Motor Cortex Stimulation: Neural Circuits and Practical Approach on Electrode Implantation Technique

Erich Talamoni Fonoff, Kleber Carlos de Azevedo Junior, and Eduardo Joaquim Lopes Alho

The electric stimulation of the human motor cortex to treat pharmacoresistant neuropathic pain has been reported in the early 1990s by Tsubokawa et al. [1, 2], and since then, the encouraging results [3–6] have led to an increasing use of motor cortex stimulation (MCS) as treatment option to drug-resistant neuropathic pain in the past three decades. Although the efficacy of MCS has been questioned because of variable results, hundreds of patients around the world have benefited by this technique in the treatment of refractory pain. It is important to highlight that most of patients referred to MCS are treatment-resistant to most techniques available in therapeutic resource presently. Patients suffering from various pain syndromes, such as trigeminal neuralgia, trigeminal neuropathy [7, 8], phantom limb pain [9], post-stroke pain [2], and complex regional pain syndrome [5, 10], among other deafferentation syndromes, have experienced alleviation of pain over the past decades. The technique consists in implanting an epidural electrode over the contralateral motor cortex connected to a battery-powered implantable pulse generator to drive transdural electrical pulses onto the neural circuits located in the primary motor cortex. As observed in most therapies in functional neurosurgery, the technical variations are always present and frequently are matter of debate. In this article the authors highlight their practical experience in the technique of MCS electrode implantation, using widely available surgical tools to solve methodological hitches while applying this ingenious treatment in refractory pain syndromes. They also give an overview and illustrations on pathways that possibly mediate the effects of MCS in alleviating pain.

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Overview on Neural Circuits

Although the precise mechanisms and circuits involved in pain relief by MCS remain unclear, some studies in humans [11] and in animal models [12–15] indicate the role of ventrolateral and medial thalamic nuclei, anterior cingulate and orbitofrontal cortices, periaqueductal gray matter (upper brainstem structures), and insula as major structures involved in chronic neuropathic pain modulation and also in the emotional aspects of pain [12, 16–18].

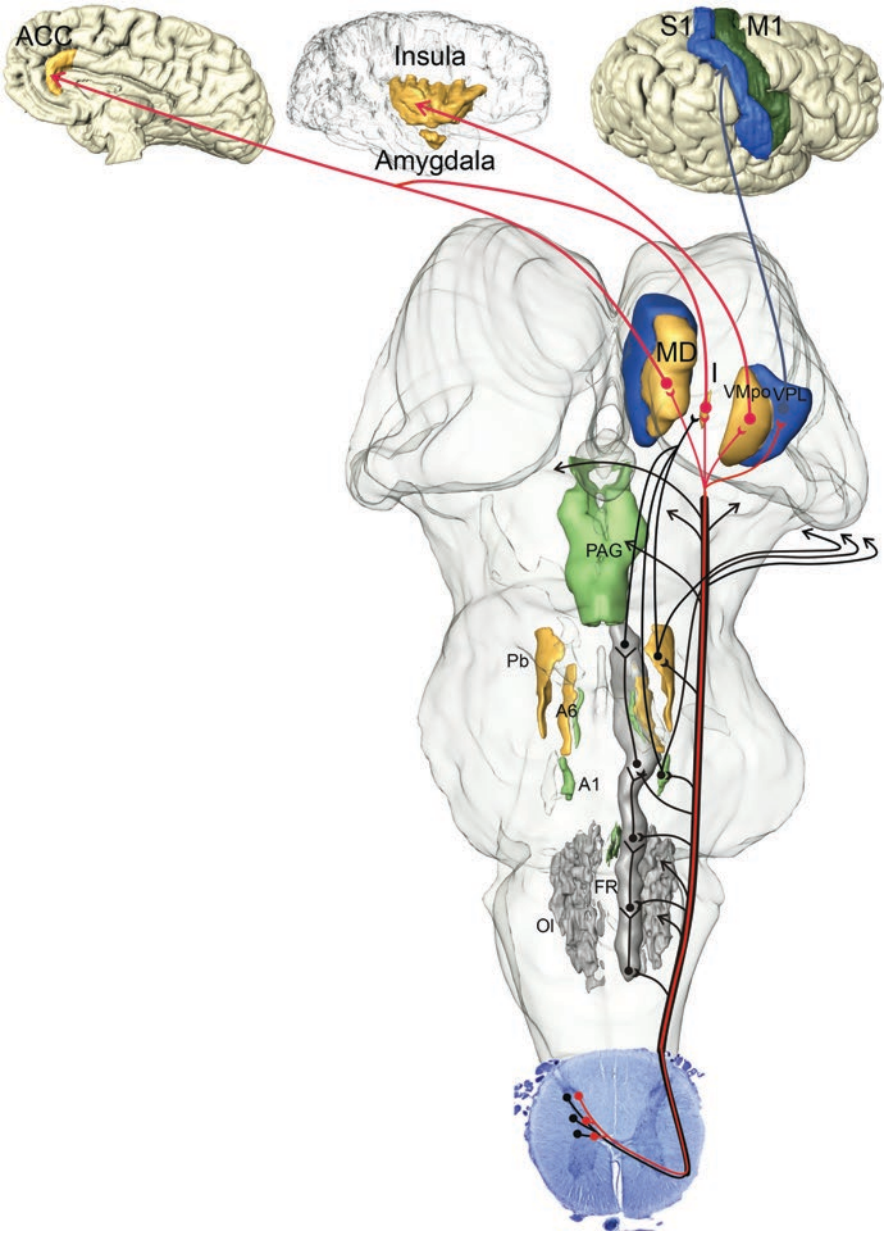
In this section, the objective is to give an overview of the anatomic structures classically involved in pain circuits and its possible relationships with motor cortex, based on the models found in the current literature.

