Changes in Sensory Hand Representation and Pain Thresholds Induced by Motor Cortex Stimulation in Humans

Bérengère Houzé[1,2], Claire Bradley[1,2], Michel Magnin[1,2] and Luis Garcia-Larrea[1,2]

[1]Central Integration of Pain lab (NeuroPain), Inserm U1028, Lyon Neuroscience Research Center, Lyon F-69000, France and
[2]University Claude Bernard Lyon 1, Villeurbanne F-69000, France

Address correspondence to Luis Garcia-Larrea, INSERM U1028, Intégration Centrale de la Douleur (NeuroPain) Hôpital Neurologique, 59 Bd Pinel, 69677 Bron Cedex, France. Email: larrea@univ-lyon1.fr

Shrinking of deafferented somatosensory regions after neural damage is thought to participate to the emergence of neuropathic pain, and pain-relieving procedures have been reported to induce the normalization of altered cortical maps. While repetitive magnetic stimulation (rTMS) of the motor cortex can lessen neuropathic pain, no evidence has been provided that this is concomitant to changes in sensory maps. Here, we assessed in healthy volunteers the ability of 2 modes of motor cortex rTMS commonly used in pain patients to induce changes in pain thresholds and plastic phenomena in the S1 cortex. Twenty minutes of high-frequency (20 Hz) rTMS significantly increased pain thresholds in the contralateral hand, and this was associated with the expansion of the cortical representation of the hand on high-density electroencephalogram source analysis. Neither of these effects were observed after sham rTMS, nor following intermittent theta-burst stimulation (iTBS). The superiority of 20-Hz rTMS over iTBS to induce sensory plasticity may reflect its better match with intrinsic cortical motor frequencies, which oscillate at around 20 Hz. rTMS-induced changes might partly counterbalance the plasticity induced by a nerve lesion, and thus substantiate the use of rTMS to treat human pain. However, a mechanistic relation between S1 plasticity and pain-relieving effects is far from being established.

Keywords: motor cortex, pain, plasticity, rTMS, somatosensory-evoked potentials

Introduction

Neuropathic pain, that is, pain resulting from a lesion or disease of the somatosensory system (Treede et al. 2008) is accompanied by modifications of somatotopic cortical maps in the primary somatosensory cortex (S1; Flor et al. 1995, 2006; Wrigley et al. 2009). In patients with pain following amputation or spinal cord injury, such changes are characterized by a "shrinking" of deafferented S1 regions, which become invaded by the representation of adjacent preserved cortical zones (Birbaumer et al. 1997; Huse et al. 2001). The extent of S1 reorganization correlated with the intensity of pain in amputees and spinal injured patients (Flor et al. 1995; Wrigley et al. 2009), and different pain-relieving procedures were reported to normalize previously altered somatotopic maps (Birbaumer et al. 1997; Lotze et al. 1999; Huse et al. 2001; Napadow et al. 2007). In contrast with this, recent data suggest that S1 plasticity may be an epiphenomenon of deafferentation without a direct relation to pain (Simoes et al. 2012).

Intracranial, epidural stimulation of the motor cortex is regularly used as a neurosurgical technique for the relief of refractory pain (Tsubokawa et al. 1991; Peyron et al. 2007;

Nguyen et al. 2011). Although less powerful than the neurosurgical technique, non-invasive procedures based on transcranial magnetic stimulation (rTMS) are now emerging as an alternative treatment of drug-resistant pain (Cruccu et al. 2007; Fregni et al. 2007; Lima and Fregni 2008; Lefaucheur, André-Obadia, et al. 2011). High-frequency rTMS has proved of greater analgesic benefit than low-frequency rTMS (Lefaucheur et al. 2001, 2008; André-Obadia et al. 2006; Saitoh et al. 2007), and the analgesic response to high-frequency rTMS may be a prognostic factor for subsequent pain relief with implanted electrodes (Canavero et al. 2002; André-Obadia et al. 2006; Lefaucheur, Ménard-Lefaucheur, et al. 2011). When used for pain relief, high-frequency rTMS is applied either as repeated stimulus trains at 10–20 Hz (conventional HF-rTMS) or, more recently, as repeated short bursts of 50 Hz stimuli recurring with theta frequency ("intermittent theta-burst" or iTBS; Huang et al. 2005; Cardenas-Morales et al. 2010).

While the analgesic efficacy of HF-rTMS appears empirically established, its underlying mechanisms remain largely unknown. It has been posited that rTMS induces rapid plastic changes within the sensorimotor cortex, which might counteract the maladaptive plasticity generating neuropathic pain (Lefaucheur et al. 2006; Antal and Paulus 2010a, 2010b), but there has not been, as yet, any direct evidence for the joint development of S1 plastic changes and antinociception in humans following motor cortex rTMS. Therefore, in this study, we evaluated 2 modalities of analgesic rTMS (conventional HF-rTMS vs. iTBS), in terms of their ability 1) to induce sensory plasticity by modifying the sensory representations in S1 and 2) to modify the sensory thresholds for innocuous and noxious experimental stimuli.

Materials and Methods

Subjects

Data were obtained from 13 healthy adult volunteers (5 men, 22–63 years old [mean age 32.2 ± 13.9 years]), who gave their informed consent prior to the study and were remunerated for their participation. All but 2 subjects were right-handed, none had a history of neurological or psychiatric disease or was under medication. The study was approved by the local ethics committee (CPP Léon Bérard-Lyon; 2008-A01437-48).

rTMS with Magnetic Resonance Imaging-Based Neuronavigation

Cortical stimulation of the right motor cortex was performed using a MagPro X100 MagOption stimulator and a figure-of-eight coil (butterfly cooled coil MCF-B65, MagVenture®, Alpine Biomed®). Each subject underwent 2 magnetic resonance imaging (MRI)-guided sessions of cortical stimulation (20 Hz and iTBS) over the hand motor

spot, delivered at a 4-week interval. Before each rTMS session, recording bipolar electrodes were placed on the left *abductor digiti minimi* (ADM) muscle. The optimum dominant representation of this muscle innervated by the ulnar nerve was determined by applying single biphasic TMS pulses with the coil held roughly perpendicular to the central sulcus, as guided by neuronavigation (VISOR, ANT®, The Netherlands). In these conditions, the handle of the coil pointed backwards at about 45° laterally and the direction of the current induced in the brain was antero-posterior when the second phase of the biphasic pulse is considered (Sommer et al. 2006; Talelli et al. 2007). The cortical point allowing best motor responses with the lowest TMS intensity was defined as the motor "hot spot." An equivalent hot spot for muscles innervated by the median nerve was not investigated. The rTMS session was then performed over the ADM hot spot, at intensity equal to 90% of the motor threshold, itself defined as the TMS intensity eliciting 5 of the 10 motor responses with 50-μV minimal amplitude at rest (Rossini et al. 1994). The anatomical position of the stimulation was controlled online during the whole session, using the subjects' individual 3D-MRI, loaded into the neuronavigation station. Strictly identical procedures of threshold determination, hot spot localization and pulse directionality were applied for 20-Hz rTMS and iTBS.

The 2 active protocols chosen have been proposed as methods of analgesia in chronic pain (Lefaucheur, André-Obadia, et al. 2011) and were applied in standard mode. Thus, the high-frequency rTMS protocol (20 Hz rTMS) consisted of 20 consecutive trains of 80 stimulations (280-μs biphasic pulses) each delivered at 20 Hz, and separated by 84-s inter-train intervals (e.g. André-Obadia et al. 2006, 2008), and the intermittent theta-burst protocol (iTBS) consisted of 20 consecutive trains of 30 identical pulses at 50 Hz, separated by 8-s inter-train intervals. Each train contained 10 bursts of 3 pulses each, with internal frequency 50 Hz and inter-burst frequency 5 Hz (e.g. Huang et al. 2005, 2007). These 2 modes of stimulation are generally accepted as increasing the excitability of the stimulated cortex (Khedr et al. 2007; Hoogendam et al. 2010; Pell et al. 2011) and were applied to each participant, with a 4-week interval between the sessions. A comparative assessment of iTBS versus conventional rTMS showed similar enhancing effects on motor cortex excitability (Zafar et al. 2008). The sham rTMS protocol was identical to the HF-rTMS session, using a placebo coil of identical shape and eliciting identical noise as the "active" coil, but not producing a significant magnetic field (Placebo coil MCF-P-B65, MagVenture®, Alpine Biomed®). The placebo coil did not generate, however, any superficial electrical stimulus and did not induce any subjective scalp perception.

