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# Modifying somatosensory processing with non-invasive brain stimulation

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Somatosensory processing is required for different activities in life. From sensorimotor integration required for accurate motor control to careful manipulation of objects and tool using. Abnormalities in somatosensory processing are associated with different behavioral and clinical entities like focal hand dystonias, a movement disorder (Cohen & Hallett, 1988; Reilly, Hallett, Cohen, Tarkka, & Dang, 1992), in which digit representations in the primary somatosensory cortex (S1) exhibit clear distortions (Byl, et al., 1997; Byl, Merzenich, & Jenkins, 1996; Wang, Merzenich, Sameshima, & Jenkins, 1995) and repetitive strain related pain (Tecchio, Padua, Aprile, & Rossini, 2002). Changes in somatosensory processing and cortical organization within S1 representations can also be linked to other types of chronic neuropathic and musculoskeletal pain (Flor, 2003). Somatosensory deafferentation results in massive reorganization of S1 cortical maps (Pons, et al., 1991). Phantom limb pain post-amputation correlates with the extent of cortical reorganization within S1 (Flor, et al., 1995) and M1 (Karl, Birbaumer, Lutzenberger, Cohen, & Flor, 2001) suggesting the hypothesis that it may play a maladaptive role, that is, contributing to the abnormal perceptions (pain).

On the other hand, cortical reorganization within sensorimotor regions can play an adaptive role, that is, be linked to behavioral gains. Greater refinement and expansion of S1 digit representations are linked to improved dexterity and motor skill (Xerri, Merzenich, Jenkins, & Santucci, 1999) as in musicians (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995), as well as possibly with improvements in motor function post-stroke (Xerri, Merzenich, Peterson, & Jenkins, 1998). Further, the highly plastic nature of somatosensory representations can support unique abilities in specific populations, such as blind subjects who rely on improved tactile discrimination when reading Braille (Amedi, Floel, Knecht, Zohar, & Cohen, 2004; Cohen, et al., 1997; Sterr, et al., 1998a, 1998b). Interestingly, early blind individual can utilize brain regions usually engaged in visual processing (occipital cortex) to process somatosensory information, a paradigm extensively studies as a form of crossmodal plasticity.

In this manner, increased cortical plasticity in primary sensorimotor regions may play adaptive or maladaptive roles. Thus, it is conceivable that purposeful manipulation of

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cortical plasticity: to augment it when it is adaptive or to downregulate it when maladaptive, represents a meaningful goal, of possible therapeutic applications.

Noninvasive brain stimulation (NBS) represents one of the tools available to manipulate cortical excitability but also cortical plasticity (Ziemann, Wittenberg, & Cohen, 2002). In clinical settings (Knotkova & Cruciani, 2010), it has been proposed that NBS is effective in the treatment of chronic neuropatic pain secondary to peripheral nerve injury when applied to primary motor cortices (M1) but also in relation to spinal cord injury and thalamic stroke, (Lefaucheur, et al., 2008) and when applied to secondary somatosensory brain regions for visceral pain (Fregni, Freedman, & Pascual-Leone, 2007) (*See in this issue: Soroush Zaghi & colleagues: "Assessment and treatment of pain with non-invasive cortical stimulation"*). Modulation of somatosensory processing in the affected and non-affected hemisphere has also been shown to improve motor recovery in chronic stroke (Conforto, Cohen, dos Santos, Scaff, & Marie, 2007; Conforto, Kaelin-Lang, & Cohen, 2002; Conforto, et al., 2008) (*See in this issue: Pablo Celnik & colleagues: TMS in the diagnosis and treatment of motor disorders*).

