Cerebral cortex modulation of pain

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Pain is a complex experience encompassing sensory-discriminative, affective-motivational and cognitive-emotional components mediated by different mechanisms. Contrary to the traditional view that the cerebral cortex is not involved in pain perception, an extensive cortical network associated with pain processing has been revealed using multiple methods over the past decades. This network consistently includes, at least, the anterior cingulate cortex, the agranular insular cortex, the primary (SΙ) and secondary somatosensory (SΠ) cortices, the ventrolateral orbital cortex and the motor cortex. These cortical structures constitute the medial and lateral pain systems, the nucleus submedius-ventrolateral orbital cortex-periaqueductal gray system and motor cortex system, respectively. Multiple neurotransmitters, including opioid, glutamate, GABA and dopamine, are involved in the modulation of pain by these cortical structures. In addition, glial cells may also be involved in cortical modulation of pain and serve as one target for pain management research. This review discusses recent studies of pain modulation by these cerebral cortical structures in animals and human.

Keywords: anterior cingulate cortex; agranular insular cortex; ventrolateral orbital cortex; periaqueductal gray; primary and secondary somatosensory cortices; motor cortex; nociception.

Introduction

Pain – which usually refers to nociceptive pain elicited by the activation of specific nociceptors or neuropathic pain resulting from injury to sensory fibers or from damage to the CNS itself – is a complex experience. It is a multidimensional phenomenon that encompasses sensory-discriminative, affective-motivational and cognitive-emotional components mediated by different mechanisms and processed in a neural network[1–3]. Recent years have seen a progressive unraveling of the neuroanatomical circuits and cellular mechanisms underlying the induction of pain. Contrary to the traditional view that the cerebral cortex is not involved in pain perception, an extensive cortical network associated with pain processing has been revealed in recent decades and is increasingly recognized as playing a major role in the representation and modulation of pain[4, 5]. Despite the recognition of cerebral structures engaged in pain transmission, however, the cerebral mechanisms involved in pain modulation are still not well understood. The cortex probably influences pain via several mechanisms. It has been proposed that the cortex may reduce pain by interrupting the transmission of noxious information from the spinal cord level by activating descending pain modulatory systems located in the brainstem[6]. Recent studies have shown that the anterior cingulate cortex (ACC), the insular cortex, the primary (SI) and secondary (SII) somatosensory cortices, the ventrolateral orbital cortex (VLO) and the motor cortex are involved in pain modulation[3–5, 7–11]. These cortical structures constitute, respectively, the medial and lateral pain systems, the nucleus submedius (Sm)-VLO-periaqueductal gray (PAG) system and the motor cortex system[3–5, 7–11]. Multiple neurotransmitters, including opioid, glutamate, GABA and dopamine transmitters, are involved in the modulation of pain by these cortical structures[11–15]. This paper reviews recent studies on pain modulation by the aforementioned cerebral cortex structures in animals and human.

Medial pain system: the ACC and the insular cortices

Nociceptive processing within the human brain takes place within at least two distinct and parallel systems: the medial pain system, which projects through medial thal-
amic nuclei to the ACC, the insular cortex, and other brain regions; and the lateral pain system, which projects through lateral thalamic nuclei to the primary and secondary somatosensory cortices (SI and SII) and other brain regions. Current thought proposes that the medial system may be involved mainly in processing the affective-motivational aspects of pain, whereas the lateral system may be involved mainly in processing the sensory-discriminative aspects of pain[2,10].

**ACC**

**Involvement of ACC in nociceptive modulation** The ACC primarily receives extensive projections from the mediodorsal thalamic nucleus and broadly connects with relevant regions of the descending modulation system, including PAG[4, 19]. Recent functional imaging data provide evidence that the rostral ACC is a crucial cortical area for placebo analgesia and that this type of endogenous pain control depends on the enhanced functional connectivity of the rostral ACC with subcortical brain structures that are crucial for conditioned learning and descending inhibition of nociception[20]. These results suggest that the ACC is involved in the transmission of pain sensation but also plays a role in processing pain-related emotion. Furthermore, using regional cerebral blood flow (rCBF) as an index, increased rCBF response in the contralateral ACC was found in noxious cutaneous/intramuscular stimuli and chronic regional pain patients[21, 22].

