UNIVERSITÉ **LAVAL**

Syndrome douloureux régional complexe: apport de la neurostimulation périphérique - Plasticité cérébrale et amélioration cliniques

Mémoire

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RÉSUMÉ

Malgré des traitements spécialisés et multidisciplinaires, les personnes souffrant du syndrome douloureux régional complexe (SDRC) peuvent conserver de la douleur et des limitations fonctionnelles qui s'expliqueraient par des changements cérébraux persistants, entre autres dans le cortex moteur primaire (M1). Étudier les changements de fonctionnement du M1 permettrait de mieux comprendre comment utiliser la neurostimulation non invasive, comme les stimulations magnétiques répétées en périphérie (rPMS des muscles, connues pour influencer la plasticité cérébrale), pour normaliser la fonction motrice corticale, réduire la douleur et augmenter les gains cliniques.

Les objectifs de ce projet de maîtrise étaient donc de mieux comprendre la place dans la littérature de la neurostimulation non invasive en SDRC, de tester le fonctionnement de M1 en parallèle à la fonction sensorimotrice d'adultes avec SDRC au membre supérieur, ainsi que de mesurer l'effet d'une séance rPMS sur ces mesures et les symptômes de douleur de cette même population.

Il a été observé que, indépendamment du côté atteint, l'excitabilité du M1 était asymétrique en SDRC avec une association avec la douleur et les troubles du mouvement. Les participants avec SDRC présentaient également une diminution et une latéralisation altérée des mesures de fonction sensorimotrice.

Les rPMS ont permis de moduler bilatéralement l'excitabilité des M1 (diminution du débalancement) et, chez les personnes présentant avant la séance rPMS une hyperexcitabilité du M1 controlatéral au membre atteint, de diminuer leur douleur. Les rPMS ont également permis une amélioration de la fonction sensorimotrice et des changements centraux reliés à la plasticité cérébrale ont été mesurés dans l'hémisphère ipsilatéral au membre avec SDRC.

Les rPMS seules ou comme adjuvant aux thérapies conventionnelles de réadaptation représentent donc une approche prometteuse pour dépasser les gains cliniques en SDRC.

ABSTRACT

Despite specialized and multidisciplinary treatments, people suffering from complex regional pain syndrome (CRPS) can present with persistent pain and functional limitations likely due to brain changes such as in the primary motor cortex (M1). Studying the changes of M1 functioning would permit to better understand how to use noninvasive neurostimulation, as repetitive peripheral magnetic stimulation (rPMS of muscles, known to influence brain plasticity) in CRPS to enable the normalization of cortical motor function, the reduction of pain and to go beyond gains already reached.

The objectives of this master's project were thus to better understand the place in the literature of the noninvasive neurostimulation in SDRC, to test the functioning of M1 concurrent with the sensorimotor function of adults with CRPS of the upper limb, and to measure the effect of one rPMS session on these measures and pain symptoms of this same population.

It has been measured that M1 excitability was asymmetrical in CRPS, regardless of the impaired side, with an association to pain and movement disorders. Participants with CRPS also exhibited a decreased and an altered lateralization of the measures of sensorimotor function.

rPMS influenced bilateral M1 excitability (decrease of the imbalance) and, with people presenting before the rPMS session hyperactivity of M1 contralateral to the impaired limb, reduced pain. rPMS also improved sensorimotor function and central changes related to brain plasticity were measured in the hemisphere ipsilateral to the CRPS limb.

rPMS alone or as adjuvant to conventional rehabilitation therapies thus represent a promising approach to overcome clinical gains in CRPS.

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AMPA (récepteurs) : α-amino-3-hydroxy-5-méthylisoazol-4-propionate (récepteurs)

ANOVA : analyses de variance, de l'anglais « analysis of variance »

EMG : électromyographie

EVA : échelle visuelle analogue

FDI : muscle premier interosseux dorsal de la main, de l'anglais « first dorsal interosseus »

FDS : muscle fléchisseur superficiel des doigts, du latin « flexor digitorum superficialis »

FIFC : formulaire d'information et de consentement

HC : hémisphère controlatéral ou contrôlant le membre avec SDRC

HI : hémisphère ipsilatéral ou contrôlant le membre sans SDRC

ICF : facilitation intracorticale, de l'anglais « intracortical facilitation »

iTBS : blocs de stimulations intermittentes de fréquence thêta, de l'anglais « intermittent theta-burst stimulations »

M1 : cortex moteur primaire

MEP : potentiel moteur évoqué dans le muscle, de l'anglais « motor evoked potentials »

MSO : intensité maximale du stimulateur, de l'anglais : « maximal stimulator output »

NMDA (récepteurs) : N-methyl-D-aspartate (récepteurs)

NOS (ou SDRC de type NOS) : qui n'est pas mieux expliqué par tout autre condition, de l'anglais « not otherwise specified »

RMT : seuil moteur de repos, de l'anglais « resting motor threshold »

SICF : facilitation intracorticale avec conditionnement à courte latence, de l'anglais « short-interval intracortical facilitation »

SICI : inhibition intracorticale avec conditionnement à courte latence, de l'anglais « short-interval intracortical inhibition »

rPMS : stimulations magnétiques répétées en périphérie, de l'anglais « repetitive Peripheral Magnetic Stimulations »

rTMS : stimulations magnétiques transcrâniennes répétitives, de l'anglais « repetitive transcranial magnetic stimulation »

SDRC : syndrome douloureux régional complexe

SENIAM : électromyographie de surface pour l'évaluation non-invasive des muscles, de l'anglais « surface electromyography for the non-invasive assessment of muscles »

SNC : système nerveux central

TMS : stimulations magnétiques transcrâniennes, de l'anglais « transcranial magnetic stimulations »

À mon fils Costa, pour avoir été une boussole lorsque j'avais perdu le nord,

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AVANT-PROPOS

Ce mémoire est le résultat de trois ans de travail et a mené à la rédaction de trois articles. Je tiens à remercier chaudement mon directeur, Cyril Schneider, PhD avec qui j'ai travaillé sur les articles qu'il a relus et corrigés ainsi que pour sa révision de mon mémoire. Comme j'ai écrit la version initiale et que j'ai été directement impliquée dans toutes les étapes de la réalisation des articles (revue de littérature, élaborations des études, recrutement des participants, prise de mesures, analyses brutes et statistiques, création des tableaux et figures, rédaction et correction), j'en suis l'autrice principale. Toutefois, j'ai eu le plaisir de collaborer avec des co-auteurs nommés ci-après que je remercie grandement pour leur travail et rétroaction.