Therefore, histological sections processed as described and analyzed to develop tridimensional reconstructions of the anatomical structures involved in pain in order to give the reader a true 3D impression of size, topography, and interrelation of nuclei and cortical regions engaged in neurophysiological processing of painful stimuli [19–21].

The neural circuits that are responsible for conduction, modulation, and interpretation of painful stimuli can be divided into afferent or ascending systems, efferent or descending systems, and pathways that connect different supraspinal centers.

Afferent Systems (See Fig. 1)

Fig. 1 *Afferent or Ascending Systems for Pain, Itch and Temperature.* The three ascending systems are shown here. The red system represents the spinothalamic tract (STT) since its origin in spinal cord gray matter (laminae I and IV to VIII), passing through its thalamic connections (MD, intralaminar nuclei, VMpo, and VPL), and finally the cortical projections (anterior cingulate cortex and anterior insula). The nuclei and cortex known to play a role in painful stimuli perception are shown in orange. The system shown in black lines is the anterolateral fascicle and its projections to principal and accessory olives, PAG, tectal structures, medial geniculate body, hypothalamus, and amygdala directly and indirectly by synapses with the A1 noradrenergic cell group and parabrachial nucleus. The synapses of the anterolateral fasciculus with the multisynaptic medial pain system in the reticular formation, parabrachial nucleus, and A1 and their projections to the thalamic intralaminar nuclei are also represented by black lines. The blue arrow represents the projection from VPL to S1. The structures represented in blue are known to have a discriminative perception of the painful stimuli, and the structures represented in green have a modulatory role in them. Full circles represent neuronal perikarya, the inverse arrowheads represent synapses, and the arrowheads represent final connections (*further details inside the text*). *In orange*: medial and lateral parabrachial nuclei (Pb); ventrocaudal medial dorsal nucleus (MD); ventromedial posterior nucleus (VMpo); intralaminar thalamic nuclei (I) insula; amygdala (Amy); and anterior cingulate cortex (ACC). *In green:* nucleus raphe magnus (RM); A1 noradrenergic cell group (A1); coeruleus and subcoeruleus complex (A6); periaqueductal gray matter (PAG); primary motor cortex (M1). *In blue*: anterior mediodorsal nucleus (MD); ventral posterior complex, with ventral posterolateral nucleus (VPL); and ventral posteromedial nucleus (VPM). *In gray:* olivary complex (O) and brainstem reticular formation (FR)


ACC
Insula
Amygdala
S1
M1
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I
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VPL
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A6
A1
FR
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So far three ascending systems have been recognized, comprising:

1. The spinothalamic tract (STT) in the anterolateral fascicle.
2. Other ascending fibers from neurons located in superficial and deeper laminae of the dorsal horn of the spinal cord that also course in the anterolateral fascicle (ALF). They are difficult to disentangle from the ascending STT.
3. A multisynaptic medial pain system [22].

