



# Modulation of somatosensation by transcranial magnetic stimulation over somatosensory cortex: a systematic review

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Received: 20 October 2022 / Accepted: 17 February 2023 / Published online: 23 March 2023  
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## Abstract

Over the last three decades, transcranial magnetic stimulation (TMS) has gained popularity as a tool to modulate human somatosensation. However, the effects of different stimulation types on the multiple distinct subdomains of somatosensation (e.g., tactile perception, proprioception and pain) have not been systematically compared. This is especially notable in the case of newer theta-burst stimulation protocols now in widespread use. Here, we aimed to systematically and critically review the existing TMS literature and provide a complete picture of current knowledge regarding the role of TMS in modulating human somatosensation across stimulation protocols and somatosensory domains. Following the PRISMA guidelines, fifty-four studies were included in the current review and were compared based on their methodologies and results. Overall, findings from these studies provide evidence that different types of somatosensation can be both disrupted and enhanced by targeted stimulation of specific somatosensory areas. Some mixed results, however, were reported in the literature. We discussed possible reasons for these mixed results, methodological limitations of existing investigations, and potential avenues for future research.

**Keywords** Somatosensory processing · Transcranial magnetic stimulation · Somatosensory cortex · Tactile perception · Proprioception

## Introduction

Over the past three decades, our understanding of brain–behavior relationships has been substantially shaped and enriched by research using non-invasive brain stimulation (NIBS). One of the most commonly used NIBS techniques is transcranial magnetic stimulation (TMS). TMS was first introduced by Barker et al. (1985), who demonstrated that a single TMS pulse applied over the primary motor

cortex (M1) elicits responses (i.e. motor evoked potentials, MEPs) in those muscles that receive corticomotor input from the stimulated motor cortical area. In brief, TMS can induce electrical currents in the brain tissue underlying the coil by creating a small, precise, rapidly-changing magnetic field around the coil. This special property of TMS thus provides a unique opportunity for researchers to directly test how experimentally-altered neural activity causally affects behavior in a non-invasive manner (see reviews, Parkin et al. 2015; Pitcher et al. 2021).

Somatosensory processing is required for various activities in daily life, from tactile and proprioceptive feedback required for precise motor control to pain perception that is critical for survival. At the level of cerebral cortex, somatosensory information converges in the somatosensory areas located in the anterior part of the parietal lobe, including the primary (S1) and secondary somatosensory cortex (S2), and provides cohesive perception of temperature change (thermoception), pain (nociception), position and movement of head and body (proprioception), and touch (mechanoreception). Damage to these somatosensory areas can result in a variety of disorders, depending on where the damage

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Communicated by Bill J Yates.

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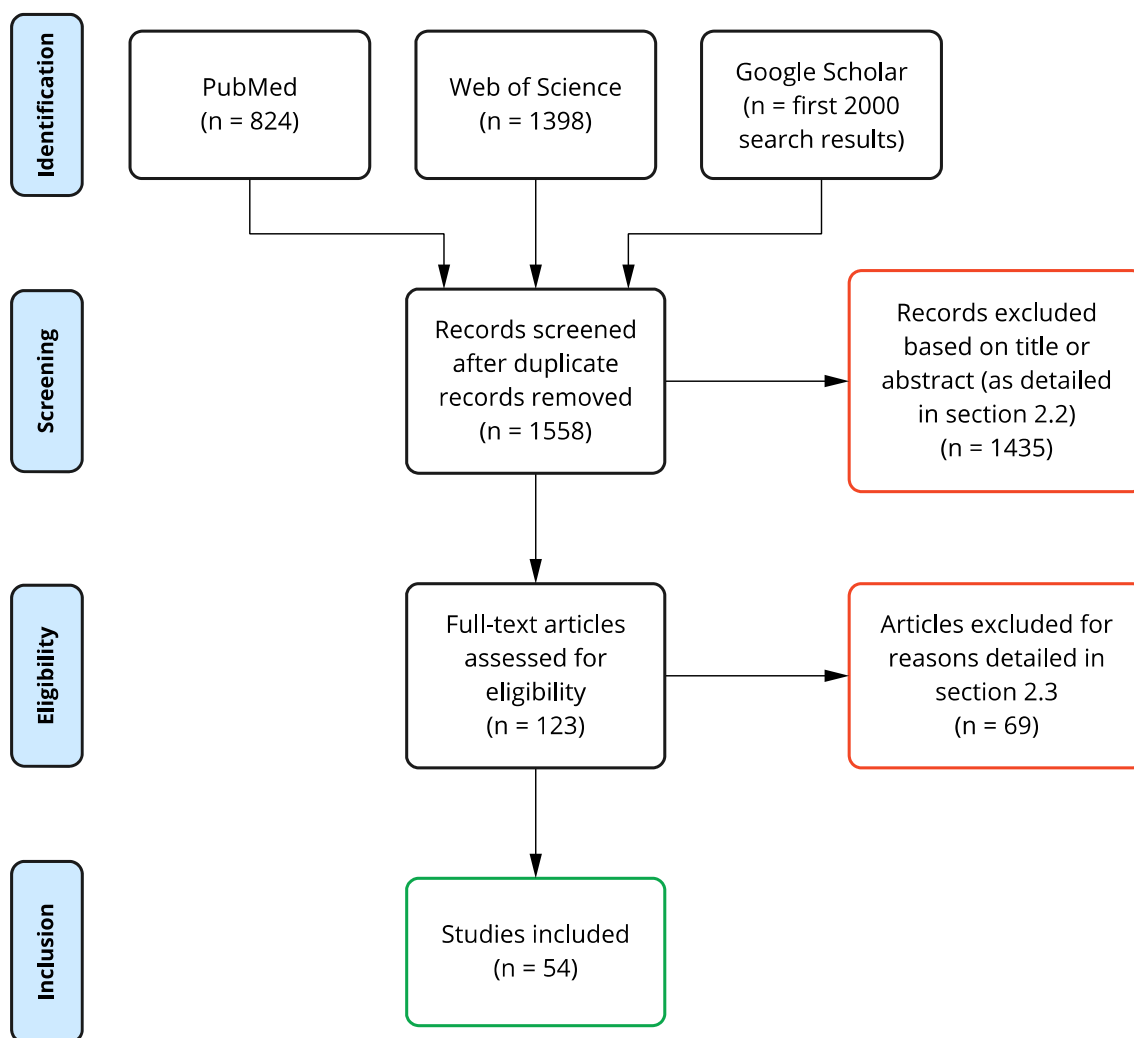
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occurs (Caselli 1993; Okuda et al. 1995). Accurate tactile and proprioceptive sensation is particularly important for the development of motor skills (Bernardi et al. 2015; Cauller 1995). Changes in cortical organization within somatosensory areas are also related to some chronic neuropathic and musculoskeletal pain (Flor 2003; Vartiainen et al. 2009).

Six years after the initial introduction of TMS, Cohen et al., (1991) first applied TMS to human somatosensory areas. Since then, TMS has been applied to these areas in a variety of different ways to study the brain–behavior relationship during somatosensory processing. For example, single-pulse TMS has been used to probe the chronometry of somatosensory processing (e.g. Hannula et al. 2005; Seyal et al. 1992), while repetitive TMS (rTMS) has been demonstrated to be an ideal tool to investigate the causal contributions of specific somatosensory areas to different somatosensory modalities or tasks (e.g. Knecht et al. 2003; Mirdamadi & Block 2021). More recently, an increasing number of

studies have used a newer form of rTMS protocols, theta-burst stimulation (TBS), to investigate somatosensory processing (e.g. Kumar et al. 2019; Rai et al. 2012; Rocchi et al. 2016). Such “patterned” rTMS protocols, where trains of short bursts of high-frequency TMS pulses are repeated at certain intervals, have been shown to have profound influences on cortical excitability and plasticity (Di Lazzaro et al. 2008; Huang et al. 2005).

While there is a large body of literature investigating the behavioral and neurophysiological effects of different TMS protocols over somatosensory areas, these studies are variable in both methodology and conclusions. The aim of the present review is to provide a comprehensive synthesis of all hitherto conducted studies that have adopted TMS to explore somatosensory processing in the healthy human brain. In particular, we integrate studies investigating the behavioral and neurophysiological effects of different TMS protocols over somatosensory areas on different types of



**Fig. 1** PRISMA flowchart depicting the process of literature search and screening

somatosensory perception (e.g. tactile perception, proprioception and pain). In doing so, we aim to reconcile the mixed results found in the primary literature as well as identify possible limitations and challenges for future research.

## Methods

We performed a systematic review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) guidelines (Liberati et al. 2009). The selection process is summarized in Fig. 1.

### Literature search

Three databases were used: PubMed/MEDLINE, Web of Science and Google Scholar. Search keywords/terms included “somatosensory cortex” AND (“transcranial magnetic stimulation” OR “TMS”). We also looked for additional references in retrieved papers and previous reviews (Azañón and Haggard 2009; Song et al. 2011; Staines and Bolton 2013).

### Screening criteria

After removing duplicate publications, 1558 were initially screened (i.e. examined title and abstract). The following exclusion criteria were used for initial screening:

- Studies using other types of non-invasive brain stimulation, including but not limited to transcranial electrical stimulation (tES), transcranial static magnetic stimulation (tSMS), and paired-associative stimulation (PAS).
- Animal studies
- Studies applying TMS over non-somatosensory areas only or dual sites (dual site paired-pulse TMS)
- Reviews, meta-analyses or book chapters
- Conference articles

### Eligibility criteria

123 full-text journal articles were further thoroughly reviewed following the eligibility criteria below:

- TMS was performed (i.e. single-pulse, paired-pulse or rTMS)
- Participants were healthy adults (i.e. without any somatosensory-related deficits)
- TMS was applied over somatosensory areas (i.e. S1 or S2)

- At least one behavioral or neurophysiological outcome measure assessing somatosensory processing was reported

## Results

Altogether, 54 TMS studies met the eligibility criteria and were included in the current review (see Table 1). 16 studies used single-pulse TMS, 3 studies used paired-pulse TMS, 11 studies used low-frequency TMS (3 of these studies also used high-frequency TMS or theta burst stimulation), 6 studies used high-frequency TMS, and 18 studies theta-burst stimulation. Risk of bias assessments were performed for all included studies using ROBINS-I, an assessment tool designed to help users to evaluate the risk of bias within different domains (i.e. distinct aspects of a study that can contribute to the risk of bias) (Sterne et al. 2016). A summary and detailed traffic light plots generated using the Cochrane robvis tool (McGuinness and Higgins 2020) are shown in Fig. 2 and Fig. S1, respectively.

