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Comprehensive review

Noninvasive cortical modulation of experimental pain

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ABSTRACT

Noninvasive cortical stimulation (NICS) can produce analgesic effects by means of repetitive transcranial magnetic stimulation or transcranial direct current stimulation (tDCS). Such effects have been demonstrated on chronic ongoing pain, as in acute provoked pain. The investigation of induced changes in the perception of experimental pain by NICS could help clinicians and researchers to better understand the mechanisms of action involved with these techniques and the role played by the cortex in the integration of nociceptive information. This review presents current literature data on the modulation of experimental pain perception by cortical stimulation. The observations found that NICS analgesic effects depend on the method used to provoke pain (referring to the type of nerve fibers and neural circuits that are recruited to mediate pain) and the parameters of cortical stimulation (especially the nature of the cortical target). The motor cortex (precentral cortical area) is the most widely used target for pain modulation. However, other targets, such as the dorsolateral prefrontal cortex, could be of particular interest to modulate various components of pain. Further developments in NICS techniques, such as image-guided navigated brain stimulation, might lead to improvement in the beneficial effects of NICS on pain. Finally, we discuss whether the results obtained in experimental pain can be transposed to the problem of chronic pain and whether they can be used to optimize cortical stimulation therapy for pain disorders.

1. Introduction

Various techniques of noninvasive cortical stimulation (NICS) have been developed for physiological and therapeutic applications in humans [54,55]. In recent years, these techniques were mainly represented by repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), which are based on different mechanisms of action. On the one hand, rTMS can generate propagated action potentials, thus activating brain neural circuits, and is therefore a stimulation technique (Fig. 1). On the other hand, tDCS can modulate rest membrane potential of axons, thus changing the endogenous excitability of brain neural circuits, and is therefore a modulation technique (Fig. 2). The patterns of stimulation used for the different NICS methods applied in experimental pain studies are presented in Fig. 3.

NICS was thus demonstrated to be able to modulate various neural processes, including pain [56,58]. However, the first use of cortical stimulation for pain relief was achieved through an invasive surgical approach: this was the treatment of chronic drug-resistant neuropathic pain syndromes by epidural cortical stimulation using implanted electrodes over the precentral gyrus (motor cortex) [113].

Noninvasive methods were also used to study the pathophysiological effects of cortical stimulation on experimental pain in healthy volunteers. Since the early 1990s, it has been demonstrated that NICS could modulate both innocuous and noxious provoked sensations. Our goal was to review the literature on the modulation of acute provoked pain by NICS. These results may help us better understand what role different cortical areas play in the integration of nociceptive information and could possibly be used to optimize cortical stimulation therapy for pain disorders [74].

The complete list of articles published to date on the modulation of experimentally provoked pain by NICS is presented in Tables 1 and 2. The articles are categorized according to the cortical

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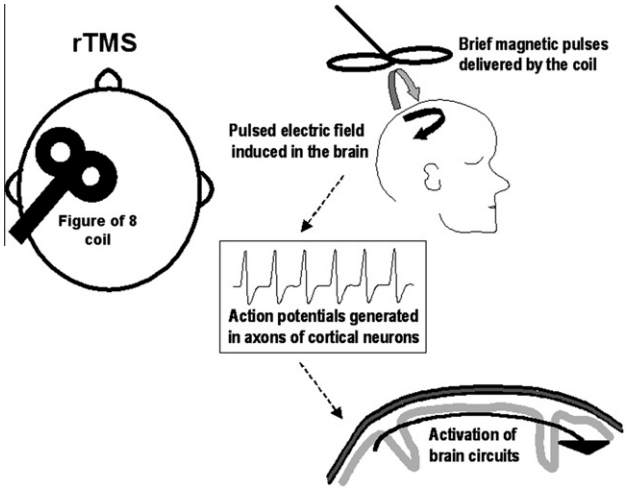

Fig. 1. Mechanism of action of repetitive transcranial magnetic stimulation (rTMS). Brief magnetic pulses are delivered by the coil placed on the scalp over a given cortical target and generate action potentials (activation) in neural circuits of the cortex.

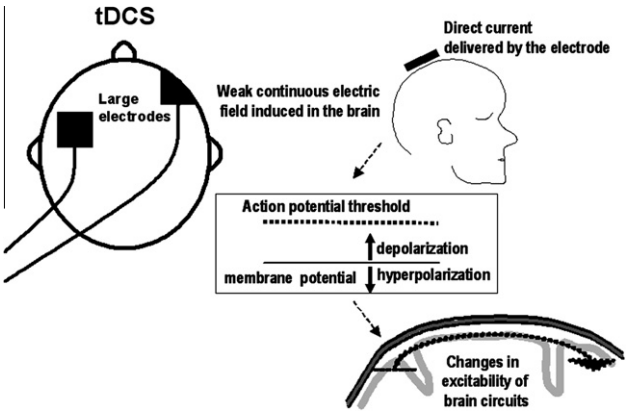

Fig. 2. Mechanism of action of transcranial direct current stimulation (tDCS). A weak direct current is delivered by electrodes placed on the scalp over a given cortical target and generates membrane potential changes (depolarization or hyperpolarization) in neural circuits of the cortex.

target and the method of stimulation. The various parameters of stimulation and evaluation used in these studies are reported. The effects of NICS on the perception of sensory stimuli are presented in Tables 3 and 4, regarding innocuous and noxious stimulations, respectively.

We begin by presenting the data provided by the stimulation of the primary motor cortex (M1), which is the most widely used target in experimental pain studies, probably because it is the only validated target for the treatment of refractory pain by cortical neurostimulation [22].

2. Modulation of provoked pain by motor (precentral) cortex stimulation

Experimental pain can be produced by various methods in humans. These methods include thermal, laser, or electrical stimulation, applied pressure, and cutaneous injection or application of capsaicin. The modulating effect of motor cortex stimulation (MCS) seemed to vary with the method used to provoke pain. In fact, these different methods reflect various mechanisms of pain production, corresponding to different types of afferent nerve fibers and neural circuits that are recruited to mediate pain.

2.1. Thermal sensation and thermal pain

2.1.1. TMS studies

Thermal stimuli allow small-diameter afferent sensory fibers to be selectively stimulated. Cold sensations are transmitted by thinly myelinated Aδ fibers, whereas warm sensations are conveyed by unmyelinated C fibers. Thermal pain involved both Aδ and C fibers, but mostly C fibers, at least for heat pain [98]. These different types of receptors and afferent fibers were found to be associated with distinct central pathways and neural structures of integration, such as the anterior and medial cingulate cortices [18,53]. Aδ-fiber-mediated first pain is thought to be mainly processed in the lateral pain pathway, whereas C-fiber-mediated second pain could be mainly processed in the medial pain pathway, thus reflecting the affective and cognitive aspects of pain [92]. However, an interaction between both types of fiber is possible, mainly leading to the inhibition of one system by the other [110]. In experimental pain, the resulting cortical activation further varies with the applied intensity of stimulation, the cortical regions involved in the emotional aspects of pain being more strongly activated at higher pain intensities [20].

The perception of different sensory modalities can be accurately evaluated in humans by techniques of quantitative sensory testing using dedicated computer-driven devices. Thermal sensory testing includes 4 main modalities that are the measurement of cold detection threshold, warm detection threshold, cold pain threshold, and heat pain threshold. In most articles, as in this review, thresholds are expressed as absolute temperatures, meaning that a reduction in the sensitivity to warm sensation or susceptibility to heat pain corresponds to an increased threshold, whereas a reduced sensitivity to cold sensation or susceptibility to cold pain corresponds to a decreased threshold.

When tested on the hand of healthy subjects, the temperature at which cold sensation is detected was lowered by rTMS delivered at 1 or 20 Hz over the hand area of M1, whereas the temperature at which cold sensation became painful was only lowered by 20 Hz rTMS [105]. Thus, 20 Hz rTMS reduced susceptibility to cold pain. A reduced cold pain threshold was also observed after the application of 10 Hz rTMS of the hand area of M1 in another series of healthy volunteers [80]. In this study, cold pain thresholds were found to be reduced in a very diffuse manner, at both upper and lower extremities after focal stimulation of the motor cortex. In contrast, 10 Hz rTMS did not change detection thresholds for cold or warm sensations, or heat pain thresholds in this study. In a third study, the reduction of cold pain threshold was only marginal after 1 Hz rTMS, but frankly significant after 10 Hz rTMS, as well as the reduction of cold detection threshold [10]. In this study, heat pain threshold was not modified by M1 rTMS, as in another study [40]. Finally, one study reported that a very brief train of 1 Hz rTMS could reduce the temperature at which cold sensation was detected without affecting the warm detection threshold [86].