Quantitative Sensory Testing

A number of somatosensory tests were performed on the first and fifth fingers of the left hand, immediately before and after each rTMS session. "Tactile thresholds" were assessed using Von Frey filaments (Somedic®, Sweden), and "2-point discrimination" on the first and fifth digits extremity using 2 blunted needles. To weigh up "joint position sense" the investigator produced slow vertical and horizontal movements (10–30°) to the first and fifth digits of the open right hand, which the subject had to reproduce in real time, eyes closed, with the corresponding digits of the contralateral hand. A separate examiner evaluated the number of correct responses out of 5 trials per digit. Ring and plastic-mounted bipolar electrodes were used to evaluate the perceptive and the nociceptive thresholds in the left first digit and ulnar nerve territories, respectively.

Cortical Representation of the Sensory Hand Using Evoked Potentials

Somatosensory-Evoked Potentials

The subjects were comfortably installed on a chair in a quiet room and were instructed to keep eyes closed while remaining awake. According to previous experiments defining the most robust method to assess the human hand representation (Houzé et al. 2011), electrical stimulations were delivered to the left first digit and ulnar nerve. The first digit was stimulated using ring electrodes and the ulnar nerve

close to its emergence near the wrist using a bipolar electrode (cathode proximal in both cases). The stimuli were square-wave pulses of 0.2 ms, delivered at 3 Hz, and with intensity 3-fold the sensory threshold. Such stimulus intensity was below pain threshold in each subject.

Somatosensory-evoked potentials (SEPs) were recorded before and after rTMS sessions with a 128-channel electroencephalogram (EEG) cap (Waveguard Cap™) in accordance with the 10–10 extended international system. All electrodes were referred to the left mastoid and a ground electrode was installed on the stimulated arm, between the stimulation site and the recording electrodes. Electrode impedance was kept below 5 kΩ. For each stimulated site, 2 runs of 950 stimuli were applied. Recordings were made using ASA® (ANT® Software, The Netherlands) with 2048 Hz sampling rate and band-pass filter 0.263–1024 Hz.

SEP Analyses

The continuous EEG was segmented into epochs of 120 ms that included a 20-ms pre-stimulus period. Before averaging, a digital band-pass filter was applied offline on each epoch (Butterworth's filter, 15–350 Hz, 24 dB/oct) together with a 50-Hz notch filter. Slow linear trends were corrected by high-pass filtering, and baseline correction was performed using the pre-stimulus period. Epochs were visually inspected and rejected from average if voltage variations exceeding ±70 μV were present on 1 of the 128 channels. Under these conditions, an average of 10.1 ± 1.81% of epochs were rejected per subject. Since source localization heavily relies on a good signal-to-noise ratio at all electrode sites, the signal from electrodes that remained of poor quality after the processing steps described above (detrending, baseline correction and filtering) was interpolated using spline functions that took into account the whole set of 128 electrodes. Less than 5 over the 128 electrodes used per subject were interpolated. Grand averages of the 2 consecutive runs for a given stimulation condition were then performed for each subject, before submitting the results to source analysis.

The earliest component arising from the primary sensory cortex (N20/P20, from area 3b; Allison et al. 1989) was identified on the basis of its latency, polarity, and scalp distribution. For each SEP recording and in each subject, the channel in the right parieto-central region exhibiting the largest negative value (around the peak of N20 SEP) was identified. Peak latency was estimated at the maximal peak amplitude and amplitude was measured from the baseline. For each stimulated site, N20 latency and amplitude were compared before and after the rTMS sessions.

S1 Source Reconstructions

Source reconstruction by dipolar modeling was performed using the whole 128-eletrode montage. Previous to source analysis, the topographical voltage distribution of the N20/P20 SEP component was assessed using 3D mapping, to ensure that its pattern was in line with the known scalp topography of this component. Dipole source analysis using BESA® (MEGIS Software GmbH, Germany) was first based on the grand average of data obtained in all subjects for each condition. The model obtained for the grand average was then used as a starting point to perform individualized source analysis in each subject and condition. BESA® correlates iteratively the scalp potential distributions generated by theoretical dipoles within the brain with the actual scalp distribution obtained experimentally, in order to estimate the location and orientation of intracranial sources best explaining the potentials recorded at the scalp surface. A model with dipole localizations coherent with current anatomo-functional knowledge and a value ≥90% for the goodness-of-fit (GOF) was accepted as reliable.

The spatial position of each dipole was characterized by its coordinates in a 3-dimensional referential: The *X*-axis corresponds to the line passing through T7 and T8 (negative values on the left hemisphere), the *Y*-axis to the line between Fpz and Oz (negative values toward the occipital region), and the *Z*-axis to the line perpendicular to the *XY* plane and passing through Cz (negative values below the head center). The origin of coordinates is defined by the intersection point of the *X*, *Y*, and *Z* axes. The head model used in BESA® was a

4-shell ellipse of 85-mm minor radius (Scherg 1990). The model used to estimate sources was a non-moving equivalent current dipole whose magnitude and orientation were allowed to vary across time. The default time-window loaded in the BESA source analysis module was 0–120 ms. A relatively long-interval fit needs to be chosen to include as much activity as possible but must be sufficiently short to be specific of the activity of interest. In the case of the N20/P20 component, the source localization was performed considering its ascending phase (i.e. 6–10 sampling points). When the subcortical P14 component was in part contained in this time-window, N20 source reconstruction was performed after a subcortical dipole taking account of the early activity was identified and fixed. In 35% of cases, a noise dipole accounting for focal electromyography (EMG) noise (neck or periocular EMG) further improved the GOF. After estimation of the best dipolar solution, co-registration of electrode coordinates within the Talairach space allowed projection of the estimated sources onto an averaged Talairach-normalized MRI (BESA® software).

Before rTMS sessions, coordinates of the N20/P20 dipole in all subjects were averaged to obtain 2 mean dipolar localizations corresponding to the first digit and ulnar nerve pre-rTMS dipoles. The 2 mean dipolar positions were projected onto an averaged Talairach-normalized MRI to specify the anatomical position of dipoles. The 2D Euclidean distance of each dipole in the sagittal plane, obtained before and after rTMS sessions, was calculated with respect to the origin of coordinates in the Talairach system, that is, the anterior commissure. In addition, 2D inter-dipole distances between the first digit and ulnar nerve were calculated for each subject before and after rTMS sessions. This dual approach allowed us evaluating possible variations in the position of dipolar sources both within the Talairach space and with respect to each other.

Control Experiments

Two control comparisons were performed. In the first ($n = 10$ subjects) control experiment, the 2 control sessions recorded before each type of rTMS (20 Hz and iTBS) were compared in terms of source localization and psychophysical results. The comparison of these 2 sessions allowed controlling for possible non-specific changes (i.e. independent from rTMS) in either the quantitative sensory testing or in source localization. The second control experiment ($n = 6$ subjects) involved the localization of SEP cortical sources before and after a sham high-frequency rTMS session. To this end, SEP recordings were performed in the same way as during actual 20-Hz rTMS sessions except that the "sham" coil was used (see above).

