effect on sensory perception, rTS has also been shown to improve motor performance, especially after brain injury related impairments. Several neurophysiological processes were proposed to underlie the improved motor performance after rTS: Firstly, the enhanced sensory perception and processing after rTS might also have a positive impact on performance in motor tasks. Sensory information influences motor output, as it is necessary to fulfil a wide range of motor tasks. The impairment of tactile acuity might deteriorate performance in those tasks (Augurelle, Smith, Lejeune, & Thonnard, 2003; Kalisch et al., 2010). Correspondingly, enhancing tactile acuity should improve especially fine motor performance (Kalisch et al., 2010). While the results on a correlation between tactile and motor performance vary (Kowalewski et al., 2012; Thonnard, Saels, Van den Bergh, & Lejeune, 1999), several studies found an interaction of motor recovery and sensory measures in stroke (for a review see: Sullivan & Hedman, 2008). For instance, recovery in motor performance was related to a normalization of the somatosensory evoked potentials from the affected limb (Peurala et al., 2002). Thus, it is probable that part of the increased motor performance bases on improved tactile abilities.

Secondly, it was proposed that improved motor performance after rTS bases on the increased connectivity between sensory and motor cortex that was observed in EEG (Freyer et al., 2012). The increased sensorimotor integration might be especially important in grasping tasks which demand a fine interplay between feedfoward and feedback control. Furthermore, enhanced interconnectivity could increase the spread of plasticity promoting processes, like increased excitability, from the sensory to the motor cortex (Freyer et al., 2012). Indeed, somatosensory input was proposed to influence plastic processes in the motor cortex, like learning and the recovery from lesions (Hummel & Cohen, 2005).

Thirdly, there are multiple evidences that rTS exerts an effect on the motor cortex itself, distinct from the effect on sensory cortex and sensorimotor integration. RTS increased activity in M1 as well as S1 was found through fMRI (Christova et al., 2012; Wu et al., 2005) and MEG (Golaszewski et al., 2010; Golaszewski et al., 2012; Kowalewski et al., 2012). Indeed, Wu et al. found an even bigger increase of activation in M1 than in S1 (Wu, van Gelderen et al. 2005). In another study the effects were longer lasting in M1 than in S1 (Golaszewski et al., 2004). This long duration of rTS effects in the motor cortex indicates the induction of plastic processes also in this area (Christova et al., 2012; Wu et al., 2005). The changes in M1 further resemble those in S1 in their spatial restriction. For instance, stimulation of the foot did not induce any changes in the cortical representations of upper extremities (Christova et al., 2011). Moreover, stimulation at specific nerves seemed to affect only motor evoked potentials (MEPs) of the muscles innervated by this specific nerve (Kaelin-Lang et al., 2002; Ridding, McKay, Thompson, & Miles, 2001). To see, whether the same rules of effectiveness from basic research can be applied to increase motor performance through rTS, it would be important to know in how far effects in the motor domain base on similar hebbian plasticity.

Research has uncovered several neurophysiological effects of rTS on the motor cortex, whereas the choice of protocols influences these various measures differently. It is beyond the scope of this review to summarize all studies dealing with a respective rTS induced plasticity in the motor cortex (Chipchase, Schabrun, & Hodges, 2011; J. R. de Kroon, IJzerman, Chae, Lankhorst, & Zilvold, 2005; for a related review see e.g. Stefan et al., 2000). Also, in case of stimulation protocols that evoke muscle contractions it is difficult to judge, whether the plastic changes in the motor cortex result from sensory input or muscle activation. We will thus focus on evaluating the effectiveness of somatosensory stimulation protocols in behavioral and neurophysiological motor changes. If these somatosensory stimulation protocols are also effective in inducing effects in the motor domain, it is possible that the respective motor effects rely on similar hebbian plasticity.

RTS induced behavioral effects on motor control and possible underlying mechanisms. Especially in stroke patients, tactile stimulation is used as a means of recovering motor impairments, including spasticity, paralysis and fine motor impairments. Spasticity is a frequent following of stroke. Because spastic cramps in stroke patients are not as clearly related to maladaptive plasticity as in writer’s cramp and dystonia (see above), stimulation protocols differ and concentrate more on activation of the muscles and motor cortex. However, there is some indication that hebbian learning is involved also in the results from these studies treating spasticity in stroke patients (see below). Thus we will also discuss some examples of stimulation over muscle points in this context. As, spastic cramps in stroke patients are related to hyperactivity and inhibition of motor commands (Levin & Hui-Chan, 1992), rTS is in this context often not used to increase excitability, but to inhibit hyperactive reflexes through somatosensory or muscle stimulation at very high frequencies (90-100 Hz). Repeated stimulation at such high frequencies, was shown to decrease hyperactivity of reflexes, ankle plantarflexor spasticity, and resistance to passive movement (Levin & Hui-Chan, 1992) as well as the overall signs of spasticity on the

Ashworth Scale of Spasticity (80 % in the upper extremity and 100 % in the lower extremity) (Adak & Göksoy, 1998). At the same time, it inhibited the spastic muscle (Levin & Hui-Chan, 1992), increased maximal voluntary contraction and ample dorsiflexion (Ng & Hui-Chan, 2007).