Somewhat different from quantitative sensory testing, but also related to the susceptibility to cold pain, was a cold immersion test performed in 2 studies to assess the analgesic effects of cortical stimulation [40,109]. In one of these studies [40], rTMS delivered at 1 Hz over M1 did not modify cold pain threshold or tolerance when produced by hand immersion in ice water. These results seem to be contradictory to the previous ones. However, the ice water test produces equivocal activation of multiple afferent fiber types and neural circuits, which limits the interpretation.

Finally, one study assessed the modulation of facial sensitivity by 10 Hz rTMS delivered over the representation of facial muscles within M1 [115]. In contrast to the aforementioned studies in which hand area was targeted, this study did not reveal any change in either thermal detection or pain thresholds (cold or warm/heat sensations) after real rTMS compared to the sham condition. Real

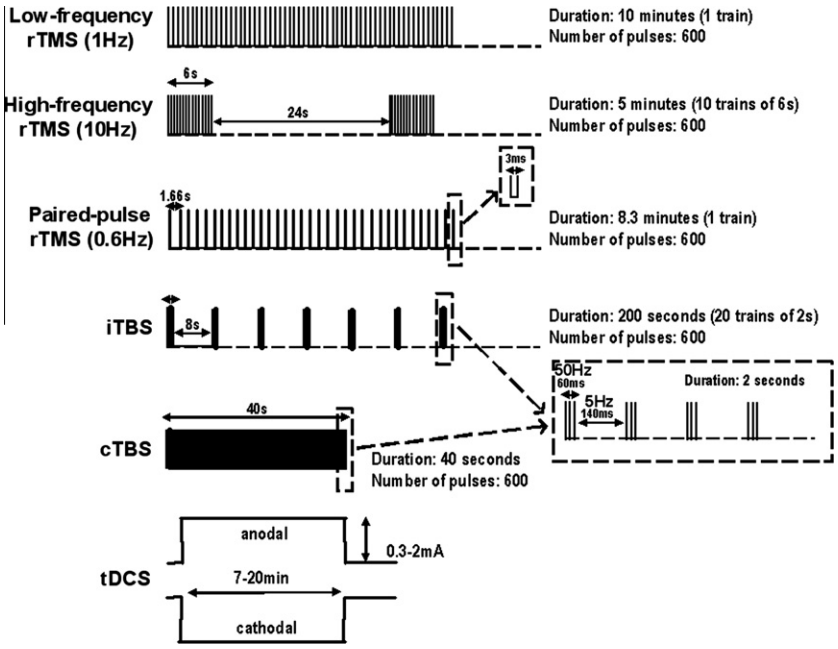

Fig. 3. Patterns of stimulation used for the different noninvasive cortical stimulation methods. Low- and high-frequency or paired-pulse repetitive transcranial magnetic stimulation (rTMS), intermittent or continuous theta burst stimulation (iTBS, cTBS), and transcranial direct current stimulation (tDCS). The duration and pattern of all TMS protocols are arbitrary examples set to correspond to a total number of 600 pulses.

Table 1
Effect of noninvasive stimulation of the primary motor cortex (M1) on experimental pain in healthy volunteers and pain patients.

Study	Type of subject/ patient	No. of active stimulations (no. of sham if different)	Type of stimulation	Frequency/ polarity (intensity)	Pulse number/ stimulation duration	Sham control	Site of stimulation	Investigated parameters
Motor cortex stimulation in normals								
High-frequency rTMS								
[86]	Normal	14	rTMS	5 Hz	50 pulses	Yes (occip. stim.)	Left M1 (hand)	Thermal (cold and warm) detection thresholds
[26]	Normal	12	rTMS	5 Hz	1800 pulses	Yes (angled coil)	Left M1 (hand)	Laser pain intensity and evoked potentials
[115]	Normal	14	rTMS	10 Hz	500 pulses	Yes (occip. stim. with angled coil)	Right M1 (face)	Thermal (cold and warm/heat) detection and pain thresholds
[80]	Normal	13	rTMS	10 Hz	1500 pulses	Yes (sham coil)	Right M1 (hand)	Thermal (cold and warm/heat) detection and pain thresholds; electrical pain reflex and tolerance thresholds
[25]	Normal	12 (12 sham)	rTMS	10 Hz	1500 pulses	Yes (sham coil)	Right M1 (hand)	Cold pain threshold
[10]	Normal	13 and 15 (2 series)	rTMS	10 Hz	2400 pulses	Yes (eSham)	Left M1 (hand)	Thermal (cold and warm/heat) detection and pain thresholds; mechanical pain threshold
[118]	Normal	8	rTMS	10 Hz	900 pulses	Yes (angled coil)	Left M1 (hand)	Electrical detection and pain tolerance thresholds
[77]	Normal	12	rTMS	10 Hz	1000 pulses	Yes (sham coil)	Dominant M1 (hand)	Electrical pain reflex threshold, intensity, and unpleasantness
[105]	Normal	20	rTMS	20 Hz	500 pulses	Yes (second coil placed away)	Left M1 (hand)	Cold detection and pain thresholds
Low-frequency rTMS								
[105]	Normal	20	rTMS	1 Hz	500 pulses	Yes (second coil placed away)	Left M1 (hand)	Cold detection and pain thresholds
[10]	Normal	12 and 13 (2 series)	rTMS	1 Hz	2400 pulses	Yes (eSham)	Left M1 (hand)	Thermal (cold and warm/heat) detection and pain thresholds; mechanical pain threshold
[40]	Normal	15 (15 sham)	rTMS	1 Hz	900 pulses	Yes (angled coil)	Right or left M1 (hand)	Thermal (cold and heat) pain thresholds; ice water immersion test; mechanical pain threshold
[107]	Normal	7	rTMS	1 Hz	300 pulses	Yes (second coil placed away)	Left M1 (hand)	Capsaicin pain intensity

Table 1 (*continued*)