## Somatosensory processing

Cortical excitability in S1 can be evaluated by measurements of somatosensory evoked potentials (SEPs) to peripheral nerve stimulation or to more ecological stimuli like touch, pain or heat (Cohen, Starr, & Pratt, 1985). For SEP measurements, typically a peripheral nerve is electrically stimulated and the subsequent EEG (or MEG) responses that follow each single stimulus are averaged over time. Measures of SEPs focus on the following short-latency low-frequency (<200Hz) components: the primary N20 component recorded from the scalp overlying somatosensory cortex, P22 and N35 components recorded from the central scalp, and P20 and N30 components recorded from the frontal scalp (Allison, McCarthy, Wood, Williamson, & Spencer, 1989). These components are believed to be generated by radially oriented cells in area 1 and tangentially oriented pyramidal cells in area 3B of S1 (Allison, et al., 1989). Studies may also employ a paired pulse SEP protocol to identify paired pulse inhibition of the N20 component. Here, the median nerve is stimulated twice with an interstimulus interval of 30 msecs, and the resultant SEPs show a reduction in the N20 component for the second pulse when compared to that for the first pulse (Ragert, Becker, Tegenthoff, Pleger, & Dinse, 2004). Some studies also focus on high frequency oscillations (HFOs) (~600Hz) believed to be partially generated by postsynaptic activities in S1 and presynaptic terminals of thalamo-cortical projections to S1 (Curio, 2000). Brain responses may be assessed by imaging modalities other than EEG such as functional magnetic resonance imaging (fMRI), which measures indirect changes in the blood oxygenation level dependent (BOLD) signal (Pleger, et al., 2006; Tegenthoff, et al., 2005; Wu, van Gelderen, Hanakawa, Yaseen, & Cohen, 2005). In pain studies, stimulation of nociceptive receptors is achieved with a laser, and the subsequent EEGs are termed laser-evoked potentials (LEPs) (Poreisz, et al., 2008).

Behaviorally, somatosensory processing can be assessed with tactile discrimination tasks. These include tactile frequency discrimination (TFD) where subjects discriminate between two frequencies of stimulation, tactile spatial discrimination with the grating orientation task

(GOT) where subjects discriminate between orthogonal and parallel presentations of gratings that vary in size (Van Boven & Johnson, 1994), or 2-point discrimination (2-point discrimination) where subjects discriminate between one or two presentations of needles that vary in thickness. For each of these tasks, a discrimination threshold is used as the measure of tactile acuity. The specific task employed by each study will be highlighted in the sections below. In pain studies, pain perception is studied with laser stimulation (Poreisz, et al., 2008). Recent studies have also used indirect means to assess somatosensory processing via multisensory influences from vision and proprioception (Azanon & Haggard, 2009).

## Transcranial Magnetic Stimulation (TMS)

TMS, a technique that relies on principles of electromagnetic induction (Barker, Jalinous, & Freeston, 1985), can be used to determine causal relations between activity in specific brain areas and particular behaviors. In TMS, a large but brief current pulse is passed through a TMS coil, typically a figure-8 coil for focal stimulation (Maccabee, Amassian, Eberle, & Cracco, 1993), which produces a rapidly shifting magnetic field that passes through the scalp and skull to induce an electric current in the cortex underneath the coil. At sufficiently high stimulation intensities, TMS will cause neuronal firing. For example, when a single pulse of TMS (spTMS) is applied to the scalp overlying the primary motor cortex (M1) with an intensity past a certain threshold (termed the resting motor threshold or RMT), a TMS pulse can produce a twitch in the contralateral extremity muscles, and a motor-evoked potential (MEP) can be recorded from the muscles with electromyography (EMG) (Barker, et al., 1985). In this way, a causal link can be established between M1 activity and muscle responses. TMS pulses can also be paired (ppTMS) to evaluate intra-cortical connnectivity within a brain region. For example, in M1, a sub-threshold conditioning pulse (CS) will either increase or decrease the MEP resultant from the subsequent supra-threshold test pulse (TS) dependent on the latencies between the two pulses (ranging between 1–15 msec). Hence, ppTMS can reveal different inhibitory or facilitatory populations of neurons within M1 (Reis, et al., 2008).