Le premier article est une revue de littérature accepté avec corrections par le journal « Frontiers in Pain Research ». Il brosse le portrait de la problématique à l'étude et explique le rationnel du projet de maîtrise. Le deuxième co-auteur, Andrea Zangrandi, a collaboré au développement de la version finale de l'article, notamment par la mise à jour de la revue de littérature entre sa rédaction et sa soumission.

Les articles deux et trois présentent des résultats originaux provenant des études cliniques réalisées dans le cadre de ma maîtrise et sont respectivement en préparation pour soumission au journal « Pain » et accepté avec corrections par le journal « Frontiers in Pain Research ». Le deuxième article présente les différences entre des participants vivant avec un syndrome douloureux régional complexe et des participants sans douleur. La deuxième co-autrice, Alicia Delisle, a participé à la prise de données et aux analyses de deux des participants. Le troisième article présente l'effet d'un traitement expérimental chez les participants avec un syndrome douloureux régional complexe (différences entre les temps avant- et après-traitement et comparés aux sujets sans douleur). Le deuxième co-auteur Andrea Zangrandi a participé à la correction de l'article.

INTRODUCTION

L'introduction du mémoire comporte deux sections.

La première est une revue de littérature narrative sur le syndrome régional douloureux complexe (SDRC) exposant la problématique, mais également la littérature et les recommandations supportant la réalisation des deux études expérimentales effectuées au cours de cette maîtrise (présentées dans les chapitres 2 et 3). Cet article de revue en anglais est en préparation pour soumission au journal Neurophysiologique Clinique */ Clinical Neurophysiology*.

La deuxième section de l'introduction expose le rationnel, les objectifs, les hypothèses et l'approche de ces deux études expérimentales.

SECTION 1 : ARTICLE 1 - *« Complex Regional Pain Syndrome (CRPS). A Comprehensive Review on Plastic Changes supporting the Use of Noninvasive Neurostimulation »*

« Syndrome douloureux régional complexe (SDRC). Une revue de littérature narrative sur les changements plastiques supportant l'utilisation de la neurostimulation noninvasive »

COMPLEX REGIONAL PAIN SYNDROME (CRPS). A COMPREHENSIVE REVIEW ON PLASTIC CHANGES SUPPORTING THE USE OF NONINVASIVE NEUROSTIMULATION

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RÉSUMÉ

Contexte : Le syndrome douloureux régional complexe (SDRC) est une pathologie rare très invalidante en raison, entre autres, des douleurs importantes affectant typiquement un (parfois plusieurs) membre(s). La physiopathologie du SDRC est complexe et multifactorielle. Les anomalies périphériques et somatosensorimotrices peuvent refléter des changements inadaptés du système nerveux central. Ces changements de volume, connectivité, activation, métabolisme, etc. pourraient être des marqueurs aidant à comprendre la chronicisation et le caractère réfractaire aux traitements conventionnels et contribuant à développer des traitements plus efficaces.

Objectif : Cette revue vise une meilleure compréhension de la physiopathologie du SDRC et des changements cérébraux associés et expliquant la chronicisation, rappelle les approches thérapeutiques conventionnelles et leurs limites et discute des écrits scientifiques récents soutenant l'utilisation de techniques de neurostimulation non invasives et non pharmacologiques en SDRC.

Conclusion : Malgré des perspectives prometteuses, plus d'études sont nécessaires pour supporter l'efficacité de la neurostimulation non invasive en SDRC. L'intégrité de la voie corticospinale et les changements cérébraux devront être documentés afin de personnaliser les protocoles de neurostimulation. La neurostimulation non invasive du cerveau ou des nerfs/ muscles/ racines spinales, seule ou combinée aux traitements conventionnels, représente un terrain fertile pour des recherches plus approfondies en vue de développer des approches plus efficaces dans la gestion de la douleur en SDRC.

Mots-clés : Syndrome douloureux régional complexe (SDRC); neurostimulation non invasive; rTMS; rPMS; tDCS; TENS; plasticité neuronale mal-adaptée; douleur chronique

ABSTRACT

Background: The complex regional pain syndrome (CRPS) is a rare debilitating disorder characterized by severe pain affecting one or more limbs. CRPS presents a complex multifactorial physiopathology. The peripheral and somatosensorimotor abnormalities may reflect maladaptive changes of the central nervous system. These changes of volume, connectivity, activation, metabolism, etc. could be keys to understand chronicization, refractoriness to conventional treatment and how to develop more efficient treatments.

Objective: This review focused on better understanding CRPS physiopathology and the brain changes explaining chronicization, recalling the conventional therapeutic approaches and their limitations, and discussing the up-to-date literature supporting the use of non-pharmacological noninvasive neurostimulation techniques in CRPS.

Conclusion: Future work is warranted to foster the evidence of the efficacy of noninvasive neurostimulation in CRPS. The integrity of corticospinal pathways and neuronal status (brain changes) will have to be documented in order to individualize protocols of neurostimulation adapted to each person. Noninvasive neurostimulation of brain or of nerve / muscles / spinal roots, alone or in combination with conventional therapy, represents a fertile ground for further investigations with a view of developing more efficient approaches for pain management in CRPS.

Keywords: Complex regional pain syndrome (CRPS); noninvasive neurostimulation; rTMS; rPMS; tDCS; TENS; maladaptive neuronal plasticity; chronic pain

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INTRODUCTION

Complex Regional Pain Syndrome (CRPS): an Overview

Complex Regional Pain Syndrome (CRPS) is a rare debilitating disorder characterized by severe and persisting pain affecting one (sometimes more) limb(s). Signs and symptoms are disproportionate owing to the inciting event, and include spontaneous and/or movement-induced pain, sensory impairment (allodynia, hyperesthesia), autonomic dysregulation (changes in skin temperature and/or colour, abnormal sweating) and motor abnormalities (joint stiffness, tremor, dystonia and muscle weakness) The inciting event is usually traumatic such as fracture, surgery, sprain or contusion, but in around 10% of cases the precipitating cause remains unknown. CRPS is divided in two main categories, based on the absence (type I, 90% of all CRPS cases) or presence (type II) of nerve lesion at the periphery (Borchers and Gershwin, 2014). A third type ("Not Otherwise Specified, or "NOS") includes patients who do not fulfil the diagnosis criteria, but whose signs and symptoms cannot be better explained by another diagnosis (Harden et al., 2010). Individuals who were diagnosed only at a later stage when some of the symptoms were resolved can also enter the NOS category (although retrospective inspection of medical history shows that they would have fulfilled all criteria for CRPS diagnosis if only they had been assessed at the acute stage). The upper limb is more often affected (almost 60% of cases) than the lower limb and many cases resolve within the first year (Bean et al., 2014, Bruehl, 2015). However, more than half of people diagnosed with CRPS still present deficiencies as diminution of strength or stiffness one year after onset (Bean et al., 2014), 62% of diagnosed people still have activities of daily living limitations 3 to 9 years after onset (Geertzen et al., 1998) and most are unable to come back to their previous occupation, need workplace adjustments or are declared officially disabled (Borchers and Gershwin, 2014). CRPS mostly occurs at the age range of 40-70 years old (median of 46 years old), three to four times more frequently in women (Veldman et al., 1993) and rarely in children (less than 10% of all cases, usually in early adolescence) (Abu-Arafeh and Abu-Arafeh, 2016). Worldwide, CRPS incidences vary from 5.5 to 26.2 per 100.000 person per year (de Mos et al., 2008, Sandroni et al., 2003). Although some psychological factors are often concomitant with the CRPS, no link has yet been drawn