Study	Type of subject/ patient	No. of active stimulations (no. of sham if different)	Type of stimulation	Frequency/ polarity (intensity)	Pulse number/ stimulation duration	Sham control	Site of stimulation	Investigated parameters
[106]	Normal	13	rTMS	1 Hz	600 pulses	Yes (second coil placed away)	Left M1 (hand)	Laser pain intensity and evoked potentials
Other TMS protocols								
[48]	Normal	8	rTMS	ppTMS	10 trials	Yes (occip. stim.)	Right M1 (hand)	Laser pain intensity
[76]	Normal	9 and 8 (8 occip.)	rTMS	ppTMS	2 to 4 trials	Yes (occip. stim.)	Left M1 (hand)	Electrical pain reflex threshold, intensity, and unpleasantness
[10]	Normal	12	rTMS	iTBS	2400 pulses	Yes (eSham)	Left M1 (hand)	Thermal (cold and warm/heat) detection and pain thresholds; mechanical pain threshold
[94]	Normal	13	rTMS	cTBS	600 pulses	Yes (sham coil)	Left M1 (hand)	Laser pain intensity
[24]	Normal	13	rTMS	cTBS	600 pulses	Yes (sham coil)	Left M1 (hand)	Laser pain intensity and evoked potentials
Anodal tDCS								
[6]	Normal	8	tDCS	Anodal (1 mA)	15 min	Yes	Left M1 (hand)	Thermal (cold and warm/heat) detection and pain thresholds; mechanical detection and pain thresholds
[46]	Normal	17	tDCS	Anodal (1 mA)	15 min	Yes	Left M1 (hand)	Thermal (cold and warm/heat) detection and pain thresholds; mechanical detection and pain thresholds
[9]	Normal	13	HD-tDCS	Anodal (2 mA)	20 min	Yes	Right M1 (hand)	Thermal (cold and warm/heat) detection and pain thresholds; mechanical pain threshold
[23]	Normal	10 and 16 (2 series)	tDCS	Anodal (1 mA)	10 min	Yes	Left M1 (hand)	Laser pain intensity and evoked potentials
[42]	Normal	19	tDCS	Anodal (1 mA)	20 min	Yes	Left M1 (hand)	Nociceptive evoked potentials
[8]	Normal	20	tDCS	Anodal (2 mA)	5 min	Yes	Left M1 (C3)	Electrical detection and pain reflex thresholds
Cathodal tDCS								
[6]	Normal	8	tDCS	Cathodal (1 mA)	15 min	Yes	Left M1 (hand)	Thermal (cold and warm/heat) detection and pain thresholds; mechanical detection and pain thresholds
[46]	Normal	17	tDCS	Cathodal (1 mA)	15 min	Yes	Left M1 (hand)	Thermal (cold and warm/heat) detection and pain thresholds; mechanical detection and pain thresholds
[108]	Normal	12	tDCS	Cathodal (1 mA)	15 min	No	Left M1 (hand)	Laser pain intensity and evoked potentials
[23]	Normal	10 and 16 (2 series)	tDCS	Cathodal (1 mA)	10 min	Yes	Left M1 (hand)	Laser pain intensity and evoked potentials
[42]	Normal	19	tDCS	Cathodal (1 mA)	20 min	Yes	Left M1 (hand)	Nociceptive evoked potentials
Motor cortex stimulation in patients								
High-frequency rTMS								
[27]	Spinal cord injury	6 (5 sham)	rTMS	5 Hz	500 pulses/d (10 d)	Yes (sham coil)	Vertex	Heat pain threshold
[26]	Migraine	13	rTMS	5 Hz	1800 pulses	Yes (angled coil)	Left M1 (hand)	Laser pain intensity and evoked potentials
[59]	Neuropathic pain	46	rTMS	10 Hz	1200 pulses	Yes (sham coil)	M1 contralateral to pain side	Thermal (cold and warm) detection thresholds
[62]	Neuropathic pain	32	rTMS	10 Hz	2000 pulses	Yes (sham coil)	M1 contralateral to pain side	Laser pain intensity and evoked potentials
[45]	Low back pain	17	rTMS	20 Hz	500 pulses	Yes (second coil placed away)	Left M1 (hand)	Thermal (cold and warm/heat) detection and pain thresholds

cTBS/iTBS = continuous/intermittent theta burst stimulation; eSham = portable electrical system that was specifically designed to produce similar scalp sensations as real TMS; (HD-)tDCS = (high density) transcranial direct current stimulation; ppTMS/rTMS = paired-pulse/repetitive transcranial magnetic stimulation.

M1 stimulation only decreased the capacity to discriminate painful heat without influencing heat pain threshold at the face.

In patients, cold pain threshold was found to decrease after M1 stimulation as in healthy control subjects, but heat pain threshold concomitantly increased. This result was observed after a session of 20 Hz rTMS administered over M1 in patients with chronic back pain [45]. This was in favor of a reduced susceptibility to both cold and heat pain. Heat pain threshold also increased after 5 Hz rTMS

Table 2
Effect of noninvasive stimulation of nonmotor cortical areas on experimental pain in healthy volunteers and pain patients.

Study	Type of subjects/ patients	Number of active stimulations (n. of sham if different)	Type of stimulation	Frequency/ polarity (intensity)	Pulse number/ stimulation duration	Sham control	Site of stimulation	Investigated parameters
Prefrontal cortex stimulation in normals								
High-frequency rTMS								
[30]	Normal	5	rTMS	5 Hz	1800 pulses	No	Left dl-PFC	Capsaicin pain intensity
[16]	Normal	16	rTMS	5 Hz	1800 pulses	No	Left dl-PFC	Capsaicin pain intensity
[16]	Normal	16	rTMS	5 Hz	1800 pulses	No	Right dl-PFC	Capsaicin pain intensity
[14]	Normal	10 (10 sham)	rTMS	10 Hz	300 pulses	Yes (sham coil)	Left dl-PFC	Heat pain threshold
[80]	Normal	13	rTMS	10 Hz	1500 pulses	Yes (sham coil)	Right dl-PFC	Thermal (cold and warm/heat) detection and pain thresholds; electrical pain reflex and tolerance thresholds
[115]	Normal	14	rTMS	10 Hz	500 pulses	Yes (occip. stim. with angled coil)	Right dl-PFC	Thermal (cold and warm/heat) detection and pain thresholds
[25]	Normal	12 (12 sham)	rTMS	10 Hz	1500 pulses	Yes (sham coil)	Right dl-PFC	Cold pain threshold
[109]	Normal	4	rTMS	15 Hz	30 pulses	No	Right or left PFC (F3, F4)	Ice water immersion test
Low-frequency rTMS								
[40]	Normal	15	rTMS	1 Hz	900 pulses	Yes (angled coil)	Right dl-PFC	Thermal (cold and heat) pain thresholds; ice water immersion test; mechanical pain threshold
[40]	Normal	15	rTMS	1 Hz	900 pulses	Yes (angled coil)	Left dl-PFC	Thermal (cold and heat) pain thresholds; ice water immersion test; mechanical pain threshold
Anodal tDCS								
[75]	Normal	12	tDCS	Anodal (2 mA)	20 min	Yes	Right dl-PFC	Thermal (cold and warm/heat) detection, pain, and tolerance (heat) thresholds
[75]	Normal	12	tDCS	Anodal (2 mA)	20 min	Yes	Left dl-PFC	Thermal (cold and warm/heat) detection, pain, and tolerance (heat) thresholds
[8]	Normal	20	tDCS	Anodal (1 mA)	5 min	Yes	Left PFC (F3)	Electrical detection and pain reflex thresholds
Cathodal tDCS								
[75]	Normal	12	tDCS	Cathodal (2 mA)	20 min	Yes	Right dl-PFC	Thermal (cold and warm/heat) detection, pain, and tolerance (heat) thresholds
[75]	Normal	12	tDCS	Cathodal (2 mA)	20 min	Yes	Left dl-PFC	Thermal (cold and warm/heat) detection, pain, and tolerance (heat) thresholds
Prefrontal cortex stimulation in patients								
High-frequency rTMS								
[13]	Neuropathic pain	4	rTMS	10 Hz	4000 pulses/ d (3 d)	Yes (sham coil)	Left dl-PFC	Heat and mechanical pain thresholds
Medial frontal cortex stimulation in normals								
High-frequency rTMS								
[118]	Normal	8	rTMS	10 Hz	900 pulses	Yes (angled coil)	MFC	Electrical detection and pain tolerance thresholds
Other TMS protocols								
[48]	Normal	8 (8 sham)	rTMS	ppTMS	10 trials	Yes (occip. stim.)	MFC	Laser pain intensity
[78]	Normal	10	rTMS	ppTMS	2 trials	No	MFC	Electrical pain intensity and unpleasantness
Inferior frontal cortex stimulation in normals								
High-frequency rTMS								
[79]	Normal	8	rTMS	10 Hz	1600 pulses	Yes (sham coil)	Right IFG	Electrical pain reflex threshold, intensity and unpleasantness
Low-frequency rTMS								
[79]	Normal	8	rTMS	1 Hz	900 pulses	Yes (sham coil)	Right IFG	Electrical pain reflex threshold, intensity and unpleasantness
Sensory cortex stimulation in normals								
High-frequency rTMS								
[115]	Normal	15 (14 sham)	rTMS	10 Hz	500 pulses	Yes (occip. stim. with angled coil)	Right S1	Thermal (cold and warm/heat) detection and pain thresholds
[115]	Normal	15 (14 sham)	rTMS	10 Hz	500 pulses	Yes (occip. stim. with angled coil)	Right S2	Thermal (cold and warm/heat) detection and pain thresholds

Table 2 (*continued*)