Statistical Analyses

After checking the normality of their distributions (Kolmogorov–Smirnov test), data from quantitative sensory testing before/after each stimulation modality were compared using paired t-tests. N20 latencies and amplitudes were submitted to 2-way repeated measures analysis of variance (ANOVA), with "time" (before vs. after rTMS stimulation) and "site" (first digit vs. ulnar nerve) followed by post hoc paired t-tests. Two-way (site and time) repeated measures ANOVA was also used for the comparison of 2D Euclidean distances. Inter-dipole distances before/after each type of cortical stimulation were compared by paired t-tests. In all cases, the level for statistically significant difference was set at $P < 0.05$, after either Greenhouse correction (ANOVA's main effects) or Tukey's correction (post hocs).

Results

Effects of 20-Hz rTMS and iTBS Sessions on Sensory Thresholds and Cortical Responses

Quantitative Sensory Testing

Figure 1 illustrates the mean ± standard error of the mean (SEM) of threshold data obtained in the ulnar nerve and first digit territories, before and after the 20-Hz rTMS (upper part) and the iTBS (lower part). Whatever the type of cortical stimulation, no statistical changes were noted in tactile, 2-point discrimination, and non-noxious sensory thresholds assessed before and after the stimulation session. Conversely, a significant increase of pain thresholds was observed following 20-Hz rTMS, for both the first digit ($t(8) = 3.58$, $P = 0.007$) and the ulnar nerve territories ($t(8) = 4.66$, $P = 0.002$). This effect was not observed following the iTBS sessions.

Latency and Amplitude Measurements of Cortical Responses

SEP responses allowing accurate measurements of N20 latency and amplitude could be obtained in 50 of the 52 recording sessions. In Subject 6, no clear SEPs could be recorded in the 2 ulnar nerve sessions, excluding him from the analyses. The N20/P20 somatosensory response had in all subjects a dipolar voltage distribution (posterior negative, anterior positive) over the hemisphere contralateral to stimulation, with the isoelectric line grossly overlapping the central region. For 20-Hz rTMS, there was a significant effect of stimulation site ($F_{1,8} = 43.85$, $P < 0.001$), since the N20 response occurred at shorter latencies for stimulation of the ulnar than the first digit, both before (20.44 ± 0.3 ms vs. 21.37 ± 0.21 ms; $t(8) = 3.34$, $P = 0.01$) and after the 20-Hz rTMS session (20.55 ± 0.37 ms vs. 22.22 ± 0.34 ms; $t(8) = 5.32$, $P = 0.001$).

Two-way repeated measures ANOVA on pre- and post-iTBS latencies revealed both site ($F_{1,8} = 29.30$, $P = 0.001$) and time effects ($F_{1,8} = 8.69$, $P = 0.018$), with no interaction. The N20 response culminated earlier after stimulation of the ulnar nerve than the first digit, both before (20.00 ± 0.38 ms vs. 21.70 ± 0.18 ms; $t(8) = 5.29$, $P = 0.001$) and after the iTBS session (20.49 ± 0.42 ms vs. 22.09 ± 0.27 ms; $t(8) = 4.77$, $P = 0.001$). The N20 latency to ulnar nerve stimulation was slightly but significantly delayed following iTBS ($t(8) = 2.80$, $P = 0.023$).

N20 amplitudes elicited by the ulnar nerve stimulation were always higher than those after first digit stimulation ($F_{1,8} = 16.12$, $P = 0.004$ and $F_{1,8} = 7.06$, $P = 0.029$, respectively in 20-Hz sessions and iTBS sessions). The amplitude of the responses remained stable during the 2 types of cortical stimulation, with no "time effect" ($F_{1,8} = 0.08$; $P = 0.78$ n.s.).

Source Analysis

The source localization of the S1 cortical response N20/P20 could be performed with a GOF >90% in 37 of the 40 recording preceding and following the active rTMS sessions. SEP sources to ulnar nerve stimulation could not be modeled appropriately in 1 subject (#6) under 20-Hz rTMS and sources to the first digit in another one (#8) under iTBS. These data were rejected from analyses and thus statistics were based on 9 subjects only for each type of cortical stimulation. The mean and SEM of the Talairach anatomical coordinates of N20/P20 equivalent dipoles for each stimulation site obtained before and after rTMS session are summarized in Table 1. Figure 2 shows the projection of the N20/P20 dipoles onto an averaged Talairach-normalized MRI before and after each modality of cortical stimulation (Fig. 2A,B—20 Hz rTMS; C,D—iTBS).

For 20-Hz rTMS, 2-way repeated measures ANOVA on 2D Euclidean distances to anterior commissure (AC) showed a strong effect of the site (first digit vs. ulnar nerve; $F_{1,8} = 62.64$, $P < 0.0001$) with significant interaction between site and time ($F_{1,8} = 18.10$, $P = 0.003$). The main effect of site reflected the fact that cortical source locations were significantly different
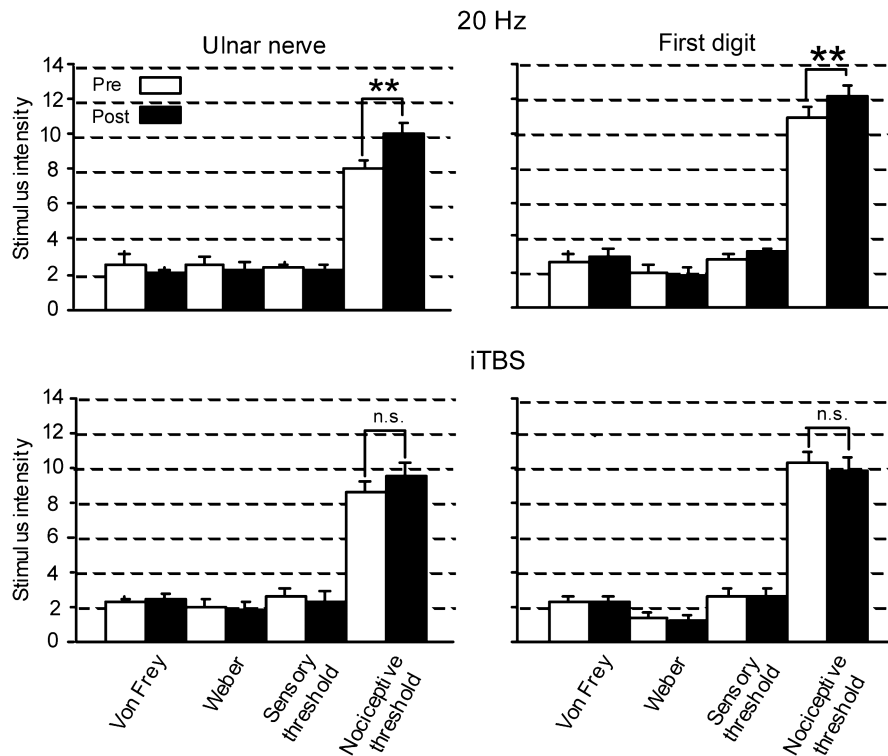
Figure 1. Data (mean ± SEM) from quantitative sensory testing obtained on ulnar nerve and first digit territories before and after 20-Hz rTMS and iTBS sessions. In ordinates, tactile thresholds are expressed in g/mm^2 for VonFrey filaments and in millimetres (mm) for 2-point discrimination. Sensory and nociceptive thresholds to electrical stimuli are expressed in milliamperes (mA). Data on joint position sense are not shown, as all subjects were at 100% performance at baseline and remained so following cortical stimulation. Nociceptive thresholds were significantly enhanced after a 20-Hz rTMS session, in both ulnar nerve and first digit territories (**$P < 0.002$ and $P < 0.007$, respectively), while they did not change significantly following the "theta-burst" (iTBS) session.

