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The clinical utility of repetitive transcranial magnetic stimulation in reducing the risks of transitioning from acute to chronic pain in traumatically injured patients

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ABSTRACT

Pain is a multifaceted condition and a major ongoing challenge for healthcare professionals having to treat patients in whom pain put them at risk of developing other conditions. Significant efforts have been invested in both clinical and research settings in an attempt to demystify the mechanisms at stake and develop optimal treatments as well as to reduce individual and societal costs. It is now universally accepted that neuroinflammation and central sensitization are two key underlying factors causing pain chronification as they result from maladaptive central nervous system plasticity. Recent research has shown that the mechanisms of action of repetitive transcranial magnetic stimulation (rTMS) make it a particularly promising avenue in treating various pain conditions. This review will first discuss the contribution of neuroinflammation and central sensitization in the transition from acute to chronic pain in traumatically injured patients. A detailed discussion on how rTMS may allow the restoration from maladaptive plasticity in addition to breaking down the chain of events leading to pain chronification will follow. Lastly, this review will provide a theoretical framework of what might constitute optimal rTMS modalities in dealing with pain symptoms in traumatically injured patients based on an integrated perspective of the physiopathological mechanisms underlying pain.

1. Introduction

Pain is a multidimensional phenomenon consisting of complex mechanisms featuring sensory and motor components (sensory-discriminative features of pain) as well as emotional and cognitive aspects (affective-motivational processing of pain) (Davis and Moayedi, 2013; Seifert and Maihofner, 2011). According to the International Association for the Study of Pain (IASP), chronic pain is characterized as persistent pain that is experienced everyday for three months over a period of six months (Merskey and Bogduk, 1994). Chronic pain constitutes a major public health concern that has deleterious effects on quality of life (Patel et al., 2012). Chronic pain afflicts, in the United States alone, > 100 million individuals suffering from a wide variety of diseases and results in more than $560 to $654 billion in total annual cost (Gaskin and Richard, 2012).

Acquired traumatic injuries represent a significant proportion of patients seeking care in the healthcare system and regroup a wide variety of injuries such as, but not limited to, musculoskeletal injuries (fractures), cranio-maxillofacial trauma (facial trauma), and traumatic brain injuries (Centers for Disease, 2011). Pain constitutes one of the most common symptoms shared among this population and is known to delay return to work even in patients suffering from minor traumas (Albrecht et al., 2013; Archer et al., 2012; MacDermid et al., 2003; Platts-Mills et al., 2016). Despite intensive research, treating pain represents a particularly challenging task considering the high heterogeneity in clinical manifestations across individuals and pathologies. Furthermore, the difficulty in predicting which patients will transition from acute to chronic pain as well as the lack of consensus as to which treatment to prioritize make it an even bigger challenge for healthcare professionals. Indeed, predictors of pain chronification following an acquired traumatic injury are not well understood, which makes it even more challenging to develop effective treatments that will maximize recovery, but recent evidence suggests the involvement of maladaptive neuroplasticity mechanisms (McGreevy et al., 2011; Miranda et al., 2015). Development of interventions aiming to prevent the installation of chronic pain is critical as persistent pain is associated with an

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increased risk of medical complications, staggering financial burdens (on personal and societal levels) and diminished quality of life (Patel et al., 2012).

Although treating pain is considered a human right for which all healthcare professionals are responsible (Lohman et al., 2010), this field of research is currently undergoing important transformations to address the multiple shortcomings associated with pharmacological treatments. Indeed, it is estimated that 30% of chronic pain patients remain symptomatic despite optimal treatment (Galhardoni et al., 2015). An increasing amount of alternative treatments are currently gaining in popularity in an attempt to reduce, and eventually replace, the use of the highly controversial prescription of opioids for its potentially serious side effects (Benyamin et al., 2008; Chou et al., 2015a, 2015b; Ray et al., 2016). Among them, repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique, appears particularly promising in alleviating pain symptoms among acquired injury patients by tackling key elements of the neurophysiopathological underpinnings of acute pain symptoms. Indeed, the modulating effects of rTMS on synaptic plasticity together with its ability to precisely target brain regions involved in pain processing has provided pain relief in several experimental pain studies (Hallett, 2000, 2007). Moreover, although very limited data exist on the clinical utility of rTMS during the acute phase, we believe that this technique would be most beneficial when applied during the early stage of the trauma given that rTMS allows to modulate the excitability of the stimulated brain region through the activation/inhibition of NMDA receptors, a central element to the excitotoxic chain reactions associated with pain chronification. To support this opinion, we will first provide a detailed description of two of the main mechanisms involved in pain chronification, namely central sensitization and neuroinflammation, in a context of acquired injuries. Secondly, this review will discuss the available literature on the mechanisms involved in rTMS as a potential treatment for reducing the risk of transition from acute to chronic pain. Furthermore, this review will provide a theoretical framework of what could reveal to be optimal rTMS modalities in order to reduce pain based on an integrated perspective of the physiopathological mechanisms underlying pain in acquired injury patients.