### Single-pulse TMS

#### Tactile perception

Single-pulse TMS applied at a specific time relative to a somatosensory stimulus has been shown to block or suppress tactile detection (Cohen et al. 1991; Seyal et al. 1992). Cohen et al (1991) showed that detection of percutaneous electrical stimuli delivered through bipolar ring electrodes was attenuated when a TMS pulse was applied over contralateral somatosensory areas (the border of the coil placed over C3 as defined by the international electroencephalography (EEG) 10–20 system, Cadwell MES-10 magnetic stimulator) 200 ms before electrical stimuli, and was blocked when a TMS pulse was applied simultaneously to or 20 ms after electrical stimuli (“The intensities of TMS were those necessary to evoke an electromyographic response smaller than 500  $\mu$ V from right abductor pollicis brevis (APB) when the coil was positioned at the optimal scalp location for motor stimulation in each subject”). Similar results were reported by Seyal et al. (1992) using the same Cadwell MES-10 magnetic stimulator and a round 9 cm diameter coil, showing that the suppression of perception was maximal when the TMS pulse (intensity: 45–55% of maximum output) over contralateral somatosensory areas (the anterior edge of the coil passing through C4) was applied either 30–90 ms before or 20–30 ms after electrical stimulation of the fingers.

To standardise stimulation intensity across participants, most later TMS studies determine the motor threshold (MT) for each participant. The MT is typically defined as the lowest stimulus intensity that is required to induce

**Table 1** All included studies are sorted by TMS types: single-pulse TMS (a), paired-pulse TMS (b), low-frequency TMS (c), high-frequency TMS (d), cTBS (e) and iTBS (f)

Study	Sample	TMS	Intensity	Site	Task	Results
Cohen et al. (1991) <sup>a</sup>	N = 7 (Exp 1)	spTMS	Intensity that necessary to evoke hand MEP	S1: Coil border over C3	YES/NO electrical stimuli detection	Suppressed tactile detection when spTMS applied 200 ms before or 20 ms after tactile stimulation
Hannula et al. (2005) <sup>a</sup>	N = 6	spTMS	120% or 130% MT	S1: the site produced at least 75% sensation block	YES/NO electrical stimuli detection	Suppressed tactile detection when spTMS applied 20 or 50 ms after tactile stimulation
Hannula et al. (2008) <sup>a</sup>	N = 6	spTMS	120% MT	Same localisation procedure as in Hannula et al. (2005)	Temporal discrimination	Tactile temporal discrimination was reduced by spTMS applied simultaneously to the first tactile stimulus
Harris et al. (2002) <sup>a</sup>	N = 14 (Exp2)	spTMS	110% AMT	S1: tactile extinction obtained by spTMS (C3 / C4)	Vibrotactile frequency discrimination	Tactile frequency discrimination was reduced by spTMS applied 300 or 600 ms after the first vibrotactile stimulus
Kujirai et al. (1993) <sup>a</sup>	N = 7	spTMS	100% RMT	Central scalp	SEP	An increase in the P25/N33 and a decrease in the later components (e.g. P40/N65) when spTMS applied 10 ms before tactile stimulation
Lockwood et al. (2013) <sup>a</sup>	N = 19	spTMS	110% RMT	S1: moving the coil posteriorly from M1 until no detectable motor twitches occurred, 2.4 ± .6 cm posterior to the M1 hotspot S2: 0.5 cm anterior and 6.5 cm superior to the right preauricular point	Pain location and intensity discrimination induced by laser stimulation	Pain intensity discrimination was disrupted by S2 stimulation, 120 ms after the nociceptive stimulus TMS over neither S1 nor S2 had any effect on pain localisation
McKay et al. (2003) <sup>a</sup>	N = 12	spTMS	115% or 135% RMT	S1: 4 cm posterior to M1 hotspot	YES/NO electrical stimuli detection	Suppressed tactile detection when spTMS applied 100 ms before or 20 ms after tactile stimulation
Morley et al. (2007) <sup>a</sup>	N = 8	Two spTMS	100% RMT	S1: 0.5–1 cm posterior to the motor hotspot, approximately to C3/C4	Vibrotactile frequency discrimination	Tactile frequency discrimination was reduced by two spTMS pulses (30 ms before and 5 ms after the second tactile stimulus)

**Table 1** (continued)

Study	Sample	TMS	Intensity	Site	Task	Results
Porro et al. (2007) <sup>a</sup>	N = 12	Three spTMS	120% RMT	S1: the same localisation procedure as described in Lockwood et al. (2013, 2 to 3.5 cm posterior to the motor hotspot)	Pain localisation	Pain localisation was disrupted by three-pulse TMS (pulses at 0–40–80 ms) applied 300 ms after a pain stimulus
Ro and Koenig 2021) <sup>a</sup>	N = 12	spTMS	115–119% MT	S1: moving coil caudally from motor hotspot until there was suppression of tactile sensations on three out of five trials	YES/NO electrical stimuli detection	spTMS over S1 decreased detection sensitivity but did not affect decision criterion
Seyal et al. (1992) <sup>a</sup>	N = 6	spTMS	45–55% of maximum output	S1: the anterior edge of the coil pass through C4	YES/NO electrical stimuli detection	Suppressed tactile detection when spTMS applied 30–90 ms before or 20–30 ms after tactile stimulation
Seyal et al. (1993) <sup>a</sup>	N = 6	spTMS	45–60% of maximum output	S1: the anterior edge of the coil was over C4	SEP	An enhancement of the N1-P1 amplitude of SEP when spTMS applied before tactile stimulation
Schurmann et al. (2001) <sup>a</sup>	N = 7	spTMS	110% MT	S1: 1.5 to 2 cm posterior to the motor hotspot	SEP	Maximal enhancement of the P25 when spTMS was applied concurrent with tactile stimulation
Tamè and Holmes 2016) <sup>a</sup>	N = 11 (Exp 1)	Dual TMS (25 and 75 ms after)	120% RMT	S1 and IPL (control site): both anatomical and functional criteria from individual fMRI localizer scan	Yes/No vibrotactile stimuli detection	Dual TMS over S1, not but IPL impaired detection sensitivity
Zangaladze et al. (1999) <sup>a</sup>	N = 6 (Exp 2)	spTMS	150% RMT	S1: coil was moved posteriorly until the motor response from hand just disappeared	Tactile spatial discrimination (grating grooves)	Both S1 and IPL stimulations changed decision criterion
Zhao et al. (2018) <sup>a</sup>	N = 15 (Exp 1)	spTMS	110% RMT	S1: 2 cm posterior to the motor hotspot	Vibrotactile frequency discrimination	Impaired tactile spatial discrimination when spTMS applied 30 ms after the onset of grating presentation
						Tactile frequency discrimination was reduced by contralateral spTMS applied 100 or 200 ms after the first vibrotactile stimulus

Table 1 (continued)

Study	Sample	TMS	Intensity	Site	Task	Results
Meehan et al. (2008) <sup>b</sup>	N = 11 (Exp1)	ppTMS	70% RMT CS + 130%; ISI (ms): 15	S1: post-central gyrus directly posterior to M1 guided by individual MRI and BrainSight neuronavigation	Vibrotactile stimulus detection	pp TMS applied 20 ms after tactile stimulus further decreased the percent of abrupt changes detected, but only when participants were required to respond discretely
Kanda et al. (2003) <sup>b</sup>	N = 9	ppTMS	120% RMT CS + 120%; ISI (ms): 50	S2: 0.5 cm anterior and 6.5 cm superior to the right preauricular point	Pain location and intensity discrimination (laser CO <sub>2</sub> stimuli)	ppTMS over S2 did not affect either pain intensity or localisation discrimination
Koch et al. (2006) <sup>b</sup>	N = 8 (Exp1)	ppTMS	70% RMT CS + 130% RMT TS; ISI (ms): 1,3,5,7,10,15	S1: 3 cm posterior to the motor hotspot	Electrical stimuli detection	Tactile detection was further suppressed by ppTMS (ISI: 10 or 15 ms) applied 20 ms after tactile stimulation
Balslev et al. (2004) <sup>c</sup>	N = 12 (Exp 1)	1 Hz rTMS (N = 6)	110% RMT—RMT defined as the lowest intensity that reliably elicited a visible twitch in the FDI muscle	S1: 3 cm posterior to the motor hotspot	Mirror tracing	Trajectory error during mirror tracing was significantly lower after real TMS than after sham stimulation
	N = 10 (Exp 2)	1 Hz rTMS	"	"	Proprioceptive acuity evaluated by a finger-matching task	1 Hz rTMS impaired proprioceptive acuity
Balslev et al. (2007) <sup>c</sup>	N = 10 (each participant received both stimulations)	1 Hz rTMS	110% RMT	S1: 3 cm posterior to the motor hotspot	Motor adaptation in response to visual perturbation	Compared to sham stimulation, 1 Hz rTMS led to slower reaction time for initiating a motor correction, presumably by causing proprioceptive deafferentation
Case et al. (2016) <sup>c</sup>	N = 19	1 Hz rTMS	110% RMT	S1: derived from each subject's peak response to the brushing and motor fMRI tasks	Two-point discrimination by aesthesiometer	Two-point discrimination accuracy was significantly reduced more by S1 rTMS than by vertex rTMS at the smallest distance tested
Enomoto et al. (2001) <sup>c</sup>	N = 7	1 Hz rTMS	110% AMT	S1: C3' (2 cm posterior to C3)	SEP	1 Hz rTMS over S1 did not affect SEP

**Table 1** (continued)

Study	Sample	TMS	Intensity	Site	Task	Results
Huh et al. (2016) <sup>c,d</sup>	N=15	1 Hz rTMS	90% RMT	S1: 2 cm posterior to the motor hotspot	Tendon vibration	1 Hz rTMS decreased both the amplitude and the velocity of replicating movements performed by the right wrist joint
		5 Hz rTMS	"	"	"	5 Hz rTMS increased both the amplitude and the velocity of replicating movements performed by the right wrist joint
Knecht et al. (2003) <sup>e</sup>	N=10 (each group)	1 Hz rTMS (stimulation time 5, 10, 20 min)		C4	Vibrotactile frequency discrimination	1 Hz rTMS train (20 min) over S1 induced a suppression of frequency discrimination for up to 8 min
Meehan et al. (2011) <sup>c,e</sup>	N=15	1 Hz rTMS	90% RMT	S1: posterior to the central sulcus 2 cm posterior and 1 cm lateral to the motor hotspot guided by individual MRI and BrainSight neuronavigation system	SEP Sensorimotor tracking task	An increase of the N20-P27 amplitude induced by tactile stimulation after a 1 Hz rTMS train 1 Hz rTMS didn't affect sensorimotor tracking task
		cTBS	80% AMT	"	"	cTBS over S1 did not affect either sensorimotor tracking task or SEP
Ogawa et al. (2004) <sup>e</sup>	N=7	0.5 Hz	80% RMT	S1: 1 cm posteriorly and 1 cm laterally to the motor hotspot	SEP	0.5 Hz rTMS did not affect SEP; but led to an increase of HFOs
Restuccia et al. (2007) <sup>c,d</sup>	N=8	1 Hz rTMS	80% RMT	S1: the anterior end of the junction of the two coil wings at a scalp site half way between C3 and P3	SEP	1 Hz rTMS did not affect the standard SEPs, it did cause both an increase in early HFO and a decrease in late HFO
		10 Hz rTMS	"	"	"	10 Hz rTMS did not affect the standard SEPs, it did cause an increase of the late HFO
Satow et al. (2003) <sup>e</sup>	N=6 (received S1 stimulation)	0.9 Hz rTMS	90% RMT	S1: 3 cm posterior to the motor hotspot	Tactile detection by von Frey monofilaments Two-point discrimination (2PD) by caliper SEP	0.9 Hz rTMS did not affect either tactile detection or two-point discrimination 0.9 Hz rTMS over S1 did not affect SEP

