The brain and behavioral correlates of motor-related analgesia (MRA)

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ABSTRACT

The human motor system has the capacity to act as an internal form of analgesia. Since the discovery of the potential influence of motor systems on analgesia in rodent models, clinical applications of targeting the motor system for analgesia have been implemented. However, a neurobiological basis for motor activation’s effects on analgesia is not well defined. Motor-related analgesia (MRA) is a phenomenon wherein a decrease in pain symptoms can be achieved through either indirect or direct activation of the motor axis. To date, research has focused on (a) evaluating the pain-motor interaction as one focused on the acute protection from painful stimuli; (b) motor cortex stimulation for chronic pain; or (c) exercise as a method of improving chronic pain in animal and human models. This review evaluates (1) current knowledge surrounding how pain interferes with canonical neurological performance throughout the motor axis; and (2) the physiological basis for motor-related analgesia as a means to reduce pain symptom loads for patients. A proposal for future research directions is provided.

1. Introduction

Preclinical and clinical research has contributed to an improved understanding of the “motor” system in pain and analgesia. While prior research has focused on the classical motor system as involving motor loops at the spinal level and thalamo-cortical-basal ganglia regions, new insights have extended the definition of motor systems to integrate connections throughout the brain connectome, especially with sensory systems. The integration and relationship of motor unit activity to endocrine responses in inflammatory molecules and neurotrophic factors,(Pedersen and The, 2019) as well as to genetic and epigenetic factors,(Di Liegro et al., 2019) provides mechanisms through which motor unit activity may contribute to pain perception. The influence of motor system activity on how pain is processed and perceived at the behavioral and brain levels has not yet been reviewed.

2. The human motor system

The human motor system is densely interconnected with other brain regions (see Fig. 1; see(Kaneko et al., 1994) in terms of anatomy and function,(Pool et al., 2015; Biswal et al., 1995) which underlie complex tasks such as motor learning(Papale and Hooks, 2016) for full review).

The primary region for motor control within the central nervous system (CNS) is the primary motor cortex (M1) and is connected to other motor-related structures such as the basal ganglia, pontine nuclei, cerebellum, thalamus, superior colliculus, brainstem, and corticospinal tract.(Papale and Hooks, 2018) Motor tasks amenable towards automation such as gait require little cognitive resources and may be controlled primarily through local spinal circuits (see central pattern generators(Minassian et al., 2017; Steuer and Guertin, 2019)). However, more complex movements as well as simple movements completed in novel environments, require greater cognitive resources where regions such as the frontal, parietal and temporal lobes may be involved for optimal sensory integration and coordination processes.(Takaku, 2017) What is more, motor learning – the process of acquiring new motor skills – guides a dynamic shift in motor connectivity that may show age-related dependence and mirror observations of critical periods in sensory and visual cortices.(Papale and Hooks, 2018) Injury along the motor axis is associated with competitive remodeling of cortical circuits.(Jones and Adams, 2015; Li et al., 2016) This remodeling has been tied to pain with maladaptive arborization of peptidergic pain afferents associated with neuropathic pain(Detloff et al., 2014) and chronic functional and structural changes in the motor cortex tied to chronic pain.(Chang et al., 2018) This innate remodeling potentiates opportunity for integration of...
motor units in pain treatment services.

3. Pain and neural networks – beyond sensory systems

The processing and perception of painful stimuli influences multisensory integration through a distributed network of peripheral and central regions. Perspectives regarding supraspinal pain processing of painful stimuli involved in cognition, sensory and motor regions. (Coghill et al., 1999) Pain processing also integrates localized descending pain mechanisms within the brain stem and spinal cord that include regions such as the periaqueductal gray. (Stroman et al., 2018) Centrally, patient-reported levels of pain have been associated with impaired visual object processing (Bingel et al., 2007) and can bias how visual processing occurs based on the side of the body affected. (Filbrich et al., 2017) Pain related sensitization of the CNS has also been found to increase activity in vision-based regions of the brain (e.g., lateral occipital cortex), again suggesting that the intensity of pain can influence visual processing of environmental stimuli. (Torta et al., 2017) Peripherally, impaired proprioception has been found in persons with low back pain relative to healthy controls. (Laird et al., 2014; Tong et al., 2017) The pain element appears to be implicated in this process as when a group of chronic idiopathic neck pain patients were evaluated, only symptomatic patients were found to have impaired proprioception. (Harvie et al., 2015; Stanton et al., 2016) As was found in a group with chronic neck pain, proprioceptive deficits appeared to be related to pain symptoms and not the structure or function of the underlying muscles. (Amiri Arimi et al., 2018) As such, the distributed nature of pain processing influences both central and peripherally mediated processes.