The spinothalamic tract is the best characterized of them. The name indicates its topography in the spinal cord. Most of the STT axons begin in lamina I, and three morphological and functional groups of neurons can be there distinguished: fusiform, pyramidal, and multipolar cells. These cells can be activated by pinch or noxious heat. The pyramidal cells are thermoceptive and are activated by innocuous cooling; multipolar neurons are a mixture of polymodal (heat, pinch, and cold sensitive) and nociceptive-specific neurons [23–25]. An additional population of lamina I spinothalamic cells, sensitive to histamine and involved in the perception of itch, was also identified [23]. The polymodal neurons of lamina I do not project to the thalamus but are involved in spinal motor or sympathetic reflex pathways [26]. The specific nociceptive fusiform and thermoceptive pyramidal cells of lamina I contribute to the spinothalamic tract. After crossing, the fibers course in the ventral white funiculus of the spinal cord. Caudal segmental fibers are shifted laterally by succeeding increments of more rostral fibers in a kind of topical lamination. During its ascending course through the brainstem, the spinothalamic tract is less well demarcated than the medial lemniscus. In general it can be found lateral to the latter and hence more superficial with respect to the surface of the spinal cord. They end in the thalamic VMPo (ventromedial posterior nucleus) and the ventrocaudal medial dorsal nucleus (MD). Other components of the STT derive from layer IV to layer VIII neurons and end in the thalamic VPL (ventral posterolateral nucleus) and in intralaminar thalamic nuclei (I).

The anterolateral fascicle (fascicle of Gowers) comprises ascending fibers arising from different laminae of the spinal gray matter and heading to the hypothalamus, the central nucleus of the amygdala, and to the intralaminar thalamic nuclei. They collateralize or end in brain stem centers including the medullary and pontine reticular formation, the olives, A1 noradrenergic cell group, parabrachial nuclei, coerulean/subcoerulean complex, mesencephalic periaqueductal gray, dorsally located tectal structures, and the diencephalic medial geniculate body. Direct hypothalamic endings parallel to efferents from A1 likewise end in the hypothalamus. Spinothalamic fibers from lamina I spinal cord neurons mainly terminate in a somatotopical fashion in the thalamic VMPo and in the ventrocaudal medial dorsal nucleus. Fiber endings subserving pain, itch, and temperature remain segregated within the VMPo. Fibers originating from deeper dorsal horn laminae end diffusely in the centrolateral intralaminar nucleus, in the adjoining lateral paralaminar region of the mediodorsal nucleus, and more sparsely in other intralaminar and midline nuclei of the thalamus [27].

The medial multisynaptic pain system is an ascending pathway parallel to STT. The neurons from spinal gray matter laminae VII and VIII via ALF send

collaterals to the brainstem reticular formation and periaqueductal gray (PAG). In the reticular formation, the signal is transmitted in a multisynaptic way. Both supraspinal centers are connected to thalamic intralaminar nuclei. This kind of transmission could represent the morphological basis of the behavioral, emotional-affective, autonomic, and endocrine aspects of pain sensation.

The thalamocortical projections and hence the cortical role in pain perception are still a matter of debate. VMpo projections are directed to the posterior insular cortex. Neurons in the ventrocaudal medial dorsal nucleus together with neurons from the intralaminar nucleus target the cortex of the anterior cingulate gyrus (ACC).

Other spinothalamic fibers end in VPM (ventral posteromedial nucleus) and VPL. Efferents from these nuclei project to S1 (primary somatosensory cortex or Brodmann areas 1, 3, and 2).

Cingulate and insular cortical regions are considered to play a role in emotional and affective assessment of pain, whereas S1 should play a role in its sensory-discriminative aspects [11].

Efferent Systems (See Fig. 2)

The primary motor cortex (Brodmann area 4 or M1) is the target of transcranial magnetic stimulation and direct electrical stimulation by epidural electrodes to treat neuropathic pain [28]. Descending axons from the primary motor cortex are long known to inhibit the activity of layer I dorsal horn neurons [29]. This is at odds with MCS-induced pain relief, which occurs after prolonged time intervals.