Table 1 (continued)

Study	Sample	TMS	Intensity	Site	Task	Results
Vidoni et al. (2010) <sup>c</sup>	N = 14	1 Hz rTMS	90% RMT	S1: one gyrus backward and approximately 1 cm laterally from the M1 hotspot guided by individual anatomical MRI and BrainSight neuronavigation system	Two-point discrimination by aesthesiometer Proprioceptive acuity evaluated by limb-position matching task	1 Hz rTMS disrupted two-point discrimination 1 Hz rTMS caused a small but non-significant ( $p = .078$ ) reduction in proprioceptive acuity
Karim et al. (2006) <sup>d</sup>	N = 26 (separate days for spatial and frequency discrimination training)	15 Hz rTMS	90% RMT	S1: 1–2 cm posterior in parasagittal direction to the motor hotspot	Temporal discrimination training (interleaved with TMS) Spatial discrimination training (interleaved with TMS)	Compared to sham stimulation, 15 Hz TMS decreased spatial discrimination threshold during training (the averaged threshold of all trials in the training blocks), but not temporal discrimination threshold 15 Hz rTMS alone without combination with tactile discrimination training, did not affect performances on either spatial or frequency task
Pleger et al. (2006) <sup>d</sup>	N = 10	5 Hz rTMS	90% RMT	S1: 2 cm posterior to the motor hotspot	Temporal discrimination performance (without task training) Spatial discrimination performance	5 Hz rTMS improved tactile frequency discrimination
Rager et al. (2004) <sup>d</sup>	N = 13	5 Hz rTMS	90% RMT	S1: 1–2 cm posterior in parasagittal direction to the motor hotspot	SEP	5 Hz rTMS reduced the paired-pulse inhibition of the N20 SEP component
Tegethoff et al. (2005) <sup>d</sup>	N = 33	5 Hz rTMS	90% RMT	S1 finger representation: 1–2 cm posterior in parasagittal direction to the motor hotspot	Two-point discrimination by pairs of needles fMRI (only 12 participants performed fMRI)	5 Hz rTMS over index finger representation improved two-point discrimination and led to an increase of brain activation of the stimulated area



**Table 1** (continued)

Study	Sample	TMS	Intensity	Site	Task	Results
Valmunen et al. (2009) <sup>d</sup>	N= 15	10 Hz rTMS	90% RMT	S1 and S2 were determined when participants underwent a functional MRI study with tactile stimulation of the left cheek	Pain and temperature perception	10 Hz rTMS over both S1 and S2 increased the warm detection threshold S1 (but not S2) stimulation reduced cool detection threshold S2 (but not S1) stimulation produced a suppression of pain sensitivity for both cold and heat
Yoon et al. (2014) <sup>d</sup>	N= 12	10 Hz rTMS (online)	110% RMT	S1: 2.5 cm posterior to the motor hotspot	Proprioceptive shift	10 Hz online rTMS increased proprioceptive shift, presumably by causing proprioceptive suppression
Annak et al. (2019) <sup>e</sup>	N= 18	cTBS	80% AMT	M1 localisations were recognized by MRI task and transferred to BrainSight	Subjective intensity of pain: verbal analogue score (VAS)	Both the M1 and the S2-spaced stimulations did not affect the ratings of the nociceptive stimuli of different strengths
Conte et al. (2012) <sup>e,f</sup>	N= 15	cTBS/iTBS	80% AMT	S2 localisations were MRI task S1: Talairach coordinate reported in a previous study (x, y, z)=(48, -28, 54)	SEP (only cTBS over right S1) Tactile temporal discrimination (whether a single or two temporally separated stimuli were perceived)	cTBS over right S1 decreased N20-P25 and P25-N33 amplitudes induced by electrical stimulation applied to the left median nerve iTBS over right S1, but not pre-SMA increased temporal discrimination threshold
Ishikawa et al. (2007) <sup>e</sup>	N= 11 (Exp1)	cTBS	80% AMT	S1: 2 cm posterior to the motor hotspot	SEP	iTBS over right S1 decreased temporal discrimination threshold cTBS significantly suppressed P25-N33 following right, but not left median nerve stimulation

Table 1 (continued)

Study	Sample	TMS	Intensity	Site	Task	Results
Jones et al. (2019) <sup>e</sup>	N = 19	cTBS	40% of maximum machine output, corresponding on average to 104% AMT	S1: MNI coordinates (-32, -35, 64)	Itch: the histamine prick test consisted of the application of a single drop of 1% histamine dihydrochloride to the right volar forearm	cTBS over S1, but not S2 or IFG, led to a significant reduction in itch intensity
Katayama et al. (2010) <sup>e,f</sup>	N = 14 (9 completed both iTBS and cTBS, a further 5 completed iTBS only)	" cTBS	" 80% AMT	S2: MNI (-47, -21, 13) S1: C3' (2 cm posterior to C3)	" SEP	cTBS did not affect SEP amplitudes following right median nerve stimulation, but facilitated the early HFO and inhibited the late HFO at 15 min after cTBS
Kumar et al. (2019) <sup>e</sup>	N = 20	iTBS	"	"	"	iTBS over S1 facilitated N20 15 min and N20-P25 at 15 and 30 min, but left HFOs unchanged
Kumar et al. (2019) <sup>e</sup>	N = 20	cTBS	70% AMT	S1: 2 cm posterior to the motor hotspot	Proprioceptive acuity evaluated by limb position matching Motor adaptive learning induced by altered somatosensory feedback	cTBS over S1 decreased participants' acuity of perceived limb position for at least 10 min cTBS over S1 delivered immediately after motor adaptive learning largely blocked the retention
Lee et al. (2013) <sup>e</sup>	N = 16 (Exp 1)	cTBS	80% AMT	S1: 2 cm posterior to the motor hotspot	Temporal order judgement Temporal order judgement with noise (low amplitude background synchronised vibration)	cTBS only significantly impaired temporal order judgement with noise
Mirdamadi and Block (2021) <sup>e</sup>	N = 18	cTBS	70% RMT	S1: 1 cm posterior and 2 cm lateral to the motor hotspot	Proprioceptive sensitivity: verbally report hand position Visuomotor learning	cTBS over S1 impaired proprioceptive sensitivity in the horizontal, but not sagittal, dimension cTBS over S1 did not significantly affect visuomotor learning

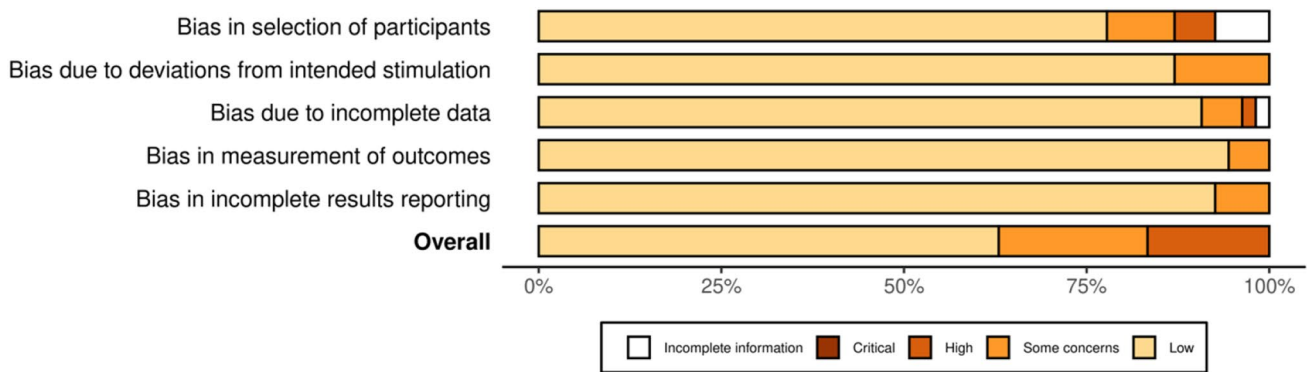
**Table 1** (continued)

Study	Sample	TMS	Intensity	Site	Task	Results
Poreisz et al. (2008) <sup>e,f</sup>	N= 12	cTBS	80% AMT	S1: Coil position was determined by anatomical MRI dataset and marked using neuronavigation system	Subjective intensity of pain: verbal analogue score (VAS) Laser-evoked potential (LEP)	All three active TBS decreased subjective pain perception. However, the decrease did not differ significantly from the sham stimulation
		tTBS	"	"	"	All active TBS stimulation significantly decreased the amplitudes of the N2 component of LEP induced by the contralateral hand laser stimulation. Sham stimulation condition had no such effect
Rao et al. (2020) <sup>e</sup>	N= 10	cTBS	80% AMT	S1: postcentral gyrus posterior to the motor hotspot guided by individual MRI and BrainSight neuronavigation system	Tactile sensitivity: the smallest filament that could be perceived on at least 70% of its applications Tactile electrical sensitivity: the lowest intensity of electrical stimulation that subjects can explicitly feel Electrical pain threshold	cTBS did not have significant effect on tactile sensitivity induced by either filament or electrical stimulus cTBS increased the perceptual threshold for electrically-induced pain for up to 40 min compared to sham stimulation
Rai et al. (2012) <sup>e</sup>	N= 16 (Exp 1) N= 14 (Exp 2)	cTBS	80% AMT	S1: 2 cm posterior to the motor hotspot	Tactile temporal discrimination	cTBS increased temporal discrimination threshold
		"	"	"	Tactile spatial amplitude discrimination	cTBS increased spatial discrimination threshold
Rocchi et al. (2016) <sup>e</sup>	N= 12 (Expts 1–3)	cTBS	80% AMT	S1: Talairach coordinate: (x, y, z) = (48, -28, 54)	Tactile temporal discrimination SEP	cTBS over S1, but not S2 impaired temporal discrimination threshold cTBS over S1 reduced N20 component of SEP
Torta et al. (2013) <sup>e</sup>	N= 11	cTBS	80% RMT	S1: One gyrus backward and approximately 1.5 cm laterally and 1.5 cm posteriorly from the M1 hotspot guided by individual MRI and BrainSight neuronavigation system	Subjective perception of nociceptive CO <sub>2</sub> laser thermal stimuli Subjective perception of non-nociceptive electrical stimuli	cTBS over S1 reduced the subjective perception of nociceptive CO <sub>2</sub> laser thermal stimuli delivered to the contralateral hand, not but subjective perception of non-nociceptive electrical stimuli

