Cognitive effects of precentral cortical stimulation for pain control: an ERP study

Effets cognitifs de la stimulation du cortex précentral à visée antalgique

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Abstract

Electrical stimulation of the motor cortex (MCS) is a promising and increasingly used neurosurgical technique for the control of refractory neuropathic pain. Although its mechanisms of action remain unknown, recent functional imaging data suggest involvement of the thalamus, brainstem and anterior cingulate/orbitofrontal cortex. Since some of these areas are also implicated in higher cognitive functions, notably attentional processes, we analysed cognitive ERPs and behavioural performance during an “oddball” auditory detection task in patients submitted to this procedure. Eleven consecutive patients undergoing MCS because of neuropathic refractory pain, ranging in age from 25 to 71 years, were included in the study. ERPs were obtained in all cases both during the application (“MCS-on”) and within the 10 min that followed discontinuation of the procedure (“MCS-off”). In five patients, ERPs could also be obtained just before the start of MCS. When the patients’ sample was taken as a whole, there were no consistent effects of MCS on the ERPs. There was, however, a significant interaction of MCS action with the patients’ age, reflecting a significant delay during MCS of the cognitive responses N2 and P3 (N200 and P300) in the group of patients older than 50 years exclusively. This effect was rapidly reversible after MCS discontinuation. No MCS-related changes were observed in the N1 component. At the individual level, the effect of MCS on the endogenous ERPs was highly variable, ranging from a total stability of ERPs (mostly in younger subjects) to latency differences of tens of milliseconds in the older group. These results, together with recent experiments showing P300 alteration during repetitive transcranial stimulation, suggest that motor cortex stimulation may interfere with relatively simple cognitive processes such as those underlying target detection, and that the risk of abnormal cognitive effects related to cortical stimulation may increase with age. Although the procedure appears on the whole remarkably safe, complementary neuropsychological studies in this category of patients are advised, as well as caution to possible adverse cognitive effects when using MCS in the elderly, notably in the presence of pre-existent cerebral lesions.

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Résumé

La stimulation électrique du cortex moteur (SCM) est une technique neurochirurgicale prometteuse et de plus en plus utilisée pour le contrôle de la douleur neuropathique pharmaco-résistante. Bien que les mécanismes d’action de cette technique demeurent inconnus, des données récentes d’imagerie fonctionnelle suggèrent la participation du thalamus, du tronc cérébral et des structures cingulaires et orbitofrontales. L’implication de certaines de ces structures dans les fonctions cognitives supérieures, notamment attentionnelles, nous a poussé

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à étudier chez des patients soumis à cette technique les potentiels évoqués cognitifs (PEC) et les performances comportementales au cours d’une tâche de détection de discordances (« oddball »). Ont été inclus dans cette étude 11 patients consécutifs, d’âge compris entre 25 et 71 ans, soumis à une SCM en raison de douleurs chroniques neuropathiques réfractaires. Les enregistrements ont eu lieu chez tous les patients pendant l’application de la SCM, et dans les 10 min qui ont suivi l’arrêt de la stimulation. Chez 5 patients, des réponses ont pu être également obtenues juste avant la mise en route du stimulateur. Lorsque le groupe de patients est pris dans son ensemble, il n’y a pas d’effet significatif de la SCM sur les PEC. Il y a, cependant, une interaction significative entre l’action de la SCM et l’âge du patient, reflétant un retard significatif des composantes cognitives N2 et P3 pendant la SCM dans le groupe des patients les plus âgés (>50 ans) exclusivement. Cet effet était rapidement réversible après l’arrêt de la SCM. Aucun changement significatif ne fut observé sur la composante N1. Au niveau individuel, l’effet de la SCM sur des ERPs endogènes était très variable, allant de la stabilité complète des PEC sous SCM (surtout chez les sujets les plus jeunes) jusqu’à des différences de latence de dizaines de millisecondes chez des patients âgés. Ces résultats, en accord avec des expériences récentes montrant des modifications du P300 au cours de la stimulation magnétique transcrânienne, suggèrent que la stimulation du cortex moteur puisse interférer avec des processus cognitifs relativement simples comme ceux sous-tendant la détection de cibles, et indique aussi que le risque d’effets cognitifs augmenterait avec l’âge. Bien que l’innocuité de la procédure soit claire dans l’ensemble, des études neuropsychologiques complémentaires semblent recommandables, ainsi que la prise en compte des effets cognitifs secondaires possibles quand on utilise de la SCM chez des sujets âgés, notamment chez des patients porteurs de lésions cérébrales préexistantes.