Several supraspinal structures are involved in the control of neuronal transmission of painful stimuli. Most of the superordinate cortical and subcortical structures converge directly or collaterally onto the mesencephalic periaqueductal grey (PAG). The periaqueductal grey is connected to aminergic brainstem nuclei including the serotoninergic raphe magnus, A1 noradrenergic cell group, and the noradrenergic coeruleus/subcoeruleus complex. These aminergic nuclei emit descending axons to the posterior horn of the spinal cord and are likely to modulate pain transmission in long-term periods. Stimulation of the mesencephalic periaqueductal gray matter activates encephalin-releasing neurons [30] that project to the nucleus raphe magnus and adjacent raphe nuclei in the brainstem [31]. The nucleus raphe magnus (RM) is located directly rostral to the raphe obscurus and receives afferent axons from the spinal cord and cerebellum connected to the motor system. The RM receives descending afferents not only from the periaqueductal gray matter but also from the paraventricular hypothalamic nucleus, central nucleus of the amygdala, lateral hypothalamic area, parvocellular reticular nucleus, and the prelimbic, infralimbic, medial, and lateral precentral cortices in rats [32].

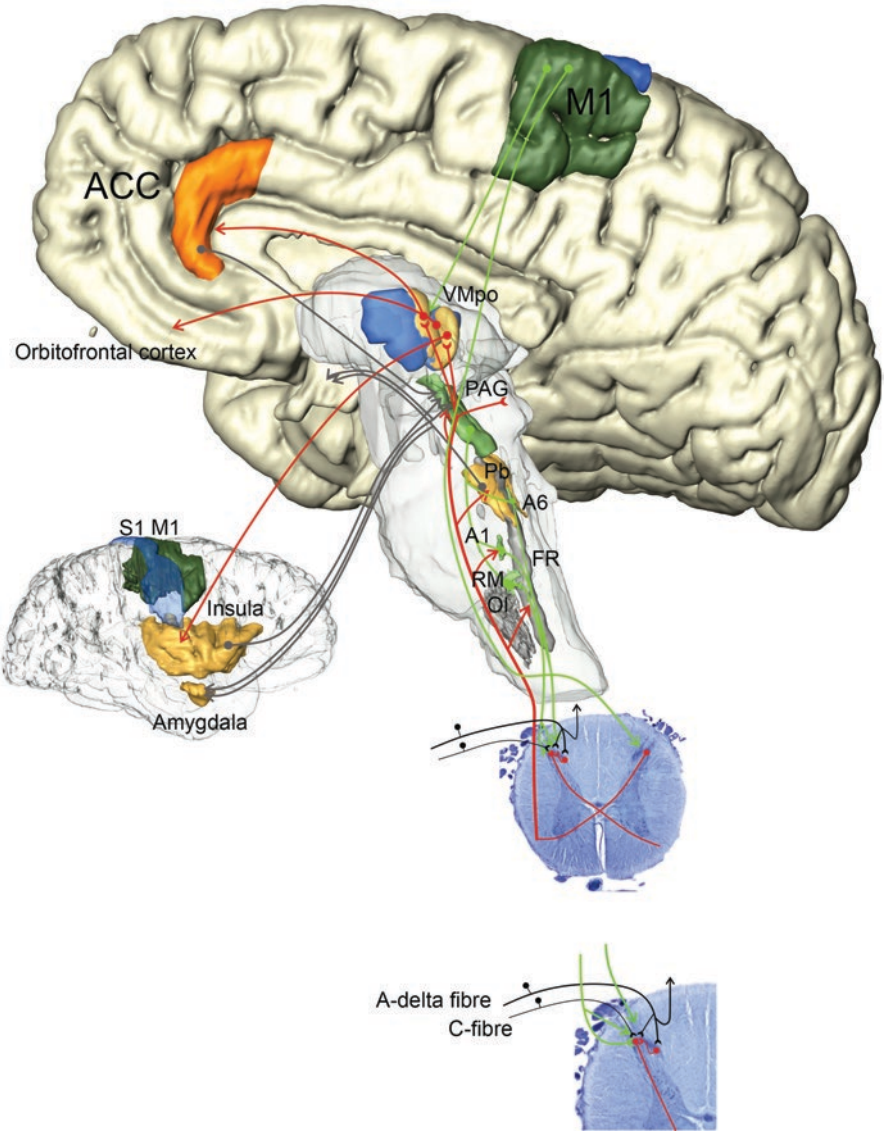
In response to raphe nuclei stimuli, serotonin is released to the dorsal horn of the spinal cord where it forms excitatory connections with the inhibitory interneurons located in lamina II (substantia gelatinosa). When activated, these interneurons release either encephalin or dynorphin, which bind to μ-opioid on the axons of incoming C and