With regard to somatosensory stimulation protocols, low frequency TENS (1.7 Hz) applied over several sessions did, not influence signs of spasticity (Sonde, Gip, Fernaeus, Nilsson, & Viitanen, 1998), even though the choice of parameters was sufficient to induce plasticity according to basic research. Also subthreshold sensory stimulation was found to be inefficient (Levin & Hui-Chan, 1992). Yet, sensory stimulation of the palm at 25 Hz reduced spasticity measured through the Ashworth scale by 10 % (Sullivan & Hedman, 2007). This might indicate that treatment of spasticity demands stronger stimulation parameters than those applied in some somatosensory stimulation protocols. However, somatosensory protocols that applied higher frequencies might still be effective to treat spasticity. One explanation for this varying effect of somatosensory stimulation protocols could be that the recovery of spasticity is also dependent on other factors but sensory input. Levin and Chan (1992) propose that the recovery of spastic reflexes is divided into several phases, relying on different mechanisms. According to the authors, hyperactive motor reflexes inhibit voluntary motor commands, which hinders the recovery of cortico-motor connections that could be induced through hebbian learning. Only after this hyperactive motor activity is diminished, these neuronal connections could possibly be re-established (Levin & Hui-Chan, 1992). Thus, hebbian mechanisms might support the recovery of spasticity after stroke, but only if recovery of more spinal mechanisms occurs beforehand. This need for a previous inhibition of muscle reflexes, could explain the relative effectiveness of protocols using very high frequencies (10-90 Hz). Especially in the beginning of treatment, these higher frequencies would be favorable, as hyperactive reflexes that suppress need to be inhibited before motor neural pathways can recover. When this recovery is enabled, hebbian learning might re-establish the neuronal connections, through unmasking of synapse connections or sprouting of new synapses (Sullivan & Hedman, 2008), both of which could be related to hebbian learning. This involvement of hebbian learning could then explain the effect induced by stimulation also at the lower frequency of 25 Hz (Sullivan & Hedman, 2007). Indeed, in this later phase of recovery, somatosensory stimulation protocols might be even more effective in inducing recovery, as they induce excitation and increase synaptic efficacy (see above).

RTS further improves motor control in stroke patients through its influence on paralysis that is the loss of function in a muscle, which is often accompanied by sensory loss in the respective area. It is difficult to judge, in how far this improvement after rTS is related to hebbian mechanisms. On the one hand, stimulation at sensory threshold and lower frequencies was more successful in recovering signs of paralysis as compared to signs of spasticity. Exemplarily 1.7 Hz TENS just above the somatosensory threshold, which is rather similar to single pulse stimulation, improved the movement velocity of the wrist, fingers and hand (Koesler, Dafotakis, Ameli, Fink, & Nowak, 2009). Also repeated electrical stimulation at 2 Hz and muscle intensity for 1 hour at 10 days, which is comparable to the parameters applied in whole hand stimulation protocols, improved the effects of this motor training on kinesthesia sense, hand functioning and hand movement (Yozbatiran, Donmez, Kayak, & Bozan, 2006).

On the other hand, one study that applied stimulation parameters resembling those of burst stimulation (35 Hz for 30 minutes) to the peroneal nerve, did not add effects to motor training in any measure of paralysis, including ample dorsiflexion, volitional movement and kinematic characteristics of gait and performance on the Brunnstorm scale of stroke recovery (Yavuzer, Öken, Atay, & Stam, 2007). Instead, stimulation of the wrist extensors at 20 Hz at motor intensity for 8 weeks did improve the wrist extension angle for at least up to 16 weeks later (Powell, Pandyan, Granat, Cameron, & Stott, 1999).

The diversity of results indicates that the protocols used in basic research have a positive effect on some dimensions of motor control, but not all of them. Stronger stimulation at muscle threshold might be needed to affect those other dimensions, like movement range and dorsiflexion. Furthermore, repeated stimulation might be necessary to improve motor performance beyond increased velocity. However, the results of studies assessing general measures of paralysis also show that lower frequency stimulation can influence some measures, like wrist extension, hand functioning and kinesthesia sense (Koesler et al., 2009; Yozbatiran et al., 2006).

Next to muscle function in the arm, also grasping strengths of the fingers could be modulated after tactile stimulation. However, most TENS protocols were ineffective, in influencing grasping forces in stroke patients. Neither low frequency TENS of the median nerve at supra- or subsensory intensity (Conforto et al., 2010) nor of the median and ulnar nerve at sensory intensity (Klaiput & Kitisomprayoonkul, 2009) influenced grasping forces. Also low frequency TENS of the arm or the wrist extensors (20 Hz) at motor intensity had no influence (Powell et al., 1999; Sawaki, Wu, Kaelin-Lang, & Cohen, 2006). Only, if the site of stimulation was increased to the median and ulnar nerve, *and* the intensity was increased to induce strong paresthesia, this led to an increase in tip grip strength by 10.35 % and in lateral pinch strength by 9.6 % (Klaiput & Kitisomprayoonkul, 2009). Also stimulation at 40 Hz, eliciting maximal contraction influence both, grip strength (15 %) and pinch strength (35 %) in stroke patients (Thrasher, Zivanovic, McIlroy, & Popovic, 2008). Thus, it seems that the parameters used in somatosensory stimulation are not sufficient to influence grasping forces.

Possibly increases in grasping strength need a high amount of stimulation that can only be reached by combining either a bigger site of stimulation or a high frequency with muscle contraction.

This variable effect of the sensory based protocols, can explain some of the variation of the rTS induced effect on general measures of motor function. The improvement in these measures is related to recovery of spasticity and paralysis. For instance, stimulation of the antagonistic muscle at 100 Hz, intended to reduce spasticity, also increased the Barthel activities of daily living, such as mobility, dressing, feeding, by 164 % (Adak & Göksoy, 1998). Stimulation at 2 Hz and motor intensity, improved the score for Barthel activities by 160 % (B. B. Johansson et al., 2001). Low frequency TENS that did not decrease spasticity, but only paralysis also had varying effects on measures of motor performance. Performance as measured through the Barthel scale did not improve after this low frequency TENS (Sonde et al., 1998). Yet Barthel scale scores stayed constant until 3 years after stimulation, whereas they deteriorated in the control group. Low frequency TENS increased performance in the Fugl Meyer Assesment of Motor Recovery, by the low amount of 11.9 % (Sonde et al., 1998).