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Keywords: Motor cortex stimulation; Event-related potentials; Cognitive potentials; P300; Pain; rTMS; Transcranial stimulation

Mots clés: Stimulation du cortex moteur; Potentiels évoqués; Potentiels cognitifs; P300; Douleur; rTMS; Stimulation transcrânienne

1. Introduction

Motor cortex stimulation for pain control (MCS) is a recent technique, developed in the last decade, which allows clinical relief to be obtained in a significant proportion of patients with neuropathic pain resistant to pharmacological therapy. The use of MCS in the management of chronic pain patients who have failed to respond to all other available therapies is steadily growing nowadays [10,42,62,63]. Experimental electrical stimulation of the central nervous system (CNS) was first shown to inhibit afferent pain transmission in the late 1950s [4,40,41] and the pain-relieving effect of stimulating CNS motor structures was first described in man in the 1970s [3,16]. During the last decade, the analgesic effect of chronic electrical stimulation of the motor cortex (pre-central gyrus) has been reported in different conditions, including central post-stroke pain [9,10,17,32,33,42,45,46,52,62] and peripheral neuralgias [10,43,46]. Depending on series, significant pain relief is obtained in 50–70% of cases of this otherwise intractable group of patients. Although attempts are being made for predicting, prior to implantation, those patients who may respond to treatment [33,38], the response, in terms of pain relief, does not appear to be specific to any one particular condition.

Despite encouraging clinical results, the mechanisms of action whereby motor cortex stimulation exerts its clinical effects are still controversial. According to Tsubokawa et al. [63] pain relief induced by MCS might be mediated through secondary activation of non-noceptive neurones in the sensory cortex, via cortico-cortical fibres, which would inhibit hyperactive nociceptive units within primary sensory cortex, and in this line histochemical changes were reported in the sensorimotor cortex of rats after chronic MCS [64]. The thalamus could be another possible target of this procedure since abnormal thalamic hyperactivity (induced by spinothalamic transection) was shown to be attenuated after MCS in the cat [24,62]. Positron emission tomography (PET) studies in patients undergoing MCS for pain control have shown an increase in regional cerebral blood flow (rCBF) mainly in the ventral lateral and ventral anterior thalamic nuclei, and subthalamic area ipsilateral to MCS, and also (to a lesser extent) in the medial thalamus, anterior cingulate/orbitofrontal cortex, the contralateral insula and the ipsilateral upper brainstem [17,18,52]. These changes were rapidly reversible after discontinuation of the procedure except for relatively long-lasting persistence in anterior cingulate/orbitofrontal area.

The anterior cingulate and orbitofrontal cortices are thought to be involved in the emotional/affective component of pain [36,52,54,69]; however, their role is not limited to pain processing and they are also implicated in a variety of higher cognitive functions. Anterior cingulate cortex is crucial for attentional orienting, motor inhibition and executive control of cognition (for reviews see [11,14,68]), while the orbitofrontal cortex represents one critical structure in a neural system (that includes other cortical and subcortical components) subserving decision-making [7]. Both structures take part in a multimodal cortical network for the detection of changes in the sensory environment [15]. Since MCS entails significant activity changes in these regions a major question arises about the possible consequences of
this therapeutic procedure on cognitive activities. Although electrical cortical stimulation can obviously disrupt the activity of underlying structures, and therefore, alter high-order information processing, no studies have been conducted so far to detect possible changes in cognitive functions related to MCS.

Transcranial magnetic stimulation of the cortex, and specially its repetitive form (rTMS), has been reported to have pain-relieving effects comparable to those of MCS, but of shorter duration. However, studies of rTMS effects on cognitive activities are rare and often contradictory. No significant changes were found in cognitive functions after the delivery of 20 Hz rTMS over the left motor cortex by Jahanshahi et al. [27], and improvement of verbal memory and of reaction time after rTMS was even reported in one study [51]. Conversely, Cohen et al. [12] showed that single-pulse TMS induced a perceptual lessening of contralateral somatic stimuli, and André-Obadia et al. [5] demonstrated that TMS-related attenuation of somatic perception was dependent on the timing of cortical activation, assessed with somatosensory-evoked potentials. Very recently, Jing et al. analysed event-related auditory potentials (P300-ERPs) before and after rTMS delivered over the left frontal area in healthy subjects [29]. These authors found a significant increase of the P300 latency after cortical stimulation, which was interpreted as an rTMS-induced delay in neuronal activities related to cognitive processing. It must be emphasised here that considerable caution is required when attempting to extrapolate the results obtained with TMS to the possible cognitive consequences of MCS. Not only are the stimulation periods always far longer for MCS than for TMS, but this latter was applied to normal subjects who underwent a single experimental stimulation, while in patients the stimulation is a chronic condition. For these reasons, if cognitive changes have been detected in some TMS studies, we can strongly suspect their existence in patients under MSC. In this context, a recent review on the effects of intracranial therapeutic stimulation stressed the importance of investigating cognitive functions putatively altered by interventional neurophysiological techniques [25].

