Motor cortex stimulation for neuropathic pain: From phenomenology to mechanisms

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Received 30 December 2006; revised 15 April 2007; accepted 8 May 2007
Available online 29 June 2007

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 synthesize 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.

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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 Ottoisson, 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...
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
Thalamus

Anterior Cingulate Area 32

Fig. 2. ROI analysis of the lateral thalamus and area pregenual ACC (BA 32) in patients with very good (>80%) or insufficient (<20%) pain relief. X axis: experimental conditions (Control 1 and Control 2, MCS off). Y axis: normalized radioactivity within ROI. While lateral thalamic CBF appears to increase in all patients (albeit to a greater extent in those with good clinical effect), pACC CBF shows very different trends in patients with good and bad clinical effect. From Garcia-Larrea et al. (1999).

regions (either by direct connection from motor cortex (Powell and Cowan, 1967) or via the reticularis and VA nuclei), were postulated to trigger a cascade of synaptic events influencing activity in other pain-related structures, including the anterior cingulate gyrus, the insula and the upper brainstem which were also activated in PET studies. It was deemed conceivable that thalamic functional changes should reach a threshold in order to activate other areas, and that a lack of clinical effect might result from failure to attain such threshold. Activation of thalamic nuclei connected with motor and premotor cortices was considered as a crucial (although not sufficient) step for allowing the pain-relieving activity of this procedure, while the rostral (perigenual) ACC and the upper brainstem appeared as more directly related to clinical effects. It was therefore, concluded that the cortical and brainstem structures activated by MCS might modify the pain experience at least at two different levels:

1) The perigenual ACC, which has been the target of neurosurgical lesions that specifically reduced the emotional component of chronic pain (e.g. Foltz and White, 1962; Talbot et al., 1995). The cingulate/orbitofrontal boundary activated by MCS appears particularly involved in the affective components of pain (Devinsky et al., 1995; Vogt et al., 1996, Vogt, 2005), and generally in the processing of emotional stimuli. It was therefore suggested that the analgesic effects of MCS might partly derive from a transient blunting of the distressful reaction to pain, rather than to an actual decrease of its intensity.

2) Changes in spinal reflexes during cortical stimulation supported the implication of descending mechanisms leading to inhibition of pain impulses at the dorsal horn level. Activation of central motor fibres can inhibit nociceptive transmission in the dorsal horn (Lindblom and Ottoisson, 1957; Andersen et al., 1962; Senapati et al., 2005), and this effect might be at the basis of flexion reflex depression in patients. This putative mechanism was postulated by authors who, in the 1970s, stimulated corticospinal fibres in the internal capsule to treat neuropathic pain in humans (Fields and Adams, 1974; Adams et al., 1974). Descending inhibition triggered by direct motor cortex stimulation was considered to explain the efficacy of the procedure upon the 'evoked components' of pain (i.e. alldynia and hyperalgesia) even in patients who may remain unsatisfied of the overall pain relief (Garcia-Larrea et al., 1999). Activations that were reported in the upper brainstem (Peyron et al., 1995; Garcia-Larrea et al., 1999) were also considered as possibly mediating such descending inhibitory processes.

Time-course of rCBF changes during MCS

A point that remained unexplained in the models described above is that the clinical effects of MCS are generally delayed relative to the actual periods of cortical stimulation. Patients almost never experience sudden pain relief concomitant with stimulation: they rather describe a progressive relief during the hours or days following utilization of the device. A clinical consequence is that MCS is generally used in discontinuous mode, with alternating “on” and “off” periods, while clinical relief, when present, remains continuous (e.g. Nuti et al., 2005). This aspect of clinical effects differs from the rapid rCBF changes investigated in classical PET-scan experiments, and needs to be investigated by addressing specially the temporal dynamics of different regional brain activities during MCS. In the first PET experiments such temporal dynamics singled out, to a certain extent, the ACC from other activated regions. While in most regions the relatively abrupt rCBF increase was reversible shortly after MCS offset, in the perigenual cingulate such increase had not yet reverted to pre-stimulation values 30 min after MCS discontinuation (Fig. 3). This aspect was confirmed by statistical comparisons between the pre- and post-stimulation control conditions, where two spots of increased rCBF during the post-stimulation period (as compared with the pre-MCS baseline) appeared in both right and left ACC/orbitofrontal boundaries, indicative of a remnant effect on CBF after MCS offset.