However, not all performance improvement in daily living tasks can be explained through decreased paralysis and spasticity. Stimulating wrist extensors for 8 weeks at 20 Hz did not influence Barthel activities of daily living, even though it decreased signs of paralysis (Powell et al., 1999). Also some stimulation parameters that were too weak to affect either spasticity or paralysis were effective in increasing the performance in daily activities. For instance, subsensory stimulation was able to induce an effect on Barthel activities, if applied at 80 Hz to the elbow region and the thenar muscle. The results were the same as after electroacupuncture or 2 Hz muscle stimulation (B. B. Johansson et al., 2001). All improved Barthel activities of daily living by approximately 160 % up to 12 months after stimulation (B. B. Johansson et al., 2001). Furthermore, one protocol, applying muscle stimulation at 40 Hz during motor tasks in sessions of 45 minutes, increased Barthel activities of daily living, but only by 50 % and performance in the Fugl Meyer Assesment by 40 % (Thrasher et al., 2008). No stimulation protocol was able to induce an effect on functional independence measures, another measure of daily living activities- neither TENS in single-session (Wu, Seo, & Cohen, 2006) nor repeated setting (Conforto et al., 2010) oor muscle stimulation at 40 Hz (Thrasher et al., 2008). This is surprising, as the Barthel scale activities of daily living and the functional independence measures are proposed to be equally responsive to recovery (Wallace, Duncan, & Lai, 2002).

Therefore, higher frequencies and intensities are not generally more efficient in increasing motor control. Part of this variation in results might be explained through the stimulation rhythm. It was suggested that rTS, if it mimics the natural EMG patterns of movement, could reactivate motorneurons in the cortex (L. E. Smith, 1990). This activation should lead to new inter-neural connections. The so induced reorganization of the neuronal network should help to compensate for the cerebrovascular damage (L. E. Smith, 1990). A protocol that applied such muscle stimulation mimicking the patterns of limb movement in hourly sessions for a year, led to a 90 % increase of volitional movement in the upper limbs and 69 % in the lower limb (L. E. Smith, 1990).

Functional abilities. Kroon et al. (2002) distincted between motor control (range and strength of movement, activities of daily living) and functional abilities (tasks requiring fine motor coordination and the movement of small objects. They did conclude on a positive effect of rTS on motor control, but stated that there were not sufficient studies on functional abilities, to make final conclusion about the effect of electric stimulation on functional abilities. Including the recent studies on this topic and the results from basic research, enables further insight into the question whether rTS is able to improve motor function on a fine motor level.

Of the studies that focused on motor control of the upper limb, only two further investigated fine motor control that is important for functional abilities. Hereby TENS failed to influence measures of dexterity, like peak wrist position or aperture and the amplitudes of finger tapping (Koesler et al., 2009). Additionally, after 2 Hz stimulation at muscle intensity, the ability to perform isolated digit movements did not improve more than after motor exercises (Yozbatiran et al., 2006). Nevertheless, there are multiple evidences for improved fine motor coordination through rTS, such as the assessment of grasping abilities. Grasping relies on several different dimensions, including grip- and pinch strength as well as modulation, preload duration and the adaption of grip force to load force during the lift. A frequent measure to assess fine motor control reflected through grasping performance is the Action Research Arm Test (ARAT), which reflects fine motor coordination, dexterity and function (McDonnell, Hillier, Miles, Thompson, & Ridding, 2007). Low frequency stimulation protocols were not able to induce changes in this task. Single Pulse (0.66 Hz) muscle stimulation only improved the adaption of grip force to load force during the lift (by approximately 16 %), which was not correlated to the ARAT scores (McDonnell et al., 2007).Also TENS over the median and ulnar nerve did not affect ARAT scores regardless of whether the intensity was set to strong paresthesias or sensory threshold (Klaiput & Kitisomprayoonkul, 2009). In opposition to that, continuous sensory stimulation of the palm at 25 Hz for 15 minutes increased ARAT performance in those 6 out of 10 participants that had the lowest baseline performance (Sullivan & Hedman, 2007). Continuous 20 Hz stimulation of the wrist extensors resulted in a 66 % improvement of the ARAT score (Powell et al., 1999), whereas this improvement based on an increase of the grasp and grip subscores, but not the pinch or gross movement. Eight weeks later, the differences between stimulation and control group had vanished. The result from studies assessing grasping abilities indicate, that improvement in the ARAT score can especially be induced by higher frequency stimulation, but does not necessarily demand muscle stimulation. However, tactile burst stimulation of the fingers did not influence grip force modulation in seniors (Voelcker-Rehage & Godde, 2010). This might be due the one-session design of this study. In both studies that did report an effect, several sessions of stimulation were applied. Besides, also in motor control, measures of dexterity changed only after repeated stimulation (see above). Notably, low frequency stimulation did improve upper extremity function, as measured through the Jebsen Taylor Hand Functioning Task (JTHFT). TENS, at an intensity inducing strong paresthesias, improved performance in this task by 15 % (Conforto et al., 2007), and at suprathreshold intensity influenced performance by 5 % in one study (Wu et al., 2006). After subthreshold stimulation, only a 3 % improvement was observed (Conforto et al., 2007), indicating a dose dependent influence of intensity. However, if it was repeated in several sessions, subthreshold stimulation was most effective in increasing JTHFT scores (43 %), whereas the improvement in the group receiving suprasensory stimulation was not significant (Conforto et al., 2010). Possibly, the efficiency of sub- and suprathreshold stimulation changes with increased stimulation time. Another explanation could be that the recovery is divided into several stages and that rTS has different effects during those different phases, as it was also proposed for spasticity.