Study	Type of subjects/ patients	Number of active stimulations (n. of sham if different)	Type of stimulation	Frequency/ polarity (intensity)	Pulse number/ stimulation duration	Sham control	Site of stimulation	Investigated parameters
[109]	Normal	4	rTMS	15 Hz	30 pulses	No	Right or left S1 (P3, P4)	Ice water immersion test
Low-frequency rTMS								
[99]	Normal	10	rTMS	1 Hz	600 pulses	Yes (angled coil)	Left PPC	Mechanical pain threshold
Other TMS protocols								
[48]	Normal	8 (8 sham)	rTMS	ppTMS	10 trials	Yes (occip. stim.)	Right S2	Laser pain intensity
[93]	Normal	12	rTMS	c, i, or imTBS	600 pulses	Yes (angled coil)	Left S1 (hand)	Laser pain intensity and evoked potentials
Anodal tDCS								
[41]	Normal	12	tDCS	Anodal (1 mA)	15 min	Yes	Left S1 (hand)	Thermal (cold and warm/heat) detection and pain thresholds; mechanical detection and pain thresholds
[2]	Normal	10	tDCS	Anodal (1 mA)	15 min	Yes	Left S1 (hand)	Laser pain intensity and evoked potentials
Cathodal tDCS								
[41]	Normal	12	tDCS	Cathodal (1 mA)	15 min	Yes	Left S1 (hand)	Thermal (cold and warm/heat) detection and pain thresholds; mechanical detection and pain thresholds
[2]	Normal	10	tDCS	Cathodal (1 mA)	15 min	Yes	Left S1 (hand)	Laser pain intensity and evoked potentials

cTBS/iTBS/imTBS = continuous/intermittent/intermediate theta burst stimulation; (dl-)PFC = (dorsolateral-)prefrontal cortex; IFG = inferior frontal gyrus; MFC = medial frontal cortex; PPC = posterior parietal cortex; ppTMS/rTMS = paired-pulse/repetitive transcranial mAgnetic stimulation; S1/S2 = primary/secondary somatosensory cortex; tDCS = transcranial direct current stimulation.

delivered over the vertex in a series of patients with lower limb pain due to spinal cord injury [27]. Regarding innocuous thermal sensation, 20 Hz rTMS of M1 lowered cold detection threshold in a series of patients with back pain [45], whereas 10 Hz (but not 1 Hz) M1 rTMS improved detection of both innocuous warm and cold sensations in a series of patients with chronic neuropathic pain [59].

Taken together, these observations seem to conflict. Nevertheless, the most robust result is probably the reduced susceptibility

Table 3
Effect of noninvasive cortical stimulation on the perception of innocuous stimuli in healthy volunteers.

Cortical target	Type of stimulation	Reduced perception for:	Unchanged perception for:
Motor (precentral) cortex (left M1, except when indicated)	High-frequency rTMS	Cold stimulations [10,86,105]; warm stimulations [10]; electrical stimulations [118]	Thermal (cold/warm) stimulations (right M1) [80,115]; warm stimulations [86]
	Low-frequency rTMS	Cold stimulations [105]	Thermal (cold/warm) stimulations [10]
	iTBS		Thermal (cold/warm) stimulations [10]
	Anodal tDCS	Thermal (cold/warm) stimulations (right M1) [9]; electrical stimulations [8]	Thermal (cold/warm) and mechanical stimulations [6,46]
	Cathodal tDCS	Cold and mechanical stimulations [6]	Thermal (cold/warm) and mechanical stimulations [46]; warm stimulations [6]
Dorsolateral prefrontal cortex (right or left side)	High-frequency rTMS		Thermal (cold/warm) stimulations [80,115]
	Anodal tDCS		Thermal (cold/warm) stimulations [75]; electrical stimulations [8]
	Cathodal tDCS		Thermal (cold/warm) stimulations [75]
Medial frontal cortex	High-frequency rTMS		Electrical stimulations [118]
Sensory (postcentral) cortex	High-frequency rTMS		Thermal (cold/warm) stimulations (right S1/S2) [115]
	Anodal tDCS		Thermal (cold/warm) and mechanical stimulations (left S1) [41]
	Cathodal tDCS	Thermal (cold/warm) stimulations (left S1) [41]	Mechanical stimulations (left S1) [41]

iTBS = intermittent theta burst stimulation; M1 = primary motor cortex; rTMS = repetitive transcranial magnetic stimulation; S1/S2 = primary/secondary somatosensory cortex; tDCS = transcranial direct current stimulation.

Table 4
Effect of noninvasive cortical stimulation on the perception of noxious stimuli in healthy volunteers.

Cortical target	Type of stimulation	Reduced perception for:	Unchanged or ∗increased perception for:
Motor (precentral) cortex (left M1, except when indicated)	High-frequency rTMS	Cold stimulations [10,105], (right M1) [25,80]; electrical stimulations [118]	Cold [115] and heat [80,115] stimulations (right M1); heat and mechanical stimulations [10]; laser stimulations [26]; electrical stimulations [77,80]
	Low-frequency rTMS	Cold stimulations [10]; capsaicin application [107]	Cold stimulations [105]; heat and mechanical stimulations [10]; thermal (cold/heat) and mechanical (right or left M1) [40]; laser stimulations∗ [106]
	ppTMS	Electrical stimulations [76]	Laser stimulations (right M1)∗ [48]; electrical stimulations∗ [76]
	iTBS		Thermal (cold/heat) and mechanical stimulations [10]
	cTBS	Laser stimulations [24,94]	
	Anodal tDCS	Cold stimulations [9]; electrical stimulations [8]	Thermal (cold/heat) and mechanical stimulations [6,46]; heat and mechanical stimulations [9]; laser stimulations [23]; electrical stimulations∗ [42]
	Cathodal tDCS	Laser stimulations [23,108]; electrical stimulations [42]; mechanical stimulations [6]	Thermal (cold/heat) stimulations [6,46]; mechanical stimulations [46]
Dorsolateral prefrontal cortex	High-frequency rTMS	Cold stimulations (right dl-PFC) [25,80]; heat stimulations (left dl-PFC) [14]; capsaicin application (left dl-PFC) [16,30]	Thermal (cold/heat) stimulations (right dl-PFC) [115]; heat and electrical stimulations (right dl-PFC) [80]; capsaicin application (right dl-PFC) [16]
	Low-frequency rTMS		Thermal (cold/heat) and mechanical stimulations (right or left dl-PFC) [40]
	Anodal tDCS	Heat stimulations (right dl-PFC) [75]; electrical stimulations (left dl-PFC) [8]	Cold (right or left dl-PFC) and heat (left dl-PFC) stimulations [75]
	Cathodal tDCS		Thermal (cold/heat) stimulations (right or left dl-PFC) [75]
Medial frontal cortex	High-frequency rTMS		Electrical stimulations∗ [118]
	ppTMS	Laser stimulations [48]	Electrical stimulations∗ [78]
Inferior frontal cortex (right side)	High-frequency rTMS		Electrical stimulations [79]
	Low-frequency rTMS		Electrical stimulations [79]
Sensory (postcentral) cortex	High-frequency rTMS	Thermal (cold/heat) stimulations (right S2) [115]	Thermal (cold/heat) stimulations (right S1) [115]
	Low-frequency rTMS		Mechanical stimulations (left ppc) [99]
	ppTMS		Laser stimulations (right S2) [48]
	c, i, or imTBS	Laser stimulations (left S1) [93]	
	Anodal tDCS		Thermal (cold/heat) and mechanical stimulations (left S1) [41]; laser stimulations (left S1) [2]
	Cathodal tDCS	Laser stimulations (left S1) [2]	Thermal (cold/heat) and mechanical stimulations (left S1) [41]

cTBS/iTBS/imTBS = continuous/intermittent/intermediate theta burst stimulation; (dl-)PFC = (dorsolateral-)prefrontal cortex; PPC = posterior parietal cortex; ppTMS/rTMS = paired-pulse/repetitive transcranial magnetic stimulation; S1/S2 = primary/secondary somatosensory cortex; tDCS = transcranial direct current stimulation.

to cold pain but not to heat pain after M1 stimulation delivered at high frequency (10–20 Hz) in healthy volunteers and pain patients [10,25,80,105]. This result is consistent with the classical view of separate sensory systems for warmth and cold, including distinct warm-sensitive and cold-sensitive spinothalamic pathways and thalamic relays [21,88]. However, in contrast to normal subjects, a concomitant reduction in susceptibility to heat and cold pain was found in patients with chronic low back pain or pain due to spinal cord injury [27,45]. This may reflect the impact of chronic ongoing pain on nociception. Central sensitization in pain pathways or dysregulation in endogenous pain inhibitory controls to heat stimuli has been found in patients with chronic pain related to spinal cord injury [117,119] and chronic back pain [38,50,51,69], as in various other chronic pain conditions, including functional gastrointestinal pain disorders [28,43,49] and fibromyalgia [102,104]. These clinical observations were correlated to the presence of functional or structural alterations in multiple brain structures [7,17,116]. Because chronic pain condition is associated with central nervous system plasticity, it is conceivable that cortical stimulation could act on a broader range of percepts (including heat pain in addition to cold pain) in chronic pain patients than in normal subjects.