between development nor aggravation of CRPS and psychological factors (Bean et al., 2015, Beerthuizen et al., 2009, de Mos et al., 2008), except for the association reported between traits of anxious personality and CRPS development (Dilek et al., 2012).

Due to the variety and complexity of its symptoms and a lack of recognition as a disease, CRPS was historically referred to by means of different names (e.g., reflex sympathetic dystrophy, algodystrophy, causalgia, shoulder-hand syndrome, etc.; see (Merskey, 1986). The 1994 International Association for the Study of Pain (IASP) adopted the appellation of CRPS and affined the diagnosis by establishing specific descriptive criteria. The latter were then improved by the "Budapest Criteria" (see Table 1) (Harden et al., 2010), still used to diagnose CRPS (Merskey and Bogduk, 1994; Harden *et al.*, 2013). Today, CRPS physiopathology remains not well understood, especially concerning the brain mechanisms responsible for its deterioration into a chronic condition. The steps of conventional treatments vary a lot depending to the culture and local practices from one establishment to another, are not well supported by evidence-based data and do not usually address the underlying maladaptive changes of brain function (O'Connell et al., 2013).

(Insert Table 1 near here)

Objectives of the Review

Therefore, the present review aims to: 1) better understand the complex physiopathology of CRPS; 2) give an overview of the brain-related changes in CRPS that could play a role in chronicization; 3) recall the conventional therapeutic approaches and their limitations; and 4) review the up-to-date literature supporting the use of non-pharmacological noninvasive neurostimulation techniques to treat CRPS*.

*Invasive stimulation has been excluded due to the impact of surgery and related pain on neural plasticity.

PHYSIOPATHOLOGY OF CRPS

To date, the pathophysiology of CRPS remains largely discussed as multifactorial (Birklein and Dimova, 2017, Bruehl, 2010b). The prevalence and intensity of each mechanism involved can vary between patients and over time, thus laying the stress on the difficulty to treat CRPS and the need for individualization of treatments (Bruehl, 2010; Marinus *et al.*, 2011). Peripheral sensitization, dysregulation of the autonomic nervous system and immune dysfunction are known to contribute to the occurrence and development of the syndrome. However, a growing line of research points out that autonomic and sensorimotor disturbances should be viewed as a manifestation of underlying plastic changes that occur in the central nervous system (CNS) (Janig and Baron, 2002, Maihofner et al., 2003, Maihofner et al., 2010). Therefore, brain changes and maladaptive neuronal plasticity will be discussed in a distinct section below.

Neuronal plasticity is the capacity of neurons to modulate the efficacy of their synaptic connections with other elements of CNS (neurons, glial cells). Long-term potentiation (**LTP**) and long-term depression (**LTD**) characterize respectively the increase and decrease of synaptic strength. LTP and LTD act via, among others, receptors of glutaminergic N-methyl-D-aspartate (**NMDA)** and neuromodulators (dopamine, serotonin, acetylcholine, norepinephrine) can influence the duration of the changes undergone (Hasselmo, 1995; Massé-Alarie and Schneider, 2011; Pell, Roth and Zangen, 2011). The more often synaptic circuits are used, the higher will be LTP. Thus, the more often pain pathways are activated, the lower will be the threshold to trigger pain messages.

Peripheral Changes and Central Sensitization

The inciting trauma of CRPS is usually responsible for the inflammation and the immune cascade that trigger the proliferation of connective tissue cells associated with contracture and of keratinocytes that produce inflammatory cytokines; the inflammatory cytokines activate osteoblasts and osteoclasts responsible for the formation and resorption of the bones (Russo et al., 2018). This results in less bone density and a sensitization of peripheral nociceptors in CRPS, i.e. a pain threshold now reached by stimuli of lower intensity (decreased pain threshold). Precisely, some C-fibers (nociceptive afferents), which usually transmit mostly nociceptive information from periphery to spinal cord, begin to produce

inflammatory neuropeptides (e.g., substance P); these neuropeptides activate mast cells that release in turn chemical mediators associated with the symptoms observed in acute phase, such as the edema, skin red coloring and warmth or the hair growth (Birklein and Schmelz, 2008, Birklein et al., 2001). It follows an oxidative stress for the patient in the acute phase, as denoted by a higher number of oxygen-free and hydroxyl radicals in the saliva and serum (Eisenberg et al., 2005). At the chronic stage (symptoms present for 6 months and more), pro-inflammatory factors are still present, but the inflammatory profile (presence among others of interleukins 1 and 6 in the cerebrospinal liquid and 1, 2 ,4 and 7 in blood samples) is different than during the acute phase (symptoms from less than 6 months; presence of interleukins 8 and TNFα receptors I and II in blood) (Parkitny et al., 2013). Neurogenic inflammation is also reported in parallel with CNS changes and reciprocal influences are suspected, likely the former influencing the latter in the acute phase and the reverse in the chronic phase (Russo et al., 2018). It is noteworthy that cutaneous innervation seems affected even in type-1 CRPS (no nerve lesion) as reflected by lower axonal density (Oaklander *et al.*, 2006), lower C-fiber and Aδ-fiber density and changes in hair follicles and sweat glands innervation (Albrecht *et al.*, 2006). It was also suggested that minimal distal nerve injury could be the initial trigger for the cascade of events leading to CRPS (Oaklander *et al.*, 2006; Bruehl, 2010b), thus likely explaining why some people do not recall any inciting trauma having led to their CRPS.