With the use of magnetic resonance imaging and positron emission tomography (PET) in humans, it has been demonstrated that painful heat causes significant activation of the contralateral ACC[5, 10]. This activation was consistent with the encoding of perceived unpleasantness[10, 23]. Taken together, these data suggest that hemodynamic responses to pain in ACC simultaneously reflect the sensory, cognitive and affective dimensions of pain, and that ACC may both respond to pain and participate in pain control[2, 4, 10]. These findings also provide direct experimental evidence in humans linking frontal-lobe limbic activity with pain effects, as originally suggested by early clinical lesion studies[23].

Furthermore, both electrophysiological and behavior studies indicate that the ACC is involved in nociceptive modulation. Two distinct synaptic circuits in the ACC were found to be activated by noxious stimuli, and two groups of laminar-specific transmembrane sink currents in ACC can be evoked by noxious electrical stimulation: an early group in layers V-VI and a more intense late group in layer II/III and layer V, and lesions in the medial thalamic nucleus blocked these evoked responses in ACC[24]. These results suggest that the medial thalamic nucleus is the major thalamic relay that transmits nociceptive information to the ACC. Both visceral- and cutaneous-specific nociceptive neurons have also frequently been found in the ACC of rabbit, suggesting that the ACC is associated with both visceral and somatic pain[25]. Electrical stimulation of ACC can facilitate the paw withdrawal and tail-flick reflexes induced by noxious heating. This facilitation can be blocked by electrolytically induced lesions in the dorsal reticular nucleus or high-intensity electrical stimulation of the rostral ventral medulla, and it can be enhanced by low-intensity electrical stimulation of the rostral ventral medulla[26, 27]. In visceral pain models, electrical stimulation or microinjection of glutamate into the rostral ACC enhanced the visceromotor response to colorectal distension in normal rats while ACC lesions caused a decrease in the visceromotor response in viscerally hypersensitive rats but had no effect in normal rats[28]. Further study in monkey revealed that the ACC neurons are also involved in the anticipation that precedes the avoidance of aversive stimuli in one pain-avoidance task[29] and that ACC nociceptive neurons are involved in attention to pain and escape from pain but not in the sensory discriminative aspect of pain[30].

**Neurotransmitter and receptor mechanisms underlying ACC involvement in nociception modulation** The involvement of the ACC in nociception modulation may be associated with the activities of a variety of neurotransmitters, including glutamate, dopamine and opioid. The mRNA expression level of metabotropic glutamate receptor 3 (mGluR3) is significantly increased in cortical areas of monoarthritic rats, including the contralateral cingulo-frontal cortex[31]. Intracortical injection of glutaminergic receptor antagonist inhibited the sink currents in the ACC evoked by noxious electrical stimuli[24]. Consistent with this finding, chemical activation of the NMDA receptor or mGluR in the ACC decreased the latency of the paw-withdrawal and tail-flick responses to heat stimulation[26, 27]. These inhibitory effects were blocked by electrolytically induced lesions in the dorsal reticular nucleus or high-intensity electrical stimulation of the rostral ventral medulla and enhanced by low-intensity electrical stimulation of the rostral ventral medulla[26, 27]. In a visceral pain model, microinjection of glutamate into the ACC increased the visceromotor response to colorectal distension (10 mmHg) in viscerally hypersensitive rats, and higher concentrations of glutamate induced more potent visceromotor responses in
viscerally hypersensitive rats than in normal rats\cite{28}. Microdialysis of AMPA and NMDA receptor antagonists also inhibited the colorectal distension-induced ACC neuronal firing in normal and sensitized rats\cite{33}. These results indicate that activation of NMDA receptor or mGluR in the ACC may facilitate spinal nociception transmission and that the dorsal reticular nucleus and rostral ventral medulla play crucial roles in mediating ACC-induced facilitation of spinal nociception. The ACC NMDA receptor-based modulation of pain is also associated with other neurotransmitters. For example, dopamine injection into the ACC dose-dependently diminished autotomy behavior in a neuropathic pain model. NMDA receptor antagonist MK801 and dopamine releaser amantadine elicited significant reductions of the autotomy score. Pre-injections of D1 and D2 receptor antagonists blocked the antinociceptive effects of amantadine on long-term nociceptive behavior, suggesting an interaction between dopaminergic and glutamatergic systems within the ACC in the genesis and maintenance of long-term nociception\cite{12}. Intra-ACC injection of endogenous D-serine-degrading enzyme, d-amino acid oxidase, and an antagonist of the glycine site of NMDA receptors, 7-chlorokynurenate, greatly attenuated formalin-induced nociception\cite{34}. These data simultaneously implicate multiple neurotransmitters in the modulation of nociception by the ACC.

