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Cognitive Brain Research 25 (2005) 153 – 160
COGNITIVE BRAIN RESEARCH
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Research Report

# Repetitive transcranial magnetic stimulation of dorsolateral prefrontal cortex increases tolerance to human experimental pain

Ariel Graff-Guerrero[a,e,*], Jorge González-Olvera[b], Ana Fresán[c], Diana Gómez-Martín[d], Juan Carlos Méndez-Núñez[a], Francisco Pellicer[a]

[a]*Instituto Nacional de Psiquiatría Ramón de la Fuente, Dirección de Investigaciones en Neurociencias (Lab. Neurofisiología Integrativa) Calz. México-Xochimilco 101, Col. San Lorenzo Huipulco, Del. Tlalpan, 14370, México, D.F. México*
[b]*Instituto Nacional de Psiquiatría Ramón de la Fuente, Dirección de Servicios Clínicos, México, D.F. México*
[c]*Instituto Nacional de Psiquiatría Ramón de la Fuente, Subdirección de Investigaciones Clínicas, México, D.F. México*
[d]*Instituto Nacional de Ciencias Médicas y de la Nutrición Salvador Zubirán, Departamento de Enseñanza. México, D.F. México*
[e]*Centre for Addiction and Mental Health, PET Centre, Toronto, Ontario, Canada*

Accepted 3 May 2005
Available online 2 June 2005

**Abstract**

Dorsolateral prefrontal cortex (DLPFCx) has been implicated in pain perception and in a pain modulation pathway. However, the precise participation of this region is not completely understood. The aim of this study was to evaluate whether 1 Hz rTMS of DLPFCx modifies threshold and tolerance in experimental pain. The effect of 1 Hz rTMS during 15 min at 100% motor threshold was tested in one hundred and eighty right-handed healthy volunteers, using a parallel-group stimulation design. The stimulation sites were right or left DLPFCx, right or left motor cortex, vertex or sham. rTMS was applied in two experimental contexts: (1) To evaluate its transitory effect (interference or facilitation) during cold pressor threshold (CPTh) and tolerance (CPTt) and (2) to evaluate its long-term effect by stimulating before CPTh, CPTt, pain heat thermal threshold, pain pressure threshold and tolerance. During rTMS of right DLPFCx, an increase in left hand CPTt (mean ± SD; 17.63 s ± 5.58 to 30.94 s ± 14.84, $P < 0.001$) and in right hand CPTt (18.65 s ± 6.47 to 26.74 s ± 11.85, $P < 0.001$) were shown. No other stimulation site modified any of the pain measures during or after rTMS. These results show that 1 Hz rTMS of right DLPFCx has a selective effect by increasing pain tolerance and also sustains a right hemisphere preference in pain processing.


*Theme:* Sensory systems
*Topic:* Pain modulation: anatomy and physiology

*Keywords:* Dorsolateral prefrontal cortex; Repetitive transcranial magnetic stimulation; Working memory; Pain; Pain threshold; Pain tolerance; Cold pressor

## 1. Introduction

Pain studies have revealed that there is not a single brain region whose destruction abolishes completely the experience of pain, consequently, it has been proposed that pain is processed by a highly distributed brain system [10].

This distributed brain system (neural network) includes parallel somatosensory, limbic and thalamocortical components that subserve the sensory–discriminative, affective–motivational and evaluative–cognitive dimensions of pain experience [46,64]. Cerebral pain studies have mainly involved the following areas in this neural network: thalamus, anterior cingulate cortex (ACC), primary (S1) and secondary (S2) somatosensory cortices, insula, dorsolateral prefrontal cortex (DLPFCx), inferior parietal cortex, primary and secondary motor cortices, cerebellum and hippocampus [11,63,65].

* Corresponding author. Fax: +52 56559980.
*E-mail addresses:* agraff@imp.edu.mx, ariel_graff@yahoo.com.mx (A. Graff-Guerrero).

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doi:10.1016/j.cogbrainres.2005.05.002

The experience of pain is difficult to ignore, and it interferes with concurrent activities. However, sometimes it is essential to ignore or disengage from pain in order to fight or escape even in the presence of body injury [47]. Among the brain areas of the pain neural network, the DLPFCx is a potential candidate region to modulate the experience of pain given that it is a critical structure for working memory (WM) and attention functions. With these properties, this structure could shift the focus of attention, hold pain information in WM and access the motor system to escape or defense.