In addition, in the case of neuropathic pain, we must consider that the structural damage of the nervous system at the origin of pain also results in sensory deficit [67]. This sensory deficit results in altered thresholds within the painful zone at baseline. This may in turn explain the difference in the modulation of sensory perception by cortical stimulation between pain patients and healthy subjects. For example, an improvement in cold and warm detection threshold, which was correlated to pain relief, was found after either invasive or noninvasive stimulation of the motor cortex in patients with neuropathic pain [29,59], but not in healthy subjects.

In terms of brain circuitry, the question is to determine on what structures of the pain matrix MCS could act to modulate experimental pain [36]. Functional activation of brain regions to noxious stimuli are reflected by an increase in the regional cerebral blood

flow (rCBF) in positron emission tomographic studies and in the blood oxygen level–dependent (BOLD) signal in functional magnetic resonance imaging (fMRI) studies. Such activation is almost constantly observed in the secondary somatosensory cortex (S2), the insula, and the anterior cingulate cortex (ACC), and less constantly in the thalamus, the primary somatosensory cortex (S1), the posterior parietal cortex (PPC), and the prefrontal cortex (PFC) [91]. The activation of lateral thalamus, S1, S2, or posterior insula relates to changes in the lateral system mediating the sensory-discriminative aspects of pain processing, whereas the activation of medial thalamus, anterior insula, ACC, PPC, or PFC is rather involved in the modulation of the medial system mediating the affective, cognitive, emotional, and attentional aspects of pain [91].

Neuroimaging studies have also focused on assessing the mechanisms of abnormal pain evoked by normally innocuous stimuli (allodynia) or exaggerated pain evoked by noxious stimuli (hyperalgesia). There are subtle differences in brain activity changes between a condition of abnormal or exaggerated pain response compared to a normal pain response to noxious stimuli [72,100]. There may be also differences depending on the type of stimulation, mechanical or thermal. In healthy subjects, central sensitization to heat pain was found to be associated with the activation of all structures of the pain matrix, such as the thalamus, S1, S2, anterior and posterior insula, ACC, and supplemental motor area [103]. However, when compared to mechanical hyperalgesia, thermal hyperalgesia led to higher ratings of the stimulus-related unpleasantness and to an increased activation of anterior insula, medial frontal cortex (MFC), and ACC, all structures rather involved in the affective and cognitive dimensions of pain [68]. The specific activation of the medial pain pathway to abnormal painful sensation to warm/heat stimuli has been almost constantly observed [63,100]. Cold allodynia also involves an increased activation of some structures of this medial pathway, including the dorsolateral PFC (dl-PFC), anterior insula, and midbrain [101].

Regarding the modulation of pain by cortical stimulation, most brain imaging data relate to the effects of invasive epidural MCS in patients with chronic spontaneous neuropathic pain. Overall, epidural MCS seems to produce activity changes in all neural structures involved in pain processing, such as the thalamus, ACC, orbitofrontal cortex, insula, S2, or the periaqueductal gray matter [36,37,90]. One recent fMRI study also revealed that 10 Hz rTMS of M1 performed in patients with poststroke pain could reduce BOLD signal in S2, insula, PFC, and putamen in those who respond to rTMS [85]. To our knowledge, only 2 studies [99,107] have assessed by neuroimaging techniques the effects of NICS on provoked pain in healthy subjects. In the first one [107], single-photon emission computed tomography (SPECT) revealed that the analgesic effects of 1 Hz rTMS of M1 on acute pain induced by intradermal capsaicin injection were associated with a relative rCBF decrease in the medial PFC corresponding to Brodmann area 9 and rCBF increase in the caudal part of the right ACC corresponding to Brodmann area 24. In the second one [99], stimulation did not involve the motor cortex: fMRI was used to assess the effects of 1 Hz rTMS of the PPC on electrically induced secondary mechanical pinprick hyperalgesia. However, compared to sham stimulation, no significant effect of active rTMS was observed.

Thus, the modulation of pain by MCS may involve brain activity changes in the various structures of both the lateral and the medial pain pathways. It was demonstrated that first pain mediated by Aδ fibers was particularly related to the activation of the lateral system, whereas second pain mediated by C fibers was more closely related to the activation of the medial system [92]. Therefore, MCS may influence the interactions between the 2 systems, eg, by reinforcing or restoring the somatotopically distributed, mutually suppressive interaction between central processing of Aδ- and C-fiber-mediated sensory afferent information [110].

In terms of neurotransmission, the functional influence of MCS on thermal pain processing may be mediated by endogenous opioids because naloxone injection was demonstrated to significantly decrease the analgesic effects of 10 Hz rTMS of M1 on provoked cold pain in healthy subjects [25]. The endogenous opioid system was also found to play a role in the analgesic effects of implanted epidural MCS in patients with chronic neuropathic pain [66]. It remains a matter of debate whether or not this system is activated by cortical stimulation to modulate descending controls down to the spinal cord via a top–down regulation of nociception [36]. The modulation of the nociceptive flexion reflex (NFR or RIII reflex) by MCS is a way to address this issue, as discussed later.

Another neurotransmission system able to support the analgesic effect of MCS is the inhibitory GABAergic system. Intracortical GABAergic inhibition is reduced in patients with chronic neuropathic pain and high-frequency rTMS was demonstrated to restore this defective inhibition in parallel with pain relief [60]. Anodal tDCS delivered to M1 was found to produce the same concomitant effects on pain ratings and intracortical inhibition in a series of patients with chronic pain [4]. The hypothesis of a GABAergic mediation of MCS-induced analgesia has been recently strengthened by an experimental study performed in a rodent model of central pain due to spinal cord lesion [65]. From this study, it can be hypothesized that MCS produces its analgesic effects by enhancing GABAergic activity in the zona incerta, resulting in an increased inhibition of thalamic neurons involved in nociceptive processing.

Finally, a recent study revealed that rTMS of right S2 was associated with a significant analgesic effect in patients with visceral pain and that this effect was correlated with an increase in excitatory neurotransmitter levels such as glutamate and N-acetyl aspartate [34]. However, most of these mechanisms regarding neurotransmission of the analgesic effects of cortical stimulation have been demonstrated in patients with chronic pain. It remains to be demonstrated that these results can be transposed to acute provoked pain in healthy subjects.

From a methodological point of view, the relief of provoked pain seems to depend on the frequency of cortical stimulation [10,105]. The frequency of stimulation is thought to be a key factor regarding the mechanism of action of rTMS. In normal subjects, rTMS tonically applied over M1 at low frequency (1 Hz or less) reduces motor corticospinal output as demonstrated by post-rTMS decrease in motor-evoked potential amplitude [19], whereas the reverse is induced by rTMS bursts delivered at high frequency (5 Hz and higher) [87]. The changes in motor-evoked potential amplitude are prolonged beyond the time of stimulation, suggesting processes of long-term depression or potentiation of synaptic transmission. However, it is not certain that we can extrapolate this frequency-dependent antagonistic modulation for cortical target other than M1, for cortical function other than motor control, and for individuals other than healthy subjects.