Another task that is used to assess fine motor abilities is the pegboard task. This task was also used to assess the effect of somatosensory stimulation protocols (Kalisch et al., 2008; Voelcker-Rehage & Godde, 2010). Hereby, single pulse stimulation of all fingers decreased the number of errors in this task by more than 80 % (Kalisch et al., 2009). Also the time needed was reduced by approximately 17 % in both forms. The induced changes lasted up to 96 hours (Kalisch et al., 2008). In opposition to that, burst stimulation had a smaller influence on this task. Repeated burst stimulation applied to all fingers reduced the number of errors by 66 % only, with no further decrease or lasting changes. However, the performance of the control group decreased between sessions. Regarding performance speed, burst stimulation induced changes after several stimulation sessions only, but for a duration of 1 week (Kalisch et al., 2010). If applied to D1 and D2 and for a single session, it improved performance only in a demanding version of the pegboard task by 5 % (Kowalewski et al., 2012), and did not have any effects on performance of an older participant's group in the intermediate version (Voelcker-Rehage & Godde, 2010). Stimulation of the wrist extensors at 20 Hz over 8 weeks did not influence performance in the 9 holes peg test (Powell et al., 1999). This delayed, weaker or lacking effects of burst stimulation in grasping measures and pegboard task, might indicate that single pulse stimulation is more successful in improving fine-motor performance, which is contradictory to the results from habtic object recognition (see Figure 3). Yet the results of the repeated stimulation study also show that an apparently absent effect after the first session might still induce some changes that form the basis for cumulative and long-term effects. Such cumulative effects would then only reveal after several sessions.

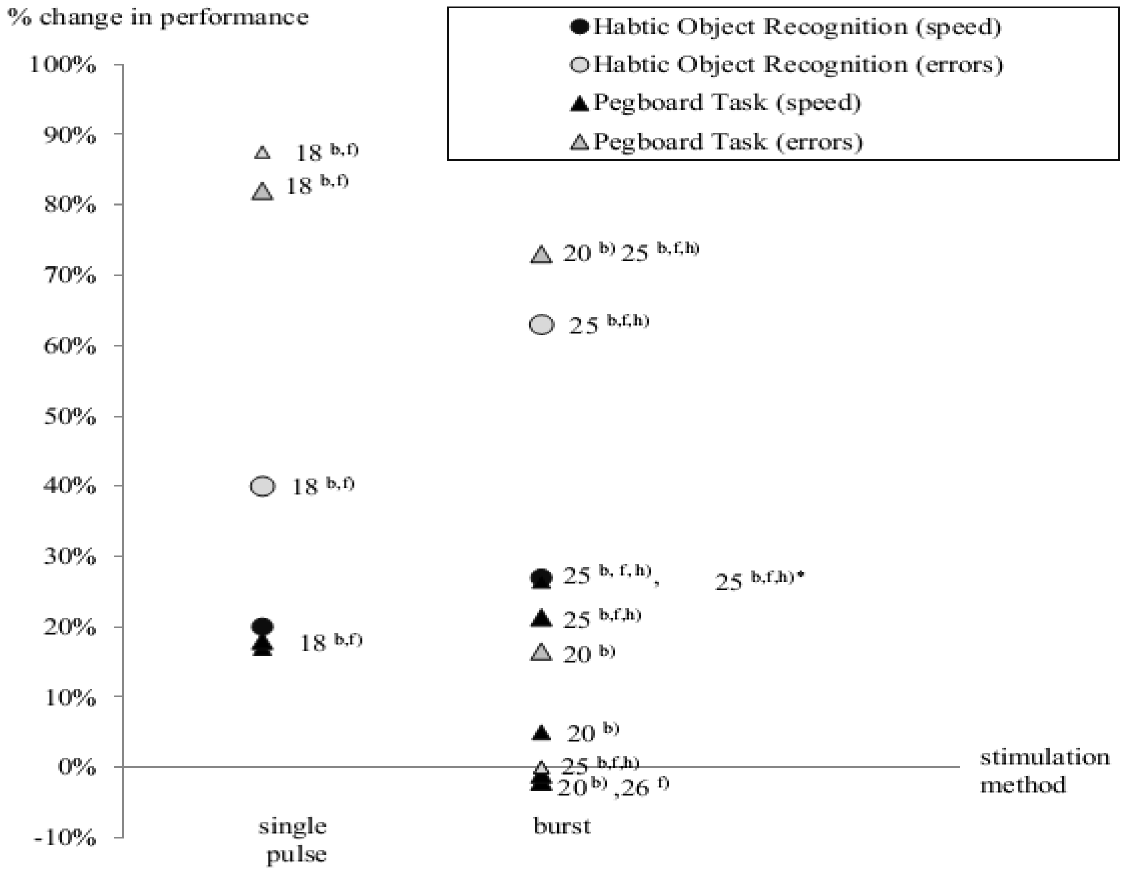

Figure 3. Influence of Single pulse and burst stimulation on pegboard performance as compared to haptic object regognition.

b) multiple fingers; f) older participants; h) repeated stimulation; *effects only occurred after several weeks; Numbers refer to the numbers assigned to each study in Table 2

The relatively big differences between protocols that were able to improve grasping abilities, ARAT, JTHFT and pegboard performance (subsensory, suprasensory as well as very strong muscle stimulation) could be due to the different forms of abilities that underlie the performance in these tasks. Grasping performance relies on grip strength, which seemed to improve only after a very strong choice of parameters, but also on sensory abilities, that were shown to improve after relatively light stimulation parameters. Respectively, studies assessing fine-motor performance found very strong effects also after the protocols used in sensory stimulation research.

