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TOPICAL REVIEW

From pulses to pain relief: an update on the mechanisms of rTMS-induced analgesic effects

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Abstract

Background: Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that allows cortical stimulation. Recent studies have shown that rTMS of the primary motor cortex or dorsolateral prefrontal cortex decreases pain in various pain conditions. The aim of this review was to summarize the main characteristics of rTMS-induced analgesic effects and to analyse the current data on its mechanisms of action.
Databases: Medline, PubMed and Web of Science were searched for studies on the analgesic effects and mechanisms of rTMS-induced analgesic effects. Studies on epidural motor cortex stimulation (EMCS) were also included when required, as several mechanisms of action are probably shared between both techniques.
Results: Stimulation site and stimulation parameters have a major impact on rTMS-related analgesic effects. Local cortical stimulation is able to elicit changes in the functioning of distant brain areas. These modifications outlast the duration of the rTMS session and probably involve LTP-like mechanisms via its influence on glutamatergic networks. Analgesic effects seem to be correlated to restoration of normal cortical excitability in chronic pain patients and depend on pain modulatory systems, in particular endogenous opioids. Dopamine, serotonin, norepinephrine and GABAergic circuitry may also be involved in its effects, as well as rostrocaudal projections.
Conclusions: rTMS activates brain areas distant from the stimulation site. LTP-like mechanisms, dependence on endogenous opioids and increase in concentration of neurotransmitters (monoamines, GABA) have all been implicated in its analgesic effects, although more studies are needed to fill in the still existing gaps in the understanding of its mechanisms of action.

1. Introduction

In addition to its uses in cognitive neuroscience, the clinical applications of repetitive transcranial magnetic stimulation (rTMS) have rapidly expanded over the last few years. This non-invasive technique was initially proposed and has been most thoroughly studied for the treatment of depression (George et al., 1995; Gaynes et al., 2014; Lefaucheur et al.,

Database
- Search of literature published from 1996 to 2014.
- Open databases (Google, Scholar, Web of Sicence, Pubmed).

What does this review add?
- Updated analysis of the main mechanisms responsible for rTMS-related analgesia based on chronic and experimental pain conditions.

2014). However, rTMS may also be useful for the treatment of other psychiatric and neurological conditions, including negative symptoms of schizophrenia, chronic motor stroke, tinnitus and auditory hallucinations (Lefaucheur et al., 2014). Furthermore, recent studies have shown that rTMS of the primary motor cortex (M1) or dorsolateral prefrontal cortex (DLPFC) decreases pain perception in healthy volunteers under various experimental models (Nahmias et al., 2009; Fierro et al., 2010; de Andrade et al., 2011; Brighina et al., 2011; Taylor et al., 2012, 2013; Ciampi de Andrade et al., 2014). Repetitive TMS of M1 has also been shown to have analgesic effects in neuropathic pain (Lefaucheur et al., 2006a), complex regional pain syndrome (Picarelli et al., 2010) and fibromyalgia (Passard et al., 2007; Mhalla et al., 2011) although conflicting results exist (Kang et al., 2009; Boyer et al., 2014). Thus, despite a large variability in the stimulation protocols used in the different studies (for review see Galhardoni et al., 2015; Lefaucheur et al., 2014), the bulk of evidence indicate that rTMS can induce analgesic effects. The mechanisms of these analgesic effects are still uncertain, but there is a rapidly growing body of data, both in humans and animals, which shed new lights on the potential mechanisms of action of rTMS-induced analgesic effects. After a brief summary of the main features of rTMS-induced analgesic effects, their putative mechanisms on both experimental and clinical pain will be addressed.

