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Motor cortex stimulation for neuropathic pain: From phenomenology to mechanisms

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Motor cortex stimulation (MCS) is relatively recent neurosurgical technique for pain control, the use of which is growing steadily since its description in the last decade. While clinical series show that at least 50% of patients with chronic, pharmacoresistant neuropathic pain may benefit from this technique, the mechanisms of action of MCS remain elusive. In this review, we synthesise a number of studies that, combining electrophysiology and functional imaging, have permitted to proceed from phenomenology to models that may account for part of such mechanisms. MCS appears to trigger rapid and phasic activation in the lateral thalamus, which leads to a cascade of events of longer time-course in medial thalamus, anterior cingulate/orbitofrontal cortices and periaqueductal grey matter. Activity in these latter structures is delayed relative to actual cortical neurostimulation and becomes maximal during the hours that follow MCS arrest. Current hypotheses suggest that MCS may act through at least two mechanisms: activation of perigenual cingulate and orbitofrontal areas may modulate the emotional appraisal of pain, rather than its intensity, while top down activation of brainstem PAG may lead to descending inhibition toward the spinal cord. Recent evidence also points to a possible secretion of endogenous opioids triggered by chronic MCS. This, along with the delayed and long-lasting activation of several brain structures, is consistent with the clinical effects of MCS, which may also last for hours or days after MCS discontinuation.

Keywords: Motor cortex stimulation; Neuropathic pain; Positron-emission tomography; Models; Central pain; Neurophysiology; Functional imaging

Introduction

Experimental studies in animals have demonstrated the strong inhibitory influences that electrical stimulation of the nervous system can exert on pain transmission, thus prompting the use of neurostimulation strategies for the relief of chronic pain in humans. The neural targets of neurostimulation have been mostly the sensory pathways mediating transmission of non-noxious information (e.g. large afferent peripheral fibres, spinal dorsal columns or thalamic sensory nuclei) and to a lesser extent brainstem structures exerting antinociceptive influences, such as the peri-aqueductal or peri-ventricular grey matter (reviews in Gybels and Kupers, 1995; Holsheimer, 1997; Wallace et al., 2004). Although stimulation of sub-cortical motor fibres was also shown to inhibit afferent transmission in the dorsal horn (Lindblom and Ottosson, 1957) and produce analgesic effects in man (Fields and Adams, 1974), the use of motor cortex stimulation (MCS) for pain control was not reported and documented until the early 1990s (Tsubokawa et al., 1991, 1993a). Since then, MCS has been progressively introduced in functional neurosurgical procedures with the aim to treat chronic pain refractory to all pharmacological approaches (Tsubokawa et al., 1993a; Meyerson et al., 1993; Mertens et al., 1999; Nguyen et al., 2000; Carroll et al., 2000; Nuti et al., 2005). Although no randomised controlled study of MCS has been published yet, a number of case series covering more than 200 patients converge in indicating that 50–60% of patients with medically refractory neuropathic pain may benefit significantly from the procedure (Cruccu et al., in press), and that an even greater proportion would be willing to be operated again, should the same result be guaranteed (Nuti et al., 2005).

The mechanisms whereby MCS attenuates neuropathic pain remain hypothetical. However, whatever the precise actions underlying this effect, these are likely to be mediated by regional changes in brain synaptic activity, which should in turn be reflected by changes in regional cerebral blood flow (rCBF) (Sokoloff et al., 1991). rCBF changes can be tagged using functional imaging procedures, such as positron-emission tomography (PET) in patients undergoing MCS. The goal of this article is to review

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critically the literature of functional imaging of motor cortex stimulation for neuropathic pain, and to describe how the combined use of metabolic and electrophysiological techniques has proceeded, from purely phenomenological grounds, to the proposal of models that describe changes in functional connectivity during MCS, and allow insight into a number of possible mechanisms of MCS-induced pain relief.

First experiences, early PET and electrophysiological studies

Following spinothalamic transection in cats, Tsubokawa et al. (1991) first showed that MCS attenuated abnormal thalamic hyperactivity. They considered this effect to be mediated by the activation, through corticocortical fibres, of non-nociceptive somatosensory neurons that in turn would inhibit hyperactive units within SI and the thalamus (Tsubokawa et al., 1993a). This view received support by the finding of histochemical changes in the sensorimotor cortex of rats exposed to chronic motor stimulation (Tsubokawa et al., 1993b); however, electrophysiological and PET-scan studies in patients receiving MCS have failed so far to demonstrate significant changes within primary motor or sensory cortices. Rather, significant increases in regional cerebral blood flow were observed in structures *distant* from the motor cortex, such as the thalamus, striatum, brainstem and anterior cingulate areas.