In sum, rTS can improve some aspects of motor recovery. Most probably, different mechanisms underlie those aspects, making it difficult to draw general conclusions about effective stimulation parameters. Motor function improved more after stimulation at higher frequencies and longer stimulation protocols. Fine motor coordination improved more after single pulse stimulation. Relatively strong stimulation parameters were most effective in decreasing spasticity and paralysis or increasing grasp forces, which might indicate other underlying mechanisms than hebbian plasticity. These different effects of stimulation parameters on different dimensions of motor tasks are reflected in the effect on performance in general motor tasks, such as the ARAT score and the JTHFT.

Facilitation of rTS treatment effects on motor abilities. The combination with motor training is a suitable way to increase the effect of rTS in stroke patients. Adding motor training to the protocol reduced the pegboard time after TENS at mild paresthesias by about 6.9 % (Celnik, Hummel, Harris-Love, Wolk, & Cohen, 2007). This effect was significantly higher than that of mere motor training and increased even more in the second measurement 24 hours later (8.9 %) (Celnik et al., 2007). Yet, there was no effect of rTS on errors in this task (Celnik et al., 2007).

In the patient group suffering from cortico-subcortical stroke, stimulation effects on pegboard performance were increased by 65 % through additional motor training (Conforto et al., 2007). The strength of effect was the same as in the group that received sham stimulation and motor training. Yet, the remaining effect after 30 days was much bigger in the group that received actual stimulation (Conforto et al., 2007). This indicates that rTS can increase the duration of effects, even if it does not increase the effect's strength. Thus, in some of the studies that found no additional effect or rTS on motor training, there might have been a delayed effect that was not revealed because no second measurement was taken.

Also in stroke patients suffering from spasticity, some positive effects on movement range and control, only occurred or lasted, if motor training was added to the treatment (Ng & Hui-Chan, 2007), indicating that motor training is a valuable addition to rTS and can lead to further effects and longer duration of improved motor performance.

Another mean to increase the effect of rTS on motor performance is to combine it with TMS. A protocol combining TMS, TENS and subsequent motor training led to a 43 % increase in performance in a keyboard typing task. If they were applied separately, TMS led to 22.7 % improvement and rTS to 15.4 % improvement only (Celnik et al., 2009). Changes did not fully recover until 6 days later, whereas the strength of effect was still bigger in the group that received all three treatments (Celnik et al., 2009). Also in basic research, TMS increased plastic changes induced through single pulse stimulation if applied in combination with rTS. This supports the assumption that motor recovery, after stroke bases on similar hebbian mechanisms.

Furthermore, the variation in the effectiveness of different stimulation protocols to induce motor recovery may be explained by inter-subject variability. A review by Kroon et al. (2002) on the effectiveness of electrical stimulation after stroke rejected an influence of the time after stroke onset or the method of stimulation. However, the authors reported a better responsiveness to treatment in patient groups that were less severely affected. Also the area affected by the stroke has an influence on the effectiveness of treatment (Conforto et al., 2007). Besides inter-subject variability, there is also a very big variation in the study protocols, which restricts comparability. Furthermore, the choice of control groups was very different between studies, because few studies used actual sham stimulation but compared participants to no-stimulation groups or groups that received another form of stimulation.

Neurophysiological processes at the motor level and relation to behavioral measures. Basic research on the influence of rTS on the motor cortex can shed some further light on the mechanisms underlying the increased motor performance after stimulation and the question, whether these rely on hebbian learning. Several studies propose an enlargement of cortical representations after rTS not only in S1 but also in M1 (Christova et al., 2012; Golaszewski et al., 1999; Golaszewski et al., 2004; Wu et al., 2005). Hereby, TENS stimulation was more successful in comparison to mechanical stimulation protocols in increasing the BOLD signal intensity as well as the activated clusters (Christova et al., 2012; Golaszewski et al., 2004; Wu et al., 2005). Also with regard to the MEP amplitudes, TENS was more or equally effective than mechanical short burst stimulation, even if the latter was combined with motor contraction (Kaelin-Lang et al., 2002; Ridding et al., 2001; Ridding, Brouwer, Miles, Pitcher, & Thompson, 2000). Notably, here increasing stimulation site by stimulating radial *and* ulnar nerve did not increase effects (Ridding et al., 2000). The increased cortical representations might give some more explanation for the stimulation-induced improvement of motor performance in stroke patients. Namely, motor impairment after stroke was indeed related to cortical representations. After stroke, these representations were shown to be smaller for the impaired side, as compared to the unimpaired side. Recovery through motor training led to an increase of these cortical representations towards normalization (Liepert, Bauder, Miltner, Taub, & Weiller, 2000).

The overall stronger effect of TENS protocols on these measures might be due to the more direct activation or the longer duration of stimulation in TENS as compared to tactile stimulation protocols. A shift of center of gravity or activational hot spots in M1 could only be seen after TENS of the radial and ulnar nerve at 3 times perceptual threshold (Ridding et al., 2001), but not after similar TENS of only the ulnar nerve (Ridding et al., 2000) or continuous high frequency stimulation over muscle points (Meesen et al., 2011). Yet this might be due to the different directions of movement of Center of Gravity that possibly cancel each other out when an average is calculated (Ridding et al., 2001).

Concerning the motor threshold, TENS had no effect, regardless of the applied intensity in either the healthy population (Chipchase et al., 2011; Kaelin-Lang et al., 2002; Mima et al., 2004; Ridding et al., 2000) or patients with subacute stroke (Celnik et al., 2007). One protocol applying motor stimulation at 0.67 Hz frequency on average for 1 hour in 9 sessions, prior to motor training could not affect either motor threshold, MEP amplitudes or recruitment curves (McDonnell et al., 2007), which might be due to the relatively low frequency and stimulation time. Stimulation of the whole *hand* at sensory intensity was only effective if it was applied at 50 Hz (2.5-3.5 % increase of motor threshold) (Golaszewski et al., 2010; Golaszewski et al., 2012), but not at 10 or 25 Hz (Christova et al., 2011). However, at *motor* intensity, stimulation of 2 Hz was sufficed to induce a strong decrease of motor threshold of about 3.9 %. Short stimulation together with voluntary contraction protocol lowered the motor threshold by 2.4 % (Christova et al., 2010). Accordingly, it seems, changes in motor threshold can only be achieved by indirect stimulation in conjunction with high frequencies or motor contraction, but not by stimulation of the nerves. Thus, affecting the motor threshold might demand a stronger choice of parameters than those applied in somatosensory stimulation. These parameters resemble those that are necessary to affect grasping force.