Table 1

The mean and SEM of ulnar nerve and first digit dipoles coordinates before and after 20-Hz rTMS and iTBS sessions

		First digit pre-rTMS				First digit post-rTMS				Ulnar nerve pre-rTMS				Ulnar nerve post-rTMS			
		X	Y	Z	GOF	X	Y	Z	GOF	X	Y	Z	GOF	X	Y	Z	GOF
20 Hz	Mean	39.2	−32.7	40.4	92.2	40.2	−29.0	35.7	92.0	35.7	−31.7	48.6	92.5	36.4	−34.3	52.6	94.3
	SEM	1.1	1.9	1.3	0.7	2.0	2.9	1.5	1.0	1.7	2.0	1.2	0.6	2.1	2.6	2.4	0.9
iTBS	Mean	38.1	−28.2	42.3	91.1	42.3	−24.2	36.4	91.4	37.2	−31.0	49.4	90.5	38.0	−29.1	49.5	92.2
	SEM	4.0	2.1	1.5	0.8	2.9	2.3	2.6	0.4	1.9	2.3	1.0	0.8	2.6	2.2	0.8	0.4

Note: GOF: goodness-of-fit.

for the first digit and the ulnar nerve, both before ($t(8) = 3.70$; $P = 0.006$) and after the 20-Hz rTMS session ($t(8) = 7.86$; $P < 0.0001$), the first digit being more lateral and inferior relative to the ulnar territory (Fig. 2A,B). The site × time interaction indicated that changes in source location following 20-Hz rTMS were dependent on the site of stimulation: While the first digit localization after 20-Hz rTMS changed in an anterior–inferior direction relative to its pre-rTMS position ($t(8) = 5.32$; $P = 0.001$), that of the ulnar territory moved in the "opposite" direction (upwards and backwards; ($t(8) = 2.05$; $P = 0.075$). As a result, the distance between the first digit and ulnar nerve sources, reflecting the extent of the sensory hand cortical representation, was significantly enhanced after 20-Hz rTMS, relative to pre-20–Hz rTMS values (9.62 ± 1.63 mm vs. 20.66 ± 2.51 mm; $t(8) = 4.45$, $P = 0.002$; Figure 3A,C).

For iTBS, 2-way ANOVA on 2D Euclidean distances from AC revealed significant site ($F_{1,8} = 14.05$, $P = 0.006$) and time

($F_{1,8} = 5.90$, $P = 0.041$) effects, as well as an interaction ($F_{1,8} = 13.38$, $P = 0.006$). The site effect reflected the fact that cortical representations of the first digit and ulnar territories were significantly disjoint, and this both before and after iTBS ($t(9) = 2.92$, $P = 0.017$ and $t(8) = 4.56$, $P = 0.002$, respectively; Fig. 3B, D). The significant [time × site] interaction effect was explained by a different iTBS effect on the first digit and ulnar nerve sources: A significant modification in localization relative to the pre-iTBS position was observed for the first digit ($t(8) = 3.18$, $P = 0.013$), but not for the ulnar SEP sources, and the inter-dipole distance reflecting the extent of the hand cortical representation did not change significantly after the iTBS session relative to the values before (9.91 ± 2.04 mm vs. 14.81 ± 2.60 mm; Fig. 3D).

As a consequence of the above, the increase of inter-dipole distance between the pre- and post-rTMS sessions was significantly greater following 20-Hz rTMS when compared
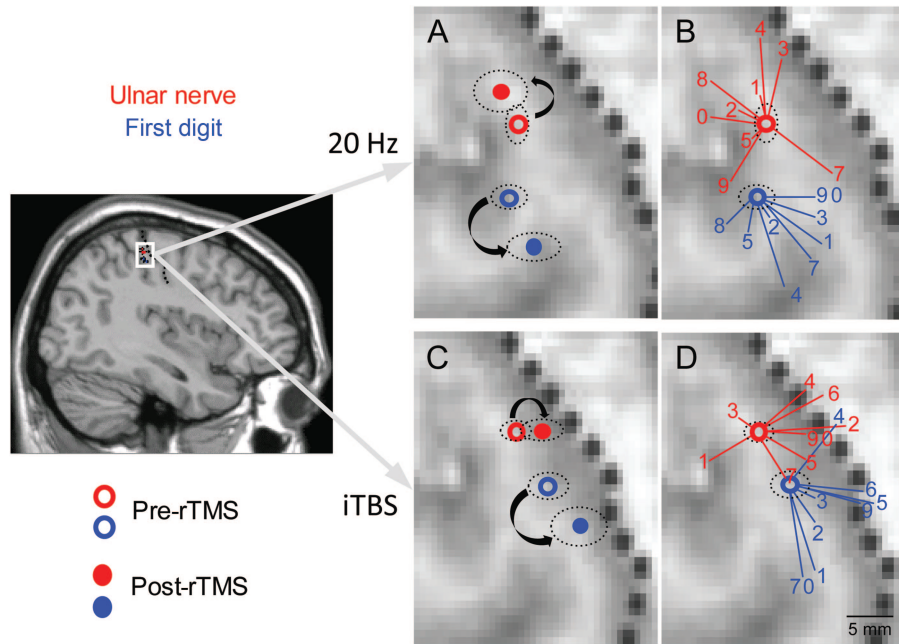
Figure 2. Projections of pre- and post-rTMS ulnar nerve, first digit averaged dipoles (A and C), and individual post-rTMS dipoles positions (B and D) onto an averaged normalized Talairach MRI after 20-Hz (A and B) and iTBS (C and D) rTMS sessions. Dotted ellipsoids indicate the 95% confidence region of dipoles location. The location of the first digit and ulnar nerve dipoles obtained after rTMS sessions in each subject is represented with respect to the mean of first digit and ulnar nerve dipole locations obtained in all subjects before the 20 Hz or iTBS session. Numbers correspond to individual post-rTMS dipole locations of ulnar nerve and first digit. Subjects 6 and 8 are not represented for the 20-Hz rTMS and iTBS sessions, respectively, due to unsatisfactory dipolar solutions. Dotted line: central sulcus.
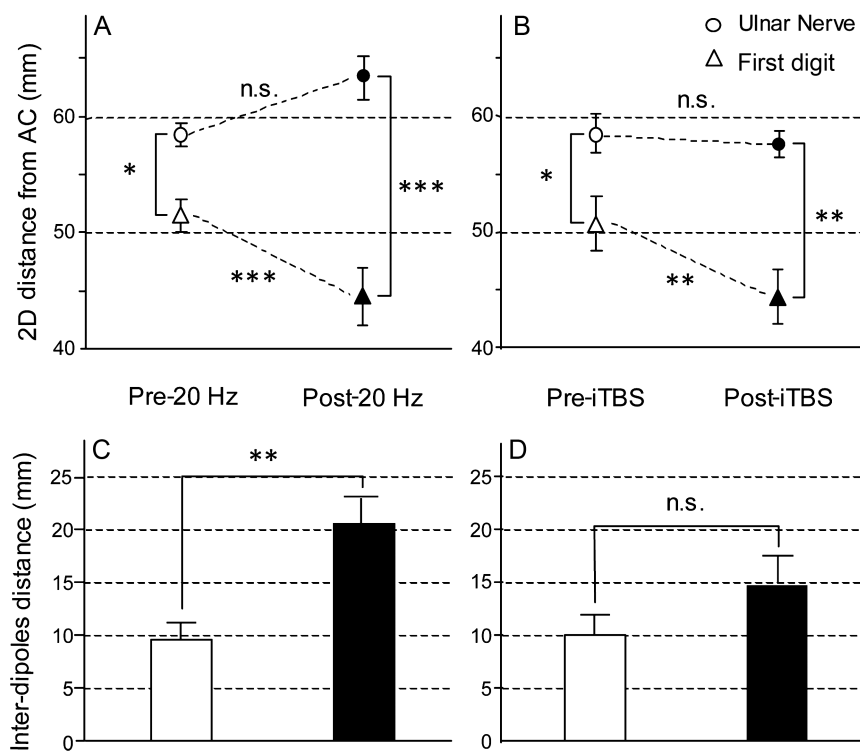

