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EXPERIMENTAL TONIC HAND PAIN MODULATES THE CORTICOSPINAL PLASTICITY INDUCED BY A SUBSEQUENT HAND DEAFFERENTATION

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Abstract—Sensorimotor reorganization is believed to play an important role in the development and maintenance of phantom limb pain, but pain itself might modulate sensorimotor plasticity induced by deafferentation. Clinical and basic research support this idea, as pain prior to amputation increases the risk of developing post-amputation pain. The aim of this study was to examine the influence of experimental tonic cutaneous hand pain on the plasticity induced by temporary ischemic hand deafferentation. Sixteen healthy subjects participated in two experimental sessions (*Pain, No Pain*) in which transcranial magnetic stimulation was used to assess corticospinal excitability in two forearm muscles (flexor carpi radialis and flexor digitorum superficialis) before (T0, T10, T20, and T40) and after (T60 and T75) inflation of a cuff around the wrist. The cuff was inflated at T45 in both sessions and in the *Pain* session capsaicin cream was applied on the dorsum of the hand at T5. Corticospinal excitability was significantly greater during the Post-inflation phase ($p = 0.002$) and increased similarly in both muscles ($p = 0.861$). Importantly, the excitability increase in the Post-inflation phase was greater for the Pain than the No-Pain condition ($p = 0.006$). Post-hoc analyses revealed a significant difference between the two conditions during the Post-inflation phase ($p = 0.030$) but no difference during the Pre-inflation phase ($p = 0.601$). In other words, the corticospinal facilitation was greater when pain was present prior to cuff inflation. These results indicate that pain can modulate the plasticity induced by another event, and could partially explain the sensorimotor reorganization often reported in chronic pain populations.

Key words: ischemic nerve bloc, experimental pain, TMS, motor cortex, phantom limb pain.

INTRODUCTION

In 90% of cases limb amputation is followed by the vivid sensation that the now-missing body part is still there, a phenomenon called "phantom limb". In addition to the sensation of a phantom limb, 50–80% of amputees also report phantom limb pain (PLP) in the missing limb and this pain often becomes chronic (Jensen et al., 1985; Kooijman et al., 2000; Flor et al., 2006; Weeks et al., 2010). Much research in both animals and humans has documented massive cortical and subcortical reorganization of the sensorimotor cortices occurs after amputation (Sanes et al., 1988; Cohen et al., 1991; Ziemann et al., 1998b; Chen et al., 2002). While various factors have been associated with the extent of this reorganization, phantom limb pain has received the most attention (Flor et al., 1995; Lotze et al., 2001; Makin et al., 2015a,b; Raffin et al., 2016). For instance, many studies have shown that in upper limb amputees the shift of the face's sensorimotor area into the deafferented hand area correlates with the severity of phantom pain (Flor et al., 1998; Lotze et al., 2001; Karl et al., 2004; MacIver et al., 2008; Raffin et al., 2016). Even though this finding has been replicated numerous times, the correlational nature of transversal patient studies makes it difficult to establish a causal relationship between these factors.

Sensorimotor reorganization is believed to play an important role in the development and maintenance of PLP. An alternative explanation for this reorganisation, although not mutually exclusive, is that pain itself modulates the sensorimotor plasticity induced by limb deafferentation. In support of this view, several longitudinal studies have shown that the presence of pain before an amputation increases the risk of developing PLP (Jensen et al., 1985; Katz and Melzack, 1990; Nikolajsen et al., 1997; Flor, 2002; but see Wall et al., 1985 and Kooijman et al., 2000 for contrasting results). Interestingly, the length of time a patient's limb has been painful before the amputation does not appear

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Abbreviations: FCR, flexor carpi radialis; FDS, flexor digitorum superficialis; MEPs, motor-evoked potentials; TMS, transcranial magnetic stimulation; ANOVA, analysis of variance; EMG, Electromyographic; GABA, gamma-aminobutyric acid; LTD, long term depression; LTP, long term potentiation; NMDA, N-methyl-D-aspartate; PLP, phantom limb pain; rTMS, repetitive transcranial magnetic stimulation; SEM, standard error of mean; SICI, short interval cortical inhibition; TES, transcranial electric stimulation.

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to be related to the persistence or recurrence of pain after amputation (Nikolajsen et al., 1997; Hanley et al., 2007). Observations from animals support these observations, as noxious stimuli applied prior to neurectomy or rhizotomy significantly enhance the development of autotomy (self-mutilation behavior thought to reflect pain) after the deafferentation, even when the noxious stimulation period is brief (Wiesenfeld and Lindblom, 1980; Katz et al., 1991; Seltzer et al., 1991). Together, these data suggest that the presence of pain at the moment of the nerve lesion might have a modulatory effect on the plasticity that will be induced by the lesion.