4. Motor-sensory interactions

The interaction between pain and motor processes can be evaluated in multiple domains. Peripheral nerve or musculoskeletal injury provides a window into efferent and afferent motor commands and how they interact with myofibril and muscular health. Factors such as central sensitization imply a unique state of brain processing wherein motor processes may be influenced by the acute and chronic processing of painful stimuli. The interaction between motor and sensory regions is significant and dependent on the voluntary nature of a movement. That is, voluntary limb movements have been shown to be coincident with a decrease sensitivity to tactile stimulation of the moving limb (Angel and Malenka, 1982; Chapman et al., 1987) and that somatoaesthesia evoked potentials are reduced during movement, more so during voluntary than passive movements. (Jiang et al., 1990; Seki and Fetz, 2012; Starr and Cohen, 1985) Functional activity within the primary sensory cortex correlates with motor activity during active but not passive movements. (Cui et al., 2014) Recently, Umeda and colleagues (Umeda et al., 2019) have shown that the sensory cortex encodes movement activity slightly after the primary motor cortex and prior to the arrival of peripheral afferent feedback (see Fig. 2 for a list of proposed mechanisms) implying a short path efference copy of motor programs (possible pathways 1 through 3). Findings underscore a significant link wherein motor cortex activity influences neurophysiological performance within the primary sensory cortex. Understanding not only how pain interferes with canonical motor performance, but also how motor performance may
Influence pain processes will likely provide unique insight into pain treatment services.

In the following sections we define (4.1) the impact of pain on motor related behavior; (4.2) clinical conditions where motor systems have been implicated in pain processing; and (4.3) Motor based analgesia and approaches used to activate such systems for scientific and therapeutic effects. directions.

### 4.1. The impact of pain on motor systems: behavioral consequences

Pain related disturbances to the motor system implicate both the central and peripheral nervous system and have varying degrees of influence on behavioral performance. In the presence of an injury, structures involved in propagating a painful stimulus develop hypersensitivity and some pain-inhibition mechanisms are less functional (Woolf and Salter, 2000) which leads to an abnormal pain response and the spread of pain to non-injured areas. In the following section and summarized in Fig. 3, we outline how pain has been shown to influence canonical motor performance at different levels of the motor system as well as how pain modulates motor activity within cortical and sub-cortical areas of the brain.

The presence of pain has a behavioral impact on motor programming. Acute painful stimuli have the capacity to influence both motor preparation processes as well as upcoming movement execution. That is, the early stages prior to a movement starting when motor programs governing the movement are being developed require more time to complete, possibly due to engagement of neurocognitive mechanisms from pain anticipation. (Neigh et al., 2018) Moreover, in the presence of an acute painful stimulus (capsaicin) attention may be increased to the early stages prior to a movement starting when motor programs governing the movement are being developed require more time to complete, possibly due to engagement of neurocognitive mechanisms from pain anticipation. (Neigh et al., 2018) These findings have shown how the motor system adapts in an anti-nociceptive manner by enhancing movement process. (Dancey et al., 2016) These findings have shown how the motor system adapts in an anti-nociceptive manner by enhancing movement process. (Dancey et al., 2016) However, this must be viewed in light of long-standing research showing that attention and arousal have a peak effect on performance, after which they begin to have negative interactions. (Yerkes and Dodson, 1908)

Indeed, prior pain episodes can negatively influence motor learning with the duration of the impairment relating to the duration of the pain episode. (Huot-Lavoie et al., 2019) In other research, pain was associated with an element of movement during the swing phase which, as the authors note, may reflect a reduction in the anticipatory strategy (i.e., movement preparation) and difficulty in transferring motor skills due to pain-related changes in motor strategy. (Bouffard et al., 2016) This is notable as learning movements in the presence of pain is associated with maintaining this adaptive strategy over time, (Lamothe et al., 2014) and that elimination of this response requires re-learning motor sequences. (Dancey et al., 2019) As such, pain has a clear influence on motor performance which largely targets motor preparation and planning.