A-δ fibers carrying pain signals from nociceptors activated in the periphery [33]. The activation of the μ-opioid receptor inhibits the release of substance P from these incoming first-order neurons and, in turn, inhibits the activation of the second-order neuron that is responsible for transmitting the pain signal via the spinothalamic tract to the thalamus and brainstem structures. The nociceptive signal is blocked before it is able to reach the cortical areas that interpret the signal as pain (such as the anterior cingulate and posterior insula). This is sometimes referred to as the gate control of pain, as first described by Melzack and Wall [34] and is supported by the fact that electrical stimulation of the PAG results in profound analgesia [35]. Four known kinds of opioid receptors have been identified: μ (mu), κ (kappa), σ (sigma), and δ (delta). Synthetic opioid and opioid-derivative drugs activate these receptors (possibly by acting on the PAG directly, where these receptors are densely expressed) to produce analgesia [36]. The neurons from noradrenergic A1 group and the noradrenergic coeruleus/subcoeruleus complex emit also descending axons to the posterior horn of the spinal cord and modulate pain transmission at this level.

Pathways Connecting Different Supraspinal Centers (See Fig. 2)

Thalamic connection patterns with motor, premotor, and supplementary motor areas of primate cortex indicate that VLa (ventral lateral nucleus, anterior subdivision) and VLp (ventral lateral nucleus, posterior subdivision) are the principal motor

Fig. 2 *Efferent or Descending Systems.* The red system is still the STT ascending system described in Fig. 1, in order to show its relationship with the descending systems and with the pathways connecting different supraspinal centers. The descending systems are shown in green, heading from M1 directly to the posterior horn of the spinal cord or terminating in the thalamic nuclei. The descending pathways from PAG to raphe magnus and from A1 noradrenergic cell group, subcoerulean region, and raphe magnus to the posterior horn are also shown in green. The arrows in gray represent the pathways connecting the anterior insula and amygdala to PAG, parabrachial nucleus and PAG to the hypothalamus, and anterior cingulate cortex to PAG. In the spinal cord section detail, these are represented: the peripherally incoming axons from C (thinner axon in black) and A-δ (thicker axons in black) fibers, the inhibitory interneuron in lamina II (small neuron in red), and the modulatory descending system from M1, PAG via raphe magnus and noradrenergic A1 and subcoeruleus (in green). Full circles represent neuronal perikarya, the inverse arrowheads represent synapses, and the arrowheads represent final connections (*further details inside the text*). *In orange*: medial and lateral parabrachial nuclei (Pb); ventrocaudal medial dorsal nucleus (MD); ventromedial posterior nucleus (VMpo); intralaminar thalamic nuclei (I); insula; amygdala (Amy); and anterior cingulate cortex (ACC). *In green:* nucleus raphe magnus (RM); A1 noradrenergic cell group (A1); coeruleus and subcoeruleus complex (A6); periaqueductal grey matter (PAG); primary motor cortex (M1). *In blue*: anterior mediodorsal nucleus (MD); ventral posterior complex, with ventral posterolateral nucleus (VPL); and ventral posteromedial nucleus (VPM). *In gray:* olivary complex (O) and brainstem reticular formation (FR)


M1
ACC
VMpo
Orbitofrontal cortex
PAG
Pb
A6
A1
FR
RM
OI
S1 M1
Insula
Amygdala
A-delta fibre
C-fibre

nuclei, with VLp contributing dense inputs to M1 but also to PMV (ventral premotor cortex), PMD (dorsal premotor cortex), and SMA (supplementary motor area). VLa projects moderately to M1 and SMA while projecting densely to PMD. Furthermore, neurons from the primary motor cortex are reciprocally linked to the thalamic VPLo (ventroposterior lateral nucleus, pars oralis) and small contingent fibers to the caudal part of MD (medial dorsal nucleus) and the adjacent intralaminar nuclei [27]. These thalamic nuclei are also connected to the orbitofrontal cortex, to the insula, and to the cortex of the anterior cingulate gyrus. In addition, by feed-forward cortical connections, the motor cortex has access via premotor, supplementary motor, and cingulate motor fields to orbitofrontal and anterior cingulate regions.