Also the increase of MEPs might rely on different mechanisms and demand for stronger stimulation parameters. In stroke patients TENS of the radial and ulnar nerve eliciting mild parenthesis did not induce any effect on the amplitude or recruitment curve of MEPs even though it sufficed to increase performance in the pegboard task (Celnik et al., 2007).

Furthermore stimulation at a very high frequency decreases MEPs (30 min, 90 Hz) (Mima et al., 2004), but increased the volume and sites of activation in fMRI (100 Hz, 60 minutes) very strongly relative to other stimulation protocols (Meesen et al., 2011; Ridding et al., 2001). Possibly high frequency stimulation has a different effect on excitability of the muscles as compared to cortical excitability and reorganization. This would also explain how continuous high frequency stimulation in patients with spasticity could first inhibit the hyperactive reflex and later increase the connectivity to the motor neurons, increasing the transfer of exciting signals. Indeed, Chipchase and colleagues (2011) state in their review on electrical stimulation parameters and MEPs that stimulation at motor intensity is more suitable to increase motor performance and excitability, but that both suprasensory and motor stimulation have a similarly variable effect on excitability of the corticomotor pathway. This supports different effects of stimulation with regard to the cortex as opposed to the corticomotor pathway. To explain the stronger effect of stimulation at motor intensity on MEPs, Chipchase and colleagues (2011) further proposed that stimulation at motor intensity is able to induce changes in other groups of the motor cortical pathway, including muscle fibers and motorspinal neurons, but stimulation at sensory intensities might have a larger effect in exciting also antagonist muscles (Chipchase et al., 2011). Besides they suggested that also differences between the corticobulbar and corticospinal pathway might play a role in the variable effects of stimulation at motor and suprasensory intensities. At last, this review also found a positive relation between stimulus duration and delayed recovery time of the induced changes.

Also intracortical facilitation and inhibition were differently influenced by stimulation intensity. Whole hand stimulation at *sensory* intensity changes ICF and ICI by the same amount, if applied at 50 Hz (Golaszewski et al., 2012). If the frequency is lowered to 25 Hz, stimulation at sensory intensity influences ICF more than ICI (Christova et al., 2011).

In opposition to that, stimulation in conjunction with motor contraction, including motor intensity rTS, affected only ICI to a similar amount as sensory stimulation, but ICF less (Golaszewski et al., 2012) and partly later (Christova et al., 2010). Also in stroke patients, TENS of the median and ulnar nerve at the level of mild paresthesias reduced ICI but not ICF beyond simple motor training (Celnik et al., 2007). Accordingly, motor stimulation might be more effective in influencing ICI as compared to ICF. With regard to ICF, sensory stimulation might be more effective. The equal effectiveness of 50 Hz sensory stimulation on ICI and ICF might be explained by the stronger muscle activation after high frequency stimulation (Sullivan & Hedman, 2008).Another study applying similar 50 Hz whole hand stimulation found a stronger effect of sensory stimulation on ICI as compared to ICF (Golaszewski et al., 2010). However, these effects appeared only in the second measurement 1 hour after stimulation offset, which might have influenced the results (Golaszewski et al., 2012).

Regardless of the stimulation intensity, a certain frequency and size stimulation site seems necessary to influence ICI as well as ICF. TENS of only a single nerve could neither influence inhibition nor facilitation, whether it was applied at motor threshold (Kaelin-Lang et al., 2002), sub- or suprathreshold intensity (Conforto et al., 2010). The only low frequency TENS study that influenced these measures was combined with motor training and stimulation of 2 nerves (Celnik et al., 2007). This indicates again that some of the parameter combinations applied in rTS are likely to be too weak to induce certain effects on the motor level.

With regard to rTS applications, stimulation-induced modification of ICI and ICF could also play a role in stroke recovery, as many patients suffer from maladaptive excitation and inhibition. It is assumed that the neuronal loss in one hemisphere of stroke patients causes and increased inhibition from the other hemisphere. One treatment option is therefore to reduce this inhibition through counter-inhibition of the intact hemisphere itself, or excitation of the impaired hemisphere (for a review see exemplary: Dancause & Nudo, 2011). For instance, Floel and colleagues (2008) showed that anaesthesia of the intact hand can decrease inhibition through the respective hemisphere and increase finger tapping speed of the impaired hand. Tactile stimulation could mimic this effect, as it can induce a similar overweight of input to the impaired hand. The importance of diminishing inhibitory processes in stroke recovery could further explain the relative effectiveness of high frequency and motor contraction protocols, because these have a stronger influence on inhibitory than excitatory processes in the cortex, as compared to sensory stimulation (see above).

Regarding the duration of the induced changes, TENS of the ulnar nerve led to changes of only 20 minutes (Ridding et al., 2000). Similar stimulation to the radial *and* ulnar nerve resulted in changes of 30 to 40 minutes (Ridding et al., 2001). Stimulation protocols using voluntary or stimulation induced motor contraction induced changes after relatively short time (10-30 minutes), but these tended to vanish faster (Christova et al., 2010) or not to build up after stimulation (Golaszewski et al., 2012), even if stimulation was sustained for 2 hours (Kaelin-Lang et al., 2002).