In the same manner, spTMS studies demonstrating that TMS over the primary somatosensory cortex (S1) masks tactile sensation (Cohen, Bandinelli, Sato, Kufta, & Hallett, 1991; Cohen, et al., 1997; Hannula, et al., 2005; McKay, Ridding, & Miles, 2003; Seyal, Siddiqui, & Hundal, 1997) and ppTMS studies demonstrating amplified masking of tactile sensation by a sub-threshold CS (Koch, Franca, Albrecht, Caltagirone, & Rothwell, 2006; Meehan, Legon, & Staines, 2008) show a direct link between activity in S1 and somatosensory processing. For example, in an spTMS study by Cohen et al. (1991), detection of electrical stimulation of the index finger was attenuated or blocked by spTMS to S1 when the TMS pulse was delivered 200 msec prior, simultaneously or 20 msec after electro-cutaneous stimulation of a contralateral finger, but was unaffected by TMS pulse delivery 200 msec after. These findings suggested that focal S1 stimulation over the hand representation, could modulate detection of a somatosensory afferent volley originating in a contralateral finger. In a ppTMS study by Koch et al. (2006), a sub-threshold CS to S1 delivered 10 to 15 msec prior to the TS to S1 led to greater attenuation of electro-cutaneous stimulation that TS to S1 alone suggesting that GABAergic corticocortical circuits within S1 may also play a role in somatosensory processing.

Depending on the form of TMS application, it can have lasting after-effects on cortical excitability (Ridding & Ziemann, 2010; Sandrini, Umiltà & Rusconi, 2011). Repetitive TMS (rTMS) protocols where TMS pulses are delivered at a constant rate up to 50Hz, and "patterned" rTMS protocols such as theta burst stimulation (TBS) where trains of short bursts of high-frequency TMS pulses are interleaved with pause periods with no stimulation (Huang, Edwards, Rounis, Bhathia, & Rothwell, 2005; Rossi, Hallett, Rossini, & Pascual-Leone, 2009) can have profound influences on cortical excitability and plasticity. The specific parameters of TMS protocols determine if the effects are excitatory or inhibitory. These parameters include frequency of stimulation for rTMS protocols, durations of pause periods for TBS protocols, and interval duration between paired peripheral and TMS pulses for PAS protocols (Ridding & Ziemann, 2010; Sandrini, et al., 2011).

TMS pulses can also be paired with electrical stimulation of a peripheral nerve in paired associative stimulation protocols (PAS) (Ridding & Ziemann, 2010). Typically, many pairs of PAS are delivered at a constant rate to elicit long lasting after-effects (Stefan, Kunesch, Cohen, Benecke, & Classen, 2000; Stefan, Kunesch, Benecke, Cohen, & Classen, 2002). Stimulation intensity is standardized across subjects by determining the motor threshold (MT) in each subject. Resting MT (RMT) is defined as the lowest intensity required to elicit MEPs of more than 50 μV peak-to-peak amplitude in at least 50% of successive trials, in resting target muscles (Rossini, et al., 1994). MT can be measured also in an active muscle (active motor threshold, AMT). In this case it is the minimal intensity of stimulation required to produce an MEP having an amplitude of about 150–200 μV on more than 5 out of 10 trials while the subject is maintaining a voluntary contraction of about 10–20% of maximum contraction using visual and/or auditory feedback.

Several methods are used to ensure focal delivery of TMS pulses to S1. Some studies first find the index finger representation in M1 and then move the TMS coil location 1 to 2 cm posterior in the parasagittal direction to approximate the index finger representation in S1 (Maldjian, Gottschalk, Patel, Detre, & Alsop, 1999). This S1 position may be confirmed by asking subjects to detect prickling or tickling sensations in their index finger when given a TMS pulse at an intensity of 90% RMT (Tegenthoff, et al., 2005). Other studies determined the stimulation site with neuronavigation software, which can stereotaxically register the participant's brain with the TMS coil (Vidoni, Acerra, Dao, Meehan, & Boyd, 2010). Other studies rely on scalp coordinates based on standard 10–20 electrode scalp positioning system (Knecht, Ellger, Breitenstein, Bernd Ringelstein, & Henningsen, 2003).