2. Main characteristics of rTMS-induced analgesic effects

2.1. Stimulation site

The primary motor cortex (M1) contralateral to the pain location has been the most frequent target in studies of the effects of rTMS on pain. This choice was related to the well-documented analgesic effects of epidural motor cortex stimulation (EMCS) in refractory neuropathic pain syndromes, evidenced more than 20 years ago by Tsubokawa et al. (1991) and subsequently confirmed by others (Nguyen et al., 1999; Nuti et al., 2005; Lefaucheur et al., 2009). Initially rTMS was envisaged as a predictive test for the identification of potential responders to EMCS. However, during this procedure it was noticed that rTMS itself could induce long-term analgesic effects lasting for more than a year by monthly maintenance sessions (Lefaucheur et al., 2004a). The analgesic effects of M1 stimulation have been confirmed in a number of studies both on clinical (Lefaucheur et al., 2004a, 2006a, 2008; Khedr et al., 2005; Passard et al., 2007; André-Obadia et al., 2008; Goto et al., 2008; Mhalla et al., 2011; Ohn et al., 2012; Hosomi et al., 2013b) and experimental pain (Summers et al., 2004; Nahmias et al., 2009; de Andrade et al., 2011; Houzé et al., 2013; Ciampi de Andrade et al., 2014; Moisset et al., 2015). In addition, studies in healthy volunteers (Nahmias et al., 2009; Fierro et al., 2010; de Andrade et al., 2011; Brighina et al., 2011; Taylor et al., 2012, 2013; Ciampi de Andrade et al., 2014) and in patients with acute (Borckardt et al., 2006, 2014) or chronic pain (Borckardt et al., 2009; Short et al., 2011) have shown that analgesic effects can also be induced by stimulation of the DLPFC. There is little information regarding the simulation of other sites. In two studies, it was suggested that stimulation of the secondary somatosensory cortex (S2) could also be effective (Valmunen et al., 2009; Fregni et al., 2011), but these findings have not been so far replicated. It remains to be shown whether other cortical areas, known to be involved in pain perception, such as the insular cortex could represent new potential targets for analgesia (Ciampi de Andrade et al., 2012).

Neuronavigation-guided rTMS has been used in several studies (Hirayama et al., 2006; Saitoh et al., 2007; Goto et al., 2008; Valmunen et al., 2009; Lefaucheur et al., 2012; Hosomi et al., 2013a; Houzé et al., 2013; Jetté et al., 2013; Matsumura et al., 2013; Hasan et al., 2014; Melchior et al., 2014; Lindholm et al., 2015; Moisset et al., 2015). Although this should allow a better reproducibility and accuracy regarding the definition of the stimulation site and potentially an increased efficacy, especially as non-motor areas are concerned (Ahdab et al., 2010), this has not yet been clearly confirmed.

2.2. Stimulation parameters

Most rTMS studies were performed with the 'figure-eight' (F8) coil, which induces a relatively focal electric current 2 cm beneath the coil surface. It has been shown that the analgesic effects are influenced by the orientation of the coil (André-Obadia et al., 2008). Other types of coils have also been used (e.g. double-cone, H-coil, etc.), but there are too few data (Ciampi de Andrade et al., 2012; Onesti et al., 2013) to conclude regarding the clinical advantages of these coils, which in principles allow to stimulate deeper brain structures than the classical F8 coil (Deng et al., 2013).

Although analgesic effects have been reported with low frequency stimulation, which is usually described as inhibitory (Fregni et al., 2011; Sampson et al., 2011), clinical and experimental studies have generally concluded that relatively high frequencies (≥5 Hz, frequently called 'excitatory rTMS') are more effective than lower frequencies. Nonetheless, this dichotomy is not entirely satisfying, and it has been shown that both high frequency and low frequency rTMS may have mixed excitatory and inhibitory effects (Houdayer et al., 2008) depending on different factors such as the length of stimulation and the network being targeted. Typical stimulation paradigms consist of 10–20 series of 10-s trains of pulses with an intra-train frequency of 10 Hz and an interval of 50 s between each train, resulting in a total of 1000–2000 pulses per session. Although the analgesic effects are probably related to the number of pulses, this has not been formally demonstrated (Cruccu et al., 2007). In most studies, the intensity of stimulation was below that of the motor threshold, but the relationships between the intensity of the stimulation and the magnitude of the analgesic effects have not been systematically studied. Recently, new rTMS paradigms consisting of theta-burst stimulation (TBS) (Huang et al., 2005) have been tested. These paradigms include short bursts of three TMS pulses with inner high frequency (50 Hz, within the gamma range) that are delivered at 5 Hz (within the theta range). The pulses are delivered continuously (cTBS) for 40 s or intermittently (iTBS) (2 s every 10 s), for a total stimulation time of 200 s. Although cTBS is usually seen as excitatory and iTBS as inhibitory, this dichotomy is rather relative. For instance, doubling the duration of stimulation can reverse the outcome from inhibition to excitation and vice versa (Gamboa et al., 2010). Studies in healthy volunteers using cTBS (Poreisz et al., 2008; Torta et al., 2013) have shown a reduction in acute pain perception whereas iTBS was not associated with any analgesic effect (Borckardt et al., 2011; Houzé et al., 2013). In patients, neither iTBS nor cTBS produced analgesic effects when used alone (Lefaucheur et al., 2012). By contrast, recent data in healthy volunteers suggest that prolonged cTBS induces larger analgesic effects than 'classical' rTMS (Moisset et al., 2015). The main parameters involved in rTMS results are summarized in Supporting Information Fig. S1.