Anterior cingulate cortex and late-onset effects of MCS

Peyron et al. (1999a,b, 2007) devised PET-scan experiments to study specifically the timing and localization of those MCS effects that outlast the actual application of the procedure. Nineteen consecutive patients were recorded during a 35-min period of MCS, and then during a 75-min period after the stimulation had been discontinued, the results being compared with a resting condition. The 35-min period following MCS activation was associated with relatively restricted spots of CBF increase in the midcingulate area 24’ and in the ipsilateral and contralateral dorsolateral prefrontal cortices (DLPF). In contrast, a much larger matrix of CBF increase developed during the 2 h that followed the end of
neurostimulation (post-stimulation period). Areas preferentially activated after MCS was stopped comprised the mid- and perigenual cingulate (MCC and pACC), the orbitofrontal cortex, thalamus, basal ganglia and rostral mesencephalon, in a location consistent with the periaqueductal grey matter (PAG) (Fig. 4). Given the important and reciprocal connections between pACC and PAG (An et al., 1998; Freedman et al., 2000), such double activation argued in favour of top-down mechanisms from ACC to PAG. This possibility was later assessed through the study of "functional connectivity", defined as the temporal correlation of neurophysiological or rCBF events between distributed brain areas. Such analysis stands on the idea that regions with covarying patterns of blood flow during a specific condition are most likely in functional exchange with each other (Friston et al., 1996, 1997). The functional connectivity analysis showed that perigenual ACC activations were significantly correlated with those of PAG, basal ganglia and lower pons, supporting the activation of descending ACC-to-PAG connections (Fig. 5). In addition, these changes in CBF were shown to correlate with the overall pain relief and were therefore considered as contributing to the analgesic effects of MCS. These results suggest that the procedure may act in part through delayed and descending (top-down) inhibitory controls that involve DLPF, orbitofrontal and pACC as well as basal ganglia, thalamus and brainstem (PAG and lower pons) (Peyron et al., 2007).

The set of activated regions during the period with MCS “On” in this latter work was notoriously smaller than that observed in previous experiments (Cfr Peyron et al., 1995; Garcia-Larrea et al., 1999), and did not include the thalamus. This could not be explained by either technical or population differences with previous studies, as spatial resolution in this latter work was rather improved, and the patients’ lesions were consistent with those previously studied. Conversely, the overall design of the different studies may have affected their relative ability to disclose thalamic activation. Indeed, by using long “On” and “Off” periods, Peyron et al. (1999a,b, 2007) privileged activities with long time constant (in ACC and upper brainstem), relative to activities with rapid onset and offset such as those previously observed in lateral thalamus (see Fig. 3). This further suggest that thalamic activation from MCS is phasic and short lasting, and may be averaged out when 35 min of electrical stimulation are lumped together and analyzed as a whole. Because of its position as first synaptic relay of corticofugal excitation, thalamic activity may be of importance as a trigger for other cortical and subcortical activations.

Anterior cingulate cortex, chronic pain and analgesia

Vogt et al. (1996) suggested that pain unpleasantness would be principally integrated in the perigenual (pACC) areas 32, 24 and 25, whereas midcingulate activation (the one most commonly seen

Fig. 3. Temporal dynamics of rCBF changes in the regions with MCS-related rCBF increase. X axis, experimental conditions; Y axis, normalized radioactivity within regions studied. In all cases there was an abrupt rCBF increase during the first MCS scan (5 min after onset), which remained rather stable during the 2nd scan (20 min after MCS onset). These effects were reversible during the second control condition (30 min after stimulation offset) except in the ACC/orbitofrontal boundary, where rCBF had not yet reverted to pre-stimulation values 30 min after MCS discontinuation. From Garcia-Larrea et al. (1999).
in PET and fMRI studies of pain) would be associated with cognitive processes, especially response selection and motor inhibition. While the implication of midcingulate cortex in orienting and attentional reactions remains a robust finding (Valet et al., 2004; reviews in Peyron et al., 2000; Garcia-Larrea et al., 2003), the concept that pain affect is strictly contingent on the pACC has not been supported by other imaging studies. Rainville et al. (1997) reported a linear relationship between hypnotically-modulated subjective unpleasantness and CBF in the mid-, rather than perigenual cingulate, and Tölle et al. (1999) found that pain unpleasantness correlated positively with activity in the mid-posterior cingulate. Also in studies assessing the reaction to the unpleasant character of stimuli such as frightful animals, facial expressions of disgust, unpleasant musical dissonance or words with negative semantic content the main increases in CBF have been observed in the middle and posterior sections of the ACC rather than in its perigenual portions (Frederikson et al., 1995; Morris et al., 1998; Blood et al., 1999).