Dysregulation of the Autonomic Nervous System

CRPS has been considered for a long time as a hyperactivity of the autonomic nervous system. This was because of the changes of color, temperature and sweating of the skin, and people were diagnosed CRPS only if symptoms were reduced by a stellate ganglion block or by a sympathetic block of the lumbar chain (Harden et al., 2013; Borchers and Gershwin, 2014; Schlereth, Drummond and Birklein, 2014). Whether the autonomic nervous system is involved in CRPS pathophysiology is controversial, some authors having reported sympathetic dysfunction in the acute phase and its normalization over three months (Wasner *et al.*, 1999; Gradl and Schürmann, 2005), others having denoted a normal activity or an increase (in both early and late stages) (Casale and Elam, 1992; Drummond, Finch and Gibbins, 1996; Goldstein, Tack and Li, 2000; Borchers and Gershwin, 2014). This warrants

other studies on that topic because dysregulation of the autonomic nervous system may at least contribute to state changes (warm vs. cold limb) that cannot be only due to local inflammation (Schlereth, Drummond and Birklein, 2014; Knudsen *et al.*, 2019)

Immune Dysfunction

The last decade research has revealed that antibodies (e.g., of adrenergic and cholinergic receptors) could be present in the serum samples of people with CRPS (likewise inflammatory markers as cytokines). This suggests that the immune system could play a role in chronicization (long-term duration) of CRPS (Kohr *et al.*, 2011; Dubuis *et al.*, 2014; Birklein and Dimova, 2017). Research in this field is booming and the upcoming advent of knowledge ought to be considered in future reviews.

BRAIN CHANGES AND MALADAPTIVE NEURONAL PLASTICITY

The brain changes mostly reported in CRPS are presented in Table 2 and illustrated in Figure 1 for grey matter volume, extent or shift of cortical maps (either sensory or motor), connectivity, activation or metabolism of brain structures and alterations of neurophysiological outcomes commonly collected by means of Transcranial magnetic stimulations (TMS) of M1.

Brain Volume Changes

Neuroimaging studies widely showed brain changes in CRPS (which are not all in agreement). This includes a decrease of the grey matter volume in the right anterior insula, orbitofrontal cortex (OFC), right ventromedial prefrontal cortex (vmPFC), cingulate cortex, putamen, sensorimotor cortices and parietal areas (Azqueta-Gavaldon et al., 2020, Geha et al., 2008, Shokouhi et al., 2018), and an increase of the grey matter volume in the two dorsal putamen, right hypothalamus, dorsomedial prefrontal cortex, primary motor cortex contralateral to the CRPS limb and choroid plexus (Barad et al., 2014, Zhou et al., 2015). These neuroanatomical changes were observed with functional significance owing to emotion, somatosensory processing and control of movement.

Brain Mapping and Functional Changes

Primary Somatosensory Cortex (S1)
Except for one study (Mancini et al., 2019), most neuroimaging studies in CRPS ─performed with magnetoencephalography (MEG), encephalography (EEG) or functional magnetic resonance imaging (fMRI)─confirmed a significant shrinking of the S1 hand representation in the hemisphere contralateral to the painful side, as compared to the unaffected hand or to pain-free subjects (Di Pietro et al., 2013, Juottonen et al., 2002, Maihofner et al., 2003, Pfannmoller et al., 2019, Pleger et al., 2004b, Vartiainen et al., 2008). One study denoted that the center of gravity of S1 hand area was shifted to the lip area (Maihofner et al., 2003). EEG recordings of the higher amplitudes of somatosensory evoked potentials (SSEP) following median / ulnar nerve stimulation on the CRPS side showed that the S1 CRPS-hand area was

more responsive to peripheral signal than on the unaffected side or in pain-free people (Juottonen et al., 2002) but peak timing was unchanged (Juottonen et al., 2002, Maihofner et al., 2003, Pleger et al., 2004b, Vartiainen et al., 2008). The results of these studies (shrinking of the S1 vs higher amplitudes of SSEP) could appear contradictory but implicate a lot of mechanisms central (cortical and spinal) as peripheral which make their interpretation difficult. Some fMRI studies reported a smaller activation and weaker blood-oxygen level-depended signal (BOLD) in the CRPS-related S1 area as compared to the other side (Pleger et al., 2005, Pleger et al., 2004b) or to pain-free subjects (Pleger et al., 2006), but other studies did not find any between-hemisphere difference (Freund et al., 2010). Somatosensory excitability was assessed by SSEP using paired-pulse evoked suppression paradigm. This technique requires the application of two asynchronous stimulation of the median nerve at the level of the wrist, with the expectation that the amplitude of the second SSEP in S1 is significantly smaller than the first. Results showed a marked bilateral reduction of cortical disinhibition in specific tasks, as compared to pain-free subjects, thus suggesting an impairment of somatosensory circuits (Galea, 2012, Lenz et al., 2011).

Motor Areas

Neuroimaging Studies. The activation of the primary motor cortex (M1) and supplementary motor area (SMA) recorded by fMRI during finger tapping with the CRPS-affected limb was shown to be increased bilaterally but more markedly on the ipsilateral side (Maihofner et al., 2007). The technique of arterial spin labelling was used to test the motor resting neural activity and it was found that blood perfusion in M1 and SMA was increased in people with chronic CRPS (Shokouhi et al., 2018). Also, the technique of positron emission tomography with F-Fluorodésoxyglucose (*FDG-PET*) tested that the metabolisms of M1 and dorsal prefrontal cortex contralateral to the CRPS-affected side was decreased as compared to pain-free people (Shiraishi et al., 2006). Two MEG studies investigated the 20-Hz rebound of M1 in response to somatosensory stimulation, which reflects the increase of M1 excitability after a period of suppressed activity due to the somatosensory stimulation. In people with CRPS, 20-Hz oscillations (associated with M1 inhibition mechanisms) did not adapt properly in response to tactile (Juottonen et al., 2002) and noxious (Kirveskari et al., 2010) stimuli, thus suggesting the alteration of M1 inhibition processes.

Transcranial Magnetic Stimulation (TMS) Studies. TMS is a reliable tool widely used to study M1 (function and mapping) and to characterize markers of M1 and corticospinal excitability in CRPS (Nardone et al., 2018). Some TMS outcomes were reported to be different in CRPS and others unchanged as compared to pain-free people. Mapping of M1 representation by single-pulse TMS in people with type-1 CRPS showed that the affected hand had a smaller M1 representation than the unaffected with a centre of gravity more variable but not significantly different between sides or compared to pain-free people (Krause et al., 2006).