In addition to the neural components, glial effects were noticed in the ACC-mediated antinociception. It was found that chronic painful stimuli induced astrocyte activation in mouse ACC\cite{42} and that mice with chronic pain exhibit anxiety-like behavior and an increase of astrocytes in ACC due to the dysfunction of cortical delta-opioid receptor systems\cite{43}.

**Rostral agranular insular cortex (RAIC)**

**Involvement of the RAIC in nociception modulation** The RAIC receives sensory information from the thalamus via the submedius nucleus, the central lateral nuclei and the parvicellular part of the ventral posterior nucleus, and sends efferent fibers to the amygdala, particularly the basal complex, lateral hypothalamus, dorsal raphe, PAG, pericentral region, rostroventral medulla, parabrachial nuclei, and the nucleus accumbens. The RAIC also has extensive reciprocal cortico-cortical connections with the orbital, infralimbic, and ACC and with the contralateral RAIC. The connectivity of RAIC suggests that it is involved in multiple aspects of pain behavior, and increasing evidence shows that the RAIC is important for the modulation of nociception in humans and rats. It is suggested that projections to the RAIC from medial thalamic nuclei are associated with motivational/affective components of pain while RAIC projections to mesolimbic/mesocortical ventral forebrain circuits are likely to participate in the sensorimotor integration of nociceptive processing, and that its brainstem projections are most likely to contribute to descending pain-inhibitory control\cite{44}.

Clinical studies have also suggested that the insular cortex is involved in pain modulation. For example, rCBF has been correlated with subjective pain experience and noxious stimuli in the insular cortex\cite{21, 22}. Painful sensations mostly in the posterior part of the insular cortex of the right hemisphere and non-painful sensations in the posterior part of the insular cortex of both hemispheres have been elicited in patients\cite{45}.
In the insular cortex, responses to painful stimulation delivered by CO₂ laser were recorded by deep intracerebral electrodes in epileptic patients, and the insular cortex reliably encoded variations in CO₂ laser stimulus intensity at painful levels. The insular cortex has also been proposed to be involved in autonomic reactions to noxious stimuli and in pain-related learning and memory.

**Neurotransmitter and receptor mechanisms underlying RAIC involvement in nociception modulation**

Increasing evidence indicates that opioid, GABA and dopamine appear to be key neurotransmitters in nociception modulation by the RAIC. Morphologically, there are mu-opioid receptors in a discretely localized cluster of densely labeled dendrite-like processes and opioid binding sites in the RAIC. Morphine application in this region produced an antinociceptive response, reduced the number of Fos-like immunoreactive neurons in the spinal cord in formalin test and reduced the noxious thermal stimulus-evoked firing of nociceptive dorsal horn neurons. These effects were blocked by naloxone, confirming that morphine can act at opioid receptors.

Our studies have also shown that morphine injection into the insular cortex induced analgesia in some formalin-tested rats. Studies in healthy humans have further shown that the presence of sustained pain induced a regionally selective release of endogenous opioids that interacted with mu-opioid receptors in the insular cortex. A preliminary study in a group of patients with central neuropathic pain demonstrated that they have significantly fewer opioid receptor binding sites in insular cortices and the thalamus, as measured by [¹¹C]diprenorphine binding and PET. In central post-stroke pain patients, interhemispheric comparisons demonstrated a significant decrease in opioid binding in the insular, temporal and prefrontal cortices contralateral to the painful side. These data suggest that the RAIC contributes to opioid-receptor-mediated pain modulation and demonstrate a central role for the mu-opioid receptors and their endogenous ligands in the regulation of sensory and affective components of the pain experience.