2.3 Delay and duration of the effects

The analgesic effects induced by rTMS appear immediately after the stimulation, but, after a single session of stimulation, their maximum magnitude can be delayed up to 2 or 3 days and they can last up to 1 week (Lefaucheur et al., 2001; André-Obadia et al., 2008). The magnitude of the analgesic effects seemed reinforced when repeated sessions of stimulation were used (Khedr et al., 2005; Passard et al., 2007; Mhalla et al., 2011; Hosomi et al., 2013b). The duration of rTMS-induced analgesic effects is also increased after repeated sessions of stimulation since the effects can be maintained for up to 4 weeks between two stimulation sessions (Lefaucheur et al., 2004a; Mhalla et al., 2011). Concerning the modulation of cortical excitability in patients with chronic pain, it can be recorded immediately after the rTMS (Lefaucheur et al., 2006a; Hosomi et al., 2013a) but can also last for weeks (Mhalla et al., 2011) and has been shown to be correlated with the analgesic effects (Lefaucheur et al., 2006a; Mhalla et al., 2011; Hosomi et al., 2013a).

2.4 Specificity of the analgesic effects

Experimental studies have indicated that the analgesic effects induced by rTMS of M1 or DLPFC are related to a preferential action on the nociceptive systems since they are not associated with changes in non painful sensation (Nahmias et al., 2009). However, in patients with chronic pain, pain relief was correlated with an improvement of initially impaired thermal detection thresholds in one study (Lefaucheur et al., 2008). Interestingly, although the analgesic effects of M1 or DLPFC have been shown on different pain models, suggesting that there is no clear modality specificities, several studies have suggested a preferential effects on experimental cold pain (Summers et al., 2004; Nahmias et al., 2009; de Andrade et al., 2011). Regarding clinical pain, it was

shown in patients with fibromyalgia that the analgesic effects were more marked on the affective dimension of pain rather than on its sensory discriminative aspects (Passard et al., 2007; Mhalla et al., 2011). This is consistent with some EMCS studies, showing also a preferential effect on the affective component (Lefaucheur et al., 2011; Nguyen et al., 2008; see however, Lefaucheur et al., 2009). Other rTMS studies have reported effects on both affective and sensory dimensions (Picarelli et al., 2010; Borckardt et al., 2014).

2.5 Somatotopic organization of the analgesic effects

Initially, rTMS of M1 was applied, like EMCS, contralaterally to the site of pain in patients with unilateral neuropathic pain. However, it was shown in these patients that the analgesic effects of unilateral rTMS of M1 were not strictly somatotopic (Lefaucheur et al., 2006b). Consistent with these data, several studies, both in healthy volunteers (Nahmias et al., 2009; Moisset et al., 2015) and patients with fibromyalgia (Passard et al., 2007; Mhalla et al., 2011; Short et al., 2011) and myofascial pain syndrome (Dall'Agnol et al., 2014), have confirmed that unilateral rTMS of M1 or DLPFC induces bilateral diffuse analgesic effects, although the magnitude of the contralateral effects may be slightly higher (Passard et al., 2007).

3. Mechanisms of action of rTMS-induced analgesic effects

The data briefly summarized above indicate that unilateral rTMS of M1 and DLPFC induces diffuse analgesic effects on both experimental and clinical pain. The magnitude of these analgesic effects, which can last several days after a single stimulation session and are reinforced by repetition of sessions, depend both on the stimulation parameters (frequency, intensity and pattern) and orientation of the coil.

Based on these clinical features it has been suggested that rTMS-induced analgesic effects results from changes in pain modulation systems related to long term changes in neuronal excitability initiated by the changes in cortical excitability induced by the stimulation.

3.1 Role of pain modulation systems

The fact that unilateral stimulation of M1 or DLPFC induces bilateral analgesic effects (Passard et al., 2007; Nahmias et al., 2009; Moisset et al., 2015) is compatible with the involvement of pain modulating systems organized in the diencephalon and/or the pain descending modulatory controls (e.g. Lefaucheur, 2008; Pagano et al., 2011; França et al., 2013).