## Repetitive TMS (rTMS)

For rTMS protocols, TMS pulses are delivered at a constant rate and this rate determines whether subsequent changes in cortical excitability are excitatory or inhibitory. The term 'low-frequency' rTMS refers to stimulus rates of 1 Hz or less (Chen et al., 1997) and 'high-frequency' rTMS refers to stimulus rates of more than 5 Hz. Such a classification is based on the different physiological effects and degrees of risk associated with low-and high-frequency stimulation (Rossi, et al., 2009). Compared to other stimulation protocols, after-effects of rTMS are relatively shortlasting (Robertson, Theoret, & Pascual-Leone, 2003; Sandrini, et al., 2011). In the somatosensory domain, it has been similarly shown that low

frequency rTMS delivered to S1 decreases cortical excitability (as measured by SEPs) and tactile acuity while high-frequency rTMS increases them.

**Low frequency repetitive TMS(≤ 1Hz)—**To investigate the effects of inhibitory, low frequency rTMS on SEPs, Enomoto et al. (2001) applied rTMS (1Hz, 200 pulses, 110% AMT) to M1 and S1 and found significant decreases in N20 and P25/N33 amplitudes but only when rTMS was delivered to M1. These effects declined linearly up to 100 minutes post-stimulation when they returned back to baseline. No changes were found when rTMS was delivered to S1. Similarly, Ogawa et al. (2004) found that rTMS to S1 (0.5Hz, 50 pulses, 80% RMT) did not affect the N20 amplitude. However, they did identify increases in HFOs. Restuccia et al. (Restuccia, Ulivelli, De Capua, Bartalini, & Rossi, 2007) again found changes in HFOs in the absence of changes in N20 amplitude with rTMS to S1 (1Hz, 1200 pulses, 80% RMT) but increases were limited to early burst activity and were otherwise coupled with sustained decreases in later burst activity. Satow et al. (2003) failed to identify changes in SEP and 2-point discrimination after rTMS to S1 (0.9Hz, 900 pulses, 90% RMT).

However, other studies have found decreases in tactile acuity after low-frequency rTMS. 1Hz rTMS (110% RMT) delivered to right S1 for durations of 5, 10, and 20 minutes reduced tactile acuity (measured by TFD) in the contralateral hand, but not in the ipsilateral hand. The duration of this reduced acuity was related to the duration of stimulation, with effects lasting 2 min with 5 min rTMS, 4 min with 10min rTMS, and 8 min with 20min rTMS (Knecht, et al., 2003). Vidoni et al. (2010) applied 1Hz rTMS (1200 pulses, 90% RMT) over S1 and again found reduced tactile acuity (2-point discrimination) but additionally found reduced motor learning on a continuous tracking task demonstrating a link between somatosensory processing and motor learning, probably as needed for sensorimotor integration tasks.

**High frequency repetitive TMS (>5Hz)—**To investigate the effects of excitatory high frequency rTMS on SEPs, Restuccia et al. (2007) applied rTMS to S1 (10Hz, 1200 pulses, 80% RMT) and found increases in later burst activity in HFOs in the absence of changes in the N20 component. However, subtle changes in the N20 component were found by a study by Ragert et al. (Ragert, Schmidt, Altenmuller, & Dinse, 2004), which used a paired-pulse SEP measure. Paired pulse inhibition in the N20 component was reduced after rTMS to S1 (5Hz, 2500 pulses in 2 sessions, 90% RMT) on the side of the stimulated S1 but not the opposite S1, suggestive of decreased inhibition and hence, spatially specific enhanced cortical excitability.

Other studies have found increases in tactile acuity in conjunction with increases in brain response after excitatory rTMS. Tegenthoff et al. (2005) applied 5Hz TMS to S1 (2500 pulses in 2 sessions, 90% RMT), and found an immediate improvement in tactile acuity (2 point discrimination) in the contralateral but not ipsilateral index finger. This benefit dissipated over the course of 2 hours at a constant rate. Using fMRI to measure brain response to electrical stimulation of the index finger, 5Hz rTMS was associated with increases in BOLD in the stimulated S1 and the extent of this increase correlated with improvements in tactile acuity (Tegenthoff, et al., 2005). Similar findings were reported by

Pleger et al. (2006) using a TFD task and event-related fMRI with 5Hz rTMS (1250 pulses, 90% RMT) improving tactile acuity and BOLD response in the stimulated S1. This BOLD increase was found during the TFD task itself, with performance improvements correlated with BOLD changes in S1 area 1/3b (Pleger, et al., 2006). With 15Hz rTMS (2400 pulses, 90% RMT), improvements were not found on the frequency discrimination based TFD task, but found in the spatial discrimination based GOT task, suggesting that different tactile discrimination tasks may display different sensitivities to rTMS intervention (Karim, et al., 2003).