On a physiological level, changes within the motor-axis appear to largely relate to neuronal excitability based on exposure to painful stimuli. Regardless of the source of the painful stimuli (e.g., muscle or cutaneous), a reduction of cortical excitability is observed within the motor cortex. (Tsay and Giummarra, 2016) However, the same authors note that muscular pain can produce a longer lasting modulation of motor cortex excitability suggesting a possible spectrum of severity. Although unique effects may be observed within the motor cortex, depending on factors such as painful stimulus, sub-modalities and location of pain, (Farina et al., 2003) they appear to be in the form of a protective response. This protection, as outlined in the Pain Adaptation Model, (Lund et al., 1991) takes the form of a reduction in activity in agonist musculature and excitation of antagonist muscle groups.

Perhaps as a means to inhibit specific muscle groups, an acute painful stimulus decreases and increases cortical excitability for agonist and antagonist muscle groups, respectively. (Neigh et al., 2018) Bilateral changes in cortical excitability have been noted. Findings from Pelletier and colleagues (Pelletier et al., 2019) has shown that in persons with a unilateral wrist/hand pain, participants demonstrated decreases in cognitive function as well as bilateral sensorimotor differences in factors such as pressure pain thresholds, grip strength and Purdue Pegboard Test results. Preserved muscle spindle length in the presence of chronic pain (Tsay and Giummarra, 2016) suggests that the structure of the motor unit remains intact in the presence of pain. Rather, the discharge rate of motor neurons may be reduced that may be mitigated by factors such as the additional recruitment of alternative (non-painful) muscle groups. (Hodges and Tucker, 2011) As such, elements such as force can be maintained through alternative motor programs that recruit different muscle groups in a learned response.

From the level of the individual motor unit, through to the motor and...
higher order cortices, pain appears to have an inhibitory influence over motor structures that are experiencing pain. The compensatory, or adaptive, response is to engage alternate muscle groups to sustain performance demands that must be learned. This compensatory increase in excitability presents a dynamic picture of evolving levels of cortical excitability that implicate other brain regions beyond the motor cortex. Behaviorally, such compensation can be appreciated as increased time spent in motor planning as novel motor programs are developed in the context of acute and chronic pain.

4.2. Insights from clinical conditions

Examples regarding the interaction of motor and sensory integration come largely from patients with motor-related disorders. We outline three separate clinical conditions from the perspective of motor neuron death (Amyotrophic Lateral Sclerosis), damage to sub-cortical motor regions (Parkinson’s Disease) and pathology resulting in a decrease or elimination of afferent feedback (spinal cord injury) and what kind of pain is experienced.

For persons with Amyotrophic Lateral Sclerosis (ALS), diffuse pathology occurs to the motor neurons within the brain and spinal cord. (Brown and Al-Chalabi, 2017) Primary types of pain resemble neuropathic features with symptoms such as burning, tingling and shooting pain whereas secondary causes are mainly nociceptive wherein atrophy and immobility lead to pain in connective tissue, bones and joints. Chronic pain can be reported in up to 85% of patients and is found to correlate with the extent of motor disability.(Chio et al., 2017) The observation of pain syndromes such as complex regional pain syndrome are observed(Ricciardi et al., 2020) in some persons with ALS and may point towards an altered sensori-motor balance associated with deviant central processing of nociceptive stimuli.