3.1.1 Brain areas involved in rTMS-induced analgesic effects

In principle, the analgesic effects of rTMS of M1 may involve a direct inhibition of the spinal transmission of nociceptive signals. Early electrophysiological studies in animals demonstrated the direct involvement of the motor cortex in modulating the processing of sensory information (Kuypers, 1987) and highlighted the role of the presynaptic inhibition of trigemino- or spino- thalamic neurons (Guo and Hu, 2014). However, the results of studies in healthy volunteers showing a lack of effects of M1 stimulation on the RIII withdrawal reflex, which is regarded as a reliable index of spinal nociception in humans (Sandrini et al., 2005) are not consistent with a modulation of the spinal transmission of nociceptive signals through the direct descending motor systems (Mylius et al., 2007; Nahmias et al., 2009). Consistent with these results, several neuroimaging studies have shown that the hemodynamic changes induced in the brain by rTMS or EMCS are not confined to the motor system, but instead involve a set of cortical and subcortical areas (cingulate, insular, orbitofrontal and prefrontal cortices, thalamus and striatum), involved in pain processing and modulation (Peyron et al., 1995, 2007; García-Larrea et al., 1999; Strafella et al., 2001, 2003; Bestmann et al., 2004). Interestingly, M1 stimulation induces significant changes in the activity in brain structures more specifically involved in the affective-emotional components of pain, such as the insular cortex and cingulate cortex, which may explain the effects of M1 stimulation on the affective dimension of pain reported in chronic pain patients (Passard et al., 2007; Picarelli et al., 2010).

The role of 'classical' descending inhibitory controls originating in the brainstem has been suggested (Lefaucheur, 2006). This hypothesis was mostly based on the potential analogy regarding the mechanisms of rTMS and EMCS which induces activation of brainstem structures involved in descending inhibitory controls structures such as the periacqueductal gray (Maarrawi et al., 2007; Peyron et al., 2007; Pagano et al., 2012) and a decrease in the RIII nociceptive reflex in neuropathic pain patients (Peyron

et al., 1995; García-Larrea et al., 1999). By contrast, the fact that rTMS of M1 did not induce changes in the RIII reflex (Mylius et al., 2007; Nahmias et al., 2009) in healthy volunteers does not support this hypothesis. However, these studies performed in healthy volunteers included only one stimulation session and therefore one cannot exclude that the activation of descending inhibitory systems requires several sessions of stimulation or that the activation of these systems has a significant role only in patients with chronic pain who may present with a pathological alteration of descending pain modulation. The results of a recent study in patients with painful diabetic polyneuropathy showing a reduction of the RIII reflex after five consecutive sessions of rTMS to the leg representation of M1 are consistent with this hypothesis (Onesti et al., 2013).

The involvement of pain descending modulation has also been tested by investigating the effects of rTMS on diffuse noxious inhibitory controls (DNIC). Animal and human studies have shown that inhibition of pain by heterotopic noxious stimuli involves the activation of DNIC sustained by a spino-bulbospinal loop and can be assessed by measuring the inhibition of a test painful stimuli induced by another concomitant heterotopic noxious stimuli. The effects of rTMS of M1 on the inhibition of a test painful heat stimulus applied to the hand induced by a conditioning heterotopic noxious cold stimuli applied to the foot have been tested in healthy volunteers. There was no significant change in the DNIC-induced inhibition during M1 stimulation, suggesting that this modulatory system is not directly involved in rTMS-induced analgesic effects (Moisset et al., 2015). Here again, these results in healthy volunteers should be interpreted with caution and do not necessarily reflect the mechanisms at play in chronic pain patients. Thus, in a recent study in patients with chronic myofascial pain syndrome it was shown that conditioned pain modulation (which does not necessarily reflect descending inhibition) was increased after rTMS (Dall'Agnol et al., 2014).

Regarding DLPFC stimulation, its role in pain modulation has been established for more than 10 years in experimental studies, through its connections with the limbic system and brainstem structures involved in descending modulation in particular (Lorenz et al., 2003; Craggs et al., 2007). Functional neuroimaging studies in humans have confirmed that, like M1 stimulation, rTMS of the DLPFC induces changes in the activity of a network of structures involved in the integration and modulation of pain signals, including the thalamus, brainstem, insular and cingulate cortices (Li et al., 2004; Martin et al., 2013). Like the stimulation of M1, the stimulation of DLPFC was not associated with changes in the RIII reflex, suggesting that the analgesic effects are not directly related to an activation of descending inhibitory controls, at least in healthy volunteers (Nahmias et al., 2009).