High-frequency TMS can also be employed to modulate the effectiveness of a different protocol. For example, Ragert et al. (2003) applied 5Hz rTMS to left S1 (2500 pulses in 2 sessions, 90% RMT) together with tactile coactivation of the right index finger. Tactile coactivation alone can lead to shifts in S1 cortical representations of the index finger which can predict improved tactile discrimination (2-point discrimination) (Pleger, et al., 2001). 5Hz rTMS plus coactivation was found to be more effective than coactivation alone in improving tactile acuity (Ragert et al., 2003).

**Theta Burst Stimulation (TBS)—**With TBS protocols, trains of 50 Hz (3 pulses applied every 200 ms (frequency of 5 Hz, in the range of theta band) are interleaved with rest periods (2 to 10 seconds) and the duration of the rest period determines whether subsequent changes in cortical excitability are excitatory or inhibitory. In the motor domain, TBS bursts delivered with 2 second rest periods (continuous TBS or cTBS) decreases cortical excitability while TBS bursts delivered with 10 second rest periods (intermittent TBS or iTBS) increases cortical excitability. Though application of TBS (typically 600 pulses total at 80% AMT) takes only 20 to 120 second, the after-effects generally last for 30 min. (Huang, et al., 2005). As to be detailed, it has been similarly shown that cTBS delivered to S1 decreases cortical excitability (as reflected in SEPs) and perceptual acuity while iTBS increases the same.

**Continuous theta burst stimulation (cTBS):** To investigate the effects of inhibitory cTBS on SEPs, Ishikawa et al. (2007) administered cTBS to both left M1 and S1 and found a decrease in the amplitude of the P25/N33 component of SEPs for the right but not left hand median nerve after S1 stimulation, with effects lasting approximately 13 minutes. Interestingly, cTBS to M1 had an opposite effect and led to an increase in the amplitude of the P25/N33 component with effects lasting about 53 minutes post-stimulation. Using near infra-red spectroscopy to measure bilateral interactions, cTBS to M1 or S1 was found to decrease oxygenated hemoglobin levels in the opposite S1 (Mochizuki, et al., 2007). cTBS to S1 was also found to decrease the amplitudes of laser-evoked potentials (LEPs), which employs a laser to induce painful stimulation.

**Intermittent theta burst stimulation (iTBS):** To investigate the effects of excitatory iTBS on SEPs, Katayama and Rothwell (2007) administered iTBS to both left M1 and S1 and found facilitation of the N20 and P25/N33 components of SEPs for the right hand median nerve after S1 stimulation, with maximal effects appearing 15 minutes post-stimulation and lasting at least 30 minutes. No changes to SEPs were found after M1 stimulation (Katayama & Rothwell, 2007). Ragert et al. (Ragert, Franzkowiak, Schwenkreis, Tegenthoff, & Dinse,

2008) used a paired pulse SEP protocol to show reduced paired pulse inhibition in the N20 component for the right but not left hand median nerve after iTBS to left S1 consistent with a facilitory effect. In addition, subjects had increased tactile acuity (2 point discrimination) post-stimulation in the right but not left hand with these effects lasting for up to 30 minutes post-stimulation. Interestingly, iTBS was shown to decrease the amplitudes of LEPs, contrary to its commonly assumed excitatory effects on cortical excitability (Poreisz, et al., 2008).