TMS paradigms enable to investigate the different mechanisms of M1 inhibition and CRPS studies showed that some inhibitory processing could be altered and others not. Paired-pulse TMS of M1 at inter-stimulus intervals below 4 msec showed that the short-interval intracortical motor inhibition (SICI, depending on GABA$_A$ receptors activity) (Di Lazzaro et al., 2017) was reduced, as compared to pain-free individuals, either in both hemispheres (Krause et al., 2004, Schwenkreis et al., 2003) or only in M1 contralateral to CRSP-side (Eisenberg et al., 2005, Lefaucheur et al., 2006, Pfannmoller et al., 2019). Also, the long-afferent inhibition (LAI), which investigates sensorimotor integration, i.e. the cholinergic inhibition of TMS-evoked motor potentials (MEP) by sensory afferents volley triggered by an electrical stimulation of a peripheral nerve (Di Lazzaro et al., 2017), was shown to be reduced in M1 contralateral to the affected hand (Morgante et al., 2017). However, at shorter inter-stimulus intervals aiming at testing the short-afferent inhibition (SAI), the MEP reduction by median nerve stimulation was unchanged as compared to pain-free subjects (Morgante et al., 2017, Turton et al., 2007). In addition, the paired associative stimulation, e.g., 180 pairs of nerve electric stimulation and TMS of M1, induced the same capacity of sensorimotor plasticity (MEP increase) in CRPS as in pain-free (Morgante et al., 2017). Thus, circuits connecting S1 and M1 seem to work properly in CRPS and may not explain differences in M1 inhibitory function and plasticity. Of note, the cortical silent period following a MEP (superimposed on background isometric contraction) is a different mechanism of M1 inhibition which depends on GABA$_B$-receptors (Rossini et al., 2015) and

which was shown to be comparable between sides in CRPS and to pain-free subjects (Krause et al., 2005, Morgante et al., 2017).

TMS studies further showed controversial findings in CRPS for M1 facilitation. Indeed, paired-pulse TMS of M1 at inter-stimulus intervals over 10 msec showed that the intracortical motor facilitation (ICF depending on NMDA glutamatergic receptors, Reis et al., 2008) is either comparable between sides in CRPS and to pain-free subjects (Schwenkreis et al., 2003), or significantly increased in the hemisphere contralateral to CRPS side (Morgante et al., 2017).

Among other TMS-of-M1 outcomes in CRPS that were unchanged between hemispheres or as compared to pain-free people is the resting motor threshold (RMT) and the amplitude of the MEP tested at 120% RMT (Krause et al., 2004, Morgante et al., 2017, Schwenkreis et al., 2003, van Velzen et al., 2015). RMT is the minimal TMS intensity required to evoke five MEP $\geq$ 50uV out of 10 successive trials in the target muscle at rest and it represents the basic M1 excitability (Rossi et al., 2009). The MEP amplitude informs on the corticospinal excitability and depends on the extent of M1 tissue responding to TMS, the motoneuronal excitability and on the synchronicity of descending volleys to excite the alpha-motoneurons in the spinal cord. Of note, the same authors showed that MEP amplitudes were either unchanged in CRPS (Krause et al., 2004) or bilaterally decreased (Krause et al., 2005), as compared to pain-free subjects. Results of these studies are summarized in the Table 2.

Non-Motor Areas
FMRI recordings during painful stimulation in people with CRPS denoted an increase (either contralateral to the site of stimulation or bilateral) of the responses in the posterior cingulate cortex (PPC), in parallel with a decrease of posterior opercular cortex (Freund et al., 2010). Several studies found a bilateral increase of the responses in SII, cingulate cortex, parietal cortex, cerebellum, as well as in the right insula and the right thalamus (Shiraishi et al., 2006). Altered thalamic perfusion was also found contralateral to the affected limb (Fukui, 2003, Fukumoto et al., 1999).

Functional Connectivity

Changes of brain activation (neuroimaging data) and M1 excitability (TMS data) reported above in CRPS could be related to a substantial reorganization of functional connectivity between brain structures. Diffusion-tensor imaging (DTI, a technique using MRI-recorded direction of water within the myelinated fibres to reconstruct brain tractography) helped detect on one side the increase of connectivity between VMPFC and insula, between putamen and pre/postcentral gyri (Azqueta-Gavaldon et al., 2020) and, on the other side, a decrease of connectivity between VMPFC and basal ganglia (BG) (Geha *et al.*, 2008) and between putamen and cerebellum (Azqueta-Gavaldon et al., 2020). Precisely, the involvement of BG in the physiopathology of CRPS was recently hypothesized (Azqueta-Gavaldon et al., 2017). In support of this hypothesis are the increase of BG activation to nociceptive stimuli in children (Lebel et al., 2008, Linnman et al., 2013) and adults with CRPS (Freund et al., 2010) and the bilateral alteration of the functional linking between the intraparietal sulcus and caudate nuclei in people with CRPS (Bolwerk et al., 2013). Resting-state fMRI (rsfMRI) studies also brought about evidence of the alteration of the default mode network in CRPS (Bolwerk et al., 2013, Kucyi et al., 2014, Zang et al., 2014).

NMDA Receptors

Studies in chronic pain also suggested that glutamate NMDA receptors could play a pivotal role in the synaptic plastic changes (Puchalski and Zyluk, 2016). Precisely, isotropic NMDA receptors work as gates for massive inflows of calcium ions in the postsynaptic neuron when previously depolarized (Purves *et al.*, 2011), thus substantially contributing to the LTP-like phenomenon of neuroplasticity. However, in chronic pain, the NMDA receptors lead to the activation of sensory and nociceptive pathways at lower threshold of peripheral stimuli (a change referred to as "central sensitization") (Woolf, 2011). In CRPS, some studies showed positive results after the administration of an NMDA-antagonist such as ketamine, either alone (Azari et al., 2012, Correll et al., 2004, Ushida et al., 2002) or in combination with other medications (Gustin et al., 2010).

(Insert Table 2 and Figure 1 near here)

Discussion on Brain Changes

Neuroanatomical and functional brain modifications in CRPS (see Table 2) rely on somatosensory, motor and emotional networks, in one or both hemispheres but are still not consensual in the literature, perhaps because studies did not test the same time-intervals after the onset of the symptoms (acute vs. chronic stage). Controversy of findings reported may be also due to the fact that it is not clear whether brain changes were related to prolonged pain, acute symptoms, non-use of the CRPS limb, or whether they were specific to CRPS or common to other chronic pain conditions. Another explanation could be that CRPS influences brain in different ways from one person to another. This different influence on brain between individuals could explain the chronicization (symptoms not resolved by treatment) and the different alteration of body perception (representation of one's body on the basis of proprioceptive, somatosensory, cutaneous and vestibular information) (Kuttikat *et al.*, 2016) present in some people but not others. S1 and M1 map distortion in CRPS (Bruehl, 2010a) can alter sensorimotor integration e.g., people with CRPS take longer to recognize their affected hand laterality (Moseley, 2004) leading to a mismatch between sensory information and movement, thus hindering motor control and generating pain. One question is whether conventional treatments in CRPS that influence sensory integration, such as rehabilitation, are sufficient to normalize these brain changes? Another question is whether brain changes in CRPS could be related to a significant reduction of sensory information and integration, as already shown in other pain conditions (e.g., phantom limb pain) for map reorganization (Bruehl, 2010a). This may lead to the new hypothesis that nurturing brain with sensory information which is coherent with painless movement of the CRPS limb could positively influence brain plasticity and decrease pain.