It has been found that changes of GABA neurotransmission in the RAIC can raise or lower the pain threshold, producing analgesia or hyperalgesia, respectively, in freely moving rats. Local increases in GABA produced by using an enzyme inhibitor or gene transfer mediated by a viral vector generated lasting analgesia by enhancing the descending inhibition of spinal nociceptive neurons. However, selective activation of GABA-B receptor-bearing RAIC neurons produced hyperalgesia via projections to the amygdala, an area involved in pain and fear. Furthermore, application of dopamine reuptake inhibitor GBR-12935 in the RAIC produced antinociceptive effects. The effect of dopamine is mediated by different receptors; i.e., the activation of D(2) and the blockade of D(1) receptors elicit antinociception, since the dopamine D(1) receptor antagonist SCH-23390 and dopamine D(2) receptor agonist TNPA caused decreases in the autotomy score and a delay in the onset in the neuropathic pain model induced by denervation. The RAIC has a higher density of dopamine fibers that arise principally from the ipsilateral ventral tegmental area/substantia nigra and from a set of neurons different from those that project to the medial prefrontal cortex. Additionally, there are close appositions between dopamine fibers and GABAergic interneurons within the RAIC. These data suggest that part of the dopaminergic modulation of the RAIC may occur through GABAergic interneurons.

**Lateral pain system: SI and SII**

**Involvement of SI and SII in nociception modulation**

In addition to the medial pain system, nociceptive processing within the human brain takes place within the lateral pain systems that consist mainly of SI and SII. Current knowledge indicates that the lateral system may be involved mainly in processing the sensory-discriminative aspects of pain. With the use of magnetic resonance imaging and PET in humans, it has been demonstrated that painful heat caused significant activation of SI and SII. In both healthy human subjects with a whole-head magnetometer and epilepsy patients with sub-dural electrodes to directly record somatosensory evoked potentials from peri-Rolandic cortex, responses to painful CO₂ laser stimulation were recorded in the SI and/or SII, implying that the pain impulse is received in the crown of the postcentral gyrus in human. Significant increases in rCBF to both noxious cutaneous and intramuscular stimulation are also found in the contralateral SII. Noxious intramuscular stimulation evoked subsignificant responses in the contralateral SI and lenticular nucleus. Electrical stimulation of SII independently reduced the number of c-Fos-positive cells in the trigeminal dorsal horn and, in combination with 7-nitro-indazole, decreased the number of c-Fos-positive cells in the spinal dorsal horn in conscious rats. Electrical stimulation of SII also reduced formalin-induced nociceptive behaviors. These results suggest that SI and SII are involved in pain modulation.

However, there are discrepancies with respect to the roles of SI and SII in the modulation of nociception. For example, in SI and thalamus, but not in SII, activation has been recorded in response to painful stimulation, although the level of activation was significantly greater in the hemisphere.
contralateral to the stimulus\textsuperscript{58}, whereas selective activation of nociceptive nerve fibers Adelta and C by thulium-laser stimulation of skin evoked cortical responses in SII but not SI\textsuperscript{59}. Further studies show that abnormal pain evoked by innocuous stimuli (alldynia) is associated with amplification of the thalamic, insular and SII responses, but not SI responses\textsuperscript{60}, and that no painful sensation was evoked in the SI of 14 patients referred for epilepsy surgery\textsuperscript{61}. Electrical stimulation of SII also reduced the c-Fos-positive cells in the trigeminal dorsal horn induced by injection of formalin into the lower lip, but electrical stimulation of SI failed to have this effect\textsuperscript{56}. However, it was shown, using partial directed coherence analysis, that SI has an enhanced descending influence on ventroposterior thalamic nuclei during pain processing\textsuperscript{62} whereas the SII area is activated by thermal stimuli in functional imaging studies. The SII response can gradually encode the intensity of stimuli from the sensory threshold up to a level next to pain, with a ceiling effect for higher painful intensities\textsuperscript{47}. These results imply different roles of SI and SII in nociception modulation. It has been proposed that the SI cortex is involved mainly in discriminative aspects of pain, whereas the SII cortex seems to have an important role in recognition, learning, and memory of painful events\textsuperscript{4, 48}.

**Neurotransmitter and receptor mechanisms underlying SI and SII involvement in modulation of nociception**

Current knowledge indicates that mGluR and opioid receptor may be involved in the modulation of acute and inflammatory pain in SI and SII. Expression of mGluR3 mRNA was significantly increased in the SI and SII cortical areas of monoarthritic rats (average increases of 50\%–75\%)\textsuperscript{32}. Similar as, in the medial pain system, nociceptive areas of the lateral pain system have high binding potentials for opioid receptors\textsuperscript{35}. However, a preliminary study in a group of patients with post-stroke pain demonstrated that there are significantly fewer opioid receptor binding opportunities in the lateral pain system within the inferior parietal cortex (Brodman area 40)\textsuperscript{36}. These results suggest that glutamate and opioid may also be involved in the lateral pain system.