Table 1 (continued)

Study	Sample	TMS	Intensity	Site	Task	Results
Zapallow et al. (2012) <sup>e</sup>	N=13 (Exp1)	cTBS	80% RMT	S1 lower limb representation (CPz)	SEP	cTBS decreased the P1-N1 at 12–16 min cTBS also suppressed the P2-N2 second cortical potential for up to 60 min following stimulation
Katayama and Rothwell (2007) <sup>f</sup>	N=11 (only 7 completed all 3 conditions: S1, M1, reverse coil S1)	iTBS	80% AMT	S1: C3' (2 cm posterior to C3)	SEP	iTBS over S1 enhanced the N20–N20, N20–P25 and P25–N33 amplitudes of SEP
Mochizuki et al. (2007) <sup>f</sup>	N=8	iTBS	80% or 100% AMT	S1: 3 cm posterior and 3 cm lateral site from the motor hotspot	fNIRS	iTBS over S1 significantly diminished oxyhemoglobin at the contralateral M1 and S1
Premji et al. (2010) <sup>f</sup>	N=11	iTBS	80% AMT	S1: 2 cm posterior to motor hotspot	SEP	Enhanced N20-P25 amplitude was observed only at 5 min after iTBS was applied over contralateral S1 and 15 to 25 min after iTBS was applied over ipsilateral S1
Ragert et al. (2008) <sup>f</sup>	N=9, (completed all behavioural tasks and SEP)	iTBS	80% AMT	S1: 1 cm posterior in parasagittal direction to the motor hotspot	Two-point discrimination by needles Paired pulse SEP	iTBS decreased tactile discrimination thresholds for up to 30 min after the end of iTBS trains iTBS over left S1 reduced paired-pulse inhibition in the N20 component for the right but not left hand median nerve

M1—primary motor cortex, IFG—inferior frontal gyrus, DLPFC—dorsolateral prefrontal cortex, IPL—inferior parietal lobule, SPL—superior parietal lobe, SMA—supplementary motor area



**Fig. 2** Risk of bias summary: judgments broken down for each risk of bias criterion across all included studies.

an MEP in at least 5 out of 10 trials (Rossini et al. 1994). The MT can be measured either at rest (RMT: resting motor threshold) or under active conditions (AMT: active motor threshold). In case of a relaxed target muscle, a reliable MEP response has been defined as an MEP with 50  $\mu$ V or greater peak-to-peak amplitude. The AMT is measured when the target muscles are contracted. Under active conditions, a cut-off value is usually set to 200  $\mu$ V peak-to-peak.

McKay et al. (2003) used a more modern magnetic stimulator (Magstim 200, Magstim Co. Dyfed, UK) and coil (figure-of-eight) that allows more focal stimulation, and verified that single-pulse TMS over contralateral S1 (4 cm posterior to M1 hotspot) before (– 100 ms) or after (20 ms) electrical stimulus interfered with tactile detection; additionally, they showed that the TMS-induced tactile suppression was larger when the TMS intensity was higher (135% vs. 115% RMT). However, a separate study by Hannula et al. (2005) found that tactile suppression induced by single-pulse TMS (120% or 130% MT) over S1 only occurred when TMS delivered after (20 or 50 ms) the electrical stimulus, but not simultaneously with (0 ms) or prior to (– 20 ms) the electrical stimulus. The S1 position in that study was preliminarily defined as the site which produced at least 75% blocking of sensation of electrical stimuli applied at threshold intensity via 120% MT single-pulse TMS. It should be noted that these two studies examined different time windows: McKay et al. found suppression at – 100 ms prior to stimulus onset, while Hannula et al. found no suppression at – 20 or 0 ms prior to onset.

Two recent studies further differentiated the effects of TMS over S1 using both tactile detection sensitivity ( $d'$ ) and decision criterion (C) with a YES/NO detection paradigm. Tamè and Holmes (2016) found that contralateral TMS over S1 significantly impaired tactile detection sensitivity and increased participants' likelihood of reporting 'no' target present regardless of finger stimulation site (two pulses: 25 ms and 75 ms after the tactile stimulus, 120%

RMT, stimulation sites were determined using both anatomical and functional criteria from individual fMRI localizer scans). The impact of TMS on detection sensitivity, but not on decision criterion, was site-specific: the same stimulation over inferior parietal lobule (IPL) affected decision criterion similarly as S1 stimulation, but left detection sensitivity unaltered. Ro and Koenig (2021) applied single-pulse TMS (115–119% MT) over S1 40 ms prior to the tactile stimulus and found that TMS did not affect decision criterion but significantly decreased detection sensitivity in the YES/NO paradigm compared to a no-TMS condition (S1 locations were determined by moving the TMS coil caudally in 0.5-cm increments from the motor hotspot until there was suppression of tactile sensations on three out of five trials; the S1 locations of four participants were later confirmed by MRI scans). Again, it should be noted that TMS was delivered in different time windows in these two studies: Tamè and Holmes applied TMS after stimulus onset, while Ro and Koenig applied TMS 40 ms prior to onset.

In addition to tactile stimulus detection, single-pulse TMS over contralateral S1 has also shown to impair the discrimination of spatial properties of cutaneous stimuli. In Zangaladze et al. (1999), participants were asked to judge whether gratings applied to their right index finger were oriented along or across the finger (orientation task) or whether the grating grooves/ridges were wide or narrow (spacing task). Results showed that TMS (150% RMT) delivered over left S1 (coil was moved posteriorly until the motor response from hand disappeared) 30 ms after the onset of grating presentation decreased discrimination performance to near chance level in both tasks.

Similar to its effects on spatial discrimination, TMS applied over S1 significantly suppresses the frequency discrimination sensitivity of participants between a standard and a comparison vibrotactile stimulus of higher or lower frequency. Morley et al. (2007) showed that frequency discrimination between two vibrotactile stimuli (200 ms each with a 500 ms inter-stimulus interval) at both high (200 Hz)

and low (30 Hz) standard frequencies was reduced by two biphasic TMS pulses (one 30 ms before and the other 5 ms after the second stimulus; 100% RMT) over contralateral S1 (0.5–1 cm posterior to the motor hotspot, approximately to C3/C4). Harris et al. (2002) extended the inter-stimulus interval to 1500 ms and tested the effect of single-pulse TMS applied at different times across the interval (300, 600, 900, or 1200 ms after the end of the first stimulus). Single-pulse TMS (110% AMT) applied over contralateral S1 (approximately C3/C4) early in the interval (at 300 or 600 ms) significantly decreased participants' performance. The same TMS did not affect tactile performance if delivered to contralateral S1 late in the retention interval (at 900 or 1200 ms), nor did TMS affect performance if delivered to the ipsilateral S1 at any time point. Zhao et al. (2018) confirmed this result using a similar vibrotactile frequency discrimination task with a 2000-ms inter-stimulus interval. They showed that single-pulse TMS (110% RMT) over the contralateral S1 (2 cm posterior to the motor hotspot) at an early delay (100 and 200 ms after the first stimulus) reduced frequency discrimination. However, in contrast to previous findings, they also found a similar impairment when TMS was delivered over the ipsilateral S1 at a late delay (1600 and 1900 ms after the first stimulus).

Hannula et al. (2008) adopted a forced-choice paradigm in which participants were asked to tell whether a single or twin cutaneous test stimulus (two inter-stimulus intervals: 50 or 90 ms) was delivered to their hands, while real (120% MT) or sham TMS (20% of the maximal output of the stimulator) was applied to S1 (same localization procedure as in Hannula et al. 2005, site which produced at least 75% blocking of sensation of electrical stimuli applied at threshold intensity via 120% MT single-pulse TMS). This study applied monophasic TMS pulses, which arguably allow more focal stimulation than the biphasic pulses used in other studies (Groppa et al. 2012). The results of this study again confirmed that TMS over contralateral S1 disrupted sensory capacity for tactile temporal discrimination. In sum, these findings together demonstrate that the somatosensory cortex is involved in processing of both spatial and temporal tactile information.

### Pain perception

The role of somatosensory cortex in pain perception has long been in debate (Bushnell et al. 1999). Moreover, previous neuroimaging studies have shown that S1 and S2 might subservise different properties of pain discrimination (Apkarian et al. 2005; Bornhövd et al. 2002). To address this, Lockwood et al. (2013) used single-pulse TMS to investigate the contributions of S1 and S2 in the perception of pain location and intensity, respectively. Participants were required to judge either the intensity (medium/high) or the spatial

location (proximal/distal) of the stimulus in a two-alternative forced choice task, while single-pulse TMS (110% RMT) was delivered to S1 (moving the coil posteriorly from M1 until no detectable motor twitches occurred,  $2.4 \pm 0.6$  cm posterior to the motor hotspot), S2 (0.5 cm anterior and 6.5 cm superior to the right preauricular point), or a control site (vertex) 120 ms after stimulation of nociceptive afferents using neodymium:yttrium-aluminum-perovskite (Nd:YAP) laser pulses. Compared to S1 and control stimulation, TMS over S2 significantly disrupted participants' ability to judge pain intensity. Surprisingly, TMS over neither S1 nor S2 had any effect on pain localization. Porro et al. (2007) applied an uncommon three-pulse TMS protocol (three single pulses within 80 ms, pulses at 0–40–80 ms, 120% RMT) over S1 and found that TMS over S1 300 ms, but not 150 ms, after a painful stimulus impaired participants' pain localization (S1 locations were decided following the same localization procedure as described in Lockwood et al. 2013, 2 to 3.5 cm posterior to the motor hotspot).