Persons with Parkinson’s disease (PD) have loss of dopaminergic neurons within the Substantia Nigra pars compacta (SNpc). (Kalia and Lang, 2015) This loss of dopaminergic neurons results in the motor features of bradykinesia and rigidity; however, more diffuse loss of neurons in motor (e.g., dorsal motor nucleus of the vagus) and non-motor (e.g., amygdala and hypothalamus) have been reported.(Dickson and Parkinson’s, 2012) Altered top-down processing of painful stimuli – reflected by an increase in activity within the midcingulate cortex and supplementary motor area during the anticipation of a painful stimulus(Martin et al., 2020) – has been reported in persons with PD in addition to decreased thresholds and tolerance towards pain (Brefel-Courbon et al., 2005; Chaudhuri and Schapira, 2009; Djaldetti et al., 2004; Schestatsky et al., 2007) and an altered central response to pain. (Brefel-Courbon et al., 2005; Schestatsky et al., 2007; Tinazzi et al., 2009) This altered central processing of painful stimuli is a possible link towards understanding pain development in persons with PD.(Silverdale et al., 2018) At a neurophysiological level, conveying sensory and motor inputs have been observed in striatal neurons(Charpier et al., 2020) providing a plausible mechanistic link between sensation and motor system performance. In support of this, an acute exercise program has been shown to impact cortical nociceptive processing in the sensorimotor cortex,(Hautasaari et al., 2020) therein connecting motor related performance to acute disruption of how a nociceptive stimulus is processed in the brain.

Spinal cord injury (SCI) is the result of a trauma along the spinal column that produces contusion, compression, and potential transection of the spinal cord and the interruption of afferent nerve signals from distal structures. Notably, in persons with SCI, there is a preservation of central motor pathways.(Hults-Reedemaker et al., 2008) and the unique situation where pain can occur both above and below the level of spinal cord injury. In persons with neuropathic pain above the level of injury, movement imagery can reduce pain symptom levels.(Moseley, 2007) However, other research has shown that in persons with below level neuropathic pain, the level of pain after movement imagery actually increases.(Gustin et al., 2008) The precise mechanistic reason for this dichotomy is unclear but does involve aberrant recruitment of pain regions (e.g., anterior cingulate cortex and bilateral insula)(Gustin et al., 2010) and demonstrates the concept that an intact sensori-motor loop (even in the case of partial SCI)(Moseley, 2007) facilitates motor related analgesia.

The presented clinical cases draw from three perspectives of complete motor pathway destruction, restricted central motor neuron degeneration and preserved efferent motor pathways in the presence of disrupted afferent feedback. Together, they highlight the role of motor unit activity in understaning patient pain levels and underscore the central as well as peripheral integration of sensorimotor circuits.

4.3. Mechanisms of activating motor-related analgesia (MRA)

Current perspectives on evaluating pain and motor systems have evaluated how pain interrupts or interferences with canonical motor performance. However, the densely interconnected (see previous section) nature of these two systems permits the reciprocal narrative, that motor systems may have a potential influence on how pain is perceived and its influence on human brain and behavior. We evaluate methods through which movement may influence pain that can be applied external and internal to the human skull and brain.

The mechanisms representing indirect forms of engaging the motor axis reflect both covert and overt motor programs. Physical movement (overt motor behaviors) has been shown to reduce pain symptom load, even when the movement itself is acutely painful.(Ambrose and Golightly, 2015; McLaughlin et al., 2011) At a physiological level using mice, Detloff and colleagues(Detloff et al., 2014) have shown that acute exercise prevents the development of neuropathic pain and the aberrant growth of non-peptidergic c-fibers after a spinal cord injury. Even when a motor task causes pain itself, an overall reduction in pain symptoms can be obtained through activation of antinoceptive pathways.(Smith et al., 2017) This concept has been shown effective in chronic pain cohorts at reducing pain symptoms(Geneen et al., 2017); however, the exercise program should be individually tailored and watched for symptom exacerbations.(Daenen et al., 2015) In line with its extensive inter-regional connectivity, the motor cortex is responsive to sensory input as is the case in mental imagery and sensory stimulation which may trigger covert motor commands in the motor cortex without producing overt movement execution.(Hatsopoulos and Amit, 2012) This area of the literature has not received much attention and reviews have pointed towards potential efficacy in chronic pain cohorts.(Bowering et al., 2013; Yap and Lim, 2019) A recent study has shown that action observation and motor imagery may counteract the reduction in cortical excitability associated with acute pain.(Larsen et al., 2019) Notably, passive forms of movement and therapy are typically engaged with for pain treatment. These include techniques such as acupuncture, massage or manipulation type treatments. However, the use of active treatments has received comparatively less research attention which can have benefits such as empowering patients with a sense of control over their pain condition.(Crawford et al., 2014) Together, findings from indirect methods of activating the motor axis support an analgesic effect; however, a mechanistic understanding of their pain-reducing effects is lacking.