These neuronal loops and intersections between M1, PM (premotor cortex), and SMA with the thalamic relays involved in pain circuits are probably engaged in pain relief by motor cortex stimulation. The connection between motor areas with the orbitofrontal and anterior cingulate cortices seems to play a defining role too, since they are linked to the mesencephalic periaqueductal gray. Other loops that may be important are the connections from anterior insula and amygdala to PAG, parabrachial nucleus and PAG to the hypothalamus, parabrachial nucleus to amygdala, and anterior cingulate cortex to PAG.

Techniques for Implantation of MCS Electrodes

Although the best approach to determine the site for implanting MCS electrodes is still a matter of debate, if the intention is to stimulate the primary motor cortex by applying transdural electrical pulses, whatever method applied has got to the make sure this occurs efficiently in all patients. The effective delivery of electrical pulses in a particular site or region of the nervous system is a common key starting point neuromodulation and should always be the core objective when choosing electrode type and method of implant. Currently, most of the authors perform the implantation procedure under general anesthesia, using different methods for the localization of motor cortex. Reports include either localization of precentral gyrus based merely on anatomic landmarks or added to intraoperative sensory evoked potentials (SEP) for functional localization. Intraoperative SEP is oriented for the localization of central sulcus, by inverted SEP wave, what indirectly leads to the precentral gyrus located immediately anteriorly. The combination of those techniques provides the functional localization of the mid-precentral gyrus, which normally corresponds to the primary motor cortex itself. However the use of SEP is limited to patients who present sensory pathways which are at least partially preserved ensuring that SEPs can be elicited by applying electrical current in median nerve and capturing evoked potentials over the central sulcus. On the other hand, there are deafferentation pain syndromes (e.g., brachial plexus avulsion or amputation) in which the peripheral sensory pathways are severely or totally injured, precluding the intraoperative use of SEP as a target refining method.

In our experience, a different and much simpler technique has been used with much success. It provides detailed functional and spatial information for target refining during implantation of electrodes capable to stimulate the motor cortex stimulation efficiently. It is totally capable of eliciting evoked motor potentials at higher current intensity and even to evoke complex segmental limb movement depending on the stimulation frequency. Although therapeutic stimulation applied in the motor cortex is always under the motor threshold, the best electrode location is the one closest to the site that makes MEPs (motor evoked potentials) occur at lowest threshold. While most of the procedures are performed under sedation, the core technique for mapping the motor cortex should be performed with patients awake and responsive. This method does not require that patients to be awake during the whole procedure but only a few minutes during the cortical mapping procedure. Having the anatomical location of the mid-precentral gyrus, more specifically the "hand knob" as a starting point situated by either image-guided navigation system to point the center of a nummular craniotomy leaving the dura completely intact. Although MEPs can be routinely elicited in patients under light sedation, the same procedure performed in an awake patient allows lower MEP thresholds and provides the possibility of mapping the motor cortex in amputees or in severely injured brachial plexus patients, as described further on this chapter.

As above cited this technique relies on stereotactic localization of the hand knob in the posterior aspects of the precentral gyrus pinpointed in MRI to guided navigation followed by intraoperative target refining by transdural stimulation of the cerebral cortex in awake patients. Standard frameless navigation system fed by volumetric MR images in dedicated software guides the localization of the precentral gyrus in each individual patient. During targeting in navigation system, the surgeon should aim at the center of the omega-shaped knob on the posterior border of the pre-central gyrus within the central sulcus, which lines up perpendicularly with the posterior ending of the superior frontal sulcus used as anatomical landmark used to guide the center of the craniotomy. This is usually the initial point in the surface of dura for the following procedure mapping the cerebral cortex. As suggested by Yousry et al. [37], the image generated by this knob in the horizontal MR images is highly specific to indicate the primary motor area of hand in normal subjects. However, this point is usually 1.5–2 cm deep into the central sulcus and 3.5 cm from midline, consequently not visible at the cortical surface. So this targeting method provides a point deep seated in the central sulcus, not the final target itself, which is immediately above at a point on the surface of cerebral cortex. However, the technique of MCS does not require dural opening, so during the procedure only anatomical landmarks guided by imaging guided navigation are the only way to ensure the target starting point in epidural space, and the final site and orientation for electrode implantation is then specified by the intraoperative cortical mapping.