### Somatosensory evoked potentials (SEPs)

The studies mentioned above have shown that single-pulse TMS applied over somatosensory areas before tactile stimuli can affect tactile thresholds. However, it remains unclear whether TMS has a direct modulatory effect on cortical excitability of S1/S2, making S1/S2 less responsive to sensory input. The cortical excitability of somatosensory areas can be examined directly by somatosensory evoked potentials (SEPs or SSEPs). SEPs are the electrical activities of the brain generated in response to a physical stimulation (usually electrical stimulation) of afferent peripheral nerves, which can be recorded by EEG. Several studies have confirmed that TMS over somatosensory areas before median nerve stimulation affected the size of SEP components (Kujirai et al. 1993; Seyal et al. 1993; Schürmann et al. 2001). Kujirai et al. (1993) reported that TMS (100% RMT) delivered over the contralateral central scalp 10 ms before median nerve stimulation induced an increase in the P25/N33 and a decrease in the later components (e.g. P40/N65), while leaving the early N20 unaffected. The null effect on the N20 might be related to the different origins of those components. The N20 component is generated at some distance from the cortical surface in Brodmann area 3b (Allison et al. 1989, 1991), while the P25/N33 component involves generators in superficial area 1. A similar P25 increase was also observed in Schürmann et al. (2001), who found that single-pulse TMS (110% MT) over S1 (1.5–2 cm posterior to the M1 hotspot) applied concurrently with the electrical stimulus (but not before) induced the largest enhancement of P25. This raises the question of why TMS stimulation enhances the magnitude of the P25 SEP component while reducing the magnitude of later components (P40/N65).



One possible explanation for the P25 increase is the brief excitation following a prolonged inhibition caused by TMS. Hyperpolarization is accompanied by a reduction in transmembrane resistance which in turn enhances synaptic currents, generating a larger P25 response (Rothwell et al. 1991; Kujirai et al. 1993). The decrease of later components (P40/N65) is consistent with findings from behavioral studies showing single-pulse TMS applied over S1 before electrical stimuli decreased somatosensory perception (e.g. McKay et al. 2003; Ro and Koenig 2021). It should be noted, however, that the timing between TMS and median nerve stimulation may affect these results. Seyal et al. (1993) found no change of the SEPs when the median nerve was stimulated 10–20 ms following TMS (45–60% of maximum output of Cadwell MES-10) over S1 (the anterior edge of the coil was placed over C4), while median nerve stimulation 30–70 ms after TMS resulted in enhancements of not only N1 (=N20), but also P1 (=P30) and N2 (=N45).

## Summary

The reviewed studies show that single-pulse TMS applied over somatosensory cortex before somatosensory stimuli is able to suppress somatosensation. Moreover, single-pulse TMS applied over somatosensory cortex can affect the size of SEP components induced by median nerve stimulation, suggesting single-pulse TMS can transiently change somatosensory cortex activity. However, future work is needed to clarify the relationship between the changes of SEP components and behavioral performance, that is, whether impaired somatosensory perception is mainly correlated with a specific SEP component or a mix of several components.

The reviewed studies also found that single-pulse TMS applied after somatosensory stimulation impaired tactile and pain perception, suggesting TMS over somatosensory cortex might affect not only detection or discrimination of somatosensory stimuli, but also maintenance of stimuli representations over time. Moreover, this TMS-induced effect might be limited to certain time windows, which vary between different types of somatosensation. For example, TMS delivered at an early delay (30 ms or 100 ms after somatosensory stimuli) reduced spatial and temporal discrimination of non-nociceptive stimuli (e.g. Zangaladze et al. 1999; Zhao et al. 2018), while TMS delivered 300 ms, but not 150 ms, after painful stimuli impaired localization discrimination of nociceptive stimuli (e.g. Porro et al. 2007). More studies are needed to further elucidate this point.

In sum, the reviewed single-pulse TMS studies provide causal evidence for the involvement of somatosensory areas at specific moments in time in processing or maintaining multiple types of somatosensory perception, including tactile and pain perception. However, we note that the

conclusions that can be drawn from these early single-pulse TMS studies are relatively limited due to methodological constraints and inconsistent results between studies. Half of the studies have a sample size less than 8, raising questions about the generalizability of these effects. Furthermore, the method used to localise S1 varies widely across studies and it is possible that some of the inconsistent results seen between studies result from stimulation of different brain areas.

## Paired-pulse TMS (ppTMS)

TMS pulses can also be paired; that is, two sequential TMS pulses of variable intensities separated by pre-defined inter-stimulus intervals (normally ranging between 1 and 20 ms). The baseline single pulse is commonly referred to as the test stimulus (TS), while the additional modifying pulse is the conditioning stimulus (CS). Paired-pulse TMS in humans has been used to investigate the excitability of inhibitory (Kujirai et al. 1993; Hanajima et al. 1998; Fisher et al. 2002) and excitatory (Tokimura et al. 1996; Di Lazzaro et al. 1999; Hanajima et al. 2002) neuronal circuits in motor cortex. Previous studies have found that the MEP evoked by a suprathreshold TS is inhibited by a subthreshold CS applied 1–6 ms before the TS (short-interval intracortical inhibition, SICI), whereas it is facilitated by the same subthreshold CS applied 8–15 ms before the TS (short-interval intracortical facilitation, SICF) (Kujirai et al. 1993; Ziemann et al. 1996). It is thought that short-interval intracortical inhibition relies on the CS activating a population of inhibitory neurons mediated by GABA receptors (Kujirai et al. 1993). In contrast, short-interval intracortical facilitation is believed to reflect direct excitation of axon initial segments of excitatory interneurons (Hanajima et al. 2002).

## Tactile perception

Koch et al. (2006) applied paired-pulse TMS, a subthreshold CS (70% RMT) followed by a suprathreshold TS (130% RMT), over the right S1 (3 cm posterior to the M1 hotspot) 20 ms after electrical stimuli delivered to the left thumb. They found that, compared to single-pulse TMS (130% RMT) alone, tactile detection was further suppressed by paired-pulse TMS when the ISI between two pulses was 10 or 15 ms. Paired pulses with shorter ISIs (1, 3, 5, and 7 ms) had no such effect. The authors suggested that one possibility for the additional tactile suppression induced by a subthreshold CS is that the CS may facilitate the excitatory action of the following TS through an intracortical network in S1, which in turn adds neural noise in the detection system, thus reducing perception. Meehan et al. (2008) used a

similar paired-pulse TMS protocol (70% RMT CS + 130% RMT TS; ISI 15 ms) and tested its effect on a sensorimotor task during which participants were required to make discrete or continuous motor responses with their left hand by detecting a vibrotactile stimulus applied to their right index finger. Compared to single-pulse conditions (subthreshold-70% RMT or suprathreshold-130% RMT), paired-pulse TMS over left S1 (post-central gyrus directly posterior to M1 guided by individual MRI and BrainSight neuronavigation) 20 ms after tactile stimulus further decreased the percentage of abrupt changes detected. However, this reduction was observed only when participants were required to respond discretely, but not continuously, to the vibrotactile changes. The authors suggested that the continuous tracking task involved inter-hemispheric interactions between S1-M1 and somatosensory cortices (Meehan and Staines 2007, 2009), which might mitigate the effects of the sub-threshold CS (presumably in local intracortical networks in S1) on task performance.

### Pain perception

Paired-pulse TMS has also been used to investigate the roles of S2 and medial frontal cortex (mFC) in pain perception. Kanda et al. (2003) applied pairs of TMS pulses (ISI: 50 ms, CS and TS: 120% RMT) over S2 (0.5 cm anterior and 6.5 cm superior to the right preauricular point), or over medial frontal cortex (mFC, Fz of 10–20 EEG system), at variable delays after the onset of a nociceptive CO<sub>2</sub> laser stimulus (50, 150, 250, and 350 ms). TMS over mFC 50 ms after the laser stimulus decreased the number of trials identified as painful, while TMS over S2 did not have such an effect, regardless of the delay. TMS had no effect on localization of pain in either stimulation target.

### Summary

Very few studies have applied paired-pulse TMS to investigate somatosensation. The only two studies examining tactile perception showed that tactile perception was additionally inhibited by paired pulses with longer ISI (10 or 15 ms) only, which is contrary to the effects of paired-pulse TMS over M1 (Kujirai et al. 1993; Ziemann et al. 1996). This may reflect a difference in local cortical circuits in different areas of the neocortex (e.g. M1 and S1). Additional studies are needed to reach a clear conclusion about the different effects of paired-pulse TMS with short (1–6 ms) and long intervals (8–15 ms) on tactile perception. Moreover, the effects of paired-pulse TMS on brain electrical activity (i.e. SEPs) are currently unknown; our search revealed no studies examining this topic.

### Low-frequency rTMS

Single-pulse TMS can depolarize neurons transiently, suppressing or masking somatosensation temporarily, while repetitive TMS (rTMS) applied at specific frequencies is able to induce relatively long-lasting modulation of cortical excitability as well as of other physiological and behavioral measures. As general rule, low-frequency rTMS (1 Hz or below) usually reduces cortical excitability at the site of stimulation and disrupts behavioral performance (Chen et al. 1997; Mottonen and Watkins 2009; Romero et al. 2002; Tang et al. 2021a, b).

### Tactile perception

Knecht et al. (2003) demonstrated that a low-frequency rTMS train (1 Hz, supra-threshold—110% RMT) over the contralateral, but not ipsilateral, S1 (C4) significantly disrupted frequency discrimination of vibrotactile stimuli. Moreover, the duration of impairment was positively correlated with TMS duration, with the inhibitory effect lasting around 8 min after a 20-min TMS train. To avoid potential effects of the afferent input evoked by TMS-induced muscle twitch, Satow et al. (2003) applied 0.9 Hz-rTMS train (around 16 min) at subthreshold level (90% RMT) over contralateral M1 or S1 (3 cm posterior to the motor hotspot). M1, but not S1, stimulation significantly increased the tactile detection threshold evaluated by von Frey monofilaments, while stimulation over neither M1 nor S1 had an effect on a two-point discrimination task using a caliper probe. In contrast, a later study using a more accurate localization method (one gyrus posterior to and approximately 1 cm laterally from the M1 hotspot guided by individual MRI and BrainSight neuronavigation) reported that 20 min of 1 Hz rTMS applied over S1 at subthreshold level (90% RMT) significantly disrupted two-point discrimination as measured with an aesthesiometer (Vidoni et al. 2010). This result was replicated by Case et al. (2016) using the same 1 Hz rTMS with suprathreshold intensity (110% RMT).

### Proprioception

Compared with tactile perception, the effects of rTMS on other types of somatosensory perception, such as proprioception, have been less studied. Balslev et al. (2004) showed that 1 Hz rTMS (15 min, 110% RMT—RMT defined as the lowest intensity that reliably elicited a visible twitch in the FDI muscle) over S1 (3 cm posterior to the motor hotspot) impaired proprioceptive acuity evaluated by a finger-matching task in which participants were asked to match their left index finger to the position of their right index finger, which was passively moved by the examiner without seeing their hands. The same rTMS protocol also improved trajectory



accuracy during a novel task of mirror tracing, confirming the authors' hypothesis that reducing proprioceptive acuity improves performance in situations with a visuoproprioceptive conflict. Balslev et al. (2007) used the same protocol to deliver 1 Hz rTMS over S1, and found that rTMS slowed down reaction time for initiating a motor correction in response to a visual perturbation in hand position, but not to a target jump. Vidoni et al. (2010), however, found that 1 Hz rTMS to S1 (see 3.3.1 for detailed TMS parameters) at subthreshold level (90% RMT) only caused a small but non-significant ( $p=0.078$ ) reduction in proprioceptive acuity evaluated by a limb-position matching task. Meehan et al. (2011) also reported a null effect of subthreshold (90% RMT) 1 Hz rTMS over contralateral S1 (posterior to the central sulcus 2 cm posterior and 1 cm lateral to the M1 hotspot guided by neuronavigation using individual structural MRIs) on a sensorimotor tracking task in which participants needed to rely on proprioceptive perception of their hands while visual feedback was limited (participants were required to use a handle bar to control the horizontal position of a white circle while the hand that controlled the cursor was occluded from view).