## Paired Associative Stimulation (PAS)

In traditional versions of PAS, an electrical pulse applied to the median nerve at the wrist (300% sensory perceptual threshold) is paired with a TMS pulse applied to M1 delivered shortly afterwards with the duration of this interval between paired pulses determining whether subsequent changes in cortical excitability are excitatory or inhibitory. In the motor domain, after-effects are inhibitory when the duration between the paired pulses is 10msec ($PAS_{10}$), while after-effects are excitatory when the duration between the paired pulses is 25msec ($PAS_{25}$). After-effects can last for 30 to 60 minutes (Ridding & Ziemann, 2010; Stefan, et al., 2000). As to be detailed, it has been similarly shown that PAS protocols with shorter intervals decrease cortical excitability (as measured by SEPs) and disrupt perceptual acuity, while those with longer intervals increase the same. However, the latencies to induce these effects are shifted by approximately 7 msec (Wolters, et al., 2005).

To investigate the effects of PAS on SEPs, Wolters et al. (2005) paired median nerve stimulation with a TMS pulse to S1 (150% RMT, 180 pairs at a rate of 0.1 Hz) and varied the latencies between the pairings. The mean individual N20 latency occurs approximately 17–21 msec after median nerve stimulation. When the interval between paired pulses is about 20 ms ($PAS_{N20}$), there is an increase in the amplitude of the P25 component which lasted up to 30 minutes post-stimulation in the absence of changes in the median nerve sensory action potentials. When PAS was applied at other latencies ranging from −40 to +20 msec after the mean N20 latency ($PAS_{N20 + x}$), a significant increase in P25 amplitude has been reported. Hence, the latency difference between excitatory and inhibitory effects of PAS protocols applied to M1 ($PAS_{10}$ inhibitory and $PAS_{25}$ excitatory) and PAS protocols applied to S1 ($PAS_{N20 - 20}$ inhibitory and $PAS_{N20, N20 - 2.5, N20 - 5}$ excitatory) was approximately 7msec (Wolters, et al., 2005). In a follow-up study, the magnitude of P25 amplitude increases induced by $PAS_{N20 - 2.5}$ correlated with post-stimulation improvements in tactile acuity (2 point discrimination) (Litvak, et al., 2007). Interestingly, Pellicciari et al. (Pellicciari, Miniussi, Rossini, & De Gennaro, 2009) found that $PAS_{N20}$ (130% RMT, 140 pairs at a rate of 0.1Hz) was more effective in enhancing P25 amplitudes in older adults as compared to younger adults possibly due to changes in inhibitory/excitatory balance in S1 with aging.

$PAS_{25}$ and $PAS_{10}$ protocols applying TMS pulses to M1 can also have significant effects on somatosensory processing as measured by SEPs. $PAS_{25}$ increased N20/P25 and P25/N33 amplitudes for approximately 40 minutes and HFOs for 60 minutes, while $PAS_{10}$ decreased N20/P25 and P25/N33 amplitudes for 40 minutes and HFOs for 60 minutes (Murakami, et al., 2008). Pairing TMS pulses to M1 with electrical stimulation of muscle afferents at the

motor point (180 pairs at a rate of 0.1Hz) can result in increased N20/P25 amplitudes as well (Tsuji & Rothwell, 2002).

PAS application can also prime subsequent induction of LTP- or LTD-like plasticity induced by high-frequency peripheral nerve stimulation (pHFS) (Ridding & Ziemann, 2010). For example, $PAS_{N20 - 2.5}$ to S1 paired with pHFS facilitated P25 amplitudes and improved tactile spatial acuity as measured with the GOT task (Werhahn, Mortensen, Van Boven, Zeuner, & Cohen, 2002) while $PAS_{N20 - 2.5}$ paired with pHFS inhibited P25 components and decreased tactile acuity. Unlike previous studies, PAS alone had no effect perhaps explained by slight differences in stimulation protocols (150% RMT, 225 pairs at a faster rate of 0.25Hz) (Bliem, Muller-Dahlhaus, Dinse, & Ziemann, 2008).