It is thus likely that the diffuse analgesic effects of rTMS induced by DLPFC (and most likely also by M1) stimulation depend on mechanisms other than the activation of 'classical' descending pain modulation, such as changes at higher levels of modulation in the diencephalon (e.g. cortico-thalamic loops). Future studies, notably in animals, are needed to further investigate these mechanisms.

3.1.2 Neuropharmacological bases of rTMS-induced analgesic effects

Pain modulatory systems involve multiple neurotransmitters (Besson, 1999; Millan, 2002). Endogenous opioids, which are widely produced throughout the somatosensory systems (Peng et al., 2012), have long been shown to play a major role in pain modulation (Besson, 1999; Millan, 2002). It has therefore been hypothesized that the endogenous opioids systems (EOS) might be involved in the analgesic action of rTMS. The role of EOS was investigated by comparing the influence of the administration of the opioid receptor antagonist naloxone or placebo on DLPFC/Premotor cortex (PMC) and M1 rTMS-induced analgesic effects in healthy volunteers (de Andrade et al., 2011). A significant reduction of the effects of M1 rTMS on cold pain was shown after naloxone administration, supporting the involvement of the EOS in rTMS and EMCS-induced analgesic effects. As stated above M1 stimulation induces changes in the activity of several diencephalic areas involved in pain perception, such as the thalamus, the anterior cingulate, insular and prefrontal cortices (Peyron et al., 1995; García-Larrea et al., 1999; Bestmann et al., 2004). All these areas are rich in opioid receptors (Peckys and Landwehrmeyer, 1999; Baumgärtner et al., 2006) and animal studies have shown that morphine microinjections directly within these structures induce antinociceptive effects (Cohen and Melzack, 1985; Ma et al., 1992). Therefore, it is possible that the analgesic effects of rTMS of M1 consists of the modulation, through opioidergic processes, of the activities of neurons located within one or several of these cortical or subcortical areas.

The neuropharmacological mechanisms of action of rTMS may depend on the stimulation site, as the analgesic effects of DLPFC/PMC rTMS were not affected by naloxone in one study (de Andrade et al., 2011). However, this conclusion needs confirmation since contradictory results have been reported recently (Taylor et al., 2012, 2013).

Overall, these results are consistent with those of Marrawi et al. (Maarrawi et al., 2007, 2013) showing that motor cortex stimulation through epidurally implanted electrodes is associated with a decrease in the availability of opioid receptors in several brain areas. These results are also consistent with recent experimental studies in rats showing that naloxone decreases the antinociceptive effects of electrical stimulation of the motor cortex (Fonoff et al., 2009). Thus, despite obvious differences in their mode of activation of the cortex, rTMS and electrical stimulation of M1 may have certain mechanisms of action in common.

There are very few other data regarding the pharmacology of rTMS-induced analgesic effects. It has been shown that the analgesic effects of both M1 and DLPFC stimulation are reduced after ketamine suggesting a role of glutamatergic systems and of N-methyl-D-aspartate (NMDA) receptors in the analgesic effects of rTMS (see below). Concerning GABA, functional MRI data in humans (Bestmann et al., 2004) and data in animal models (Lucas et al., 2011; Pagano et al., 2012; Cha et al., 2013) have shown a modulation of thalamic activity after M1 stimulation, possibly involving GABA mediation via the inhibitory nucleus zona incerta.

Both M1 and DLPFC/PMC rTMS are able to induce dopamine release in subcortical or cortical structures including the anterior cingulate and insula (Strafella et al., 2001, 2003; Viisanen et al., 2012). Nonetheless, it has recently been suggested that pain inhibits rather than activates descending dopaminergic controls to produce an antinociceptive effect (Abdallah et al., 2015). Although the exact mode of action of dopamine in pain modulation is only partly understood, it has been shown that variation of the dopamine D2 receptor gene seems to contribute to individual differences in analgesic efficacy of rTMS in healthy humans (Jääskeläinen et al., 2014).

It is likely that other neurotransmitters, participating in pain modulation (Benarroch, 2008), are involved in rTMS-induced analgesic effects. For example, it has been shown that M1 stimulation results in the release of serotonine (Viisanen and Pertovaara, 2010a; Lee et al., 2013) while the coeruleospinal noradrenergic pathway seems to play only a minimal, if any, role in spinal antinociception induced by M1 stimulation (Viisanen and Pertovaara, 2010b), but there are still very few data regarding the specific role of these neurotransmitters in rTMS-induced analgesic effects. The main results concerning the mode of action of cortical stimulation are summarized in Fig. 1 and Supporting Information Table S1.