In the present work, we report a study of auditory cognitive potentials and error rates during a typical auditory oddball paradigm administered concomitant to electrical MCS for pain control, as compared with those obtained in the absence of MCS in the same subjects. Our objective was to assess any systematic variation in one or several of these parameters directly attributable to the cortical stimulation. Long-latency evoked potentials to attended (‘target’) stimuli are thought to reflect different aspects of cognitive processing, namely primary evaluation and feature extraction (P1, N1, P2) [23], detection/discrimination of actively attended stimuli (N2) [34,47,56], and categorisation/closure of the stimulus processing (P3 or P300) [21,22,53,61,66]. The structures which have shown PET changes in patients undergoing MCS, contain areas thought to underlie the N2 and P300 generation also [6,8,15,19], which stresses the possibility that changes in their activity might too induce changes in stimulus processing.

2. Patients and methods

2.1. Patients

Were included in this study 11 consecutive patients (six women), ranging in age from 25 to 71 years (mean 47.6, S.D. 11.4 years) suffering from severe and long-lasting neuropathic refractory pain resistant to pharmacological therapy for more than 2 years, and who underwent motor cortex stimulation for pain control.

Pain was secondary to ischemic or haemorrhagic stroke in eight patients (two patients with parietal, two with thalamic and four with capsulo-thalamic stroke), and to brachial plexus avulsion in the other three cases. Clinical characteristics of the patients are summarised in Table 1. Of the 11 patients, five had a good or satisfactory relief of pain (≥ 50%) at the moment of the ERP recordings, which were performed between 25 days and 6 months after surgery (mean 2.5, S.D. 1.7 months). The stimulating electrode (Resume Medtronic®, four poles at 20 mm intervals) was implanted epidurally, in the precentral gyrus contralateral to the painful side. Identification of the central sulcus was achieved using the phase inversion of somatosensory-evoked potentials (N20 and P20) recorded intraoperatively with epidural electrodes. The multi-plot electrode for precentral stimulation was placed in the suprasylvian region for pain predominant in the face and the upper limb. In addition, a second electrode was placed over the medial wall of the precentral cortex in the seven patients with pain involving the lower limb also. All the patients were also evaluated by means of PET scan using 15O-labeled water during precentral cortex stimulation, and changes in the regional cerebral blood flow (rCBF) of these patients have been reported elsewhere ([18] see Introduction).