More recently, Huh et al. (2016) examined the role of S1 in the perception of body position and movement separately using a task in which participants tried to replicate the amplitude (in degrees) and the velocity (in degrees per second) of an illusory movement induced by tendon vibration on the left wrist using their right wrist. A low-frequency rTMS train (1 Hz, 20 min, 90% RMT) delivered to S1 (2 cm posterior to the motor hotspot) significantly decreased both the amplitude and the velocity of replicating movements performed by the right wrist.

### Somatosensory-evoked potentials (SEPs)

When applied over M1, a train of low-frequency rTMS can reduce M1 excitability (as measured by MEPs) for minutes to hours (e.g. Chen et al. 1997; Lyer et al. 2003). In contrast, when applied over S1, most studies have found that standard low-frequency SEP measures remain mostly unaffected (Enomoto et al. 2001; Ogawa et al. 2004; Satow et al. 2003). Instead, two studies observed that low-frequency rTMS over S1 led to significant changes in high-frequency oscillations (HFOs, around 600 Hz) of SEPs (Ogawa et al. 2004; Restuccia et al. 2007). HFOs have similar latency window as the primary N20 response (Curio et al. 2000; Haueisen et al. 2001) and are thought to represent a localized activity of GABAergic inhibitory interneurons in layer 4 of area 3b of S1 (Hashimoto et al. 1996). Therefore, these results suggest that low-frequency rTMS might affect the excitability of somatosensory cortex via modulating localized activity of GABAergic inhibitory interneurons. The lack of an effect on standard SEP components suggests that SEPs (N20) and

HFOs might reflect two parallel and partly independent steps in somatosensory processing: SEPs represent a more stable somatosensory input while HFOs are more sensitive to rapid changes, such as attention variations (Klostermann et al. 2001; Restuccia et al. 2004). Low-frequency rTMS might specifically affect this more variable component of somatosensory information processing. It should be noted, however, that these two studies observed different HFOs changes after low-frequency rTMS: Ogawa et al. (2004) observed an overall increase of HFOs after 0.5 Hz rTMS (50 pulses, 80% RMT) over S1 (1 cm posteriorly and 1 cm laterally to the motor hotspot), while Restuccia et al. (2007) found an increase in early HFO (peaking during ascending slope of N20) and a decrease in late HFO (peaking during descending slope of N20) after 1 Hz rTMS (20 min, 80% RMT) over S1 (the anterior end of the junction of the two coil wings at a scalp site halfway between C3 and P3). The different effects on early and late HFOs has been thought to provide support for the dissociations of generators for early and late HFOs: one is at presynaptic level (early), while the other is at postsynaptic level (late). In contrast to studies mentioned above, one study (Meehan et al. 2011) reported an increase of the N20-P27 amplitude induced by median nerve stimulation after a 1 Hz rTMS train (20 min, 90% RMT) over S1 (following the same localization as in Vidoni et al. 2010). It is possible that modulating the more stable N20 component by low-frequency rTMS requires a higher stimulation intensity (90% RMT vs. 80% RMT) and longer stimulation length (1200 pulses vs. 50 or 200 pulses). More studies are needed to clarify this point.

### Summary

In sum, existing work has shown that a low-frequency rTMS train is able to modulate cortical excitability of somatosensory cortex, likely through modulating localized activity of GABAergic inhibitory interneurons. However, there is mixed evidence regarding the effects of low-frequency rTMS over somatosensory cortex on somatosensory sensitivity measured by psychophysical tests. Some studies showed that low-frequency rTMS with supra-threshold (110% RMT) over S1 reduced tactile and proprioceptive acuity (e.g. Knecht et al. 2003; Balslev et al. 2004; Case et al. 2016), while some other studies reported a null effect of sub-threshold (90% RMT) low-frequency rTMS (e.g. Satow et al. 2003; Meehan et al. 2011). One possibility for these results is that the impaired somatosensory perception induced by low-frequency rTMS with supra-threshold is a joint effect of direct S1 action and an indirect action of M1. Previous work has established the inhibitory effect on S1 of rTMS to M1 (Enomoto et al. 2001), likely via projections from M1 to superficial areas 1 and 2 of S1 (Jones et al. 1978). Although the effects of TMS are relatively focal and maximal at the

stimulated area, regions located adjacently or more distally that are functionally connected to the stimulated site can be affected, especially with high stimulation intensity (Paus et al. 1997). In general, a lower stimulation intensity is associated with less unwanted spread of stimulation (Mottonen et al. 2013; Mottonen and Watkins 2009; Tang et al. 2021a, b; Tang et al. 2021a, b). Further work exploring the influence of different stimulation intensities on somatosensory inhibition induced by low-frequency TMS could clarify this point. The effects of rTMS on pain perception are currently unknown; we did not find any available studies that investigated pain perception using low-frequency rTMS applied over S1/S2.

## High-frequency TMS

### Tactile perception

In contrast to the inhibitory effect of low-frequency rTMS, high-frequency rTMS (5 Hz or above) increases excitability of the stimulated population of neurons and usually results in an improvement of behavioral or perceptual change (Pascual-Leone et al. 1994; Siebner and Rothwell 2003). Most of the somatosensory-related studies employed 5 Hz offline rTMS at subthreshold level (80% or 90% MT) and found that it significantly improved tactile perception (Pleger et al. 2006; Ragert et al. 2003; Tegenthoff et al. 2005). Tegenthoff et al. (2005) reported that 5 Hz rTMS (two TMS sessions separated by 45 min, each session included 25 TMS trains for a total of 1250 pulses, 90% RMT) over the index finger representation in contralateral, but not ipsilateral, S1 (1–2 cm posterior in parasagittal direction to the motor hotspot) led to a reduction of the discrimination threshold in a two-finger discrimination task and an enhancement of the stimulated area assessed using functional magnetic resonance imaging (fMRI). The TMS-induced reduction of threshold lasted around 90 min and exhibited a relatively high spatial specificity: the same stimulation over the lower leg representation did not affect the threshold of the left or right index finger. In line with previous studies, Pleger et al. (2006) found that 5 Hz rTMS (25 TMS trains for a total of 1250 pulses, 90% RMT) applied to S1 (2 cm posterior to the motor hotspot) significantly improved contralateral tactile frequency discrimination. Interestingly, participants who showed the largest behavioral improvement exhibited the highest TMS-evoked activation gain in S1 and the lowest activation gain in M1, as measured by fMRI. The authors thus suggested that 5 Hz TMS might enhance tactile discrimination by increasing S1 excitability (self-connection) and effective connectivity from S1 and M1. Karim et al. (2006) adopted an uncommon TMS-training design in which 80 trains of 15 Hz rTMS (each train consisted of 30 single pulses with a repetition

rate of 15 Hz lasting 2 s) were applied interleaved with 40 tactile training blocks (two trains were applied in each training block with an intertrain interval of 10 s, one before and one in the middle of training block). They found that, compared to sham stimulation, 15 Hz TMS over contralateral S1 (1–2 cm posterior in parasagittal direction to motor hotspot) decreased spatial discrimination thresholds during training (the averaged threshold of all trials in the training blocks), but not temporal discrimination thresholds. They additionally tested another group of participants who received the same 15 Hz rTMS protocol but without tactile discrimination training. In contrast to previous studies, 15 Hz rTMS did not significantly modulate participants' performances on either a spatial or frequency discrimination task. This negative result could be due to the different stimulation frequency used (15 Hz vs the more typical 5 Hz). However, a higher frequency is normally associated with stronger facilitatory effect. Another more likely reason could be the uncommon TMS protocol used (2-s trains with 10-s intertrain interval vs. 250-s continuous trains).

### Proprioception

Very few studies have applied high-frequency rTMS to investigate proprioception; the few studies that do exist have shown mixed results. By combining rTMS with a prism adaptation task, Yoon et al. (2014) found that proprioceptive shift increased after 10 Hz online rTMS (10 Hz, 500 ms rTMS train applied at the beginning of each movement) over S1 (2.5 cm posterior to the motor hotspot), but only with terminal, not continuous, visual feedback. The authors argued that such increased proprioceptive shift was caused by a proprioceptive suppression effect induced by 10 Hz online rTMS. It is worth mentioning that instead of using an offline TMS protocol with subthreshold intensity (i.e. 80% or 90% MT in other high-frequency rTMS studies), this study applied online rTMS at suprathreshold level (i.e. 110% RMT). A later study reported a facilitatory effect of 5 Hz offline rTMS (25 trains for a total of 1250 pulses, 90% RMT) over S1 (2 cm posterior to the motor hotspot) on the perception of joint motion, as induced by tendon vibration illusion (Huh et al. 2016).

### Pain and temperature perception

Valmunen et al. (2009) examined the causal roles of S1 and S2 in both thermal sensory (cool and warm) and pain detection (cold-pain and heat-pain) thresholds. 10 Hz rTMS (500 pulses in total, 90% RMT) over both S1 and S2 (individual TMS stimulation sites were determined when participants underwent a functional MRI study with tactile stimulation of the left cheek) significantly increased the warm detection threshold. In contrast, S1 (but not S2) stimulation led to a

decrease in cool detection threshold. Additionally, S2 (but not S1) stimulation caused an increase in thresholds for pain sensitivity for both cold and heat.

### Somatosensory-evoked potentials (SEPs)

Two previous studies have examined the effect of high-frequency rTMS on cortical excitability of S1 assessed by SEP recording. Ragert et al. (2004) found that 5 Hz rTMS (a total of 2500 pulses, 90% RMT, the same TMS protocol as Tegenthoff et al. (2005) over left S1 (1–2 cm posterior in parasagittal direction to motor hotspot) reduced the paired-pulse inhibition of the N20 SEP component induced by right index finger stimulation for up to 1 h. Restuccia et al. (2007) did not find a modulatory effect of 10 Hz rTMS (12 TMS trains for a total of 1200 pulses, 80% RMT) over contralateral S1 (anterior end of the junction of the two coil wings placed at a scalp site halfway between C3 and P3) on standard low-frequency SEP. Instead, they found that 10 Hz rTMS induced an increase of late HFO, which is thought to reflect activity of GABAergic inhibitory interneurons. These findings are consistent with results from previous studies using low-frequency rTMS, suggesting that the N20 is more stable compared to HFOs. To induce changes in the N20 component by high-frequency rTMS, a higher stimulation intensity (90% RMT vs. 80% RMT) or longer stimulation length (2500 pulses vs. 1200 pulses) may be necessary.