Structural and functional changes in the perigenual and subgenual ACC have been, on the contrary, consistently associated with mood alterations. In the pACC of depressed or bipolar patients, rCBF decreases at rest (Drevets et al., 1997), as well as reduction of grey and white-matter cortical volume (Lopez-Larson et al., 2002), and reduced glial cell number and density (Rajkowska, 2002) have been described. Although these and other studies have not distinguished between abnormalities associated with the depressive and manic phases of the disorder, the subgenual cingulate and associated ventral prefrontal cortex is considered critical for the production of affective states and related behavior (Phillips et al., 2003; Vogt et al., 2003). For instance, anxious expectation of aversive and unpredictable events, including pain, entails decreased blood flow in perigenual ACC and medial prefrontal cortex (Simpson et al., 2001; Porro et al., 2002) while anticipation of aversive but predictable events results in activity increase in these same areas (review in Ploghaus et al., 2003). Whatever the interpretation, mood alteration, stress and anxiety appear as the subjective states most closely associated to rCBF changes in perigenual ACC, and support the conceptual view that makes of these areas a part of a “ventral affective system” involved in identification of the emotional significance of a stimulus, production of affective states, and automatic regulation of emotional responses, and comprising also the amygdala, anterior insula and ventral striatum (Phillips et al., 2003).

While acute experimental pain is generally associated with activation of the midcingulate cortex (BA 24) (Peyron et al., 2000; Derbyshire, 2000), the perigenual cingulate has generally failed to show any consistent increase to experimental pain in healthy subjects, and has on the contrary shown an inverse relation with clinical pain. Thus, Hsieh et al. (1995) reported a decrease of subgenual cingulate blood flow in chronic neuropathic pain patients at rest, and an absent or ‘blunted’ response in this region has been observed during dynamic allodynia (Hsieh et al., 1995; Peyron et al., 1998; Schweinhardt et al., 2006; Ducrex et al., 2006). It has been proposed that the lessened reaction of these regions to alldynic stimuli might represent one adaptive mechanism characteristic of patients with chronic pain (Peyron et al., 2000). An alternative (or complementary) view comes from data showing rCBF decrease in perigenual ACC and medial prefrontal cortices during or after

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Fig. 4. Midsagittal views of PET scans obtained sequentially, 5 to 35 min following MCS onset (left sequence, “ON”), and then 15 to 75 min following MCS discontinuation (right sequence, “OFF”). Note the late increase in rCBF in the pACC is maximal at 30–45 min following MCS arrest, and the protracted activation of the posterior mesencephalon, consistent with PAG 60 min after MCS arrest. The red arrows point to the perigenual cingulate cortex (pACC) and the periaqueductal grey matter (PAG), the two key-areas that were increasingly activated after stimulation was OFF.
anticipation of pain (Hsieh et al., 1999; Simpson et al., 2001; Porro et al., 2002; Creac’h et al., 2006). The question arises as to whether anticipation of an intensely distressful and well-learned sensation, rather than the sensation itself, might also contribute to the blunted rostral ACC response in allodynia.

More recently, it has been shown that a number of procedures that relieve pain tend to correct these abnormalities, and thus increase rCBF within the perigenual ACC and orbitofrontal cortices. This has been observed both in response to pharmacological interventions (Hsieh et al., 1995), neurostimulation procedures of various types (Peyron et al., 1995; Duncan et al., 1998; Davis et al., 2000; Willoch et al., 2003) and other non-pharmacological interventions entailing analgesia, such as conscious distraction from the nociceptive stimulus (Frankenstein et al., 2001; Valet et al., 2004).