Figure 3. (A and B) 2D Euclidean distances (mean ± SEM) of ulnar nerve and first digit dipoles relative to the anterior commissure assessed before and after 20-Hz (A) rTMS and (B) iTBS, respectively (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$). (C and D) Inter-dipole distances (mean ± SEM) before and after the 20-Hz iTBS or rTMS sessions (**$P < 0.01$). Note the absence of any significant variation between inter-dipole distances observed before the first and the second rTMS sessions indicating a good reproducibility of our data at a 4-week interval.
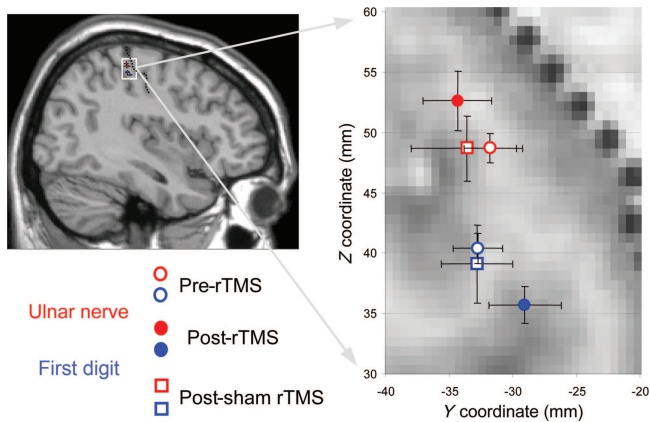
Figure 4. Locations (mean ± SEM) of ulnar nerve and first digit dipoles before (open circles) and after (full circles) active 20-Hz rTMS session together with data obtained after sham session (open square). After the active 20-Hz rTMS session, ulnar nerve and first digit dipole positions significantly moved toward a postero-superior and an antero-inferior position, respectively. Such a displacement did not occur after the sham rTMS session. Dotted line: central sulcus.

with iTBS (11.05 ± 2.48 mm vs. 4.56 ± 1.57 mm; $t(7) = 2.591$, $P = 0.036$; Fig. 3C,D).

Control Comparisons

Control SEPs Recorded Before each type of Cortical Stimulation

Neither the individual source location, nor the cortical size of hand representation, estimated by the distance between first digit and ulnar cortical sources, showed any significant variation when the 2 recordings performed before the first and before the second rTMS sessions in each subject were directly compared (9.62 ± 1.63 mm vs. 9.91 ± 2.04 mm, $t(8) = 0.365$, $P = 0.725$). The same was true for quantitative sensory testing, the results of which did not show significant differences between the 2 pre-rTMS sessions.

Placebo rTMS

In the 6 subjects submitted to sham rTMS, the latter did not induce significant differences in discrimination, sensory, or pain thresholds. The sham session did not have any effect on N20/P20 latencies and amplitudes either and did not entail significant changes in hand representation in the subjects in whom it was tested (Fig. 4).

Discussion

A 20-min session of 20-Hz rTMS applied on the primary motor cortex significantly expanded the somatosensory cortical representation of the contralateral hand, and increased pain thresholds in this same hand. Following iTBS stimulation, changes in hand representation did not reach significance and were not associated with increased pain thresholds. These results were derived from high-density SEP recordings and source dipole reconstruction, the reliability of which is maximal when neural sources are located near the cortical convexity (Scherg 1990; Nuñez and Srinivasan 2006), which is indeed the case for the N20/P20 somatosensory response that was modeled.

A number of procedures were followed to ensure that rTMS was strictly applied to the motor cortex, and did not spread to somatosensory areas. 1) Stimulation was always performed under guidance of a 3D-MRI-neuronavigation system, and 2) the stimulated spot was strictly rostral to the central sulcus; 3) both HF-rTMS and iTBS were delivered at subthreshold values, as suprathreshold stimuli tend to activate the depth of central sulcus and to enhance the probability of S1 contamination (Fox et al. 2004); 4) stimulation never created paresthesiae or other somatic sensations in the hand, contrary to what is reported when S1 is stimulated using TMS at similar frequencies as ours (e.g. Sugishita and Takayama 1993). In addition to these technical items, an important point is that HF-rTMS significantly increased pain thresholds, and was therefore anti-nociceptive, whereas stimulation addressed to S1 is known to be ineffective for inducing pain relief (Hirayama et al. 2006), can obstruct the analgesic effects of motor cortex stimulation (Peyron et al. 1995; Fukaya et al. 2003), and even exacerbate painful symptoms in post-stroke pain (Tsubokawa et al. 1993). Thus, based on both technical data and behavioral effects, we can reasonably conclude that our stimulations were specifically directed at the motor cortex, and spared the adjacent SI area.

Mechanisms Leading to rTMS-Induced Cortical Plasticity

Plasticity is a highly dynamic property of the central nervous system, and it is currently accepted that cortical body representations continuously change in response to external demands. Sensory representational changes can be induced not only by long-lasting motor training (Hänggi et al. 2010), but also acutely by simple maneuvers like selective attention to body parts (Iguchi et al. 2001) or segment immobilization (Weibull et al. 2011). In our subjects, some somatotopic action of motor 20-Hz rTMS onto sensory maps can be suggested since plastic changes involved a sensory region corresponding with the stimulated motor area. Reciprocal connections between primates' sensory and motor areas (Leichnetz 1986; Krubitzer and Kaas 1990; Mountcastle 2005) may provide the anatomical support of the plastic changes observed herein. Alternatively (or concomitantly), rTMS over the motor cortex may influence sensory patterns via cortico-thalamo-cortical indirect pathways. Corticothalamic connections from M1 in primates mainly reach the ventral lateral, ventral anterior, centromedian and centrolateral, and ventroposterolateral oralis nuclei (Künzle 1976; Rouiller and Welker 2000; Kultas-Ilinsky et al. 2003) and could modulate ascending sensory signals as it occurs in rodents (Lee et al. 2008). In humans, subthreshold motor cortex stimulation induces greater metabolic and BOLD changes in the lateral thalamus than in sensorimotor cortex, and this whether the stimulation is epidural (Garcia-Larrea and Peyron 2007) or transcranial (Bestmann et al. 2004), lending support to the hypothesis of significant cortico-thalamo-cortical loops. Feed-forward corticothalamic projections have been described, by which activity from the motor cortex is distributed via the thalamus to other parts of the cerebral cortex (Rouiller and Welker 2000). However, the feed-forward projections from M1 to the thalamus end up in so-called "giant terminals", which represent a tiny minority relative to the much more prevalent small terminals conveying feedback signals (Rouiller et al. 1998; Rouiller and Welker 2000). This, together with

the fact that projections from M1 reach the thalamus via motor, rather than sensory nuclei (Kultas-Ilinsky et al. 2003) suggests that a precise somatotopic mapping of motor onto sensory cortical areas through these feed-forward connections is unlikely, and that the role of cortico-thalamo-cortical loops on plastic changes might be modulatory and general, rather than precisely somatotopic.

Differential Effects of High-Frequency Versus "Theta-Burst" Stimulation

iTBS was less effective than 20-Hz rTMS in inducing somato-sensory plasticity and did not succeed in expanding significantly the cortical representation of the sensory hand (Fig. 3D). Also, while 20-Hz rTMS attenuated pain perception in our subjects, iTBS failed to do so. Poreisz et al. (2008) and Antal and Paulus (2010a) also reported the inability of motor cortex iTBS to produce antinociception in humans, and while "continuous" (rather than intermittent) TBS decreased the amplitude of laser-evoked potentials, it did not attenuate nociception beyond sham stimulation levels (Poreisz et al. 2008). Further, Katayama and Rothwell (2007) failed to demonstrate any amplitude modulation of early SEPs N20/P20 under motor cortex iTBS. Although in this study, iTBS was delivered at 90% motor threshold, compared with 80% in the original protocols (Huang et al. 2005, 2007), it is difficult to ascribe a lesser effect to such intensity enhancement. The lower number of pulses delivered in iTBS protocols (Huang et al. 2005, 2007) when compared with standard 20-Hz rTMS (600 vs. 1600 pulses, respectively) may have participated to the smaller ability of the former to induce cortical changes and pain relief. However, a recent systematic comparison of different motor TMS modalities also reported a lack of analgesic efficacy of iTBS, relative to standard rTMS, even when exactly the same number of pulses were used, leading the authors to suggest that intermittent theta-burst settings might even be "counter therapeutic" (Borckardt et al. 2011).