2. Mechanisms of central sensitization

Central sensitization is a pain-facilitatory state resulting from the amplification of membrane excitability and synaptic efficacy within the CNS (Koltzenburg et al., 1994; Latremoliere and Woolf, 2009). The resulting chain reaction makes the brain overly reactive (sensory amplification) to noxious stimuli (pain hypersensitivity and hyperalgesia) and non-noxious stimuli (allodynia) (Baron et al., 2010; Latremoliere and Woolf, 2009; Sandkuhler, 2009; Woolf, 2011). When the tissue or nerve insults result from peripheral damage, such as following a fracture, this central mechanism of pain chronification mainly occurs as a consequence of both peripheral and central nervous system markers (Clauw, 2015; McGreevy et al., 2011). Indeed, nociceptors at the site of injury become overly activated due to inflammation, which creates short-lasting synaptic plasticity called “wind-up” within the spinal cord (D'Mello and Dickenson, 2008; Herrero et al., 2000). This phenomenon mainly results from excitatory amino acids and neuropeptides release taking place via the spinothalamic tract of the dorsal horn in the spinal cord ultimately leading to excitotoxicity (D'Mello and Dickenson, 2008; Xu et al., 2008). Excitotoxicity is defined as prolonged overactivation of excitatory neurotransmitters such as glutamate and can lead to neuronal damage or death (Yi and Hazell, 2006). The excitotoxicity state occurring within the spinal cord also facilitates the transitioning of nociceptive afferent signals to the brain (Hanakawa, 2012) resulting in central sensitization.

Multiple other pain-facilitating mechanisms are at stake in central sensitization, such as overactivation of *N*-methyl-D-aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Hains et al., 2004; Ultenius et al., 2006). The up-regulation of NMDA receptors, a type of glutamate receptor, triggers and facilitates peripheral and central sensitization by lowering the firing threshold, therefore making the spinal cord overly reactive to pain stimuli (Latremoliere and Woolf, 2009; Petrenko et al., 2003). Similarly, up-regulated AMPA receptors also contribute to increasing nociceptive synaptic plasticity within the spinal cord (Garry et al., 2003), but more so during the initial acute phase (D'Mello and Dickenson, 2008; Voscopoulos and Lema, 2010). There is also an increased activation of voltage-gated sodium channels in the second-order nociceptive neurons, which act as facilitators for glutamate and substance P release (Luo et al., 2001), further promoting an excitatory state (Naro et al., 2016). Furthermore, this excitatory state also negatively affects GABAergic activity within the CNS (the spinal cord and the cortex), the main inhibitory neurotransmitter of the human body, which can no longer produce sufficient inhibitory influence to compensate for the excessive excitability and play its usual neuroprotective role (Baba et al., 2003; Lin et al., 1996). For this reason, inefficient GABA inhibition further contributes to central sensitization (Baron et al., 2010; Castro-Lopes et al., 1993). Indeed, GABAergic transmission and efficacy are suppressed by overly represented NMDA receptors and their excitatory neurotoxic effects, which eventually lead to disinhibition (Latremoliere and Woolf, 2009). This is supported by studies showing that NMDA receptor antagonists can successfully reduce various central sensitization symptoms such as allodynia (painful reaction to non-noxious stimuli) and hyperalgesia (exaggerated reaction to pain in response to noxious stimuli) (Bennett, 2000). Unfortunately, long-term use of NMDA receptors-based substances is contraindicated due to adverse non-specific side effects (Niesters et al., 2014) but they remain an important therapeutic target (Corasaniti et al., 2006). Taken together, secretion of excitatory neuropeptides and amino acids within the dorsal horn and reduction of inhibitory mechanisms generate an unbalanced state within the CNS, which represents a putative risk for developing central sensitization and maladaptive neuroplasticity (Naro et al., 2016; Petrenko et al., 2003).

Other studies have shown that ongoing excitatory discharge in chronic pain induces LTP-like synaptic plasticity changes (Nijs et al., 2015), which ultimately give rise to maladaptive plasticity. The latter was recently associated with significant facilitation of neuronal pain transmission and, again, possibly excitotoxicity (Costigan et al., 2009). Interestingly, transcranial magnetic stimulation (TMS) applied over the primary motor cortex (M1) allows the modulation of long-term potentiation (LTP) and long-term depression (LTD) mechanisms, therefore appearing as a highly pertinent and reliable measure for studying the mechanisms involved in central sensitization (Stefan et al., 2000). Of note, glutamatergic and GABAergic neurotransmission play a key regulating role on LTP and LTD bidirectional plasticity mechanisms (Caillard et al., 1999; Hasan et al., 2012; Pavlov et al., 2004). Most chronic pain studies describe a disinhibition state partly due to deficiency in GABA-dependent intracortical inhibition (ICI) and the latter is associated with the intensity of pain levels (Caumo et al., 2016; Lefaucheur et al., 2006; Lenz et al., 2011; Mhalla et al., 2011; Parker et al., 2016; Schwenkreis et al., 2010). Accordingly, TMS markers of cortical excitability strongly correlate with the magnitude of pain, depression, catastrophizing, motor deficits and fatigue (Mhalla et al., 2011). In the latter study, cortical excitability restoration following a 14-day rTMS protocol was associated with significant symptoms relief including pain symptoms. Furthermore, brain-derived neurotrophic factor (BDNF), a protein capable of modulating neuronal excitability (Desai et al., 1999), can further promote the process of pain chronification from a very early stage following the injury (Caumo et al., 2016). Indeed, BDNF has the potential to increase levels of available excitatory neurotransmitters (glutamate), or LTP, as well as to inversely reduce levels of inhibitory neurotransmitters (GABA) within the spinal cord and the brain (Caumo et al., 2016; Nijs et al., 2015; Smith, 2014). Given that BDNF is indiscriminately release immediately after an