The anatomical connections between ACC, insular cortex, SI and SII suggest that these regions do not function independently in encoding different aspects of pain but are highly interactive (Figure 1). Such interactions are reflected in the experiences of pain itself. For example, pain intensity, location, and quality (sensory features) are major factors in determining unpleasantness. Nevertheless, despite these associations, there appears to be at least a partial segregation of function between pain affect and sensation. The detailed mechanisms of neurotransmitter activities in these cortical regions remain to be determined.

**Ventrolateral orbital cortex (VLO)**

Anatomic studies in rat and cat have indicated that the VLO receives ascending afferent fibers from Sm\textsuperscript{63–65}. In addition to the afferent inputs from Sm, the VLO also receives 5-HTergic ascending afferents from PAG and the dorsal raphe nucleus, and the latter two nuclei also send descending fibers to the caudal spinal trigeminal nucleus (Vc) or the principal sensory trigeminal nucleus\textsuperscript{66}. Furthermore, the VLO sends efferents to the PAG, Sm and the lateral hypothalamus\textsuperscript{63, 67–70}. These studies imply that the VLO is involved in pain modulation, since PAG is an important nociception modulation center that modulates noxious informative input at the trigeminal/spinal cord level via the descending inhibition system. Recently, a series of experiments further extend and confirm this hypothesis, i.e., that there is a nociception modulation circuit that includes the trigeminal/spinal cord, Sm, VLO and PAG to modulate the nociceptive information input at the trigeminal/spinal cord level.

**Involvement of VLO in nociception modulation**

Early work on experimental animals and patients suggested involvement of the orbito-frontal area in the modulation of nociceptive behavior. Surgical lesion of the orbital cortex in patients has been shown to provide relief from chronic pain\textsuperscript{71}, and its blockade by injection of local anesthetic in rats has been reported to decrease the thresholds of nociceptive reflexes\textsuperscript{72}. Using single extracellular recordings, different types of neurons responsive to visceral or somatic noxious stimuli were recorded in the VLO\textsuperscript{73–77}. Furthermore, the tail-flick reflex and the jaw-open reflex were markedly...
inhibited by unilateral electrical stimulation of the VLO in an intensity-dependent manner, and this inhibition developed and persisted throughout the stimulation and disappeared rapidly after its termination\textsuperscript{78, 79}. Chemical inhibition of the VLO by application of morphine, GABA or lidocaine attenuated the nociceptive behavior induced by dilute formalin injection into the hind paw\textsuperscript{50}, mirrored neuropathic pain (hypersensitivity induced by contralateral L5 and L6 spinal nerve ligation) and allodynia in awake rats\textsuperscript{80, 81}, inhibited the tail-flick reflex and formalin-evoked c-Fos expression in spinal cord\textsuperscript{82, 83} and blocked tactile and cold allodynia and heat hyperalgesia\textsuperscript{84}. These results correlate well with the imaging study in patients with chronic pain that demonstrated significant activation of the prefrontal cortex, including the orbital area\textsuperscript{85}.

In addition, electrical or chemical stimulation of Sm can inhibit the tail-flick reflex evoked by radiant thermal stimuli and the jaw-open reflex by tooth pulp or facial skin stimuli, while microinjection of inhibitory neurotransmitter GABA or electrolytic lesions of the VLO or PAG can attenuate this inhibitory effect\textsuperscript{86, 87}, suggesting that the inhibitory effects of the activation of Sm are mediated by the VLO and the PAG in rats. Furthermore, electrical or chemical stimulation of the VLO can inhibit the tail-flick and jaw-open reflexes, which can be attenuated by electrolytic lesions or GABA injection into the PAG\textsuperscript{78, 79, 88}. Hutchinson et al\textsuperscript{89} found that short-train stimulation of the VLO (100–400 mA) excited PAG ON-cells (the firing rate of which increases just before the tail-flick reflex) and inhibited the ongoing activity of PAG OFF-cells (the firing rate of which suddenly decreases or stops just prior to the tail-flick reflex after tail heating), while long-train VLO stimulation enhanced the noxious evoked responses of ON-cells, prolonged the noxious heat-evoked pause of OFF-cells and decreased the tail-flick latency (pronociception). These results indicate that the VLO regulation of the descending inhibition pathway of nociception is mediated through PAG ON-/OFF-cells. Our unpublished data show that the VLO neurons showed excitatory or inhibitory responses to Sm injection of glutamate that were similar to those to noxious stimuli. All these data suggest that the combined effects of Sm, VLO and PAG may constitute one nociception modulation pathway that modulates nociceptive information input at the trigeminal/spinal cord level.