The differences in efficacy between iTBS and 20-Hz rTMS procedures might be partly dependent on a differential matching between external stimulation and internal properties of sensorimotor networks. Repetitive cortical stimulation imposes trains of oscillatory pulses to the underlying cortex, the resulting modification of cortical activity being at the basis of activity-dependent synaptic plasticity (Bear and Kirkwood 1993; Morris et al. 2003). After Hebbian models (e.g. Scarpetta et al. 2002), the relative phases between an oscillating network and an external driving frequency should shape the resulting synaptic modifications, which in turn determine the nature of the network dynamics. It is expected that synaptic efficacy would increase when phase locking between the driving and the intrinsic network frequency is high, as this strengthens the impact of the synchronously firing neurons onto common targets (Fries 2005; Axmacher et al. 2006). Motor networks oscillate spontaneously at around 20 Hz, and sensory networks at 10–12 Hz (Salmelin et al. 1995; Niedermeyer 1999; Tamura et al. 2005; Feurra et al. 2011). Thus, while standard rTMS is delivered at rates closely matching such intrinsic frequency (20 Hz in the present study), the frequency contents of iTBS trains are 5 and 50 Hz, hence respectively, lower and higher than those of to-be-driven motor cortex. Although increasingly used for motor cortex stimulation, the 5–50-Hz pattern of iTBS is not based on any

sensorimotor properties, but rather on the firing arrangement of hippocampal neurons in cats and rats, particularly when exploring novel environments, with high-frequency trains in the gamma range (around 50 Hz) being reset at theta frequencies (around 5 Hz), which is the spontaneous frequency in the hippocampus (Buzsáki 2002; Axmacher et al. 2006). Thus, a better correspondence of 20-Hz rTMS with the intrinsic properties of the underlying motor networks might explain its superiority over iTBS to induce synaptic plasticity, via a combination of increased local excitability and of M1–S1 efficacy of functional connections.

Notwithstanding the global advantage of 20-Hz rTMS to drive sensory changes, it should be noted the marked inter-subject variations in the extent of the plastic modifications that were observed, some subjects showing extensive changes while others exhibiting very limited or no plasticity at all (Fig. 2B,D). This stresses the fact that individual susceptibility to neural plasticity is variable, modulated by a huge number of intrinsic and contextual factors including age, attentional state, endogenous brain oscillations, circadian rhythm, and pre-TMS excitability state (Sale et al. 2010; Todd and Ridding 2010; Ridding and Ziemann 2010), and probably also genetically determined in part (Cheeran et al. 2008; Antal et al. 2010; Missitzi et al. 2011). A greater understanding of these determinants, together with the adequate use of optimal frequencies, should decrease variance in the response to therapeutic applications of non-invasive brain stimulation in the rehabilitation from brain injury.

The Relation Between rTMS-Induced Plastic Changes and Pain Relief

It is tempting to consider that local plastic modifications in S1 may explain some pain-relieving effects of rTMS in patients; however, no evidence of such direct relation can be presently drawn. Albeit subjects with less plastic response had also the least changes in pain perception, no significant correlation could be drawn between the magnitude of plastic sensory changes and pain thresholds, suggesting that the relation between the two may not have been a direct one. It is also noteworthy that the enhancement of sensory representations in S1 may not be accompanied by changes in nociceptive perception (Simoes et al. 2012). For instance, direct stimulation of the somatosensory cortex can expand the sensory hand representation (Tegenthoff et al. 2005; Pleger et al. 2006), but does not attenuate pain perception (Hirayama et al. 2006), and may even exacerbate pain (Tsubokawa et al. 1991, 1993). These data suggest that high-frequency rTMS in motor cortex may induce a number of functional modifications within the somatosensory system, some of which are directly responsible for, and others just parallel to changes in pain perception. The induction of S1 plastic changes, while being a reliable marker of functional reorganization in somatosensory networks, may not be mechanistically responsible for changes in pain perception (Simoes et al. 2012). This view is supported by the fact that primary somatosensory cortex is not a crucial region for the processing of nociceptive afferents: <4% of spinothalamic system projections may reach S1, while >70% of them project to the opercular and posterior insular cortices (Dum et al. 2009). In accordance, selective lesions of S1 rarely entail deficits in pain perception in humans (Kim 2007), while operculo-insular injury consistently attenuates

nociception (Greenspan et al. 1999; Garcia-Larrea et al. 2010). This suggests that the pain-relieving effects of rTMS may be exerted via functional changes acting not only on S1, but also and particularly at more distant sites including the parasylvian operculo-insular cortex (S2, posterior insula) which also receives direct projections from the motor cortex (Künzle 1978; Leichnetz 1986) and probably through cortico-thalamo-cortical loops (see above). Functional changes within S1 might then be viewed as a "marker of the ability of rTMS to exert influences over other cortical networks,"—not only nociceptive but also linked to sensorimotor control (Tsuboka-wa et al. 1991; Garcia-Larrea et al. 1999), which may in some cases exceed the effects on pain (e.g. Nguyen et al. 1998).

The results herein were obtained in healthy subjects responding to experimental nociceptive stimuli; extrapolation to patients suffering from chronic spontaneous pain should be done with caution. While the analgesic effects of rTMS in chronic pain have been consistently reported (review O'Connell et al. 2010), plastic changes in the somatosensory cortex have never been concomitantly assessed in patients as we did here in healthy subjects. There is also evidence to suggest that at least a portion of analgesic effects of motor cortex stimulation may reflect changes in midfrontal-limbic activity associated with the affective dimensions of pain experience (Bestmann et al. 2004; Garcia-Larrea and Peyron 2007), and perhaps to endogenous opioid secretion (Maarrawi et al. 2007; Ciampi de Andrade et al. 2011). Clearly, further clinical studies are needed to establish whether sensory plasticity, as demonstrated in this work, is a crucial step toward significant pain relief. Should it be the case, major efforts should be devoted to devise clinical standard protocols maximizing this effect?

Notes

Conflict of Interest: None declared.

References

Allison T, McCarthy G, Wood CC, Darcey TM, Spencer DD, Williamson PD. 1989. Human cortical potentials evoked by stimulation of the median nerve. I. Cytoarchitectonic areas generating short-latency activity. J Neurophysiol. 62:694–710.

André-Obadia N, Mertens P, Gueguen A, Peyron R, Garcia-Larrea L. 2008. Pain relief by rTMS: differential effect of current flow but no specific action on pain subtypes. Neurology. 71:833–840.

André-Obadia N, Peyron R, Mertens P, Mauguière F, Laurent B, Garcia-Larrea L. 2006. Transcranial magnetic stimulation for pain control. Double-blind study of different frequencies against placebo, and correlation with motor cortex stimulation efficacy. Clin Neurophysiol. 117:1536–1544.

Antal A, Chaieb L, Moliadze V, Monte-Silva K, Poreisz C, Thirugnanasambandam N, Nitsche MA, Shoukier M, Ludwig H, Paulus W. 2010. Brain-derived neurotrophic factor (BDNF) gene polymorphisms shape cortical plasticity in humans. Brain Stim. 3:230–237.

Antal A, Paulus W. 2010a. Effects of transcranial theta-burst stimulation on acute pain perception. Restor Neurol Neurosci. 28:477–484.

Antal A, Paulus W. 2010b. Transcranial magnetic and direct current stimulation in the therapy of pain. Schmerz. 24:161–166.

Axmacher N, Mormann F, Fernández G, Elger CE, Fell J. 2006. Memory formation by neuronal synchronization. Brain Res Rev. 52:170–182.

Bear MF, Kirkwood A. 1993. Neocortical long-term potentiation. Curr Opin Neurobiol. 3:197–202.

Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J. 2004. Subthreshold high-frequency TMS of human primary motor cortex modulates interconnected frontal motor areas as detected by interleaved fMRI-TMS. Neuroimage. 20:1685–1696.