Conventional Treatment in CRPS and Limitations Owing to Brain Changes

Multidisciplinary Management

Treatment in CRPS which is conventionally thought as optimal includes pharmacotherapy, rehabilitation (physical and/or occupational therapy) and psychotherapy. Indeed, it is generally acknowledged that multidisciplinary care and follow-up in CRPS would be the most efficient to improve the condition, but no randomized controlled trial yet supports this view (Ballantyne *et al.*, 2012; Gatchel *et al.*, 2014; Bruehl, 2015). A multi-facetted treatment should address the multi-dimension aspects of chronic pain related to the brain web interconnectivity between circuits of pain, stress, emotions, even addiction and memory. Stress or negative emotions experienced by people render pain intolerable, more suffering (Burgess et al., 2019). Thus, health practitioners should avoid words or sentences that can be easily misinterpreted, stressful and that can lead to pain catastrophization (e.g., "your limb's control is screwed up", "your vertebra is displaced", "you have a tear in the intervertebral disc", etc.), thus worsening the patient's condition. Rather, and in parallel to treatment presented below, health professionals should explain and normalize deficiencies and symptoms in relation to the pain condition (e.g., by acknowledging the presence of depressed mood), teach pain (understanding the reason why one suffers reduces anxiety and interferences in daily activities; learn to manage their energy and daily activities, etc.), break misconceptions, teach relaxation or breathing techniques, etc. (Moseley and Butler, 2015).

Medical Intervention

Combination of Medication

In acute stage particularly, pharmacological treatment includes steroids, bisphosphonates, and dimethylsulfoxide cream (Birklein and Dimova, 2017). Guidelines for neuropathic pain treatment (including CRPS) advise, if simple medication does not reduce pain in the first three to four weeks, the use of one drug among this four: amitriptyline, duloxetine, gabapentin or pregabalin and to try one of the other three medications if the first one did not help (National Institute for Health and Care Excellence (NICE), 2013; Royal College of Physicians, 2018). Combining medication usually aims at reducing pain intensity with

limited side effects. In general, people diagnosed with CRPS are prescribed with one pain killer (acetaminophen) or nonsteroidal anti-inflammatory drug (AINS) and/or a selective inhibitor of cyclooxygenase-2 (COX-2) with one serotonin-noradrenaline reuptake inhibitor (SNRI) or tricyclic antidepressants (TCA antidepressants); if not yet relieved, they add one gabapentinoid and/or opioid (Truchon and Marquette, 2015).

Anaesthesia

Two Cochrane systematic reviews in CRPS reported, respectively, no evidence of reduction of pain with local anesthetic sympathetic blockade and adverse effects in almost half of the studies analysed (Stanton *et al.*, 2013), and moderate evidence of no efficacy of intravenous regional blockage with guanethidine with risks of significant adverse events and low quality evidence of no efficacy of local anesthetic sympathetic blockade (O'Connell *et al.*, 2015). It seems however that topic creams, even local anesthetic patches, could be useful clinically even if not supported by data-based evidence (Palmer, 2015).

Ketamine Injection

A few studies reported that pain was reduced after ketamine injections in people with CRPS (Kiefer *et al.*, 2008; Schwartzman *et al.*, 2009; Azari *et al.*, 2012; Puchalski and Zyluk, 2016; Sorel *et al.*, 2018; Zhao, Wang and Wang, 2018) but only low-quality evidence supports its use (O'Connell et al., 2013). There is recent evidence however that ketamine, which is an antagonist of the NMDA receptors (via the blockade of the receptors canals pores), can decrease central sensitization (Puchalski and Zyluk, 2016) but with few side effects (systemic effect).

Rehabilitation

Physical or occupational therapy usually combines different modalities which are specific to the person's deficits and symptoms. Indeed, the CRPS treatment in rehabilitation includes teaching the patient how to monitor the mechanical stress on the painful joint, how to manage energy, sleep or working postures, etc., proposes personalised physical exercises, manual therapy (movement driven by the therapist, soft tissue and myofascial techniques, etc.), electrotherapy or thermotherapy (transcutaneous electrical nerve stimulation or TENS;

ultrasound, interference current, etc.) and CRPS-specific sensorimotor strategies: desensitization, graded motor imagery (GMI, with its three phases: discriminating laterality, mental motor imagery and mirror therapy), tactile sensory discrimination training, etc. (Smart et al., 2016) Given all the cortical sensory and motor changes reported in CRPS (see previous section), the sensorimotor strategies should be efficient to resolve CRPS, as already supported by a few original works (Maihöfner et al., 2010; Lagueux *et al.*, 2012; Cossins *et al.*, 2013; de Souza *et al.*, 2015). However, two systematic reviews reported low-quality evidence for the efficacy of GMI or mirror therapy for pain reduction and function improvement in CRPS (O'Connell *et al.*, 2015) and very low-quality evidence for long-term efficacy of GMI, multimodal physiotherapy and mirror therapy (Smart et al., 2016). The two reviews further noticed that the lack of high-quality data-based evidence challenges the development of guidelines to treat CRPS. The present work suggests that the lack of evidence could be due to the fact that one size does not fit all, i.e. people experiencing pain differently and responding to treatment differently, thus a same treatment being not efficient for everyone. That lays the stress on the fact that a better understanding of individual brain changes will allow the development of personalized rehabilitation protocols to be tested in research.

Psychological Therapy

As introduced above, pain is multi-facetted and CRPS has been considered by some as a global and excessive body's response to the perception of a threat (via an injury) to tissues integrity (Bean *et al.*, 2015). Psychological therapies can help solve CRPS by intervening on the predisposing factors: stress, anxiety, depression, fear of movement, addictions (drugs, alcohol, video games, etc.), self-esteem, social participation, etc. Psychotherapy usually also encourages patients to be involved actively in their rehabilitation and treatment plan (Bean *et al.*, 2015; Goh, Chidambaram and Ma, 2017).

Conventional Treatment Evidence

CRPS remains difficult to cure and there is almost no evidence to support therapies currently used (Bruehl, 2015, O'Connell et al., 2013, Truchon and Marquette, 2015). This lack of efficacy may rely on two limitations. First, most people with CRPS experience pain only by

the thoughts of moving the painful part, thus the conventional treatments usually create temporary additional pain that can maintain neural maladaptive plasticity of pathways, connectivity and structures, and reduce treatment after-effects. Then, despite the knowledge of brain changes in CRPS, literature is scarce about maladaptive plasticity normalization with clinical significance. The way CRPS is treated should be revisited by implementing approaches able to influence sufficiently the neuroplasticity at the origin of functional improvement. That is why, noninvasive painless neurostimulation techniques are such a promising avenue in CRPS.