The stimulation was delivered at a frequency of 25–50 Hz, with intensity below the threshold of motor responses and/or sensitive symptoms (ranging between 1.5 and 4.5 V), pulse width of 60–80 μs and a mean cycle of stimulation “on” for 30 min and “off” 90 min. After a follow-up of more than 5 years since implantation (range 5–9, mean of 6.8, S.D. 1.5 years), the treatment is still evaluated as satisfactory (>50% of pain relief) by four patients, rather satisfactory (40%) by one patient and “medium”, “rather unsatisfactory” or “ineffective” by the others. No side effects were described during chronic...
<table>
<thead>
<tr>
<th>No.</th>
<th>Diagnosis (lesion)/Date</th>
<th>Side</th>
<th>Site of pain/Characteristics</th>
<th>Age</th>
<th>Sex</th>
<th>Onset of pain (year)</th>
<th>MCS (year)</th>
<th>% pain relief at the moment record</th>
<th>Current pain relief</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-CM</td>
<td>Ischemic ictus parietal (large cav)/1987</td>
<td>Left</td>
<td>R Hemi-body (mainly under knee and forearm)/Constant pain</td>
<td>71</td>
<td>F</td>
<td>1990</td>
<td>1992</td>
<td>90%</td>
<td>Satisfied</td>
<td></td>
</tr>
<tr>
<td>2-GI</td>
<td>Haemorrhagic thalamic (lac infarct)/1989</td>
<td>Right</td>
<td>L Lower limb/first electrical discharge, later constant pain</td>
<td>54</td>
<td>F</td>
<td>1989</td>
<td>1993</td>
<td>20%</td>
<td>Ineffective</td>
<td>Now SCM induce burning sensation in LLL</td>
</tr>
<tr>
<td>3-RC</td>
<td>Ischemic ictus capsulothalamic/1989</td>
<td>Right</td>
<td>L Hemi-body (mainly forearm)/constant and intense pain</td>
<td>54</td>
<td>M</td>
<td>1990</td>
<td>1993</td>
<td>40%</td>
<td>Rather unsatisfied</td>
<td></td>
</tr>
<tr>
<td>4-AS</td>
<td>Brachial plexus avulsion/1976</td>
<td>Left</td>
<td>L Upper limb/constant pain</td>
<td>53</td>
<td>M</td>
<td>1978</td>
<td>1993</td>
<td>?</td>
<td>Unsatisfied but he refuses discontinuation</td>
<td></td>
</tr>
<tr>
<td>5-BM</td>
<td>Brachial plexus avulsion Phantom limb/1970</td>
<td>Left</td>
<td>L Upper limb/constant pain</td>
<td>44</td>
<td>M</td>
<td>1984</td>
<td>1994</td>
<td>80%</td>
<td>Satisfied, although relief decreased</td>
<td></td>
</tr>
<tr>
<td>6-MA</td>
<td>Haemorrhagic ictus capsulothalamic/1991</td>
<td>Left</td>
<td>R Upper limb/constant pain</td>
<td>40</td>
<td>F</td>
<td>1991</td>
<td>1995</td>
<td>100%</td>
<td>Ineffective</td>
<td></td>
</tr>
<tr>
<td>7-VC</td>
<td>Haemorrhagic ictus capsulothalamic/1989</td>
<td>Right</td>
<td>L Hemi-body/constant and intense pain</td>
<td>49</td>
<td>F</td>
<td>1993</td>
<td>1996</td>
<td>30%</td>
<td>Relief decreased</td>
<td>Relief on provoked pain, not on spont.</td>
</tr>
<tr>
<td>8-SA</td>
<td>Ischemic ictus Parietal (large cav)/1988</td>
<td>Right</td>
<td>L Hemi-body/constant and intense pain</td>
<td>46</td>
<td>F</td>
<td>1989</td>
<td>1995</td>
<td>20%</td>
<td>Relief progressively decreased</td>
<td></td>
</tr>
<tr>
<td>9-AA</td>
<td>Haemorrhagic ictus capsulothalamic/1993</td>
<td>Left</td>
<td>R Hemi-body/burning and dysaesthesia sensation</td>
<td>40</td>
<td>M</td>
<td>1994</td>
<td>1996</td>
<td>50%</td>
<td>Rather satisfied</td>
<td></td>
</tr>
<tr>
<td>10-BH</td>
<td>Ischemic ictus thalamic (lac infarct)</td>
<td>Left</td>
<td>R Hemo-body/spontaneous and allodynia</td>
<td>46</td>
<td>F</td>
<td>1994</td>
<td>1996</td>
<td>70%</td>
<td>Satisfied</td>
<td>Better results for RSL</td>
</tr>
</tbody>
</table>
stimulation, except in patient number 5, who suffered one epileptic focal motor seizure on MCS reintroduction, following general anaesthesia for an unrelated surgical problem.

2.2. Stimuli and procedure

Pure-tone pips of 60 ms duration (10 ms rise and fall times) and 70 dB HL were applied binaurally by means of inserted earphones. Subjects had to count silently the "target" tones (2000 Hz) and ignore the "standard" (1000 Hz) tones. Target tone probability of occurrence was 10%. Between 15 and 30 targets were averaged per run, except for patient number 1, who received multiple short (n < 10 targets) series due to rapid fatigue. At least two consecutive sequences of this oddball-counting task were obtained for each condition (with and without concomitant MCS). The inter-block interval ranged between 2 and 3 min.

ERPs were obtained under three different conditions:
- “Control-1”: At rest, before continuous motor cortex stimulation, presentation of two consecutive blocks of the standard oddball paradigm. Recordings were carried out at rest, approximately 60 min after discontinuation of MCS.
- “MCS”: During continuous motor cortex stimulation, presentation of two or three consecutive blocks of the oddball paradigm.
- “Control-2”: At rest, 3–5 min after discontinuation of MCS, presentation of two consecutive blocks of the standard oddball paradigm.