Birbaumer N, Lutzenberger W, Montoya P, Larbig W, Unertl K, Töpfner S, Grodd W, Taub E, Flor H. 1997. Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization. J Neurosci. 17:5503–5508.

Borckardt JJ, Reeves ST, Beam W, Jensen MP, Gracely RH, Katz S, Smith AR, Madan A, Patterson D, George MS. 2011. A randomized, controlled investigation of motor cortex transcranial magnetic stimulation (TMS) effects on quantitative sensory measures in healthy adults: evaluation of TMS device parameters. Clin J Pain. 27:486–494.

Buzsáki G. 2002. Theta oscillations in the hippocampus. Neuron. 33:325–340.

Canavero S, Bonicalzi V, Dotta M, Vighetti S, Asteggiano G, Cocito D. 2002. Transcranial magnetic cortical stimulation relieves central pain. Stereotact Funct Neurosurg. 78:192–196.

Cardenas-Morales L, Nowak DA, Kammer T, Wolf RC, Schönfeldt-Lecuona C. 2010. Mechanisms and applications of theta-burst rTMS on the human motor cortex. Brain Topogr. 22:294–306.

Cheeran B, Talelli P, Mori F, Koch G, Suppa A, Edwards M, Houlden H, Bhatia K, Greenwood R, Rothwell JC. 2008. A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. J Physiol. 586:5717–5725.

Ciampi de Andrade DC, Mhalla A, Adam F, Texeira MJ, Bouhassira D. 2011. Neuropharmacological basis of rTMS-induced analgesia: the role of endogenous opioids. Pain. 152:320–326.

Cruccu G, Aziz TZ, Garcia-Larrea L, Hansson P, Jensen TS, Lefaucheur JP, Simpson BA, Taylor RS. 2007. EFNS guidelines on neurostimulation therapy for neuropathic pain. Eur J Neurol. 14:952–970.

Dum RP, Levinthal DJ, Strick PL. 2009. The spinothalamic system targets motor and sensory areas in the cerebral cortex of monkeys. J Neurosci. 29:14223–14235.

Feurra M, Bianco G, Santarnecchi E, Del Testa M, Rossi A, Rossi S. 2011. Frequency-dependent tuning of the human motor system induced by transcranial oscillatory potentials. J Neurosci. 31:12165–12170.

Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, Larbig W, Taub E. 1995. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature. 375:482–484.

Flor H, Nikolajsen L, Staehelin Jensen T. 2006. Phantom limb pain: a case of maladaptive CNS plasticity? Nat Rev Neurosci. 7:873–881.

Fox PT, Narayana S, Tandon N, Sandoval H, Fox SP, Kochunov P, Lancaster JL. 2004. Column-based model of electric field excitation of cerebral cortex. Hum Brain Mapp. 22:1–14.

Fregni F, Freedman S, Pascual-Leone A. 2007. Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. Lancet Neurol. 6:188–191.

Fries PA. 2005. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn Sci. 9:474–480.

Fukaya C, Katayama Y, Yamamoto T, Kobayashi K, Kasai M, Oshima H. 2003. Motor cortex stimulation in patients with post-stroke pain: conscious somatosensory response and pain control. Neurol Res. 25:153–156.

Garcia-Larrea L, Perchet C, Creac'h C, Convers P, Peyron R, Laurent B, Mauguière F, Magnin M. 2010. Operculo-insular pain (parasylvian pain): a distinct central pain syndrome. Brain. 133:2528–2539.

Garcia-Larrea L, Peyron R. 2007. Motor cortex stimulation for neuropathic pain: from phenomenology to mechanisms. Neuroimage. 37(S1):71–79.

Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, Convers P, Mauguière F, Sindou M, Laurent B. 1999. Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain. 83:259–273.

Greenspan JD, Lee RR, Lenz FA. 1999. Pain sensitivity alterations as a function of lesion location in the parasylvian cortex. Pain. 81:273–282.

Hänggi J, Koeneke S, Bezzola L, Jäncke L. 2010. Structural neuroplasticity in the sensorimotor network of professional female ballet dancers. Hum Brain Mapp. 31:1196–1206.

Hirayama A, Saitoh Y, Kishima H, Shimokawa T, Oshino S, Hirata M, Kato A, Yoshimine T. 2006. Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex. Pain. 122:22–27.

Hoogendam J, Ramakers GMJ, Di Lazzaro V. 2010. Physiology of repetitive transcranial magnetic stimulation of the human brain. Brain Stim. 3:95–118.

Houzé B, Perchet C, Magnin M, Garcia-Larrea L. 2011. Cortical representation of the human hand assessed by two levels of high-resolution EEG recordings. Hum Brain Mapp. 32:1894–1904.

Huang YZ, Chen RS, Rothwell JC, Wen HY. 2007. The after-effect of human theta burst stimulation is NMDA receptor dependent. Clin Neurophysiol. 118:1028–1032.

Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. 2005. Theta burst stimulation of the human motor cortex. Neuron. 45:201–206.

Huse E, Larbig W, Flor H, Birbaumer N. 2001. The effect of opioids on phantom limb pain and cortical reorganization. Pain. 90:47–55.

Iguchi Y, Hoshi Y, Hashimoto I. 2001. Selective spatial attention induces short-term plasticity in human somatosensory cortex. Neuroreport. 12:3133–3136.

Katayama T, Rothwell JC. 2007. Modulation of somatosensory evoked potentials using transcranial magnetic intermittent theta burst stimulation. Clin Neurophysiol. 118:2506–2511.

Khedr EM, Rothwell JC, Ahmed MA, Shawky OA, Farouk M. 2007. Modulation of motor cortical excitability following rapid-rate transcranial magnetic stimulation. Clin Neurophysiol. 118:140–145.

Kim JS. 2007. Patterns of sensory abnormality in cortical stroke: evidence for a dichotomized sensory system. Neurology. 68:174–180.

Krubitzer LA, Kaas JH. 1990. The organization and connections of somatosensory cortex in marmosets. J Neurosci. 10:952–974.

Kultas-Ilinsky K, Sivan-Loukianova E, Ilinsky IA. 2003. Reevaluation of the primary motor cortex connections with the thalamus in primates. J Comp Neurol. 457:133–158.

Künzle H. 1978. Cortico-cortical efferents of primary motor and somatosensory regions of the cerebral cortex in Macaca Fascicularis. Neuroscience. 3:25–39.

Künzle H. 1976. Thalamic projections from the precentral motor cortex in Macaca Fascicularis. Brain Res. 105:253–267.

Lee S, Carvell GE, Simons DJ. 2008. Motor modulation of afferent somatosensory circuits. Nat Neurosci. 11:1430–1438.

Lefaucheur JP, André-Obadia N, Poulet E, Devanne H, Haffen E, Londero A, Cretin B, Leroi AM, Radtchenko A, Saba G et al. 2011. French guidelines on the use of repetitive transcranial magnetic stimulation (rTMS): safety and therapeutic indications. Neurophysiol Clin. 41:221–295.

Lefaucheur JP, Antal A, Ahdab R, Ciampi de Andrade D, Fregni F, Khedr EM, Nitsche M, Paulus W. 2008. The use of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to relieve pain. Brain Stimul. 1:337–344.

Lefaucheur JP, Drouot X, Nguyen JP. 2001. Interventional neurophysiology for pain control: duration of pain relief following repetitive transcranial magnetic stimulation of the motor cortex. Neurophysiol Clin. 31:247–252.

Lefaucheur JP, Hatem S, Nineb A, Ménard-Lefaucheur I, Wendling S, Keravel Y, Nguyen JP. 2006. Somatotopic organization of the analgesic effects of motor cortex rTMS in neuropathic pain. Neurology. 67:1998–2004.

Lefaucheur JP, Ménard-Lefaucheur I, Goujon C, Keravel Y, Nguyen JP. 2011. Predictive value of rTMS in the identification of responders to epidural motor cortex stimulation therapy for pain. J Pain. 12:1102–1111.