**Neurotransmitter and receptor mechanisms underlying VLO involvement in nociception modulation**

Recently, studies in cat and rat have indicated that several biochemical activities are involved in the modulatory mechanisms of the VLO. The VLO contains a considerable number of mu-opioid receptor subtype 1-like immunoreactive neurons\textsuperscript{49, 90} and GABAergic neurons that also express mu-opioid receptors\textsuperscript{91}. Behavioral studies indicate that application of opioid to the VLO inhibited the tail-flick reflex evoked by thermal stimulation\textsuperscript{82}, formalin-evoked nociceptive behaviors\textsuperscript{50} and mirrored neuropathic pain and allodynia induced by L5 and L6 spinal nerve ligation\textsuperscript{80, 81} in rat, and that these effects were mediated mainly by mu-opioid receptors in the VLO\textsuperscript{50, 80, 81}. Furthermore, GABA-A receptor antagonist bicuculline depressed the tail-flick reflex in a dose-dependent fashion, although this effect was blocked by microinjection of the opioid receptor antagonist naloxone into the same site. Subthreshold doses of bicuculline microinjected into the VLO significantly enhanced the morphine-evoked inhibition of the tail-flick reflex. In contrast, administration of GABA-A receptor agonist muscimol or THIP did not influence the tail-flick reflex in the control rats but significantly attenuated the opioid receptor or 5-HT\textsubscript{1A} receptor agonist-induced antinociception\textsuperscript{83, 92}. These results provide evidence for the hypothesis that opioid-induced antinociception in the VLO might be produced by opioid via the mu opioid receptor subtype 1, which exerts inhibitory effects on GABAergic inhibitory neurons, resulting in disinhibition of VLO projection neurons and leading to activation of the VLO-PAG brainstem descending pain control system to depress the nociceptive inputs at the trigeminal/spinal cord level. A similar disinhibitory effect has been found in the rostral ventral medulla\textsuperscript{93}.

In summary, there exists one feedback nociceptive pathway, consisting of spinal cord/trigeminal-Sm-VLO-PAG-trigeminal/spinal cord, that is regulated by opioidergic, serotonergic and GABAergic components and interactive mechanisms (Figure 2). Of course, the delicate mechanism of this nociception modulation pathway and the putative involvement of other neurotransmitters like dopamine remain to be further explored, as this neurochemical has been shown to play a role in other pain-related cortical areas (see other sections).

**Motor cortex**

**Involvement of motor cortex in nociception modulation**

The evidence of involvement of the motor cortex in pain modulation is derived mainly from clinical studies. Motor cortex stimulation (MCS) was first proposed by Tsubokawa in 1991 for the treatment of post-stroke thalamic pain and has emerged as a promising technique for the management of pain in patients with difficult neuropathic and central pain conditions\textsuperscript{7, 94–96}. The MCS effects are significantly influenced by the origin and site of pain and the stimulus condi-
With respect to pain origin, it was reported that results are worse in patients with brainstem stroke, regardless of the site of pain. This is consistent with a descending modulation within the brainstem, triggered by the motor corticothalamic output. Regarding pain sites, better results are obtained for facial pain, although stimulation is targeted on the hand cortical area. Thus, in contrast to implanted stimulation, the target for repetitive transcranial magnetic stimulation (rTMS) in pain control may not be the area corresponding to the painful zone but rather an adjacent region[95, 96]. The MCS effect is also related to the stimulus condition. For example, high-frequency (5- or 10-Hz) stimulus of the precentral gyrus can reduce intractable deafferentation pain, but low-frequency stimulation (at 1 Hz) cannot[97]. These parameters should be taken into account in any further study of rTMS application in pain control.