**Coupling of ACC and PAG in analgesia from motor cortex stimulation?**

Areas on the perigenual ACC and orbitofrontal cortex receive direct and indirect information from both the external and the internal milieu, via interconnections including (but not restricted to) the amygdala, hypothalamus, anterior insula, striatum and PAG (Carmichael and Price, 1995; Phillips et al., 2003). Such anatomical relationships suggest a role in the integration of information gathered from the internal and external environment, as well as an “effector” role in generating affective states. MCS, by imposing a different metabolic activity in these areas, may bias the production of affective states and change the end-line interpretation of neuropathic pain signals. While the precise mechanisms underlying such effects are unknown, the notion that MCS may activate simultaneously a ventral affective network in supported by the results of functional connectivity obtained in patients, in whom protracted activity in perigenual areas was significantly correlated with that of the striatum, the orbitofrontal cortex and the PAG (Peyron et al., 2007). Interestingly, such connections and coupling of activities can be generalized to several analgesic procedures including (exogenous) opioid effect, placebo (Petrovic et al., 2002), attentional manipulation (Valet et al., 2004), and hypnosis (Faymonville et al., 2003).

The strong connections between the perigenual ACC and the PAG, as well as the activity coupling of the two structures following MCS, seem to confirm the early suggestion that descending inhibitory controls may play a role in the pain relieving effects of MCS. The PAG, the nucleus raphe magnus and adjacent structures of the rostral ventromedial medulla constitute the efferent channel of a pain-control system that descends onto the spinal cord. In addition to the effects on spinal nociceptive reflexes, recent evidence indicates that endogenous motor cortex activation inhibits neurons to the dorsal horn in primates (Seki et al., 2003), and that such inhibition may become specific for pain inputs in case of electrical MCS (Senapati et al., 2005).
Can MCS trigger secretion of endogenous opioids?

Both pACC and PAG activations were positively related to clinical pain relief (Garcia-Larrea et al., 1999; Peyron et al., 2007), thus making these regions a pivotal area for the passage from neurophysiological to clinical effects. Since the effects upon ACC and PAG are protracted relative to actual MCS, they are not likely to represent simple on/off consequences of stimulation periods, and might rather reflect a long-term modulation of endogenous neurotransmitters. Three distinctive features of these areas are noteworthy: (a) they correspond to regions with high density of opioid receptors (Kuhar et al., 1973; Jones et al., 1991); (b) they are included in the cortical–subcortical network activated during opioid analgesia in humans (Adler et al., 1997; Firestone et al., 1996; Casey et al., 2000; Petrovic et al., 2002), and (c) they have been shown to undergo changes in opioid receptor density in patients with central neuropathic pain (Willoch et al., 2004; Jones et al., 2004; Maarrawi et al., 2007). The question whether long-lasting MCS effects are associated to tonic changes in opioid metabolism was recently addressed by comparing, using PET, the binding of the exogenous opioid ligand 11C-diprenorphine before and after chronic MCS administration. The level of 11C-diprenorphine binding to opioid receptors remained stable between and after chronic MCS administration. The level of 11C-diprenorphine binding to opioid receptors remained stable between and after chronic MCS administration. The level of 11C-diprenorphine binding to opioid receptors remained stable between and after chronic MCS administration. The level of 11C-diprenorphine binding to opioid receptors remained stable between and after chronic MCS administration. The level of 11C-diprenorphine binding to opioid receptors remained stable between and after chronic MCS administration. The level of 11C-diprenorphine binding to opioid receptors remained stable between and after chronic MCS administration. The level of 11C-diprenorphine binding to opioid receptors remained stable between and after chronic MCS administration. The level of 11C-diprenorphine binding to opioid receptors remained stable between and after chronic MCS administration. The level of 11C-diprenorphine binding to opioid receptors remained stable between and after chronic MCS administration. The level of 11C-diprenorphine binding to opioid receptors remained stable between and after chronic MCS administration. The level of 11C-diprenorphine binding to opioid receptors remained stable between and after chronic MCS administration. The level of 11C-diprenorphine binding to opioid receptors remained stable between and after chronic MCS administration. The level of 11C-diprenorphine binding to opioid receptors remained stable between and after chronic MCS administration. The level of 11C-diprenorphine binding to opioid receptors remained stable between and after chronic MCS administration. The level of 11C-diprenorphine binding to opioid receptors remained stable between and after chronic MCS administration. The level of 11C-diprenorphine binding to opioid receptors remained stable between and after chronic MCS administration.

Although binding decrease in a number of structures was correlated with clinical pain relief, these studies remain preliminary. Whether the long-lasting clinical effect of MCS are mediated by endogenous opioids or through other neurotransmitter remains an open question, whose resolution will need many future studies.

Acknowledgments

This work was supported by the Projet Hospitalier de Recherche Clinique (PHRC, 1996–1999), the Mécénat CNP (CNP Foundation against pain), the Fondation Benoît, and the Fondation pour la Recherche Médicale (FRM).

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