3.2 Role of neuronal plasticity

The fact that the maximum magnitude of rTMS-induced analgesic effects can be delayed up to 2–3 days and that these effects can last up to 1 week after a single session of stimulation (Lefaucheur et al., 2001; André-Obadia et al., 2008), strongly suggests the involvement of plastic processes inducing long-term changes in neuronal excitability. In particular, the effects of rTMS, which are initiated by changes in cortical excitability induced by the magnetic field (Lefaucheur, 2009) may have mechanisms in common with classical long-term potentiation (LTP) and long-term depression (LTD) phenomena (for an extensive review, see Pell et al., 2011). LTP and LTD are characterized by a strong dependence on the frequency of the stimulation used to induce synaptic plasticity and duration exceeding that of the stimulation period, typically by several hours to a few weeks (Cooke and Bliss, 2006). Similarly, rTMS-induced analgesic effects is highly dependent on the frequency of stimulation (André-Obadia et al., 2006).

The mechanisms of LTP and LTD are complex and involve multiple neurotransmitters. However, the NMDA receptor, a major excitatory ligand-gated ion channel in the CNS, has long been known to be one of the predominant molecular gateways controlling synaptic plasticity (Brown et al., 1988). Unlike the alpha-amino-3-hydroxy-5-methyl-4isox-azole propionate glutamate receptor, which requires only glutamate for opening, NMDA receptors require concurrent depolarization for opening and functionality (Rao and Finkbeiner, 2007). As rTMS induces a rapid depolarization of cortical neurons and long-term analgesic effects extending beyond the stimulation period, it has been hypothesized that glutamate NMDA receptors might be involved in its analgesic effects (Pell et al., 2011) and this point is consistent with data obtained in humans (Ciampi de Andrade et al., 2014). These data are compatible with the idea that rTMS-induced analgesic effects involves LTP-like mechanisms. The role of the neurotrophin brain derived neurotrophic factor, a mediator of activity-dependent modifications of synaptic