Methods of modulating motor system activity applied external to the skull are dissociated from natural reflexive or voluntary motor programs. Different techniques and devices have been used to generate a motor response. Such methods generate temporary magnetic or electric fields causing a depolarization of neurons in the brain. Depending on the strength of the technique and which method is used, different areas of the cortex are accessible; although deep gray matter and sub-cortical structure are typically out of reach. An overview is provided regarding how different modalities may be applied in the context of pain-treatment.
4.3.1. Repetitive transcranial magnetic stimulation

Research to date has provided evidence in support of the use of repetitive transcranial magnetic stimulation to reduce pain symptoms. For example, it was found by Lefaucheur and colleagues (Lefaucheur et al., 2008) that rTMS (applied at 10 Hz) applied to the motor cortex was able to reduce pain scores in participants with chronic neuropathic pain. It was observed that thermal, but not mechanical sensory thresholds were also altered using rTMS demonstrating the interconnectivity between motor and sensory brain regions. In a study by Lee and colleagues, (Lee et al., 2012) although positive pain-modulation effects were found in both a high and low frequency protocol, authors observed that low frequency (1 Hz) rTMS was associated with longer suppression of pain symptoms than a high frequency (10 Hz) protocol. An n-of-1 trial showed the efficacy of using rTMS to promote increased functional connectivity within the sensory-motor network that coincided with a reduction of pain rating on a Visual Analogue Scale (VAS). (Scibilia et al., 2018) Prefrontal circuits share extensive connectivity with pain processing regions such as the periaqueductal gray, thalamus and amygdala. (Fagg et al., 2019) Recent findings suggest that an rTMS protocol to the left dorsolateral prefrontal cortex (DLPFC) was capable of modulating pain-induced changes in sensorimotor adaptation to artificially induced muscular pain via connectivity with basal ganglia and sensorimotor regions of the brain. However, in a recent Cochrane review, low quality of evidence was found for high frequency rTMS of the motor cortex to have short lasting effects on chronic pain and low-frequency rTMS, and rTMS applied to DLPFC were not found to be effective for reducing pain intensity in chronic pain. (O’Connell et al., 2018) Findings may therefore support a potential motor-cortex specific mechanism of pain reduction.