2.1.2. tDCS studies

Regarding the modulation of thermal pain by tDCS delivered to the motor cortex, few data have been reported in the literature. The first study was performed in only 8 healthy subjects who underwent quantitative sensory testing before and after cathodal, anodal, and sham tDCS sessions, performed in a random order [6]. The active electrode was placed over the left M1 and the reference electrode above the right orbit. Cathodal tDCS lowered cold detection threshold, corresponding to a reduced sensitivity to Aδ-fiber-mediated somatosensory inputs. No other change was observed, especially after anodal tDCS session. However, this result was not confirmed in a subsequent study with the same design but a larger series of subjects [46].

A third tDCS study was characterized by the use of a new tDCS design, called high-definition tDCS (HD-tDCS) [9]. With this meth-

od, 4 cathodes are placed equidistant (7 cm) from each other and from the anode, which serves as the active electrode. This montage increases the spatial selectivity of the stimulation. Anodal HD-tDCS delivered to the left M1 decreased cold detection and pain thresholds, and increased warm sensory thresholds, but did not alter heat pain thresholds. This antinociceptive effect of anodal HD-tDCS runs counter the absence of effect of anodal tDCS in the other studies performed in healthy subjects [6,46], but fits well with the proved analgesic effect of anodal (but not of cathodal) tDCS in chronic pain, of either neuropathic or nonneuropathic origin [4,31,33,95,114].

This observation could illustrate the respective influence of disease-related homeoplastic cortical plasticity and stimulation polarity on tDCS efficacy. In general, anodal tDCS tends to reproduce the main effect of high-frequency rTMS that is a decreased sensitivity to cold stimuli and a reduced susceptibility to cold pain. It is generally accepted that cortical excitability is reduced by cathodal tDCS and increased by anodal tDCS because of induced processes of axonal hyperpolarization and depolarization, respectively [81]. Because high-frequency rTMS is thought to increase cortical excitability, the similarity between the effects of high-frequency rTMS and those of anodal tDCS on thermal sensation seems logical. Both methods likely activate some cortical neural circuits running through the precentral gyrus and involved in cold sensation processing. However, this simple approximation should be viewed with caution because, as mentioned above, it is difficult to take the effect on motor corticospinal output as a general rule of action of a type of cortical stimulation. In addition, even if anodal stimulation is exciting and cathodal stimulation is inhibiting, the efficacy of the stimulation depends on the orientation of the axons in the induced electrical field. Moreover, the site of induced biological effects is thought to locate under the active electrode because it is assumed that the other electrode is a reference. This assumption is probably wrong if we consider that in most of tDCS studies, the reference electrode is placed at the forehead or over the orbit, and thus quite close to the orbitofrontal cortex. In these cases, what is interpreted as the effect of anodal stimulation of M1 may be in fact the effect of cathodal stimulation of orbitofrontal cortex. The use of HD-tDCS will be of great help to address this issue.

2.2. Laser stimulation and capsaicin application

Laser stimulation was introduced in the mid-1970s in the armamentarium of clinical neurophysiologists to perform specific stimulation of thin afferent Aδ and C nerve fibers in the skin [73]. Noxious cutaneous laser stimulation was used to measure pain thresholds and subsequently to evoke pain-related cortical potentials (laser-evoked potentials, LEPs) that are widely used to investigate peripheral and central pain pathways in pain research and clinical studies [47,111]. In general, standard LEPs assess the activation of Aδ fibers, whereas C fiber investigation requires specific protocols [112].

2.2.1. TMS studies

In healthy subjects, experimental pain induced by cutaneous Tm:YAG laser stimulation as well as the amplitude of the resulting LEPs were found to be reduced by a protocol of continuous theta burst stimulation (cTBS) [24,94], but increased by a protocol of 1 Hz rTMS [106], both applied to M1 representation of the hand that was stimulated by the laser beam. Trains of paired TMS pulses delivered over M1 also increased Aδ-fiber-mediated cutaneous pain produced by CO_2 laser stimulation [48]. In contrast, 5 Hz rTMS delivered over the hand motor cortex of the left hemisphere did not significantly modify pain scores and LEP amplitude to CO_2 laser stimulation of the contralateral hand or face, compared to sham rTMS [26].

Whereas Aδ-fiber-mediated pain produced by laser stimulation was increased by 1 Hz rTMS of M1 [106], the same team using the same protocol reported an analgesic effect of rTMS on capsaicin-induced pain, a C-fiber-mediated tonic pain: rTMS was found to induce earlier recovery from acute pain produced by intradermal capsaicin application [107]. The discrepancy between the results of these 2 studies could be attributed to a difference in the influence of cortical stimulation on the processing of first pain (Aδ fiber mediated) and second pain (C fiber mediated) through the lateral and the medial pain pathways, respectively [92]. As mentioned above, SPECT results supports this point of view by demonstrating an association between M1 rTMS-induced pain relief and rCBF changes in cortical structures belonging to the medial pain pathway [107]. These changes could reveal an impact of M1 stimulation on the affective–emotional component of pain, probably through the activation of multiple neural circuits [56].

In contrast to the concomitant increase in laser-induced pain and LEP amplitude produced by 1 Hz rTMS delivered to M1 in healthy subjects, 10 Hz rTMS delivered to M1 in a series of patients with chronic neuropathic pain was found to reduce both Nd:YAG LEP amplitude and laser-induced pain scores [62]. In addition, the preferential change in the N2 component of the LEPs suggested a modulation of the sensory-discriminative aspect of laser-induced pain and therefore could be attributed to changes affecting the lateral rather than the medial pain pathways, in contrast to what was proposed in healthy subjects [107], as discussed above. This discrepancy could reflect the existence of different mechanisms of rTMS-induced analgesia between patients and healthy control subjects. However, the N2 component of the LEPs does not reflect solely the sensory-discriminative of pain but also may originate to other brain sources, such as parasylvian areas and ACC [35,83,84]. A more significant decrease of the amplitude of N2 compared to N1 component of the LEPs after tDCS delivered to M1 was even considered to reflect a preferential impact of cortical stimulation on the ACC origin of N2 [108]. Thus, it is difficult to definitively determine the primary mechanism of action of cortical stimulation on a specific aspect of pain processing associated with various pathophysiological conditions.

Methodological differences, mainly regarding stimulation frequency, may also explain the differences between healthy subjects and patients in how rTMS modulates LEPs [62,106]. As previously found for thermal pain [10,105], stimulation pattern and frequency may have an impact on the analgesic effects of M1 rTMS. This is clearly illustrated by the opposite results obtained on laser-induced pain after 1 Hz rTMS vs cTBS [24,94,107].

Taken together, these observations suggest that the analgesic efficacy of M1 rTMS could depend on the type of rTMS protocol according to the nature of the nociceptive afferents involved in provoked pain, and maybe to homeoplastic cortical plasticity (healthy subjects vs neuropathic patients). For instance, subtle differences in the ability of M1 rTMS to modulate laser-induced pain were reported between healthy control subjects and patients with migraine [26].

2.2.2. tDCS studies

The modulation of laser-induced pain by tDCS of M1 was investigated in only 2 studies, both issued from the same team [23,108]. In both studies, cathodal tDCS of M1 reduced both laser-induced pain and the amplitude of the resulting LEPs for the hand contralateral to the side of tDCS. One of these studies found that this analgesic effect was specific for cathodal tDCS, whereas anodal tDCS only modified the sensitivity to laser stimuli below the pain threshold (increased warm sensation to subthreshold stimuli) [23]. The other study demonstrated that the antinociceptive modulation produced by cathodal tDCS could be prolonged and amplified by the administration of pergolide, a dopaminergic drug (D2

agonist) [108]. This may result from a consolidation of tDCS effects on the long-term modulation of synaptic transmission mediated by N-methyl-D-aspartate (NMDA) receptors, which is known to be enhanced by dopaminergic drugs [82].

Recently, cathodal tDCS was also found to reduce the amplitude of trigeminal and extracranial pain-related evoked potentials, whereas anodal tDCS increased it [42]. This modulation of provoked pain in the trigeminal area may be considered as an argument to investigate the value of tDCS to treat facial pain.