### Summary

Overall, existing studies have provided fairly consistent evidence that high-frequency offline rTMS over S1 is able to increase excitability of S1 and hence improve tactile perception. Moreover, these facilitatory effects last much longer than the effects of low-frequency offline rTMS (up to 1–2 h vs. less than 30 min). However, the effects of high-frequency TMS over S1 on other types of somatosensory perception, such as proprioception and pain perception, remain less clear. Two studies investigated proprioception by high-frequency rTMS and reported opposite effects: an inhibitory effect of 10 Hz online rTMS and a facilitatory effect of 5 Hz offline rTMS. The only study that examined the effects of high-frequency rTMS over somatosensory cortex on pain perception generally found an inhibitory effect of high-frequency TMS over S2 on pain sensitivity, which is contrary to the facilitatory effect of high-frequency rTMS that is commonly observed in other high-frequency rTMS studies.

There are multiple possible mechanisms by which high-frequency rTMS may suppress pain responses. One possibility is that the high-frequency rTMS causes a change of localized activity of GABAergic inhibitory interneurons, which in turn interferes with processing of pain signals and induces

analgesia. Alternatively, the high-frequency rTMS may have induced subcortical release of various neurotransmitters, such as dopamine and serotonin, which affect the descending modulation of pain perception (Valmunen et al. 2009).

### Theta-burst stimulation

Around 15 years ago, a newer form of rTMS, termed theta-burst stimulation (TBS), was introduced by Huang and colleagues (Huang et al. 2005; Huang and Rothwell 2004), and has become an increasingly popular tool to modulate neural activity and behavior in healthy and clinical populations. The main advantage of TBS over standard rTMS protocols is that it is able to produce powerful and long-lasting effects to the stimulated brain areas with a much shorter stimulation time (less than 3 min in most studies) and lower stimulation intensity (80% AMT in most studies). TBS can be applied continuously or intermittently to induce either facilitatory or inhibitory effects, respectively (Di Lazzaro et al. 2008; Huang et al. 2005).

### Continuous theta burst stimulation (cTBS)

**Tactile perception** Several studies examined the influence of cTBS over S1 on temporal and spatial tactile acuity (Conte et al. 2012; Rai et al. 2012; Rao et al. 2020; Rocchi et al. 2016). Rai et al. (2012) found that, compared to sham stimulation, cTBS (a burst of 3 stimuli at 50 Hz, repeated every 200 ms for a total of 600 pulses, 80% AMT) over S1 (2 cm posterior to the motor hotspot) significantly increased temporal discrimination thresholds (the inter-stimulus interval needed to perceive two stimuli as being sequential) and spatial amplitude discrimination thresholds (the vibration amplitude difference needed to discriminate two simultaneous vibrations) for up to 18 min. It is worth mentioning that the increased temporal discrimination threshold was observed following stimulation at 3–7 and 15–18 min, but not 7–10 or 11–14 min. Two later studies confirmed the inhibitory effects induced by cTBS over contralateral S1 (Talairach coordinates: 48, – 28, 54), and further showed that such cTBS-induced temporal discrimination inhibition was restricted to S1, as the same stimulation over S2 (Rocchi et al. 2016) or pre-SMA (Conte et al. 2012) did not affect temporal discrimination. Moreover, the change in tactile temporal acuity correlated with reduced paired-pulse N20 suppression and HFOs (Rocchi et al. 2016). Lee et al. (2013), however, found that tactile temporal acuity (measured as a judgment of the temporal order of two sequential events) was unaltered following cTBS (80% AMT) over S1 (2 cm posterior to the motor hotspot). Instead, they observed a reduction of temporal order judgment accuracy performed in the presence of low amplitude background synchronized vibration for up to 18 min following the same cTBS. This

reduction was observed 3–6, 7–10, and 15–18 min, but not 11–14 min, after cTBS. It is worth mentioning that inhibitory interneurons are thought to play an important role when temporal order judgment is performed in the presence of low amplitude background vibration (Singer 1996).

Rao et al. (2020) investigated the effect of cTBS on tactile detection sensitivity and did not find a significant effect of cTBS (80% AMT) over S1 (postcentral gyrus posterior to the motor hotspot guided by individual MRI and BrainSight neuronavigation) on either electrical sensory threshold (the lowest intensity of electrical stimulation that subjects can explicitly feel) or tactile sensitivity (the smallest filament that could be perceived on at least 70% of its applications).

**Proprioception and motor learning** The influence of cTBS over S1 on proprioceptive sensitivity and/or associated motor learning has been examined in three more recent studies (Kumar et al. 2019; Mirdamadi and Block 2021; Platz et al. 2012). Kumar et al. (2019) provided the first evidence for the inhibitory effects of cTBS over S1 on proprioception and motor learning consolidation. They found that cTBS over S1 (2 cm posterior to the motor hotspot) significantly decreased participants' acuity of perceived limb position for at least 10 min. Moreover, cTBS over S1 delivered immediately after motor adaptation induced by altered somatosensory feedback largely blocked learning retention, measured 24 h later. However, it should be noted that this study adopted an uncommon cTBS protocol, in that cTBS was applied at 70% AMT (compared to the 80% AMT in most other cTBS studies) in two trains (10 min apart, each train consisting of a standard cTBS sequence of 600 pulses). Similarly, Mirdamadi and Block (2021) revealed that cTBS (70% RMT) over S1 (1 cm posterior and 2 cm lateral to the M1 hotspot) impaired proprioceptive sensitivity in the horizontal, but not sagittal, dimension. However, they did not find a significant difference between S1 and sham stimulation in the magnitude of visuomotor adaptation. The authors suggest that this negative result might be due to the time at which stimulation was delivered. Stimulation was applied at the end of each training day when participants had finished all motor training and proprioceptive tasks in the study, rather than immediately after the motor learning task as in Kumar et al. 2019.

**Pain perception and itch** Although a number of studies have investigated the effects of cTBS over S1 on pain perception, the results are inconsistent. Poreisz et al. (2008) applied cTBS (80% AMT) over S1 (coil position was determined by anatomical MRI dataset and marked using neuronavigation) and recorded both psychophysical (verbal analogue score of pain intensity) and electrophysiological responses (EEG recording, laser-evoked potential) to painful laser stimulation. Compared to sham stimulation, cTBS over S1 signifi-

cantly reduced the amplitude of the N2 component of the evoked potential when the contralateral hand site was laser-stimulated. The subjective pain perception also decreased after cTBS over S1, but did not differ significantly from the sham stimulation. Similarly, Annak et al. (2019) showed that cTBS (80% AMT) over either M1 or S2 (as defined by fMRI functional localizers) failed to produce change in subjective pain perception induced by CO<sub>2</sub> laser stimulation. In contrast, Torta et al. (2013) found that cTBS applied over either M1 or S1 (one gyrus posterior to and approximately 1.5 cm laterally and 1.5 cm posteriorly from the M1 hotspot guided by individual MRI and BrainSight neuronavigation) significantly reduced the subjective perception of nociceptive CO<sub>2</sub> laser thermal stimuli delivered to the contralateral hand, as compared to similar stimulation of the ipsilateral hand. Surprisingly, the same stimulation did not modulate subjective perception of non-nociceptive electrical stimuli delivered to the contralateral hand. Instead of focusing on nociception induced by laser thermal stimuli, Rao et al. (2020) showed that cTBS (80% AMT) over S1 (MRI-guided) increased the perceptual threshold for electrically-induced pain for up to 40 min compared to sham stimulation.

The role of somatosensory areas in itch, a complex sensory experience, remains poorly understood. Jones et al. (2019) used cTBS to test whether contralateral S1 (MNI coordinates: -32, -35, 64) and S2 (MNI coordinates: -47, -21, 13) and ipsilateral inferior frontal gyrus (IFG) are causally involved in the neural processing of acute itch induced by a histamine prick. Results showed that cTBS (804 pulses in total, each burst consisting of three pulses at 30 Hz, repeated at intervals of 100 ms, 104% AMT) over S1, but not S2 or IFG, led to a significant reduction in itch intensity.

**Somatosensory-evoked potentials (SEPs)** TBS was first applied to S1 by Ishikawa et al. (2007), who found that amplitudes of the P25-N33 SEP component following right, but not left, median nerve stimulation were significantly suppressed for up to 13 min after cTBS (80% AMT) over left S1 (2 cm posterior to the motor hotspot). This was confirmed by two later studies (Conte et al. 2012; Rocchi et al. 2016), who further showed that the same cTBS over right S1 (Talairach coordinates: 48, -28, 54) decreased both N20-P25 and P25-N33 amplitudes induced by electrical stimulation applied to the left median nerve. Zapallow et al. (2012) showed that cTBS over S1 has similar effect on SEPs from the lower limb (tibial nerve electrical stimulation): following cTBS (80% RMT) over S1 lower limb representation (CPz), the P1-N1 first cortical potential and P2-N2 second cortical potential were suppressed at 12–16 min and for up to 30 min following stimulation, respectively. A recent animal study has confirmed that cTBS is able to produce a pronounced and long-lasting reduction in neuronal excita-



bility in macaque parietal neurons (Romero et al. 2022). The observed decrease in SEP components therefore most probably reflects the summed decrease of neuronal excitability.

However, null effects of cTBS over S1 on SEPs were also reported by two other studies (Katayama et al. 2010; Meehan et al. 2011). Katayama et al. (2010) reported that cTBS (80% AMT) over left S1 (C3', 2 cm posterior to C3) did not affect the amplitudes of either the N20-N20 or N20-P25 SEP components following right median nerve stimulation, but did facilitate early HFO and inhibit late HFO at 15 min after cTBS. Similar early increases and late decreases in HFOs were also observed after low-frequency rTMS over S1 (Restuccia et al. 2007). When taken together, this suggests that, similar to low-frequency rTMS, cTBS produces prolonged effects on the excitability of GABAergic inhibitory interneurons, which is reflected by the increased late HFO, and also cause a disinhibition of the thalamus, which is reflected by the decreased early HFO (Katayama et al. 2010).