All patients underwent ERP recordings in Conditions 2 and 3, but only five of them could be recorded during the “Control-1” condition (as they arrived at the laboratory with the stimulator “on”).

2.3. ERP recordings

Electroencephalographic (EEG) activity was recorded at 19 scalp sites of the international “10–20” System of the International Federation for Clinical Neurophysiology [28,35], using tin electrodes inserted in an ‘electrocap’ (Electro-Cap International, Inc.) and referred to the nose. The electro-oculogram (EOG) was monitored by a silver–silver chloride cup electrode attached to the supero-lateral margin of the right superciliary arch, also referred to the nose. A ground electrode was placed on the forehead. EEG activity was filtered with a band pass of 0.3–30 Hz (12 dB roll-off) and amplified 30k. Impedances were kept below 2 kΩ. Signals were sampled at a rate of 256 Hz (4 ms between-points resolution) during an epoch length of 1024 ms (including 80 ms of pre-stimulus baseline). Individual averages were digitally re-filtered between 0.5 and 30 Hz in the “MCS-condition” to eliminate the high-frequency interference induced by the stimulator (frequency of 25–50 Hz).

2.4. Component identification and data analysis

The ERP amplitude, duration and latency values used for this study were computed at Cz for the different blocks, conditions (“off-before”, “on” and “off-after” MCS) and stimulus category (target/non-target). Amplitude and duration measurements of the different ERP components were calculated with reference to the pre-stimulus baseline, itself estimated through the average of the 80 ms pre-stimulus. Three components were visually identified: N1, N2 and P3 (P300). The N1 was scored in the ERP waveform to non-target stimuli, while N2 and P3 were identified in the waveform to target stimuli. N1 was identified as the negative wave peaking between 80 and 120 ms in both target and non-target responses, and showing fronto-central distribution. N2 was recognised as the negative-going response to target stimuli, peaking between 180 and 250 ms in central or frontal midline leads. P300 was identified as the largest positive peak between 250 and 650 ms, with centro-parietal scalp distribution and appearing to target stimuli only. In cases where the P3 wave was split into two or more peaks of similar topography and amplitude within the appropriate window, P3 latency was estimated by prolongation of the ascending and descending limbs of the complex, and P3 amplitude taken at the peak of maximal positivity. Only in a few patients was it possible to separate the P3a from the P3b component, on the basis of latency, topography and reproducibility across different runs. The number of patients showing this aspect was too small to allow statistical analyses; however, two cases are illustrated in Figs. 4 and 5. Error percentages in the performance of the counting task were also evaluated for each condition, and quantified as the ratio of errors related to the total number of target stimuli in each sequence. The possible correlations between performance scores (error %) and latency or amplitude of the different components of the auditory event related potentials were calculated exclusively in the MCS condition using Pearson’s correlation coefficient.

Separate analyses were carried out for each component latency, amplitude and duration. Significant effects were first examined with repeated measures ANOVA with the “experimental condition” as a single ‘within’ factor. Since age is known to exert significant effects on ERP amplitude and latency [2,49], and since this parameter varied greatly in our patients (25–71 years), the subjects’ age was then introduced as a covariate in ANOVA. When a significant main effect of condition was evidenced, Scheffe’s and paired t-tests were used for post-hoc comparisons. A level of P < 0.05 was considered statistically significant.
2.5. Single-subject analysis

The possible significance of MCS-induced ERP changes within a single subject were estimated using the average latency change in two successive control runs, and taking the mean latency change ±2 S.D. as the range of "physiological variation" between runs. The mean latency variation of P300 in two consecutive control runs was –0.5 ± 15.2 ms, and the range of "physiological variation" between runs was consequently drawn at ±30 ms. Values exceeding these limits were considered abnormal.

3. Results

3.1. Task performance

The percentage of counting errors was 0.38% (range 0–1.9%, S.D. 0.85) before cortical stimulation; it increased to 4.16% (range 0–16.6%, S.D. 5.94) during cortical stimulation, and abated again to 2.55% (range 0–13.3, S.D. 4.88) immediately after cortical stimulation. The averaged error rate across the two control conditions was 1.48% (range 0–7.14%, S.D. 2.63), i.e. lower than that under MCS, although the differences were not statistically significant.