As for thermal pain, all these results were in favour of an analgesic efficacy of cathodal tDCS, whereas anodal tDCS was ineffective or even deleterious. Again, this runs counter the results observed in patients with chronic pain, in whom anodal (but not cathodal) tDCS is able to reduce chronic spontaneous pain [31,33]. Interestingly, the same team that demonstrated an effect of cathodal tDCS of M1 on acute provoked pain prolonged by pergolide [108] found an effect of anodal tDCS of M1 on chronic persistent orofacial pain, also prolonged by cycloserine, an NMDA agonist [3]. Whether this discrepancy reveals the influence of disease-related plasticity or differences in the mechanisms of pain processing between provoked and spontaneous pain remains to be studied.

2.3. Electrical stimulation

Experimental pain induced by electrical sensation presents various particularities compared to the other types of provoked pain previously described in this review. First, this is not a natural sensation, and nociceptive Aδ fiber activation is associated with concomitant stimulation of nonnociceptive Aβ fibers. This is because Aβ fibers are larger than Aδ fibers and therefore are primarily recruited by electrical shocks.

2.3.1. TMS studies

In one study, M1 rTMS performed at 10 Hz was found to increase the threshold and the tolerance to pain produced by a mode of electrical stimulation of the skin up to 30 min after cortical stimulation [118]. By contrast, in another study, the same rTMS protocol was found to increase the unpleasantness of another type of painful electrical stimuli immediately after cortical stimulation [77]. The unpleasantness of electrical stimuli was also increased when the painful stimulation was applied shortly before or after paired TMS pulses delivered over M1, whereas pain intensity was decreased in case of preceding paired TMS [76]. In these 2 latter studies, as in a third one [80], the nociceptive flexion reflex (RIII) was not concomitantly modified, in threshold, latency, amplitude or area, by rTMS application. This runs counter to the idea of activation of descending inhibitory controls down to the spinal cord and rather suggests intraencephalic modulation of pain by cortical stimulation, likely involving limbic structures, as also demonstrated by various imaging data [36,107]. In contrast, it has been demonstrated that epidural MCS was able to modulate the RIII reflex in some patients with chronic neuropathic pain [37]. Thus, the recruitment of descending pathways involved in pain control and the production of descending spinal volleys probably play a role in the analgesic effect provided by cortical stimulation, at least in the case of neuropathic pain treated by implanted MCS [61]. Again, differences between healthy control subjects and patients with chronic neuropathic pain may exist, presumably depending on the presence of functional changes in thalamic relays, medial pain pathways, or descending inhibitory controls [36].

2.3.2. tDCS studies

Regarding tDCS, only one study has been published to date, reporting that anodal tDCS of M1 in normal subjects increased both perception and pain thresholds in response to electrical shocks delivered to the index finger at gradually increasing intensities [8]. This result was consistent with the relief of spontaneous pain induced by anodal tDCS that was demonstrated in chronic pain patients by the same team [31,33]. However, the effect of cathodal tDCS on electrical pain has not been assessed.

2.4. Mechanical stimulation

The impact of M1 stimulation on mechanical pain has been rarely investigated. Two studies found no changes in mechanical detection or pain threshold after various rTMS protocols delivered to healthy subjects [10,40]. There was also no change in the perception of mechanical stimuli after either anodal or cathodal tDCS [9,46]. Only one team found in a small series of normal subjects an increase in mechanical detection and pain thresholds after cathodal tDCS [6], but this result was not reproduced in a larger series that used the same methodology [46].

These data are not conclusive, but one may assume that MCS is able to modulate thermal pain, especially cold pain, more than mechanical pain. This could mean that MCS acts more specifically on the spinothalamic pathway in which thermal sensation is processed and on the medial pain pathway than on other sensory and pain pathways. Interestingly, diffusion tensor imaging studies revealed in patients with central poststroke pain that pain relief induced by motor cortex rTMS required the integrity of thalamocortical tracts in the ipsilesional hemisphere [39,85]. On the other hand, MCS certainly does not produce analgesia by reinforcing the gate control of pain processing mediated by Aβ afferents and lemniscal pathways [37].

3. Modulation of provoked pain by PFC stimulation

Low-frequency rTMS delivered to the right dl-PFC, but not to the left dl-PFC, was demonstrated to increase the tolerance to pain induced by a prolonged immersion of the hand in ice water, a model of C-fiber-mediated pain [40]. Such a result was not observed in a series of subjects after high-frequency rTMS of the right or left dl-PFC [109], but this study only included 4 subjects who received a very small number of stimuli.

By contrast, high-frequency rTMS (5 or 10 Hz) of the dl-PFC was demonstrated to reduce the susceptibility to cold pain [25,80] or heat pain [14]. The right dl-PFC was stimulated in the first case, whereas the left dl-PFC was stimulated in the second case. The reduction of susceptibility to heat pain after high-frequency rTMS of the left dl-PFC was also observed in a pilot study of 4 patients with chronic neuropathic pain [13]. This study revealed that dl-PFC rTMS could significantly improve daily pain independent of mood changes but in association with increases in thermal and mechanical pain thresholds. Similar to these observations, capsaicin-induced pain was found to be reduced by 5 Hz rTMS applied to the left dl-PFC, but not to the right dl-PFC [16,30]. It is tempting to attribute a specific effect of dl-PFC rTMS as a function of the stimulated hemisphere: analgesia induced by high-frequency rTMS would correspond to Aδ-fiber-mediated pain for the right dl-PFC target (cold pain) and to C-fiber-mediated pain for the left dl-PFC target (heat pain, capsaicin-induced pain). Such a hypothesis deserves confirmation in further studies. However, this cannot be extrapolated to tDCS effects; in another study performed in healthy subjects, the heat pain tolerance threshold was increased by anodal tDCS delivered to the right dl-PFC, whereas cathodal tDCS or left dl-PFC stimulation did not modulate any innocuous or noxious thermal sensation [75].

The role played by an interhemispheric unbalance of dl-PFC activities is the basis of the rTMS protocols used to treat depression: antidepressant effects can be obtained by excitatory high-frequency rTMS of the left dl-PFC to reinforce the relatively defective

activity in this hemisphere or by inhibitory low-frequency rTMS of the right dl-PFC to reduce the relatively excessive activity in the other hemisphere. The dl-PFC is one of the neural structures connected with the medial pain pathways and involved in the affective and motivational aspects of pain. With respect to depression, which is a clinical condition closely linked to chronic pain and sharing some common neuroanatomical substrates, a differential modulation of various aspects of pain between right and left dl-PFC stimulation could also be considered.

However, in contrast to depression, large controlled rTMS studies comparing the respective value of high and low frequency of stimulation applied to the right or left dl-PFC are lacking in the pain domain. In small series of patients with chronic pain, associated or not with depression, analgesic effects were observed for 1 Hz rTMS applied over the right dl-PFC [96,97] and for 10 Hz rTMS applied over the left dl-PFC [5,13]. In addition, high-frequency stimulation of the left dl-PFC was also found to reduce the morphine requirement in the postoperative period [12,15].

The respective ability of M1 and dl-PFC stimulation to relieve pain has been rarely compared. One tDCS study revealed a better analgesic effect of M1 vs dl-PFC stimulation on a type of chronic spontaneous pain [33]. In contrast, regarding experimental pain, the same team found that anodal tDCS of either left M1 or left dl-PFC could similarly reduce susceptibility to electrical pain, but that only M1 stimulation could modulate sensory perception thresholds, suggesting different mechanisms of action [8]. In one study, tolerance to cold pain was increased by low-frequency rTMS when delivered to the right dl-PFC, but not to the right or left M1 [40]. Finally, regarding high-frequency rTMS, a similar reduction of cold pain threshold was observed after either M1 or dl-PFC stimulation [25,80], whereas neither M1 nor dl-PFC stimulation could modulate thermal-induced pain provoked at the face in another study [115].

The mechanisms by which dl-PFC stimulation could induce analgesia remain largely unknown. One point is that M1 and dl-PFC stimulations were found to produce similar changes in intracortical inhibition with respect to pain modulation. As mentioned previously, intracortical inhibition, a GABAergic parameter, is defective in chronic pain patients and can be restored by 10 Hz rTMS [60] or anodal tDCS [4] delivered to M1 in parallel with pain relief. Left dl-PFC rTMS was also found to be able to normalize intracortical inhibition in parallel with the reduction of experimental pain provoked in healthy subjects by the application of capsaicin [30]. These observations suggest that the reinforcement of intracortical GABAergic inhibitory control could be a major common mechanism involved in pain control resulting from the activation of neural circuits in response to the stimulation of various cortical sites.