In sum, stimulation at motor intensity seems to induce more decrease in motor threshold, while stimulation at sensory intensity was more successful in increasing MEPs. Again, the choice of parameters influences the outcome of distinct neurophysiological and behavioral measures differently, which might also indicate different underlying mechanisms. Yet, the findings on neurophysiologogical and behavioral effects show that also the protocols used in somatosensory stimulation can be sufficient to induce certain changes in the motor domain. With regard to recovery after stroke, this might be especially useful concerning the reestablishment of neural connections and interhemispheric balances, both of which are assumed to be crucial for recovery (Sullivan & Hedman, 2008). However, there is only one study yet, applying an exact rTS protocol from basic research (burst stimulation) to stroke patients. In this study, the results were very promising, including improvement in pegboard performance, haptic object recognition and sensory recovery (P. S. Smith et al., 2009). Yet, due to the small number of participants in this study, no general conclusions can be drawn.

Conclusions

Comparing the outcome of different stimulation protocols shows that the choice of parameters indeed has a big influence on the induced effects. Firstly, some of the protocols were able to induce effects that others failed to show. Secondly, the protocols interacted differently with variations of the procedure, like adding TMS, pharmacological treatments, or motor training as well as changing the frequency or duration of stimulation. Thirdly, the protocols differed in the longevity of the changes they induced.

From these differences, we can provide some general recommendations for effective simulation protocols. The effectiveness of parameter choice seems to rely on a balance of frequency, duration and intensity. Taken together, they need to induce a certain minimum of excitation.

Decreasing the intensity of one of these parameters, either frequency intensity or duration, can suffice to diminish the effect (Christova et al., 2011; Golaszewski et al., 2012). Similarly, increasing the strength of another parameter like intensity (Golaszewski et al., 2012) or frequency (Christova et al., 2011) could re-establish this effect. Besides few studies, that emphasized the importance of the rhythm in which interstimulus intervals and stimuli are combined (e.g. Ragert et al., 2008; Walsh et al., 1998), all other studies concentrate on these three factors (duration, frequency and intensity).

The minimal strength of parameters needed to induce plastic changes is relatively stable in those studies. Stimulation at frequencies below 1 Hz was only sufficed to induce changes if it was applied repeatedly on several days (McDonnell et al., 2007; Schweizer et al., 2001).

Low frequency stimulation of 1-10 Hz at sensory threshold can induce changes after minimal 2 hours (Christova et al., 2011). Shorter stimulation time can be used if the intensity of stimulation is increased to motor, or stimulation is repeated (Huse et al., 2001). Stimulation of 20-50 Hz can induce cortical and behavioral changes after 20-30 minutes of suprathreshold stimulation (Freyer et al., 2012). Again, if applied repeatedly over a longer period, the stimulation duration of the single sessions needed to induce plasticity is reduced (Sullivan & Hedman, 2007).

It is difficult to assess the parameters necessary to induce plasticity in the range between 50 and 110 Hz, as there are only two studies applying frequencies in between this range. They are hardly comparable, as one worked in conjunction with muscle contraction and one used a repeated protocol (Christova et al., 2010; Meesen et al., 2011). Probably, duration between 10 and 20 minutes is necessary, depending on the involvement of muscles in the stimulation.

Furthermore, the induced effects vary with higher frequencies. Some effects indicate increased and some decreased excitability (Adak & Göksoy, 1998; Meesen et al., 2011; Mima et al., 2004; Ridding et al., 2001). High frequency stimulation might thus have inhibiting as well as excitatory effects, depending on the duration of stimulation and the outcome measure. It might also be influenced by the site of stimulation. For instance stimulation of the pharynx resulted in inhibition already after relatively low frequency (10 Hz) stimulation (Fraser et al., 2002).

Increasing the parameters more than in these combinations does not seem to increase the strength of effects much further, but also not to weaken them. Instead, the results from TMS studies show that there are restrictions to the amount of excitability that can be induced in the brain (Ragert et al., 2003; Tossi et al., 2013). Repeated application seems to influence the duration of the effects as well as the parameters necessary to induce them. Not only could repeated application enable effects with parameters that are otherwise not sufficient to induce any changes, but it also rendered some usually effective parameters ineffective (Conforto et al., 2010; Huse et al., 2001; Schweizer et al., 2001). Furthermore, repeated stimulation might influence the further development of performance in a long-term perspective, even though no effects were seen directly after stimulation (Sonde et al., 1998). This is in line with a generally weak relation between, the duration and the size of effects. It is possible to boost performance without increasing longevity (Dinse et al., 2003) and a longer lasting effect might not be especially strong (Godde et al., 2000). Also if no effects of rTS were found, it can still increase the longevity of the effect induced by motor training (Conforto et al., 2007) or delay deterioration in that measure (Sonde et al., 1998). Also the effect of subsensory stimulation varies and needs further investigation. While some studies rejected an effect of subsensory stimulation and used it as a means to stimulate the control group (Kroon, Lee, IJzerman, & Lankhorst, 2002), subsensory stimulation was actually shown to be effective if applied to the whole hand or in repeated application (Conforto et al., 2010;

Golaszewski et al., 2004; B. B. Johansson et al., 2001). The speculation that subsensory stimulation is only sufficient to induce changes in the sensory, but not the motor cortex is questionable with regard to its effect on the JTHFT (Conforto et al., 2010).