The DLPFCx is a neocortical region that corresponds to the dorsolateral region of the prefrontal cortex (PFCx). It is most elaborated in primates, animals characterized for their diverse and flexible behavioral repertories [39,49,50]. Furthermore, it has been claimed that the DLPFCx developed much later than the other PFCx structures; it evolved from motor regions, supporting the notion that the DLPFCx is involved in cognitive actions [18,19,49]. Its anatomical position enables it to coordinate a wide range of neuronal processes; it has reciprocal connections with brain regions that are associated with motor control (basal ganglia, premotor cortex and supplementary motor area), performance and monitoring (cingulate cortex) and higher-order sensory processing (somatosensory cortices and parietal cortex). It also has reciprocal connections with the ventromedial PFCx which supports the integration of information regarding emotions and memory [49,84].

The neuronal cells in the DLPFCx are particularly capable of firing over extended periods of time across events and respond to both internally generated and observed behaviors [17,20,35,36,39,70]. These single-unit recordings indicate that DLPFCx neuronal cells can maintain stimulus representations "on line" [17,20], enabling a subject to engage in behavior involving long-term goals. In addition, pyramidal cells in the macaque PFCx have more spines than cells of other cortical areas, suggesting that they are capable of integrating a great number of excitatory inputs which may be important for their role in memory and cognition [13].

Hence, it is clear that, given the evolutionary principles of the DLPFCx, connectivity and physiological properties of its neurons, it plays a crucial role not only in integrating information, but also in higher cognitive skills.

There is agreement in the literature [39,84] that the DLPFCx is essential for WM and attention functions. The role of DLPFCx in WM is to maintain information in a highly active, easily accessible state. This maintenance is particularly important in the presence of interference, and it may be crucial in blocking the effects of distractions. The attentional function is referred as the ability to focus mental effort on a subset of all available information. The DLPFCx is not critical for performing simple, automatic behaviors, such as our propensity to automatically orient to an unexpected sound or escape from an unpleasant stimulus. This type of automatic behaviors can be interpreted as "bottom–up" processes; that is, they are determined largely by the nature of the sensory stimuli and have well-established neuronal pathways that connect these stimuli with the corresponding responses. In contrast, the DLPFCx is important when "top–down" processing is needed; that is, when behavior must be guided by internal states or intentions. This structure is essential for the efficient handling of situations in which various types of information–sensory, emotional and behavioral (actions)–are implicated in a rapidly changing context. This is when we need to use the "rules of the game" and the internal representations of goals [25,48,50].

Functional neuroimaging pain studies have linked DLPFCx to cerebral blood flow (cbf) or BOLD response independent of pain intensity [4,10,62]. This response (on–off type) is initiated when the painful stimulus is perceived as such and is consistent with cognitive processes primarily handled by DLPFCx, such as focus of attention and keeping pain information in WM. Lorenz et al. [42,43] claim that the DLPFCx may have a "top–down" mode of inhibition of neuronal coupling along the ascending midbrain–thalamic–cingulate pathway through descending fibers from the PFCx which may modulate pain perception [43]. This "top–down" modulation of the DLPFCx is related to the perceived pain intensity during sensitization with capsaicin [2,29,42]. This is in agreement with a "top–down" processing in which the abnormal tissue status (sensitization) is considered a sustained sensory input. This may generate an internal state that engages DLPFCx mechanisms to guarantee optimal adaptation.

The role of DLPFCx in pain modulation is based on correlation analysis of functional neuroimaging studies [2,4,10,29,42,62]. Therefore, an intervention approach is required to test further the association between DLPFCx activity and pain modulation. The interventional approach can be done using repetitive transcranial magnetic stimulation (rTMS). This method has been developed as a noninvasive technique that, through the application of intermittent magnetic fields, induces small electrical currents in focal regions of the cerebral cortex. It transiently interferes or enhances task performance, and its application induces outlasting changes in both brain blood flow and electrical activity at the stimulation region and distal sites [34]. rTMS may induce transient changes in cortical excitability. While trains of low-frequency stimulation (<1 Hz) induce a reduction in motor cortex excitability [9], high frequency stimulation (>1 Hz) enhances the excitability of this structure [55].

The aim of this study was to evaluate whether rTMS of DLPFCx modifies experimental pain threshold and tolerance in comparison with rTMS over motor cortex. We chose the motor cortex because it has been electrically stimulated in the treatment of chronic pain [8,79]. In addition, sham stimulation and vertex stimulation were performed, as a control of placebo effect and as a region unrelated to pain processing, respectively. One experimental pain evaluation was carried out during rTMS when a transitory effect on performance was induced. Other pain evaluation was carried out immediately after one rTMS session to evaluate the lasting cortical excitability effect, using 1 Hz as stimulation frequency.