One methodological limitation of dl-PFC stimulation is the imprecision of the targeting. There are 2 classical ways to determine the location of the dl-PFC for rTMS application. The first (standard procedure) is to target the dl-PFC 5 cm anterior to the motor hot spot of the hand. This procedure was found to be inaccurate in a majority of patients, resulting in premotor rather than PFC stimulation [1]. The second is to use the 10–20 International System of EEG electrode placement that proposes to locate the dl-PFC at F3 or F4 [8,109]. However, the best way remains to use a navigation system dedicated to the practice of rTMS, incorporating individual imaging data [57].

Three studies targeted the MFC rather than the dl-PFC. One study demonstrated a reduced tolerance to pain induced by nociceptive electrical stimuli after 10 Hz rTMS delivered to the MFC [118]. A second study demonstrated an increased sensitivity to electrical pain after paired TMS pulses delivered to the MFC [78]. In contrast, the third study reported a significant analgesic effect of paired TMS pulses delivered to the MFC on laser induced pain [48]. These conflicting results may be due to targeting imprecision or rTMS protocol differences. In any case, the MFC target is probably less interesting than the dl-PFC target to provide analgesic effects and to control provoked pain.

To conclude, the dl-PFC is surely a relevant target for pain treatment through cortical stimulation, especially regarding the affective and motivational aspects of pain. The possibility that this target could be more valuable for the treatment of chronic pain (often associated with depression) than for the control of provoked pain deserves attention. In addition, it has been recently reported that 1 Hz rTMS delivered to either the right or the left dl-PFC could completely block placebo analgesia, suggesting that expectation-induced placebo analgesia is mediated by symmetric PFC activities [52].

Another study found that 10 Hz rTMS of the left dl-PFC could interrupt the perceived-controllability effect on the emotional dimension of pain experience [11]. This suggests that left dl-PFC rTMS may produce analgesic effects by acting through the limbic system and medial pain pathways, maybe including top–down regulation of brainstem structures [64]. All these observations reinforce the value of studying the dl-PFC as a target for the neuromodulation of pain disorders by means of cortical stimulation.

4. Modulation of provoked pain by sensory cortex stimulation

The sensory cortex is not classically considered as a relevant target for pain modulation compared to M1 and dl-PFC. This is rather paradoxical because of the obviously large involvement of sensory cortical structures (S1, S2) in pain processing [92]. However, no encouraging results could support the use of sensory cortical targets to date, in contrast to M1 and dl-PFC.

The sensory cortical targets that have been studied so far include S1, S2, and PPC. Actually, there is more imprecision regarding the location of these structures by TMS targeting without the aid of an image-guided navigation system, compared to motor areas that can be more accurately defined by recording motor-evoked potentials.

Analgesic effects of S1 stimulation were mostly investigated in tDCS studies. Two studies (from the same team) found a reduced sensitivity to innocuous thermal stimuli and painful laser stimuli after cathodal but not anodal tDCS of S1 [2,41]. Various TBS protocols delivered to S1 were also able to reduce LEP amplitude [93]. In contrast, 2 studies did not find any change in thermal sensation or cold- or heat-induced pain after high-frequency rTMS delivered to S1 [109,115]. Another study investigated the effects of MRI-guided neuronavigated rTMS delivered to S1 in a series of chronic neuropathic pain [44]: the stimulation of this target did not produce any significant analgesia (as the stimulation of supplemental motor area and premotor areas) compared to M1 stimulation.

Regarding S2 stimulation, one study found a clear reduction of thermal induced pain at the face (both cold and heat pain) after high-frequency rTMS of S2 that was not observed after high-frequency rTMS of M1, S1, or dl-PFC [115]. S2 is thought to be the most effective target for the treatment of visceral pain by cortical stimulation in patients [32,34]. In contrast, paired TMS pulses delivered over S2 were found to be ineffective to modulate acute pain provoked by laser stimulation [48].

Finally, one study has investigated the effects of 1 Hz rTMS of the PPC on pinprick hyperalgesia [99]. Pinprick hyperalgesia was induced by the application of a calibrated pinprick stimulator to a skin surface previously sensitized by performing a prolonged painful electrical stimulation. Stimulation of the PPC did not change any aspect of the experimental pain, except the size of the area of hyperalgesia. In contrast, one study assessed the poten-

tial analgesic effect of a brief train (2 s) of high-frequency (15 Hz) suprathreshold rTMS over various cortical sites in 2 patients with chronic refractory upper limb pain resulting from cervical root avulsion [109]. The authors found that only the stimulation of the contralateral PPC led to a reproducible reduction in pain intensity lasting up to 10 min after the stimulation. However, both 1 and 10 Hz rTMS trains applied to this target on weekdays for 3 consecutive weeks did not lead to significant changes in chronic pain intensity.

All these observations do not encourage the view that sensory cortical regions could offer valuable targets to modulate experimental pain by cortical stimulation. However, one important target remains to be studied: the insula, which plays a key role in brain processing of noxious and innocuous thermal stimuli [89]. The anterior insula belongs to the medial pain system and is involved in the regulation of affective and cognitive processing of pain, whereas the posterior insula is rather connected with structures involved in the sensory-discriminative processing of noxious stimuli in the lateral pain pathways, especially for thermal pain [70,89]. Insula is a particularly attractive target because this brain region is one of the main areas where epidural MCS produces activity changes in neuroimaging studies [36]. In addition, the posterior insula and the adjacent opercular cortex are the only areas where direct electrical stimulation is able to produce the experience of somatic pain in humans [71]. However, this region is rather deep, and it will be necessary to find suitable NICS methods to excite it transcranially.

It remains to mention 2 additional targets evaluated for their potential to modulate experimental pain but that did not indicate significant results. First, it was found that acute pain provoked by electrical stimulation could not be modulated by low- or high-frequency rTMS delivered over the right inferior frontal gyrus, a region involved in the anticipation of expected pain and in pain memory processes and cognitive inhibitory control [79]. In contrast, suprathreshold 1 Hz rTMS delivered over the lateral cerebellum was found to produce significant changes on temperature detection and pain thresholds (decreased cold detection and increased heat pain thresholds), but the same results could be obtained by stimulating the neck, indicating the peripheral and not cerebellar origin of these effects [120].

4.1. Conclusion

M1. remains the most studied target of cortical stimulation to modulate provoked pain in healthy volunteers in the line of the results obtained in chronic pain patients. Analgesic effects seem to depend on various parameters such as stimulation pattern or frequency, or the fiber type recruited by the protocol of provoked pain (Aδ or C fibers). However, the most robust effect seems to be a reduced susceptibility to cold pain induced by high-frequency rTMS of M1 in healthy subjects. Regarding tDCS effects, it seems that cathodal tDCS is more effective than anodal tDCS in reducing provoked pain, in contrast to what was observed on spontaneous chronic pain. In fact, there are probably huge differences in the pattern and mechanisms of pain relief produced by cortical stimulation between acute pain provoked in healthy subjects and in patients with chronic pain. This may relate to the influence of disease-related processes of cortical plasticity on the recruited circuits and the resulting effects of cortical stimulation.

The dl-PFC seems to be a promising target for pain modulation, especially regarding the affective, emotional, and motivational dimensions of pain. The relationship between the site of cortical stimulation, the type of pain, and the aspect of pain affected by the stimulation deserves further attention.

Thus, the different results observed in acute provoked pain and chronic pain of either neuropathic or nonneuropathic origin suggest that cortical stimulation may modulate various aspects of pain according to the activation of various neural circuits. To determine which circuit should be recruited by cortical stimulation to obtain pain relief with respect to the origin of pain, the clinical presentation of pain, or the underlying pathological condition is a real challenge for therapeutic purposes. Further studies of the modulation of experimental pain by cortical stimulation could help achieve this goal. In particular, it would be of great benefit to evaluate new targets, new parameters, and new pain conditions to better understand the mechanisms of action of cortical modulation of pain processing.

Conflict of interest statement

None declared.

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