### Intermittent theta burst stimulation (iTBS)

**Tactile perception** Compared to cTBS, fewer studies have examined the effects of iTBS (a burst of 3 stimuli at 50 Hz, repeated every 10 s for 600 total pulses) on tactile perception. Ragert et al. (2008) assessed tactile discrimination threshold using a two-point discrimination task on the right and left index fingers before and after iTBS (80% AMT) over the hand representation of left S1 (1 cm posterior in parasagittal direction to the motor hotspot). A significant decrease in tactile discrimination thresholds was observed in the right (contralateral), but not left (ipsilateral), index finger for up to 30 min after the end of the iTBS train. At the neurophysiological level, the authors found that iTBS over left S1 reduced paired-pulse inhibition in the N20 component for the right but not left hand median nerve. However, there was no correlation between tactile improvement and reduction in paired-pulse inhibition. In line with iTBS-induced enhancement of tactile spatial discrimination, Conte et al. (2012) showed that iTBS (80% AMT) applied over right S1 (Talairach coordinates: 48, -28, 54) significantly improved the tactile temporal discrimination of the left index finger.

**Pain perception** As mentioned before, Poreisz et al. (2008) tested the effects of three TBS protocols (cTBS, iTBS, imTBS: a burst of 3 stimuli at 50 Hz, repeated every 15 s for 600 total pulses) over S1 on subjective pain perception induced by laser stimulation. All three active TBS reduced subjective pain sensitivity. However, in no condition did this decrease differ significantly from the sham stimulation.

**Somatosensory-evoked potentials and near-infrared spectroscopy** Sub-threshold (80% AMT) iTBS over S1 (C3') has been demonstrated to enhance the amplitudes of several

SEPs components (e.g. N20–P20, N20–P25 and P25–N33) induced by median nerve stimulation (Katayama et al. 2010; Katayama and Rothwell 2007; Premji et al. 2010). Such modulatory effects on SEPs were not seen after cTBS over S1 in the same studies (Katayama et al. 2010; Katayama and Rothwell 2007). Instead, they found that cTBS affected the amplitudes of HFOs. The authors thus concluded that both iTBS and cTBS applied over S1 were able to produce lasting changes in the cortical excitability of S1, but likely through different mechanisms.

Interestingly, the facilitatory effect induced by iTBS appeared at different time points: Katayama et al. (2010) found that the facilitatory effect did not appear immediately after the stimulation, but only at 15 and 30 min after the stimulation, with stronger effects found in the 15 min compared to the 30 min window, while Premji et al. (2010) reported that the facilitatory effect was observed only 5 min after iTBS was applied over contralateral S1 (2 cm posterior to motor hotspot). Two other studies, however, reported an inhibition, rather than a facilitation, of cortical activities after S1 iTBS (Mochizuki et al. 2007; Poreisz et al. 2008). Poreisz et al. (2008) found that compared to sham stimulation, cTBS, iTBS, and imTBS all (delivered at 80% AMT) significantly reduced the amplitude of the N2 component when the contralateral hand site was laser-stimulated to induce a pain response. Using functional near-infrared spectroscopy, Mochizuki et al. (2007) showed that iTBS over S1 (3 cm posterior and 3 cm lateral site from the motor hotspot) significantly diminished oxyhemoglobin at the contralateral M1 and S1. Moreover, the effect of iTBS delivered at an intensity of 80% AMT was larger than that at 100% AMT.

### Summary of the effects of theta-burst stimulation

To sum up, over the past ten years, TBS has gained increasing popularity in studies aiming to investigate S1 and S2 plasticity. The advantages of TBS are its short duration and use of low intensity pulses, making it more tolerable to participants than low-frequency TMS protocols. Previous work has shown that short TBS trains (less than 3 min in most of studies) over S1/S2 are able to enhance or inhibit tactile acuity for up to 40 min, depending on the stimulation protocols (cTBS vs. iTBS). Findings from SEP recordings indicate that cTBS and iTBS may have different effects on excitatory and inhibitory cortical networks. Animal studies of M1 stimulation suggest that iTBS may increase cortical excitability by reducing inhibition of pyramidal cells by PV + fast-spiking interneurons (Benali et al. 2011). Yet there are still many unknowns. For example, it remains unclear why TBS-induced (maximal) effects on SEPs or tactile threshold only appear at certain time periods (e.g., 3–5 min and 15–18 min but not 7–14 min after stimulation). Future studies are needed to clarify the physiological effect of TBS

over somatosensory areas and its relationship with behavioral performance. In addition, the effects of both cTBS and iTBS over S1/S2 on pain perception merit further investigation. Several studies have found a decrease of subjective pain perception after cTBS over S1, but the decrease was not significantly different from the sham stimulation. The only study which examined the effect of iTBS on pain perception surprisingly found an inhibitory effect. It remains unclear whether TBS has similar or different effects on perception of non-nociceptive and nociceptive stimuli. We did not find any studies that investigated the effect of iTBS over S1/S2 on proprioception.

## Discussion, conclusions, limitations and future directions

In conclusion, TMS has proved to be a useful tool to investigate the human somatosensory system. Single-pulse TMS offers opportunities to closely examine the chronometry of somatosensory processing, while paired-pulse TMS allows researchers to investigate the intracortical inhibitory and excitatory circuits in somatosensory areas. Repetitive low-frequency TMS can be used to create longer-lasting changes in cortical excitability with relatively high spatial accuracy (“virtual lesions”), complementing functional neuroimaging and patient studies. This makes TMS a unique tool for studying the causal relationship between a specific brain area and somatosensory tasks. Innovative protocols, such as TBS, have been shown to produce stronger and longer-lasting changes in somatosensory areas with reduced stimulation time compared to traditional rTMS protocols. This not only allows for more extensive testing within the stimulation effectiveness window in experimental protocols, but also offers potential for enhancing recovery processes and aiding rehabilitation for patients with somatosensory and motor deficits.

Prolonged cortical excitability changes measured by SEP recordings have been reported after various rTMS protocols (low-frequency, high-frequency rTMS and TBS). Excitability decreases induced by low-frequency rTMS and cTBS have been discussed in terms of increased activity of GABAergic inhibitory interneurons, which presumably can be measured by late HFOs, or in terms of a disinhibition of the thalamus, which is thought to be related to early HFOs. Based on animal data, high-frequency rTMS has been thought to induce LTP (long-term potentiation)-like mechanisms, compatible with an increase of glutamatergic excitatory neurons. The reviewed studies have shown high-frequency rTMS and iTBS significantly increased the amplitudes of SEPs, which likely reflect a summed increase of glutamatergic excitatory neurons. However, the exact underlying mechanisms that drive the effects of rTMS on

S1/S2 excitability are not fully understood. The observed excitability changes might be due to one of the mechanisms mentioned above or a mixture of both, or even other unknown mechanisms, which can not be resolved by SEP recordings alone. Animal TMS models would be especially useful for understanding the underlying neurophysiological mechanisms of TMS.

Mixed results have been reported from different studies, which may stem from large variability among participants, methodological limitations, and research bias arising from various sources, such as selection of participants and deviations from intended stimulation (see Fig. 2 and Fig. S1). For instance, even though the response to TMS stimulation is highly variable across participants in most TMS studies, a sample size of 10 (or less) per group is typical for the somatosensory-related TMS studies we reviewed. It seems probable that a substantially larger sample size is necessary to produce reproducible results given the heterogeneous response to TMS across individuals. A priori power analyses should be used to prevent underpowered or overpowered studies and improve reproducibility. Moreover, as shown in Fig. 2, around 25% of the reviewed studies raised moderate to high concerns regarding the selection of participants (e.g. data from experimenters was included). In the future, selection criteria should be clearly defined and be applied consistently and transparently to reduce the risk of selection bias and increase the validity of the results.

Few studies have used the exact same experimental task and TMS parameters, leaving open the possibility that the mixed results across studies could be driven by these differences. Variability in TMS parameters can be found in the procedures used for localising S1 and S2, stimulation intensity, stimulation duration, and the number of pulses delivered. Perhaps the most critical of these is stimulation location: at least three types of localization methods have been used to determine S1 position in the TMS studies reviewed. Some studies rely on scalp coordinates based on international 10–20 system of electrode placement (e.g. Seyal et al. 1993; Restuccia et al. 2007; Knecht et al. 2003; Katayama et al. 2010). Different electrode positions, however, have been selected in different studies (e.g. C3/C4, or C3'/C4', i.e., 2 cm posterior to C3/C4). A considerable number of studies first find the motor hotspot by single-pulse TMS and move the TMS coil 1–4 cm posterior to the motor hotspot (e.g. McKay et al. 2003; Tegenthoff et al. 2005; Koch et al. 2006; Rai et al. 2012; Huh et al. 2016; Kumar et al. 2019). This S1 position has been further confirmed by asking participants to report detectable sensations in their index finger induced by single pulse TMS at 90% RMT (Tegenthoff et al. 2005). Other studies obtained anatomical MRI for each participant and imported them into the BrainSight neuronavigation system to stereotaxically register participants' brains with the TMS coil (e.g. Conte et al. 2012; Jones et al. 2019;

Meehan et al. 2011; Rao et al. 2020; Torta et al. 2013; Vidoni et al. 2010). In this approach, the TMS coil was placed above the postcentral gyrus posterior to the motor hotspot (e.g. Vidoni et al. 2010; Meehan et al. 2011; Torta et al. 2013; Rao et al. 2020) or at specific MNI/Talairach coordinates (e.g. Conte et al. 2012; Rocchi et al. 2016; Jones et al. 2019). It should be also noted that some studies adopted uncommon localization methods or stimulation protocols, which could have resulted in deviations from the intended stimulation.

Using standardized protocols for stimulation parameters, such as frequency, intensity, and duration, can help to reduce potential sources of bias and increase the comparability of results across studies (Polanía et al. 2018). Moreover, as suggested by these authors, a methods-reporting checklist should be encouraged. We note that some studies failed to report important TMS parameters (e.g. biphasic or monophasic, active or resting motor threshold, etc.), adding difficulty for later studies aiming to replicate the results. Encouraging and promoting replication of human NIBS research can help to reduce the potential for bias, as other researchers can evaluate the validity of the findings. To summarize, avoiding bias in human NIBS research requires a combination of careful study design, adequate sample size, standardized stimulation protocols and transparent reporting.

The large number of TMS studies conducted in the healthy brain to date have demonstrated that different types of somatosensation can be both disrupted and enhanced by targeted stimulation of specific somatosensory areas, depending on specific parameters of the stimulation protocol. However, the specific neurophysiological mechanisms of TMS-induced effects during human somatosensory processing still remain unclear. Recent developments in the combination of TMS and other imaging modalities such as PET, fMRI and EEG/MEG could help further our understanding.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s00221-023-06579-9>.

**Acknowledgements** This work was supported in part by NIH grant R01 DC019134 and a core grant to the Waisman Center from the National Institute of Child Health and Human Development (P50HD105353). On behalf of all authors, the corresponding author states that there is no conflict of interest.

**Funding** National Institutes of Health R01 DC019134 (Caroline Niziolek and Benjamin Parrell) and P50 HD105353 (Waisman Center).

**Data availability statement** Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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