Mechanism of motor cortex involvement in nociception modulation Although the MCS is showing promising effects in pain therapy, the mechanism underlying its involvement is not very clear. Several hypotheses have been proposed for the MCS mechanism. For example, it was found that the MCS is associated with CBF increases in the contralateral (anterior) midcingulate cortex (BA24 and 32) and in the dorsolateral prefrontal (BA10) cortices. The most important changes in CBF are observed in the 75 minutes after discontinuation of MCS. This post-stimulation period is associated with CBF increases in a large set of cortical and subcortical regions (from the posterior midcingulate cortex to pregenual ACC, orbitofrontal cortex, putamen, thalami, posterior cingulate and prefrontal areas) and in the brainstem (mesencephalon/PAG and pons), and these CBF changes in the post-stimulation period correlate with pain relief[98]. Functional connectivity analysis showed significant correlation between pregenual ACC and PAG, basal ganglia and lower pons activities, supporting the activation of descending ACC-to-PAG connections[98]. Furthermore, using PET and rCBF, significant rCBF increases in the contralateral rectus gyrus (BA11), superior frontal lobe (BA9), anterior cingulate gyms (BA32), and thalamus were observed. On the other hand, there were significant decreases in rCBF in the ipsilateral superior temporal gyrus (BA22) and the contralateral middle occipital gyrus (BA19)[99]. Based on these results, it is postulated 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; and top-down activation of brainstem PAG may lead to descending inhibition toward the spinal cord (Figure 1). In addition, it was found that the effects of rTMS in the motor cortex are more long-lasting for affective than for sensory pain[100]. Active rTMS significantly reduced pain and improved several aspects of quality of life (including fatigue, morning tiredness, general activity, walking and sleep) for up to 2 weeks after treatment had ended[100]. These results suggest that MCS may also interfere with the emotional component of nociceptive perception.

It is thought that biochemical processes involving opioid and GABAergic activities may also be implicated in the mechanism of MCS pain modulation[101]. Recent evidence points to a possible secretion of endogenous opioids triggered by chronic MCS[7]. MCS significantly decreases $^{11}$C]diprenorphine binding in the anterior middle cingulate cortex, PAG, prefrontal cortex, and cerebellum, and the binding changes in the anterior middle cingulate cortex and PAG are significantly correlated with pain relief. This decrease in binding of the exogenous ligand is most likely explained by receptor occupancy due to enhanced secretion of endogenous opioids. MCS may thus induce release of endogenous opioids in brain structures involved in the processing of acute and chronic pain[102]. Lefaucheur et al found that chronic neuropathic pain is associated with motor cortex disinhibition, suggesting impaired GABAergic neurotransmission related to some aspects of pain or to underlying sensory or motor disturbances, and that the analgesic effects produced by MCS could result, at least partly, from the restoration of defective intracortical inhibitory processes[103]. In addition, mGlur3 mRNA expression was significantly increased in cortical areas of monoarthritic rats, and higher changes were detected bilaterally at 4 days post-stimulation in the motor cortex.
cortex\textsuperscript{[32]}, suggesting that the glutamatergic receptor may be involved in the MCS effect.

**Perspective**

Although we have made great progress in understanding the cortical modulation of pain and several therapies such as MCS have emerged as promising invasive techniques to relieve some types of pain, optimized non-invasive management of pain – especially pharmaceutical therapy for chronic inflammatory and neuropathic pain – is a key objective for pain researchers. As a highly orchestrated structure, the cortex can integrate pain information from multiple areas. For example, in addition to the aforementioned cortical structures, recent studies have indicated that other cortical structures may be involved in pain modulation\textsuperscript{[104, 105]} and that this involvement is associated with cholinergic and GABAergic activities\textsuperscript{[104, 105]}. Therefore, the interactions between these cortical structures and different neurotransmitters need to be further elucidated. Elaboration of the mechanism of pain modulation by cerebral cortex structures and their interactions may be helpful for the field of pain treatment.

Another problem is how to integrate studies between animals and humans, because some cortical structures are not identical among the mammals studied. The animal models and human studies should be mutually verifiable and thus facilitate progress in understanding mechanisms of normal and pathological pain. The best way to integrate these studies and their occasionally paradoxical results remains to be determined.

Recent studies indicate that glial cells are closely associated with pain modulation at subcortical levels\textsuperscript{[106, 107]} and are activated in the cortex in some pain conditions\textsuperscript{[42, 43, 108–110]} as well as decreased in number and density in mood-disordered subjects\textsuperscript{[111]}. Contrarily, a study by Zhang\textsuperscript{[112]} indicates that the microglia in cerebral cortex are not activated by peroneal nerve (CPN) ligation in heterozygous Cx3cr1GFP/+mice. However, glial cells may still serve as one prospective target for pain research at the cortical level, and this avenue of inquiry may be helpful for clarifying cortical modulation mechanisms.

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