4.3.2. Transcranial direct current stimulation

Findings from research using transcranial direct current stimulation (tDCS) reflect both anodal (excitatory) and cathodal (inhibitory) stimulation parameters. For example, anodal tDCS over M1 was shown to significantly decrease pain intensity which was proposed to be due to the descending influence of the motor cortex over descending pain modulation systems. (Nguyen et al., 2015) In persons with phantom limb pain, application of anodal tDCS appears to produce a short-lasting decrease in pain from the increase in excitability, (Bolognini et al., 2013) counteracting the decreased cortical excitability in M1 typically observed from a painful stimulus. Application of anodal tDCS to M1 has been shown to improve pain in individuals with chronic lower back pain when completed in conjunction with a postural training program. (Jafarzadeh et al., 2019) That is, the combination of tDCS with aerobic exercise is superior compared with each individual intervention and also had positive effects on anxiety and mood in persons with fibromyalgia. (Mendonca et al., 2016) Other studies have also evaluated combination therapy. In one study, both anodal tDCS and a diffuse noxious inhibitory control (DNIC) paradigm significantly increased pain thresholds and the combination of the two produced additive effects. This finding was related to baseline levels of n-acetyl aspartate (a marker of neuronal integrity) in the cingulate cortex and negatively correlated with baseline glutamate levels in the thalamus, suggesting that the beneficial effect of M1 stimulation is not isolated to one region of the brain. (Reidler et al., 2012) It is important to consider that in other research, stronger baseline functional connectivity between M1 and the ventrolateral thalamus, primary sensory cortex and anterior insula, and ventrolateral thalamus and periaqueductal gray predicted greater analgesia after tDCS and real tDCS. Repetitive M1 tDCS causes distinct changes in functional connectivity that last beyond the stimulation period and may produce analgesia by altering thalamic connectivity. (Cummingford et al., 2016) Therefore, the potential for a placebo response is real. As shown by Sankarasubramania and colleagues, (Sankarasubramanian et al., 2017) changes in FC from active M1 anodal tDCS did not correlate with baseline pain thresholds, whereas FC changes from stimulation of the DLPFC were. Together, a review of the literature suggested that anodal tDCS of the left M1 (contralateral to the pain side) in persons with chronic lower limb neuropathic pain (secondary to spinal cord lesion) still has to have its possible therapeutic effect verified (clinically meaningful) and the optimal stimulation parameters outlined. (Lefaucheur et al., 2017)

4.3.3. Deep brain stimulation / motor cortex stimulation

The application of deep brain stimulation (DBS) is invasive, requiring neurosurgical intervention, and has most routinely been associated with treatment of movement disorders in persons with PD. However, use of DBS has shown benefit in reducing pain symptoms in persons with PD by a number of authors. (Hwynn et al., 2011; Dellapina et al., 2012; Giampaoli et al., 2012; Giampaoli et al., 2012; Kim et al., 2012; Kirkeby et al., 2013; Marques et al., 2013; Kim et al., 2008; Pellegrati et al., 2014; Cury et al., 2014; Jung et al. 2015) that lasted months to years following surgery and whose benefit may be independent of motor symptom changes. What is more, a number of targets are possible using DBS including sensory nuclei of the thalamus, periaqueductal gray, and anterior cingulate cortex, each implicated in different aspects of pain processing and offering varying degrees of success (see (Boccard et al., 2015) for review). For persons with dystonia for example, targeting of the globus pallidus internus (GPI-DBS) – a region connecting the basal ganglia with the prefrontal cortex (Karachi et al., 2002) – may reduce pain symptoms associated with dystonia and may be independent of dystonia-related symptoms. (Figgink et al., 2018)

Motor cortex stimulation is a separate method and also requires invasive intervention, using electrodes that are implanted under the skull. Using a subdural electrode in the context of deafferentation pain, Kishima and colleagues (Kishima et al., 2007) found decreased pain-related VAS scores. MCS stimulation was associated with modulation of two pathways: (1) from the posterior insula and orbitofrontal cortex to the posterior thalamus to upregulate the pain threshold as well as (2) from the posterior insula to the caudal acc to modulate emotional perception. MCS has been shown to have a mean rate of pain relief of 48% for treatment refractory neuropathic pain with a ‘good’ or ‘satisfactory’ level of efficacy. The level of pain relief at the one-year period showed a correlation with pain scores at the one-month postoperative period, suggesting that the long-term efficacy could be determined early after treatment. (Lefaucheur et al., 2009) Notably, these numbers are in line with other findings showing that only 10% of persons with refractory neuropathic pain showed a > 70% pain relief at four years although the treatment itself was found to be well accepted by patients (Nuti et al., 2005) and other showing 40–64% efficacy. (Hussein et al., 2018)

Together, data from diverse brain stimulation techniques offer insight into how applied methods of motor unit activation can influence pain perception through stimulating the motor cortex. A major issue remains the standardization of protocols and evaluation criteria being undefined (Thomas et al., 2009); however, as shown in Supplementary Table 1, this is an emerging field. There is potential for clinical application of motor cortex stimulation to produce analgesic effects and future research should be targeted at refining paradigms and determining mechanisms that bridge motor and pain treatment services.