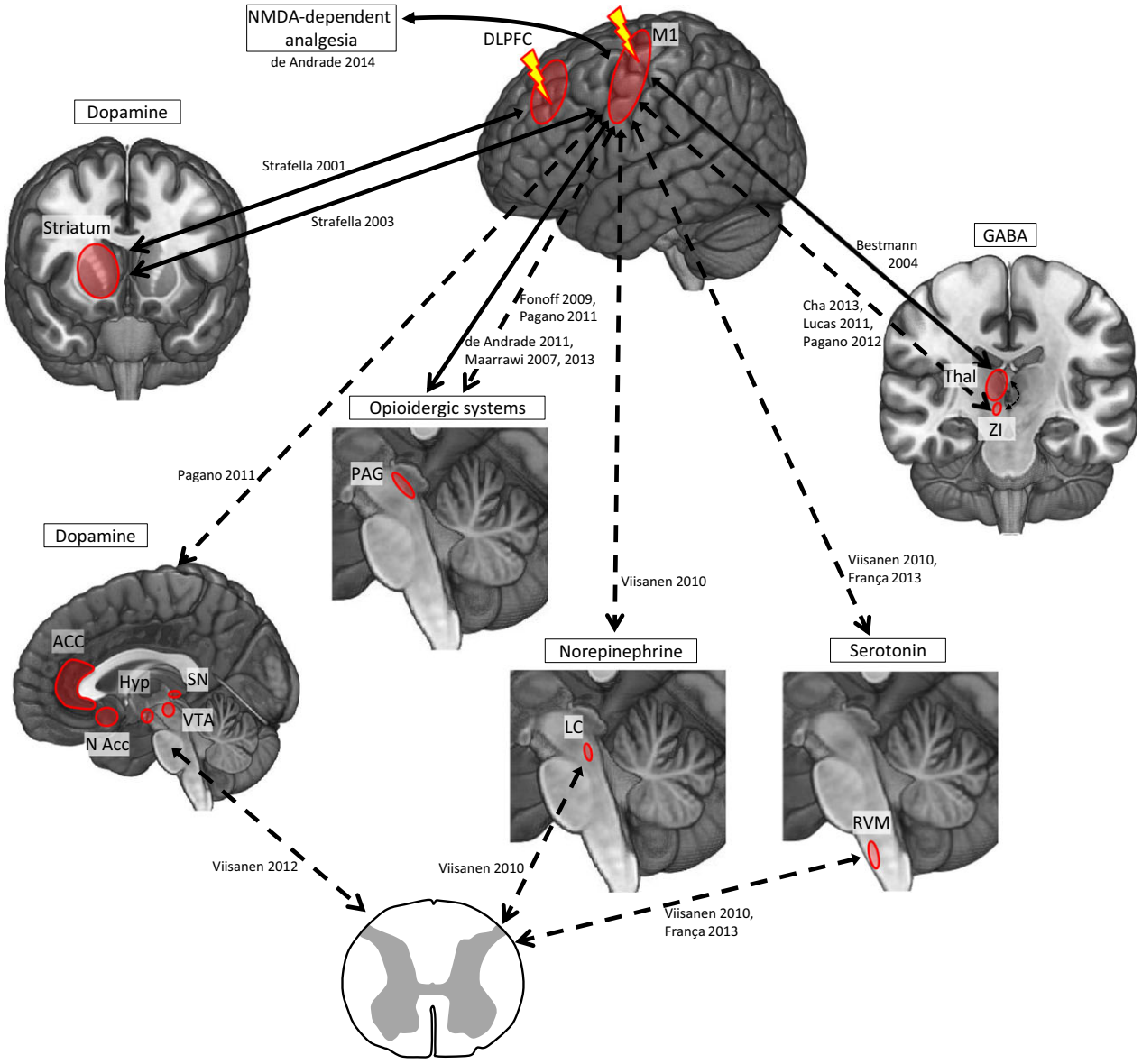

Figure 1 Main systems modified by DLPFC and M1 stimulations and probably involved in analgesic effects. Complete arrows indicate results obtained in humans and dotted arrows those obtained in animals. ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; Hyp, hypothalamus; ISI, inter-stimulus interval; LC, locus coeruleus; M1, primary motor cortex; N Acc, Nucleus accumbens; RVM, rostral ventromedial medulla; SN, Substancia nigra; Thal, thalamus; VTA, ventral tegmental area; ZI, zona incerta.

strength in the central nervous system (Tyler and Pozzo-Miller, 2001), has also been suggested, but contradictory result have been reported with a slight increase in one study (Dall'Agnol et al., 2014) and a decrease in two others (Gaede et al., 2014; Schaller et al., 2014).

However, the cellular mechanisms underlying the changes in excitability of cortical neurons initially induced by stimulation, and their relationships with the changes in the activity of neurons involved in pain modulatory systems is still unclear. This issue was addressed in some studies, by measuring the effects of rTMS on cortical excitability and intra-cortical modulation (Kobayashi and Pascual-Leone, 2003). A potential role of changes in intra-cortical excitability and modulation was suggested because the alterations of these parameters, reported in several chronic pain conditions, including neuropathic pain (Lefaucheur et al., 2006a; Schwenkreis et al., 2010), fibromyalgia (Mhalla et al., 2010) and complex regional pain syndrome (Schwenkreis et al., 2003; Kirveskari et al., 2010), are improved after

rTMS (Lefaucheur et al., 2004b, 2006a; Passard et al., 2007; Picarelli et al., 2010; Mhalla et al., 2011; Hosomi et al., 2013b). In addition, a correlation was reported between the analgesic effects and the changes in cortical excitability (Lefaucheur et al., 2006a; Mhalla et al., 2011; Hosomi et al., 2013a).

Inhibitory and facilitatory interactions in the cortex can be studied by combining a subthreshold conditioning stimulus with a suprathreshold test stimulus at different short (1–20 ms) interstimulus intervals (ISI) through the same TMS coil (Kobayashi and Pascual-Leone, 2003; Rossini et al., 2015) (Fig. 2). This method called paired-pulse TMS is used for the study of the cortical excitability of the motor cortex. Intracortical facilitation (ICF, also named paired pulse facilitation) is a phenomenon in which postsynaptic potentials evoked by an impulse are increased when that impulse closely follows a prior impulse. ICF is thus regarded by some authors (Zucker and Regehr, 2002) as a form of short-term synaptic plasticity. The mechanisms underlying neural facilitation are exclusively pre-synaptic; broadly speaking, ICF arises due to increased presynaptic Ca^{2+} concentration leading to a greater release of neurotransmitter-containing synaptic vesicles (Zucker and Regehr, 2002). Concerning intra-cortical inhibition (ICI, also named paired-pulse depression), it seems to be attributable to a modification or refractoriness of the neurotransmitter release process related to GABAergic interneuronal influence in the generation of corticofugal spikes from M1 (Waldeck et al., 2000).