PRINCIPLES SUPPORTING THE USE OF NONINVASIVE NEUROSTIMULATION IN CRPS

The noninvasive neurostimulation techniques for pain management aim at influencing the neuronal plasticity that enables clinical improvement. These techniques include cortical and peripheral repetitive magnetic stimulation (rTMS/rPMS), transcranial direct current stimulation (tDCS) and transcutaneous electrical nerve stimulation (TENS).

rTMS and rPMS

Repetitive magnetic stimulation approaches consist of painless magnetic pulse trains administrated either transcranially (rTMS) over M1 or dorsal prefrontal cortex, or peripherally (rPMS) over nerve or muscles. The manipulation of the stimulation parameters, such as frequency (from 0.1 Hz up to 50 Hz), train duration, inter-train interval, coil positioning and cortical/peripheral target enables to modify the actual net after-effects in the neural tissues beneath the coil, i.e. facilitating or inhibiting effect (for details, see Pell et al., 2011; Beaulieu and Schneider, 2015). In clinical pain studies, rTMS is usually applied over M1 at subthreshold intensity (below the intensity eliciting a muscle response via the corticospinal pathway). The after-effects (LTP-like excitation or LTD-like inhibition) can last from minutes to several hours, depending on the protocol and the task tested, and can induce changes of excitability and function in remote areas (Lefaucheur et al., 2008). Long-lasting rTMS-induced analgesic effects likely rely on LTP-like mechanisms (see the previous section on central sensitization) via an influence on glutamatergic networks (Moisset et al., 2016). rPMS is commonly applied over a spinal root, nerve or muscle belly at a suprathreshold intensity to trigger muscle contraction (Massé-Alarie and Schneider, 2011). It is hypothesized that it may recruit proprioceptive afferents directly by the depolarization of sensory fiber terminals and indirectly via the induction of repeated contractions and joint movements (Beaulieu and Schneider, 2015). Also, due to minimal recruitment of nociceptive receptors (the magnetic pulse bypasses skin without resistance), it is painless and the proprioceptive message mediated to brain is not "contaminated" by cutaneous information (Beaulieu and Schneider, 2015). Thus, rPMS nicely mimics the contraction / relaxation process of one muscle or a group of muscles and the pure proprioceptive information generated is coherent with the appropriate motor control to influence sensorimotor plasticity at the origin of motor improvement or pain reduction (Beaulieu and Schneider, 2015). In

support, it is shown in motor disorders or in chronic pain that rPMS influence the cortical markers with clinical significance (Krause and Straube, 2008).

tDCS

tDCS is administered by means of two electrodes (the anode and the cathode) fixed on the scalp. Many studies have shown a greater reduction of pain when the anode is positioned above M1, as compared to S1 or the dorsolateral prefrontal cortex (O'Connell et al., 2018, Plow et al., 2012). The cathode is usually positioned on the forehead, over the supraorbital area, contralateral to M1 stimulated. M1 stimulation by tDCS may activate corticospinal and corticothalamic projections which in turn influence the activity of regions of the diencephalon, brain stem and spinal cord involved in pain modulation mechanisms (Cuypers et al., 2013, Martel et al., 2017). Specifically, studies show that the effectiveness of tDCS in relieving chronic pain and maintaining effects depends on key stimulation parameters such as electrode position (anodal M1 montage), stimulation intensity (2 mA), and number of weekly sessions (O'Connell et al., 2018, Plow et al., 2012).

TENS

TENS can be applied at high frequency (HF>50 Hz) with subthreshold intensity (no muscle contraction) or at low frequency (LF<10 Hz) with suprathreshold intensity (producing muscle contraction) (Sluka and Walsh, 2003). In humans, both protocols can reduce chronic pain by the addition of somatosensory inputs and the release of endogenous opioids (Leonard et al., 2010), but their respective mechanisms of action seem different owing to different after-effects related to the frequencies used (Peng et al., 2019). Also, low-intensity conventional TENS can have maximal analgesic effects homotopically, i.e. on the stimulated side, whereas high-intensity TENS can induce spatially diffused analgesic effects. It has also been shown that only high-intensity TENS produced long-lasting changes in S1 and M1 areas and in their connectivity to vmPFC, which is part of the pain inhibition descending system (Peng et al., 2019). This activation of the pain inhibition systems promotes the release of endogenous opioids, thus explaining the diffuse analgesic effects (Choi et al., 2016, DeSantana et al., 2008, Ottoson and Lundeberg, 1988).

Current Evidence for Noninvasive Neurostimulation in CRPS

Fourteen studies have been published to date on the use of noninvasive neurostimulation in CRPS, either alone and combined with other therapies. The details of these rTMS, tDCS, rPMS and TENS studies are reported in Table 3.

rTMS

Only three studies to date have tested the after-effects of rTMS in people with CRPS: two studies focused on type I (Pleger et al., 2004a) and the third on mixed types I and II CRPS (Gaertner et al., 2018). All three administrated rTMS over M1 contralateral to the CRPS hand. The first two studies used 10-Hz rTMS in a one single session with 10 patients (Pleger et al., 2004) or in 10 sessions with 12 patients, once a day for 10 days in a row (Pleger et al., 2004a). Precisely, Pleger et al. (2004) reported that pain intensity could be reduced after one rTMS session (as measured on the visual analogue scale or VAS), as compared to sham stimulation, with the VAS scores being the lowest at 15 min after the end stimulation, but back to baseline at 45 min. Picarelli et al., (2010) applied rTMS as an add-on intervention of a standard pharmacological and rehabilitation treatment for 10 consecutive sessions (10 days in a row). Of note, the pharmacological and rehabilitation treatment was first followed during a month before adding on rTMS. The authors reported a reduction of pain (scores of VAS and McGill Pain Questionnaire or MPQ) and improvements of affective and emotional scores (SF-36 and Hamilton Depression Scale) during the period of rTMS treatment, but the effects had vanished at follow-ups of one week and three months. The third study (Gaertner et al, 2018) was conducted in a mixed cohort (CRPS types I and II). The authors used an open-label and nonrandomized design to investigate the after-effects of the priming of 10-Hz rTMS by intermittent theta burst (iTBS). The protocol of iTBS (5-Hz bursts of three pulses delivered at 50 Hz) was delivered at an intensity of 70% the resting motor threshold (RMT) and was followed immediately by the 10-Hz rTMS (10-sec trains with 30 sec inter-train interval) delivered at 80% RMT with the coil guided by online neuronavigation. A decrease of the pain VAS scores was reported immediately after the end of the stimulation and two weeks after. Of note, the magnitude of pain reduction was similar between patients having undergone a single session (n=6) and those having been enrolled in five sessions once a day (n=15).