## Transcranial Direct Current Stimulation (tDCS)

In contrast to TMS, tDCS relies on application of direct currents at low intensities (1–2 mA) over a sustained period of time (5–30 minutes) to achieve tonic modulation of cortical excitability and influence spontaneous neural activity (Nitsche, et al., 2008) that also influences synaptic function (Fritsch et al., 2010). Less focal than TMS, and generally delivered over the scalp through relatively large electrodes (20–35 $cm^2$), tDCS does not allow evaluation of cause-effect links in the milliseconds range (Gandiga, Hummel, & Cohen, 2006). In the motor domain, cathodal polarization reduces motor cortex excitability, whereas anodal polarization increases it, and these changes, like those induced by rTMS, last beyond the end of stimulation (Nitsche & Paulus, 2000). Stimulus duration is not the only determining factor in effect size. Current strength and electrode size both determine current density ($mA/cm^2$), the factor that ultimately determines the resultant strength of the induced electric field. The location of the reference electrode can also be an important factor. Cephalic montages place the reference electrode on the forehead orbit contralateral to the stimulating electrode, while extracephalic montages place the reference electrode over the shoulder or otherwise outside of the head (Nitsche, et al., 2008). As to be detailed, cathodal tDCS with the stimulating electrode centered on S1 can also decrease cortical excitability (as reflected in SEPs) and disrupt perceptual acuity while anodal tDCS increases the same.

### Cathodal tDCS

Dieckhofer et al. (2006) reported decreased N20 amplitudes after cathodal tDCS applied to S1 (9 minutes, current density 1/1.5 $mA/cm^2$ in 16 electrodes, montage= cephalic). Cathodal tDCS to S1 (7 minutes, current density = 1/30 $mA/cm^2$, montage = cephalic) was also found to exert an inhibitory effect on tactile acuity (TFD) both during and up to 14 minutes post-stimulation (Rogalewski, Breitenstein, Nitsche, Paulus, & Knecht, 2004). Antal et al. (2008) applied cathodal tDCS to S1 (15 minutes, current density = 1/30 $mA/cm^2$, montage = cephalic) and found decreases in LEP amplitudes as well as diminished pain perception. Cathodal tDCS to M1 (15 minutes, current density = 1/30 $mA/cm^2$, montage = cephalic) could also do the same, with effects lasting up to 2 hours, and longer with additional pharmacological manipulation (Terney, et al., 2008).

### Anodal tDCS

Application of anodal tDCS (10 minutes, current density = 1/35 mA/cm$^2$, montage = cephalic) resulted in larger P25/N33 amplitudes for up to 60 minutes post-training while cathodal tDCS had no effect on SEPs in line with other studies showing greater efficacy of anodal as compared to cathodal tDCS when applied to M1 (Matsunaga, Nitsche, Tsuji, & Rothwell, 2004). However, when applied to S1, anodal tDCS seems to induce lesser changes than cathodal tDCS. In the studies discussed above, anodal tDCS had no significant effects on SEPs (Dieckhofer, et al., 2006), tactile acuity (Rogalewski, et al., 2004), on LEPs or pain perception (Antal, et al., 2008). However, a positive effect of excitatory anodal tDCS was found by Ragert et al. (2008) who applied it to the left S1 for a longer period of time (20 minutes, current density = 1/25 mA/cm$^2$, montage = cephalic) leading to a reported improvement of tactile acuity (GOT) in the right but not left index finger, with benefits beginning during tDCS delivery and lasting until at least 40 minutes post-stimulation (Ragert, Vandermeeren, Camus, & Cohen, 2008).

## Modulating multisensory integration?

Recent work reported the possibility of modulating integration of somatosensory, visual and proprioceptive input (Azanon & Haggard, 2009). The rubber hand illusion (RHI) presents one such opportunity (Tsakiris & Haggard, 2005). In RHI, a rubber hand presented in the subject's visual field is stroked in synchrony with stroking of the subject's own unseen hand. As a result, the subject's perception of the position of his own hand shifts towards the position of the rubber hand (proprioceptive shift). In addition to the behavioral manipulation described above, it is possible to further modulate such processing through cortical stimulation. Tsakiris et al. (Tsakiris, Costantini, & Haggard, 2008) applied disruptive spTMS to the right temporal-parietal junction (TPJ) 350 msec after induction of the rubber hand illusion in half of the trials and reported a decrease in proprioceptive shift as compared to no-TMS trials. Hence, the TPJ plays a role in this multisensory phenomenon.