Individual values of performance (error rates) and neurophysiological data (values of latency and amplitude of the different ERP components) are summarised in Fig. 1. Lack of enough variance of error rates in the control conditions (where zero errors predominated) precluded the estimation of valid correlation coefficients. Such estimation was attempted in the MCS condition where the variance of error rates increased. The latency of both the N2 and P3 components correlated significantly and positively with the error rates during MCS, while no significant correlation was observed between error rates and N1 latency.

3.2. Effect of MCS on latency and amplitude of ERPs

Since the number of measures performed during each experimental condition was not balanced (five subjects before MCS vs. 11 subjects during and after MCS), the two control conditions (before and after MCS) were pooled together before entering statistical analyses (ANOVA). This was done after verifying that no significant difference existed between the pre- and post-MCS control values in any of the five subjects concerned, and in any of the measures considered (ERP latency or amplitude). Thus, the factor “condition” in ANOVA analyses had two levels: control vs. MCS.

3.3. Latency measures

When N1, N2 and P3 latencies were submitted to repeated measures ANOVA with the experimental condition (control vs. MCS) as a within factor, no significant effect was obtained on any ERP component. Conversely, when the patients’ age was introduced as a covariate, ANOVA showed a significant main effect of condition for P3 (F(1,9) = 9.001, P = 0.015), and a marginal significant effect for N2 (F(1,9) = 4.259, P = 0.069) with latency being in both cases longer during MCS than in control conditions. A very significant condition × age (covariate) interaction was also evidenced for both N2 and P3 (F(1,9) = 5.482, P = 0.044; F(1,9) = 11.954, P = 0.007), suggesting a modulation of the
'condition' effect by the patients' age (Tables 2 and 3). This was also suggested by the relationship between patients' age and latency change between conditions (Fig. 2), which showed an increase of latency modification with age, with an inflexion point at about 50 years on visual inspection.

Since the latency changes induced by the experimental condition were more marked in subjects older than 50 years (see Fig. 2), ANOVA was reconducted with the age covariate changed into a between subjects "age" factor with two levels (above and below 50 years). Again, ANOVA showed a significant "condition" × "age group" interaction for both N2 \( (F(1,9) = 7.22, P = 0.025) \) and P3 \( (F(1,9) = 8.59, P = 0.017) \) but not for N1 latency \( (F(1,9) = 2.52, P = 0.147) \). Scheffe's test confirmed that a significant increase of the N2 \( (P = 0.02) \) and P3 \( (P = 0.02) \) latencies during MCS existed in the group of patients older than 50 years (related to the group of patients younger than 50 years). In contrast, no significant changes between these two groups of patients were apparent in the absence of MCS (Fig. 3).

No significant difference relative to the effect of MCS on ERPs was observed between "responders" (i.e. patients who got adequate pain relief from the procedure) and "non responders". Similar negative results were obtained between patients with peripheral lesions as compared with those suffering from central neuropathic pain.

3.4. Amplitude and duration measures

Amplitudes and durations of the components N1, N2 and P3 were also submitted to repeated measures ANOVA with the "experimental condition" as within factor (control vs. MCS), and the patients' age as a covariate. No significant effects were obtained for any component, and no significant condition × age (covariate) interaction was found.

Fig. 4 shows examples of two patients, one showing a clear, MCS-related P300 delay without amplitude changes, reversible after discontinuation of the procedure (upper panel), and a second who did not undergo any significant ERP changes during cortical stimulation. Although the different subcomponents of the P300 (notably P3a and P3b) could not be separately evaluated in all patients, a tendency was observed in the sense of a more selective affectation of the later, more posteriorly distributed portions of the waveform (presumably related to P3b activity). Fig. 5 illustrates the case of a third patient in whom P3a and P3b subcomponents could be correctly identified. In this case, only the late, posteriorly distributed P3b was affected by the stimulating procedure, whereas the earlier and more frontally distributed subcomponent (P3a) remained stable.
3.5. Individual (single subject) analysis

Inspection of individual waveforms showed that the ERP changes in latency and amplitude during MCS were indeed highly variable across patients. The possible significance of MCS-induced ERP changes within a single subject was estimated using the average latency change in two successive control runs (see Methods). Mean latency variation of P300 in two consecutive control runs was $-0.5 \pm 15.2$ ms, and the range of “physiological variation” between runs was consequently drawn at $\pm 30$ ms. On these premises, MCS was considered to modify significantly the P300 in three patients of the group if values at Cz were exclusively considered, and four patients if values at Pz were also entered. P300 latency increase in these patients ranged from 40 to more than 200 ms. Fig. 4 illustrates examples of one patient showing MCS-related changes in ERPs, as compared with another case in whom MCS did not entail significant modifications.