Peyron et al. (1995) used PET-scan in two patients, and described rCBF changes directly related to MCS for pain control. In each patient, MCS-related increases in rCBF, ranging from 6% to 16%, were noted within the thalamus, ACC/orbitofrontal cortex, and brainstem. Subsequent group analysis of 10 consecutive patients confirmed these data: the most significant increases in rCBF during a short MCS session were found within the ventral–lateral thalamus, in regions directly connected with the stimulated motor cortex, followed by the medial thalamus, insula, subgenual cingulate and brainstem (Garcia-Larrea et al., 1999, Fig. 1). No significant modifications of rCBF were observed in the sensorimotor cortex, and the somatosensory evoked potentials (SEPs) were not affected by MCS, suggesting that SI excitability did not change during application of the procedure. It was therefore concluded that descending axons, rather than apical dendrites or cell bodies, were primarily activated by MCS, in accordance with previous theoretical considerations and empirical studies (Katayama et al., 1988; Nowak and Bullier, 1998a,b).

Considering the correlation between rCBF changes and the amount of pain relief, rCBF in the lateral thalamus of each patient (calculated using regions of interest (ROI)) was not significantly different in patients with good clinical effect of MCS (pain relief >80%) relative to those with poor to very poor efficacy (pain relief <30%). Conversely, blood flow increase in the perigenual cingulate and orbitofrontal areas during MCS was significantly higher in patients with good analgesic efficacy than in the others (Garcia-Larrea et al., 1999) as shown in Fig. 2. These results suggested that thalamic activation, although probably important, was not a *sufficient* condition for clinical effect, and that activity changes in rostral cingulate and/or orbitofrontal regions might be of greater relevance for MCS-induced pain relief.

To test the possibility of descending inhibitory action of MCS, spinal nociceptive reflexes were investigated in 7 patients receiving MCS with varying clinical effect. In 3 of them, spinal nociceptive reflexes were significantly depressed during MCS in a similar manner as it had been described during spinal cord stimulation. In no instance was an *enhancement* of such nociceptive responses observed during MCS. Two of the three patients with MCS-related reflex attenuation experienced good or very good clinical pain relief from the procedure, while the other reported a selective decrease in allodynic pain during MCS, although the procedure was unsatisfactory on spontaneous pain (Garcia-Larrea et al., 1999, 2000). None of the four patients whose nociceptive reflexes remained unmodified by MCS was satisfied with the clinical effect of neurostimulation.

The effects of MCS on attentional mechanisms was investigated by Montes et al. (2002), who analyzed event-related potentials and behavioral performance during an auditory target-detection task in 11 consecutive patients. While sensory responses remained unaffected by MCS, there was a significant delay of brain potentials reflecting target detection in the older patients, rapidly reversible after MCS discontinuation. No effect was observed in patients younger than 50 years. Cognitive effects of MCS appeared as mild and non-specific, directly related to the stimulation period (i.e. with no post-effect), in a manner reminding of cognitive effects reported during transcranial magnetic motor cortex stimulation (Jing et al., 2001).

First models of MCS mechanisms

Models of MCS activation had to be adjusted to account for these results: Although primary thalamic changes appeared to concern the lateral thalamus (and perhaps basal ganglia if we take into account the low spatial resolution of first generation PET scanners), parallel or secondary activation of medial thalamic

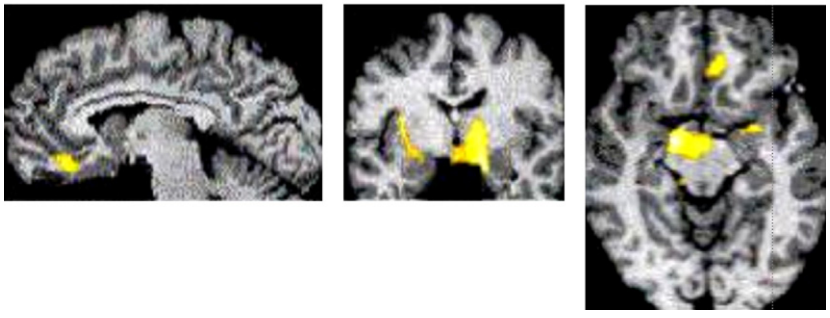

Fig. 1. MRI sections normalized according to the Talairach space, showing regions with significant ($z>3.5$) increases of blood flow during motor cortex stimulation, including the thalamus ipsilateral to stimulation, the insular and subgenual cingulate/orbitofrontal cortices, and the brainstem. No significant rCBF change was observed in the motor or somatosensory cortices directly underlying the stimulator (reprinted with permission from Garcia-Larrea et al., 1999).