Another illusion used to study visual-tactile integration is the enhancement of tactile sensitivity in an unstimulated hand in the presence of visual information suggesting the hand has been stimulated. This is accomplished through the use of a mirror, and tactile stimulation of the opposite hand. This increased tactile sensitivity was abolished in the unstimulated hand after spTMS to the right posterior parietal cortex (PPC) 50 msec prior, suggesting that the PPC plays a role in integrating visual and tactile perceptions (Ro, Wallace, Hagedorn, Farne, & Pienkos, 2004).

In another example of manipulation of multisensory processing, Bolognini and Maravita (2007) applied inhibitory low-frequency rTMS to the PPC and S1 prior to assessments of visual-tactile-proprioceptive integration. In this study, one index finger was stimulated with suprathreshold vibrations (tactile input) at the same time that visual phosphenes were induced with TMS to the occipital cortex (visual input). When the stimulated finger was placed in the same perceived space as the phosphene location, perception of the phosphene was enhanced compared to when it was not aligned. This was true even when hands were crossed, suggesting that proprioceptive input updated hand position in allocentric space to support this tactile-visual integration. When 1Hz TMS (1200 pulses, 65% of the maximum

stimulator output) was applied to S1, phosphene perceptual enhancement by somatosensory input was disrupted in both uncrossed and crossed hand conditions suggestive of a non-specific disruption of somatosensory input. Interestingly, 1Hz TMS to PPC switched the direction of phosphene perceptual enhancement specifically in the crossed hand condition. In other words, the enhancement was based on hand representations in egocentric space, rather than proprioceptively updated hand position in allocentric space. Hence, inhibition of the PPC selectively impaired the ability of proprioceptive input to spatially remap visual-tactile relationships (Bolognini & Maravita, 2007). A study by Merabet et al. (2004) also employed low-frequency rTMS to S1 and occipital cortex (V1) to explore visual-tactile relationships. Subjects were asked to rate the roughness and distance spacing of raised dots after tactile exploration. 1Hz rTMS (600 pulses, 110% RMT) to S1 impaired roughness subjects while 1Hz rTMS to V1 (600 pulses, 110% RMT) impaired spacing judgments, suggesting visual inputs play a role in somatosensory-based judgments of distance. Interestingly, the same impairment in spatial judgment was found in a blind subject with bilateral damage to V1 areas and Braille alexia, although it was preserved in congenitally blind subjects (Merabet, et al., 2004). A previous TMS (10Hz, 30 pulses, 110% RMT) study discussed above proved V1 involvement in somatosensory processing particularly in early blind subjects (Cohen, et al., 1997). In this study, both healthy and early blind subjects were asked to identify embossed Roman letters by touch. TMS to S1 impaired letter identification in both groups, but TMS to V1 only impaired letter identification in the early blind group. This was also true when the early blind subjects identified Braille letters.

One general issue to keep in mind is that while cortical stimulation is delivered to target specific brain regions, the behavioral effects of such stimulation may represent the consequence of focal activity in the stimulated region and/or effects on remote but interconnected brain regions. Dual site paired-pulse TMS (Koch & Rothwell, 2009; O'Shea, Taylor, & Rushworth, 2008) and concurrent brain stimulation and fMRI could be powerful tools to study these differences in more detail (Blankenburg, et al., 2010). In conclusion, somatosensory processing can be facilitated or downregulated by different NBS techniques resulting in different duration of effects in primary somatosensory or motor areas as well as in multi-sensory areas. When applied to S1, low-frequency rTMS, continuous TBS, $PAS_{N20\ -\ 20}$ and cathodal tDCS tend to induce inhibitory effects on cortical excitability and tactile acuity, while high-frequency rTMS, intermittent TBS, $PAS_{N20\text{-}5\ to\ 0}$ and anodal tDCS demonstrate facilitatory effects. Application of NBS techniques to M1 can modify SEPs and tactile acuity due to the substantial interactions between the motor and somatosensory systems and has been the primary target in the treatment of chronic neuropathic pain (Lefaucher, et al., 2008). Finally, application of NBS techniques to parietal and occipital regions can modify somatosensory processing through modulation of multisensory integration areas. This wide array of strategies to influence somatosensory processing suggests promise for NBS in both research and clinical domains.

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