4. Discussion

The present study addressed the question of the possible existence of cognitive impairment during stimulation of the precentral cortex, by evaluating both cognitive ERPs and performance during an “oddball” counting paradigm with the stimulator “on” and “off”. Contrary to previous studies evaluating ERPs in the context of transcranial stimulation (TMS), which could not be conducted strictly concomitant to TMS for technical reasons [29], we were able to assess both ERPs and performance during the cortical stimulation period itself. This permitted to detect transient changes appearing simultaneously to the stimulation of the human motor cortex, and disappearing shortly after MCS discontinuation. In brief, our results showed that, (a) during MCS, the stimulus processing time, as assessed by ERPs, was significantly prolonged in a proportion of patients, while in other patients it remained strictly unchanged; (b) when ERP alterations existed, they were reversible after discontinuation of the cortical stimulation, and (c) the MCS effects on cognitive ERPs were age-dependent, and affected particularly the group of patients older than 50 years.

The present results demonstrate that MCS can produce significant changes in neurophysiological indexes of cognitive stimulus processing (N2 and P3 ERP components) while leaving unaffected earlier waves such as N1. ERPs are accepted as objective tools evaluating both the sensory and cognitive processing of external stimuli. Responses within the first 150 ms post-stimulus, including the N1, are considered to reflect early sensory processing and feature extraction [23], while the subsequent N2 wave (or N200)
signals the detection/discrimination of attended stimuli [47,57,60], and the P3 (or P300) reflects a post-decisional cognitive closure mechanism [13,67], probably related to memory encoding [21,22,53,61]. The finding of a selective effect of MCS on the ‘cognitive’ N2–P3 components, but not on earlier potentials, suggests a genuine disruption of high-order mechanisms of stimulus processing. Our results also suggest that the ERP and behavioural changes cannot be explained by reasons other than cortical stimulation, and that they did not witness a stable dysfunction since they...
were reversible after stopping the stimulator: the fact that all changes were reversible after MCS discontinuation also stands against a general fatigue effect at the basis of ERP changes in this study.

The mechanism whereby motor cortex stimulation may create transient cognitive impairment in selected patients is not clear. No other study has, to our knowledge, evaluated so far event-related potentials or cognitive behaviour during MCS; however, several studies have shown that transcranial magnetic stimulation of the cerebral cortex (TMS) can induce inhibition of specific cortical regions and produce perceptual and/or cognitive impairment. For example, transient visual suppression has been described during application of magnetic pulses to the occipital human cortex [1,30]. Also, transcranial stimulation attenuated the perception of a contralateral somatic stimulus [5,12], and induced speech arrest when applied over the left frontal cortex [50]. In this latter example, the authors also described an increase of counting errors concomitant to the stimulation. If both single shock and repetitive TMS can temporally disrupt brain activity in normal subjects, the impairment can be supposed as potentially more important following MCS, which stimulates directly the cortical surface, leads to a more prolonged exposition (at least 15 min/h) and is often applied to patients with underlying cerebral lesions.

A number of TMS studies have underscored a general, non-specific disruption of sensory processing by the cortical stimulation, rather than a specific alteration of the stimulus' cognitive evaluation. For instance, EEG changes were detected by Izumi et al. [26] during the 1-s-period that

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**Fig. 5.** Illustration of the ERPs recorded from Fz, Cz and Pz in one patient showing changes in P300 during MCS. ERP changes concerned the posteriorly distributed P3b component, while the P3a wave, of earlier latency and frontal predominance, was spared.
followed vertex TMS, but nothing indicated whether such changes could entail specific cognitive disruption. In some cases, perceptual changes were clearly pre-cognitive in origin: for example, perceptual attenuation observed by André-Obadia et al. [5] was maximal when TMS occurred simultaneously with the arrival of the afferent input to the primary sensory cortex (i.e. concomitant with the N20 wave of the SEP), suggesting that TMS ‘blocked’ stimulus perception by acting at a very low level of processing. Also Amassian et al. [1] showed that the proportion of visual stimuli suppression was maximal when the magnetic pulse was simultaneous with the cortical visual input (i.e. with a delay of 60–120 ms related to the stimulus). In contrast with this, the effects observed in this study concerned exclusively the cognitive N2 and P3 components of the ERP, without any effect on the sensory response generated in the temporal auditory cortex [39]. Thus, besides possible non specific effects linked to cortical stimulation, MCS can entail specific alteration of the stages of stimulus discrimination and post-perceptual encoding (reflected by N2 and P3) without affecting the early sensory processing in primary areas. The only study that has shown comparable results using transcranial stimulation of the cortex was recently published by Jing et al. [29], who reported latency increase of P300 (but not of N100) following a 2 × 3 s session of rTMS over the frontal cortex. Interestingly, in this study P300 latency changes, although significant, were very small, notably smaller than the standard deviation around the mean in control conditions. This suggests that, in healthy volunteers also, the cognitive effects of cortical stimulation may concern only a subset of the stimulated subjects, and leave the other unaffected.