So the coordinates of the hand knob are then perpendicularly projected onto the surface of the scalp to guide the skin incision, further projected onto the surface of the skull to point the center of the craniotomy, and finally the same projection was made onto the dural surface in order to provide the initial point for cortical mapping by transdural electrical stimulation. A small craniotomy (3 cm) encompassing the

region of the anatomical target can be performed under local anesthesia and light sedation. After the craniotomy is performed, sedation can be completely withdrawn so the patient is found completely awake and responsive. Transdural bipolar stimulation of the cortex can be conducted at current amplitudes up to 4–6 mA, 1 ms, and 30–60 Hz using a bipolar stimulator. Our largest experience is using bipolar probes with tips 7–10 mm apart, although a monopolar probe can also be used with a distant reference plate. Usually protocols that include MEP peripheral myograms evoked by focalized cortical simulation do not require patients to be awake, as described elsewhere [38] and mentioned above. However, patients who suffer from severe deafferentation or amputees do not benefit from this technique because MEPs record from muscles cannot be performed either due to severe sensorimotor or, in case of proximal amputation, absence of the limb itself. So the technique described earlier in this text was designed for patients with severe injuries in the affected limb. In our experience stimulation of the motor cortex does evoke movements as early descriptions of Wilder Penfield and many other authors; however in severely injured patients, movements cannot be recorded. In the last few years, our team operated close to 50 patients for implanting MDS electrode. Some of them had severe brachial plexus injury and some were amputees. So in those patients we had a different protocol. The most effective method to map the cortex was to have the patients describe in details the sensation after each stimulation pulse. Patients describe very well sensations of pressure or paresthesias with consequent interpretations of stimulation the sensory cortex, while descriptions of sensation of movements in the inexistent or flail limb with no actual muscle activity are clearly described by patients. The consequent interpretation in this case is that stimulations have been applied over the primary motor cortex. So during the stimulation session, the patient was required to describe any sensation different from the resting state, after each short period of stimulation (1–2 s). Stimulation can be then repeated in targets that generate any sensation of interest over a longer period (2–5 s). The repeated stimulation allowed patients to improve the description of the sensation in a more detailed manner, including the part of the limb involved and the type of movement. To help the description of movements and the joints involved, as well as the speed and repetition of the entire movement, the patient used the contralateral limb to mimic the sensation of movement on the affected side. In patients with severe brachial plexus injuries or amputees, electrical stimulation at 4.0–6.0 mA, 30–60 Hz, and 1 ms of pulse width evokes a vivid sensation of movement in the nonexistent hand, forearm, and arm. The sensation of wrist flexion is usually elicited in all patients, while two-thirds of patients can make clear distinction of thumb and index movements and differentiate from the wrist flexion and from the other fingers' movements. Phantom movements of the remaining fingers (third to fifth) are usually describes in one-third of patients. The cortical area responsive to thumb tends to occupy a lateral position related to the areas of the other fingers, following the maps of normal homunculus. The evoked sensation is restricted to the period of stimulation, and it stopped as soon as that was discontinued. However some of the patients refer intense emotions because the sensation of movements can be quite vivid and the feeling of the sensation of inexistent of severely injured limb is compared as if it became healthy and

active again. All patients are warned that sensations like those may be evoked and that it does not mean that the limb can be recovered unfortunately.

Once mapping was finished, an epidural paddle electrode can be implanted following the map generated over the area of the greatest evoked motor sensation. The center contacts of the paddle electrode are then placed over the area, which elicited sensation of movement, related to the area affected by the pain syndrome. The contacts in the two extremities of the electrode covered adjacent areas of the motor cortex also elicited by stimulation, the forearm, arm, face, and so on. Eventually, two stripes of electrodes are implanted in order to expand the spatial combinations and topographically refine the therapeutic stimulation. Currently, new types of electrodes with multiple are available, so the possible combinations are numerous.

Based in our experience, this technique was useful for target refining during of implantation of electrode for motor cortex stimulation. However, comparative studies are required to investigate whether target refining by intraoperative mapping significantly improves the results of therapeutic MCS for refractory pain.

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