Experimental models of pain and deafferentation provide an opportunity to better understand the interactions between pain and sensorimotor plasticity, something that is impossible to study in a controlled manner in clinical populations. Temporary ischemic deafferentation provides a good model for addressing this question as, similar to what is observed in amputees (Cohen et al., 1991), muscles proximal to the block have both increased corticospinal excitability (Brasil-Neto et al., 1992, 1993; Ridding and Rothwell, 1995; Ziemann et al., 1998a; McNulty et al., 2002) and enlarged motor maps (Ridding and Rothwell, 1995). Although corticospinal excitability changes have not been used to show associations between amputation-induced reorganization and pain, it remains an interesting marker of plasticity for several reasons. At the practical level, it can be measured rapidly and repeatedly, which permits investigation of the time-course of the acute effect of temporary deafferentation. At the theoretical level, the increase in corticospinal excitability induced by temporary deafferentation has been shown to be mediated by gamma-aminobutyric acid (GABA) (Ziemann et al., 1996, 1998b), and GABAergic inhibition is believed to play an important role in the dynamic organization of motor maps and alterations in these maps in response to nerve lesion (Farkas et al., 2000; Sanes and Donoghue, 2000).

The aim of the present study was therefore to test the influence of experimental tonic cutaneous pain on the plasticity induced by a temporary ischemic deafferentation. Transcranial magnetic stimulation (TMS) was used to measure changes in corticospinal excitability of two forearm muscles before and after temporary ischemic deafferentation of the hand in the presence or absence of hand pain prior to deafferentation. It was hypothesized: (1) that temporary ischemic deafferentation of the hand would increase corticospinal excitability in both the presence and absence of hand pain and (2) that the presence of hand pain prior to the deafferentation would lead to a greater increase in corticospinal excitability.

EXPERIMENTAL PROCEDURES

Subjects

16 subjects (10 males) with an average age of 30 years (standard deviation = 5.25) took part in two experimental sessions (*Pain*, *no Pain*) separated by 1–2 weeks and counterbalanced for session order. Subjects completed a medical questionnaire and were excluded if they presented any history of neurological or psychiatric disorders, physical problems (including pain, or neurological and musculoskeletal disorders) or contraindications for TMS (e.g. metallic or electronic implants, pregnancy, history of epilepsy). The study was approved by the local ethics committee (CER-2009-173, Institut de réadaptation en déficience physique de Québec) and subjects provided written informed consent in accordance with the Declaration of Helsinki.

Experimental design

Subjects sat comfortably in a relaxed position with their neck and head supported and with both forearms resting comfortably on a table. In both experimental sessions (*Pain, No Pain*) TMS measurements of corticospinal excitability were taken at four time points before inflation of a pediatric blood pressure cuff around the wrist (T0, T10, T20, and T40) and twice after cuff inflation (T60 and T75 – corresponding to 15 and 30 min after cuff inflation). Motor-evoked potentials (MEPs) were recorded from two muscles proximal to the cuff: flexor carpi radialis (FCR) and flexor digitorum superficialis (FDS). Electromyographic (EMG) activity was visually monitored (see below for off-line quantitative analysis) throughout the experiment to ensure that all measures were taken with the muscles completely relaxed. Using a numerical scale from 0 (no pain) to 10 (maximum imaginable pain) subjects verbally rated the level of pain in their hand at 11 time points (T0, 10, 15, 20, 25, 30, 35, 40, 50, 60, and 75).

In both experimental sessions the cuff was positioned just proximal to the right wrist and inflated to 220 mmHg from T45 to T80. The same inflation time was used for all subjects as previous studies have shown that changes in corticospinal excitability begin as soon as 15 min after cuff inflation and plateau prior to total deafferentation (Brasil-Neto et al., 1993; Vallence et al., 2012). An oximeter was placed on the right ring finger to confirm the absence of a pulse in the hand when the cuff was inflated and deafferentation was monitored using application of a 1.56-mN Semmes Weinstein monofilament. The majority of the participants (13/16 in each condition) did not reach complete deafferentation at the moment the cuff was deflated. In the *Pain* session a thin layer (~1 mm) of 1% capsaicin cream was applied on the dorsum of the right hand over a surface of ~8 cm^2. Based on previous studies with the capsaicin pain model (Bouffard et al., 2014; Lamothe et al., 2014) the cream was applied at T5 (40 min prior to cuff inflation) so that a sufficient level of capsaicin-induced pain would be attained prior to cuff inflation.

EMG recording and TMS stimulation

Surface Ag/AgCl electrodes (1 cm^2 recording area) were placed in a bipolar configuration over right FCR and FDS. EMG signals were amplified, band-pass filtered (20–1000 Hz) and digitized at a sampling rate of 2000 Hz (CED 1401 interface; Cambridge Electronic Design, Cambridge, UK).

Monophasic TMS was applied over the left motor cortex using a Magstim Bistim^2 with a 70-mm figure-of-eight coil