The effects of the conditioning TMS on the size of a test motor evoked potential (MEP) depend on the stimulus intensity and the ISI. Maximum ICI is found at short ISIs of 1–4 ms and conditioning stimuli of around 80% of the resting motor threshold. The maximum ICI results commonly in MEP amplitude between 20 and 40% of the test MEP. γ-butyric acid (GABA) type A receptors agonists, such as benzodiazepines, enhance ICI and depress MEP amplitude but have no effect on resting motor threshold (RMT) (Ziemann, 2013). ICF can be observed at ISIs of 7–20 ms. The magnitude of this facilitation can be quite variable (from 110 to 300% of the test MEPs) and is even absent in some individuals (Kobayashi and Pascual-Leone, 2003).

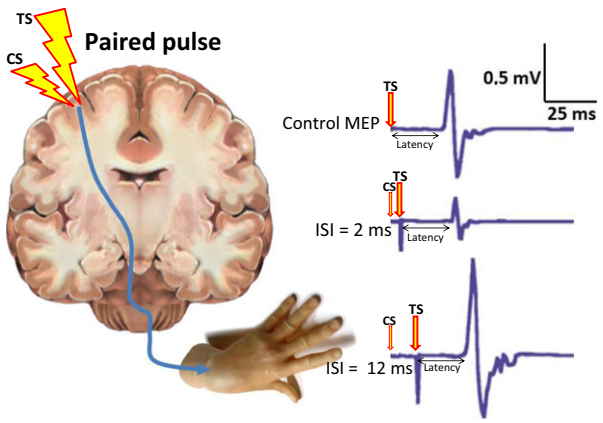

Figure 2 Principles of paired-pulse transcranial magnetic stimulation to explore cortical excitability. Paired pulses delivered at short interstimulus intervals (ISIs) (from 1 to 4 ms) explore intra-cortical inhibition whereas longer ISIs (from 7 to 20 ms) assess intra-cortical facilitation. CS, conditioning stimulus; TS, test stimulus.

However, by contrast with studies in chronic pain patients, in healthy volunteers, several studies reported no evidence of significant changes in cortical excitability after rTMS of M1 or DLPFC, although conflicting results have also been reported (Daskalakis et al., 2006; Fitzgerald et al., 2006; Arai et al., 2007; Jung et al., 2008; Ciampi de Andrade et al., 2014; de Jesus et al., 2014; Moisset et al., 2015). In particular, the blockade of rTMS-induced analgesic effects by ketamine was not associated with changes in intra-cortical modulation (Ciampi de Andrade et al., 2014). The discrepancies between the experimental and clinical studies might be due to the observation that in almost all studies on chronic pain, cortical excitability parameters have not been reported to increase above normal values after rTMS, but to increase from abnormally low values. This suggests that cortical excitability may be subject to homeostatic regulation (Turrigiano, 2008), potentially accounting for the lack of significant changes in cortical excitability reported in several studies on healthy volunteers. Thus, it would be important to perform pharmacological studies directly in patients to further investigate the mechanisms of action or rTMS-induced analgesic effects.

3.3 Importance of the placebo effect and recommendation for research protocols

As for every treatment, a part of the analgesic effect of the technique relies on placebo effect (André-Obadia et al., 2011). This point must systematically be taken into account and double-blinded studies must be systematically realized. Recommendations on rTMS use for pain treatment research have recently been published and should always be followed (Klein et al., 2015). Similarly, recommendation for the safe use of the technique must be followed (Rossi et al., 2009; Groppa et al., 2012).

4. Conclusions

The analgesic effects of rTMS of primary motor cortex and DLPFC are now well-documented, both on experimental pain and in various chronic pain conditions. The long-term effects evidenced in some chronic pain conditions suggest that rTMS may represent a valuable treatment option in some patients. Although the mechanisms of action of rTMS-induced analgesic effects remain unclear, recent studies have suggested that these effects involve a large number of brain structures and depend on pain modulatory systems, in particular endogenous opioids. The fact that these analgesic effects also depend on glutamatergic systems is compatible with the involvement of LTP-like mechanisms. However, further studies, in particular in experimental animal models, are needed to better characterize the cellular and molecular mechanisms of action of rTMS-induced analgesic effects, and the role of other substances (GABA, dopamine, serotonine, norepinephrine,...).

Author contributions

XM and DCDA involved in data search, data analyses and manuscript writing. DB involved in manuscript designing, writing and editing. All authors approved the final manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Parameters involved in rTMS results.

Table S1. Summary of the main characteristics of studies cited in the chapter 3 'Mechanisms of action of rTMS-induced analgesic effects'.