From a theoretical point of view, failure of intracortical connections has been proposed as one possible mechanism for TMS-related cognitive dysfunction [27]. In our patients, a PET examination performed during MCS (in a different session) allowed to assess regional changes in blood flow (rCBF), supposed to reflect changes in brain synaptic activity during MCS [59]. Significant increases in rCBF were evidenced in the ventral lateral and ventral anterior thalamic nuclei, and subthalamic area ipsilateral to MCS, and also (to a lesser extent) in the medial thalamus, anterior cingulate/orbitofrontal cortex, insula and upper brainstem [18]. These changes were rapidly reversible after discontinuation of the procedure except for relatively long-lasting persistence in anterior cingulate/orbitofrontal area [52]. The implication of these cortical structures, notably the anterior cingulate and orbitofrontal regions, in cognitive functions is clear (for review see [11,14]), and their role in the co-operated generation of the scalp-recorded P300 has also been widely reported [19,20,6,8,55]. Subcortical neuronal correlates of the P3 component have also been described from the posterior [37,55,65] and medial (intralaminar) thalamus [31]. In addition, the latency of P300 has been recently shown to correlate with thalamic rCBF [44], and P300 delay has been reported in patients affected by thalamic lesions [48]. The existence of MCS-related activity changes, assessed by PET, in both cortical and subcortical structures linked to cognition, and putatively implicated in P3 generation, provides some cues as to the possible mechanisms of cognitive impairment during the MCS procedure. In this respect, it is noteworthy that, in the group of patients with MCS-related changes in whom P300 sub-components could be individualised, a tendency toward selective affectation of the P3b and a relative preservation of the P3a was identified (Figs. 4 and 5) although not quantified. This might be interpreted as a relative preservation of the frontally-dependent orienting function, classically associated to P3a, and a greater impairment by MCS of stimulus encoding mechanisms, largely relying upon cortico-limbic interaction and associated with the P3b (reviews in [21,49,53]).

In our patients, MCS effects on cognitive ERPs were age-dependent and affected particularly the group of patients older than 50 years. Cognitive evoked potentials, and notably the latency of P300, are known to be affected by ageing, and this whatever the sensory modality considered (review in [49]). In several reports conducted in normal individuals, the relation between age and P300 latency has been described as quadratic [2,58], and, interestingly, the inflexion point where the slope of the latency versus age function becomes suddenly steeper often occurs near the age of 50 years the MCS-related changes in P3 latency become increased over the age of 50 years [2,49]. In our study ageing should probably be seen as a risk factor for cognitive impairment, but with additive contribution to other possible cognitive effects of stimulation because the two groups of patients were quite homogeneous, in what concerns ERPs, during control conditions. The background cerebral pathology that provoked the intractable pain in several patients probably contributed to decrease the ‘security margin’ in some cases and allowed MCS to induce clear P300 changes that should have not occurred in an intact brain. Thus, the conjunction of advanced age and an abnormal background CNS function is the more likely explanation of the increased MCS cognitive effects in our older patients. This is all the more so that we were unable to find any significant relationship between the laterality or type of lesion (central vs. peripheral) and the P300 changes without taking into account the age of the subjects.

5. Conclusion

This study has shown that significant increases of the N2 and P3 latencies obtained in an auditory oddball paradigm
can be detected in a proportion of patients during electrical motor cortex stimulation for pain control. These changes were only significant in the group of patients with more advanced ages, and were reversible after stopping the stimulator. The small size of our patients’ sample clearly limits the possibility of generalisation of these results to other data sets, and therefore, complementary studies in a greater group of patients are desirable. Our results are, however, important in that they suggest that the probability of abnormal cognitive effects linked to cortical neurostimulation clearly increases with age. We propose that elderly patients submitted to MCS, especially those with underlying cerebral lesions, should benefit from close neuropsychological and neurophysiological follow-up in order to detect any possible deficit the procedure might entail.

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