4. Integration

Understanding how activity along the motor axis could influence pain processing and perception has the ability to reshape how we approach pain treatment services. The impact of pain on motor performance is widely disseminated; however, the influence of motor activity on pain processing appears to interact with distinct areas throughout the motor axis. In this review, we outlined how (1) motor unit structure remains preserved in the presence of pain, (2) motor system activity appears to be capable of influencing both psychological as well as physiological aspects of pain processing, and (3) combination of external and internal forms of motor-related analgesia may be optimal towards improving patient care in pain settings.
5. Making sense of pain-motor interactions

Motor-related analgesia produces an independent, anti-nociceptive effect on pain processing that occurs in both the peripheral and central nervous system. Evaluating the impact of pain on the motor system is inherently difficult as the response of the CNS towards pain is protective and largely inhibitory. That is, recurrent observations have been made that outline a decrease in excitability within the motor cortex, a decrease in the firing rate of neurons innervating damaged muscles, and changes in spinal cord excitability. Compensatory changes are also observed wherein increases in excitability are found in antagonistic muscle groups as well as brain regions that may regulate attention, cognitive arousal, or other brain regions associated with pain processing (see reviews of the pain matrix (Legrain et al., 2011; Salomons et al., 2016)).

Methods of activating the motor cortex external to the human skull provides a means through which the impact of motor system activity on pain processing can be evaluated without the influence of higher order brain activity. In multiple reviews and independent studies, paradigms targeted at increasing excitability of the motor cortex have been associated with decreases in pain symptom reporting. This was accomplished through anodal TDCS, high and low frequency rTMS, and more invasive methods such as MCS and DBS. However, the significance and length of the analgesic effect is poorly understood at this point. Pain symptom reporting can indeed be decreased at the one-year mark after a motor-based paradigm, but this is not necessarily tied to the intervention. Investigations that have targeted modulation of motor cortex excitability have evinced changes in activity in cortical and sub-cortical brain structures that are functionally connected. For example, spectroscopic markers of healthy neuron concentration (N-Acetyl Aspartate) and glutamine have been correlated with the success of an anodal TDCS paradigm (Reidler et al., 2012) and stronger baseline FC between M1 and the ventrolateral thalamus and other insular, and descending pain modulation centers predicted response to a sham controlled TDCS study. (Cummiford et al., 2016) The perspective that multiple brain regions are implicated in the response to brain stimulation is consistent with the position of distributed pain processing in the brain wherein multiple brain regions are responsible for processing of pain stimuli, rather than focal nodes (e.g., somatosensory cortex) themselves. (Coghill et al., 1999) Together, it is possible that a discrete set of brain regions – that may or may not be implicated in the canonical pain experience – are involved in modulating the response to neuromodulation techniques.

Several mechanisms have been proposed that could account for the analgesic impact of motor system activity (see Fig. 4). For example, Ngernyam and colleagues (Ngernyam et al., 2015) suggested that the pain suppression impact of brain stimulation was derived from the interaction between motor cortex and brain regions through mechanisms of descending pain modulation such as the periaqueductal gray. Ascending forms of pain modulation through motor system activation have also been proposed. High frequency rTMS may act by inhibiting thalamic projections and dampening the pain response. (Ngernyam et al., 2015; Castillo Saavedra et al., 2014) Notably, the connectivity between the thalamus and motor cortex has been proposed by others as well to be the mediating source of analgesia from motor cortex stimulation (Cummiford et al., 2016) in addition to connectivity between the thalamus and insula and orbitofrontal cortex using MCS. (Kishima et al., 2007) Several neurotransmitters appear to be implicated in the MRA response. As found by Reidler and colleagues. (Reidler et al., 2012) aside from the levels of NAA within the cingulate cortex, the concentration of glutamine was correlated with the success of an anodal TDCS paradigm for reducing pain symptoms. Also, the level of serotonin – a hormone acting here as a neurotransmitter – has been implicated, wherein motor

![Fig. 4. Overview of possible mechanisms that may account for motor-related analgesia. M1 = Primary Motor Cortex; PAG = Periaqueductal Gray; + = Excitatory effects; − = Inhibitory effects.](image-url)
Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2020.105158.

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