In order to decide which stimulation protocol to use, it is important to consider the intended effects and applications. It seems that the variety of effects that were observed after rTS and other forms of peripheral stimulation can be divided into three distinct groups. The first group of effects reflects induction of plasticity in the sensory cortex, including cortical reorganization and increased excitability. Several applications of rTS rely on these somatosensory effects, including the recovery of sensory loss, phantom limb pain or complex pain syndrome. Also the treatment of certain forms of motor impairment can rely on sensory input, including for instance the recovery of focal hand dystonia or fine-motor impairment. In this first group of somatosensory effects as well as the respective applications, the protocols and rules for effective somatosensory stimulation can be applied. The second group of effects might rely on a combination of sensory input and other mechanisms, such as changes in spinal pathways. These effects include the modification of muscle reflexes and motor command transfer. This group of effects that relies only in part on sensory stimulation might underlie the treatment of spasticity and paralysis. Here, the influence of somatosensory stimulation varies. Possibly, effectiveness differs, because tactile input alone is not sufficient to induce the intended effect. The third group of effects does not seem to rely on tactile input. This group includes for instance the modification of grasping force. Also improvement in more general measures of motor control, such as the Barthel score, or the Fugl Meyer Research task, was mostly seen after repeated indirect stimulation, as opposed to single sessions or TENS. Especially in stroke recovery, stimulation is applied to induce an effect on these measures. However, this third group of effects can probably not be influenced through classical rTS protocols. Instead, higher levels of frequency or intensity are necessary to induce respective effects.

Cortical effects rely on the same distinction. While plasticity in the sensory cortex is induced by all protocols applied in basic research, some forms of plasticity in the motor cortex can be induced by largely the same protocols (ICF, BOLD signal intensity) and other aspects demand stronger activation or muscle stimulation (MEPs, motor threshold).

With regard to protocols relying on tactile stimulation, direct stimulation of the nerve might induce stronger effects. With regard to activated clusters and paired pulse ratio, a lower choice of parameters such as frequency and intensity seems favorable. However, this did not apply to BOLD signal intensity and changes in dipoles.

Burst stimulation might be more suitable than single pulse stimulation to improve sensorimotor integration (as reflected through haptic object regongnition), induce a longer duration of effects or affect sensory performance in older participants, However, single pulse stimulation might work better to increase performance in the pegboard task and possibly also the 2PD. These differences between burst and single pulse stimulation raise the question, whether there is a general difference in the plastic effects induced by the two methods. Notably, some effects could not be provoked by single pulse stimulation but by burst as well as muscle stimulation. Another difference seems to lie between TENS and mechanical stimulation, as some effects could not be induced by any form of TENS protocol, but through stimulation of limbs or fingers. This indicates that there are some general differences between nerve and limb stimulation as well as burst and single pulse stimulation. A possible differentiation might be the excitation of muscles during the stimulation. It has been proposed that burst stimulation activates muscles more strongly than single pulse stimulation (Sullivan &

Hedman, 2008). Also indirect stimulation might reach more muscle groups than TENS stimulation, even if it is applied at motor intensity. A difference in muscle stimulation would explain why differences between the protocols become most apparent in tasks that involve the motor domain. For instance, the difference between single pulse and burst stimulation is rather small with regard to 2PD, but stronger if haptic object recognition and pegboard task are concerned.

However, even if the similar protocols are applied, there is still some variation between the results, which might be due to other influencing variables (Kalisch et al., 2007; e.g. Tossi et al., 2013). For instance, it has been shown in an EEG study that resting state brain activity influences the effectiveness of stimulation (Freyer et al., 2013). This effect of brain states might explain some of the variation in studies using the same stimulation protocols. Notably it has only been found with regard to electrical, as opposed to mechanical stimulation. However, this might be due to the small sample size of the group receiving mechanical stimulation (Freyer et al., 2013). Also baseline excitability influences stimulation effects (Tossi et al., 2013).

In conclusion, the effectiveness of stimulation protocols follows relatively clear rules. The rules underlying this choice of parameters can be used to increase stimulation effects also in several practical applications of rTS, as long as these applications base on the induction of hebbian mechanisms.

Future Outlook and further research

Further research is needed especially with regard to practical applications of rTS. Several sensory and motor impairments, such as complex regional pain syndrome as well as some forms of motor impairment in stroke were related to maladaptive organization of cortical representations. It seems promising to treat these impairments with somatosensory stimulation and use neurophysiological measures to assess the role of cortical representations in their recovery. With regard to impairments that demand treatment on a cortical as well as corticospinal and/or muscular level, such as spasticity, a combination of different stimulation protocols might be a further treatment option. Hereby, muscle stimulation could be combined with rTS. For the further application of rTS, it would further be helpful to systematically investigate on the duration of the induced changes in basic research. It is not yet clear what other mechanisms, apart from the strength of effect define this duration. Even though repeated stimulation seems to be a suitable method to increase longevity, no study compares the effectiveness of different stimulation rhythms (weekly, daily, etc.) yet. Also other promising factors to increase longevity should be further investigated, for instance the consolidating role of sleep, motor training or stimulus duration.

At last, it would be interesting to assess the effect of a wider range of stimulation parameters on the somatosensory cortex. Thereby it could be tested, in how far stimulation at high frequency or intensities has a different effect on performance in sensory and motor tasks. Also a systematic comparison of electrical and mechanical stimulation as well as stimulation over the fingers or the nerves should be made. There are several evidences that these factors have an influence on the stimulation-induced effects (see above). Nevertheless, it is not yet clear what mechanisms underlie these differences in effects. A different activation of nerve afferents or muscle fibers might be a possible explanation, but no study further investigates what role this activation of muscle fibres might play in hebbian learning. A systematic comparison of a wider range of stimulation parameters could also indicate, whether burst and single pulse stimulation lead to different patterns of activation. Such differences in activation would explain the different effectiveness in populations of different age groups and in tasks demanding sensorimotor integration as opposed to motor performance. Knowledge about these differences in activation would help to choose an optimal stimulation protocol with regard to the characteristics of the participants (e.g. their age group) and the intended outcome. A further variation and comparison of different stimulation protocols would thus be relevant for basic research as well as applications purposes.

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