Leichnetz GE. 1986. Afferent and efferent connections of the dorsolateral precentral gyrus (area 4, hand/arm region) in the macaque monkey, with comparisons to area 8. J Comp Neurol. 254:460–492.

Lima MC, Fregni F. 2008. Motor cortex stimulation for chronic pain: systematic review and meta-analysis of the literature. Neurology. 70:2329–2337.

Lotze M, Grodd W, Birbaumer N, Erb M, Huse E, Flor H. 1999. Does use of a myoelectric prosthesis prevent cortical reorganization and phantom limb pain? Nat Neurosci. 2:501–502.

Maarrawi J, Peyron R, Mertens P, Costes N, Magnin M, Sindou M, Laurent B, Garcia-Larrea L. 2007. Motor cortex stimulation for pain control induces changes in the endogenous opioid system. Neurology. 69:827–834.

Missitzi J, Gentner R, Geladas N, Politis P, Karandreas N, Classen J, Klissouras V. 2011. Plasticity in human motor cortex is in part genetically determined. J Physiol. 589:297–306.

Morris RG, Moser EI, Riedel G, Martin SJ, Sandin J, Day M, O'Carroll C. 2003. Elements of a neurobiological theory of the hippocampus: the role of activity-dependent synaptic plasticity in memory. Philos Trans R Soc Lond B Biol Sci. 358:773–786.

Mountcastle VS. 2005. The sensory hand. Cambridge, MA: Harvard University Press.

Napadow V, Liu J, Li M, Kettner N, Ryan A, Kwong KK, Hui KK, Audette JF. 2007. Somatosensory cortical plasticity in carpal tunnel syndrome treated by acupuncture. Hum Brain Mapp. 28:159–171.

Nguyen JP, Nizard J, Keravel Y, Lefaucheur JP. 2011. Invasive brain stimulation for the treatment of neuropathic pain. Nat Rev Neurol. 7:699–709.

Nguyen JP, Pollin B, Feve A, Geny C, Cesaro P. 1998. Improvement of action tremor by chronic cortical stimulation. Mov Disord. 13:84–88.

Niedermeyer E. 1999. The normal EEG of the waking adult. In: Niedermeyer E, Lopes da Silva F, editors. Electroencephalography: basic principles, clinical applications and related fields. Baltimore: Lippincott, Williams & Wilkins. p. 149–173.

Nuñez PL, Srinivasan R. 2006. Electric fields of the brain: the neurophysics of EEG. Oxford University Press.

O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH. 2010. Non-invasive brain stimulation techniques for chronic pain. Cochrane Database Syst Rev. 8(9):CD008208.

Pell GS, Roth Y, Zangen A. 2011. Modulation of cortical excitability induced by repetitive transcranial magnetic stimulation: influence of timing and geometrical parameters and underlying mechanisms. Progr Neurobiol. 93:59–98.

Peyron R, Faillenot I, Mertens P, Laurent B, Garcia-Larrea L. 2007. Motor cortex stimulation in neuropathic pain. Correlations between analgesic effect and hemodynamic changes in the brain. A PET study. Neuroimage. 34:310–321.

Peyron R, Garcia-Larrea L, Deiber MP, Cinotti L, Convers P, Sindou M, Mauguière F, Laurent B. 1995. Electrical stimulation of precentral cortical area in the treatment of central pain: electrophysiological and PET study. Pain. 62:275–286.

Pleger B, Blankenburg F, Bestmann S, Ruff CC, Wiech K, Stephan KE, Friston KJ, Dolan RJ. 2006. Repetitive transcranial magnetic stimulation-induced changes in sensorimotor coupling parallel improvements of somatosensation in humans. J Neurosci. 26:1945–1952.

Poreisz C, Csifcsák G, Antal A, Levold M, Hillers F, Paulus W. 2008. Theta burst stimulation of the motor cortex reduces laser-evoked pain perception. Neuroreport. 19:193–196.

Ridding MC, Ziemann U. 2010. Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. J Physiol. 588:2291–2304.

Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijević MR, Hallett M, Katayama Y, Lücking CH et al. 1994. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol. 91:79–92.

Rouiller EM, Tanné J, Moret V, Kermadi I, Boussaoud D, Welker E. 1998. Dual morphology and topography of the corticothalamic terminals originating from the primary, supplementary motor, and dorsal premotor cortical areas in macaque monkeys. J Comp Neurol. 396:169–185.

Rouiller EM, Welker E. 2000. A comparative analysis of the morphology of corticothalamic projections in mammals. Brain Res Bull. 53:727–741.

Saitoh Y, Hirayama A, Kishima H, Shimokawa T, Oshino S, Hirata M, Tani N, Kato A, Yoshimine T. 2007. Reduction of intractable deafferentation pain due to spinal cord or peripheral lesion by high-frequency repetitive transcranial magnetic stimulation of the primary motor cortex. J Neurosurg. 107:555–559.

Sale MV, Ridding MC, Nordstrom MA. 2010. Circadian modulation of neuroplasticity in humans and potential therapeutic implications. Rev Neurosci. 21:55–66.

Salmelin R, Hämäläinen M, Kajola M, Hari R. 1995. Functional segregation of movement-related rhythmic activity in the human brain. Neuroimage. 2:237–243.

Scarpetta S, Zhaoping L, Hertz J. 2002. Hebbian imprinting and retrieval in oscillatory neural networks. Neural Comput. 14:2371–2396.

Scherg M. 1990. Fundamentals of dipole source potentiel analysis. Adv Audiol. 6:40–69.

Simoes EL, Bramati I, Rodrigues E, Franzoi A, Moll J, Lent R, Tovar-Moll F. 2012. Functional expansion of sensorimotor representation and structural reorganization of callosal connections in lower limb amputees. J Neurosci. 2:3211–3220.

Sommer M, Alfaro A, Rummel M, Speck S, Lang N, Tings T, Paulus W. 2006. Half sine, monophasic and biphasic transcranial magnetic stimulation of the human motor cortex. Clin Neurophysiol. 17(4):838–844.

Sugishita M, Takayama Y. 1993. Paraesthesia elicited by repetitive magnetic stimulation of the postcentral gyrus. Neuroreport. 4:569–570.

Talelli P, Cheeran BJ, Teo JT, Rothwell JC. 2007. Pattern-specific role of the current orientation used to deliver Theta Burst Stimulation. Clin Neurophysiol. 118(8):1815–1823.

Tamura Y, Hoshiyama M, Nakata H, Hiroe N, Inui K, Kaneoke Y, Inoue K, Kakigi R. 2005. Functional relationship between human rolandic oscillations and motor cortical excitability. Eur J Neurosci. 21:2555–2562.

Tegenthoff M, Ragert P, Pleger B, Schwenkreis P, Förster AF, Nicolas V, Dinse HR. 2005. Improvement of tactile discrimination performance and enlargement of cortical somatosensory maps after 5 Hz rTMS. PLoS Biol. 3(11):e362.

Todd G, Ridding MC. 2010. The response to repetitive stimulation of human motor cortex is influenced by the history of synaptic activity. Restor Neurol Neurosci. 28:459–467.

Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. 2008. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology. 70:1630–1635.

Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. 1993. Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg. 78:393–401.

Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. 1991. Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir Suppl (Wien). 52:137–139.

Weibull A, Flondell M, Rosén B, Björkman A. 2011. Cerebral and clinical effects of short-term hand immobilisation. Eur J Neurosci. 33:699–704.

Wrigley PJ, Press SR, Gustin SM, Macefield VG, Gandevia SC, Cousins MJ, Middleton JW, Henderson LA, Siddall PJ. 2009. Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. Pain. 141:52–59.

Zafar N, Paulus W, Sommer M. 2008. Comparative assessment of best conventional with best theta burst repetitive transcranial magnetic stimulation protocols on human motor cortex excitability. Clin Neurophysiol. 119:1393–1399.