rPMS

To date, only one study used rPMS in CRPS (Krause et al., 2005). Ten series of 10 sec of 20-Hz rPMS at 120% of spinal RMT were applied over the cervical nerve roots innervating muscles of the painful area. The after-effects of rPMS in this study were limited to the lengthening, in pain-free participants only, of the duration of the contralateral and ipsilateral cortical silent periods which informs on the level of M1 and interhemispheric inhibition, respectively. Unfortunately, this study did not collect any clinical outcomes.

tDCS

Three studies investigated the after-effects of anodal tDCS applied over M1 contralateral to the CRPS hand, two case studies (Schmid et al., 2011) and one randomized parallel single blind study (Lagueux et al., 2018). Of note, these studies used tDCS as an add-on of sensorimotor training (ST) (Schmid et al., 2011), TENS over the painful area (Houde et al., 2020) and graded motor imagery (GMI) (Lagueux et al., 2018). Schmid et al. (2011) reported that anodal tDCS + ST reduced pain intensity and improved the pattern identification during ST, as compared to sham tDCS + ST. Houde et al. (2020) reported that anodal tDCS + TENS once a day for five consecutive days slightly reduced pain intensity and unpleasantness, as compared to tDCS alone. Lagueux et al. (2018) tested tDCS + GMI in 11 people with CRPS type I. Precisely, the participants underwent six weeks of GMI and anodal tDCS of M1 was added once a day for five days in a row in the first 2 weeks of GMI, then once a week for the remaining four weeks of GMI. The authors reported that this did not reduce pain more than in the control group of 11 other patients having undergone sham tDCS + GMI with same parameters (Lagueux et al., 2018). Of note, it has never been reported yet that protocols of tDCS alone could improve on pain management in CRPS (O'Connell et al., 2018).

TENS

TENS after-effects in CRPS pain management have been described in numerous interesting case reports and case series since the late '70s, both in children and adults. However, robust data-evidence based studies are missing and the efficacy of TENS has not yet been

established. Current evidence is limited by case report designs, a large variety of protocols employed or missing details, heterogeneous cohorts of patients, and lack of appropriate control condition in most cases. However, given the high acceptance and safety of this device, it is almost always worthwhile to consider TENS as part of a multi-disciplinary approach (Wilder, 2006). Precisely, three case studies in children aged 10, 6 and 3.5 years old, respectively (Leo, 1983) and one case report in a 43-year old woman (Bodenheim and Bennett, 1983) reported that TENS applied over acupuncture points or painful areas, at low or high frequencies and for one or several sessions, decreased pain, hyperesthesia, hyperalgesia, oedema, cyanosis if any, and, in parallel, improved the range of motion at the painful joint. Two other series of cases used various stimulation protocols between children and with limited details provided in the articles: TENS coupled with home-based physical therapy reduced pain symptoms in 9/10 cases with complete remission within 2 months in 7/10 cases (Kesler et al., 1988) and TENS reduced pain in 20/29 cases (Robaina et al., 1989). More recently, a randomized clinical trial tested 100-Hz TENS as add-on to a standard physical therapy program (SPT: contrast bath, whirlpool bath and physical exercise) in 15 people with CRPS type 1. The authors showed that 15 sessions of TENS + SPT reduced pain scores and oedema and increased the 2nd–3rd fingers range of motion more than in a group of 15 other patients who underwent sham TENS + SPT. It was concluded that the addition of TENS to SPT significantly contributed to clinical recovery in CRPS (Bilgili et al., 2016).

Conclusion

Two systematic reviews rated the therapeutic effects of noninvasive neurostimulation techniques in CRPS on pain intensity with very low quality of evidence, and this may be mainly due to small sample size, short follow-up, and small/short-term analgesic effect (Cossins et al., 2013, O'Connell et al., 2013).

(Insert Table 3 near here)

Why Use Noninvasive Neurostimulation in CRPS?

Insights from Other Chronic Pain Conditions

Noninvasive neurostimulation techniques have already been reported to influence neurophysiological markers in various chronic pain conditions, such as fybromyalgia (Mhalla et al., 2011, Passard et al., 2007), neuropathic pain (Gibson et al., 2017, Hirayama et al., 2006, Khedr et al., 2005, Kumru et al., 2017, Lefaucheur, 2006, Lefaucheur et al., 2004), low back pain (Ambriz-Tututi et al., 2016, Binny et al., 2019, Masse-Alarie et al., 2013, Masse-Alarie et al., 2017, Jin et al., 2015; Galhardoni et al., 2015; Moisset et al., 2016), phantom limb pain (Töpper et al., 2003), etc. Evidence is slowly piling up in parallel with a better understanding of the pathologies. The review from Moisset et al. (2016) related the analgesic effects of rTMS (over M1 or dorsolateral prefrontal cortex in patients with chronic pain) with the changes of corticospinal excitability that can last for weeks. In a recent systematic review (Baptista et al., 2019), the use of high-frequency rTMS over M1 was acknowledged level A of evidence in neuropathic pain, level B in CRPS and the use of high-frequency rTMS over the left dorsolateral prefrontal cortex was acknowledged level B of evidence in the control of pain.

Surprisingly, despite promising data from noninvasive neurostimulation in other chronic pain conditions, only a few randomized clinical studies tested these techniques in CRPS (O'Connell et al., 2018). A possible explanation is that CRPS is a rare syndrome charaterized by a large variabilty of clinical profile, making it difficult to run larger studies with randomized placebo-controlled designs.

Chronic CPRS and Brain Changes

Maladaptive neuronal plasticity has been described as a primary cause of symptoms chronicization in CRPS (Costigan et al., 2009, Marinus et al., 2011). Pain intensity was found to be positively correlated with volume changes of the left posterior hippocampus and left amygdala (Barad et al., 2014), and negatively correlated with volume changes of bilateral dorsolateral prefrontal cortex, putamen, and other areas associated with pain processing (Barad et al., 2014, Shokouhi et al., 2018; Azqueta-Gavaldon et al., 2020). Also, on the CRPS

side, the shrinkage of the S1 hand representation was associated with the intensity of pain and the presence of hyperalgesia (Maihofner et al., 2004), and motor threshold to TMS of M1 hand area was found significantly lower in the presence of allodynia (Krause et al., 2004). Most importantly, brain changes could reverse, even normalize, concomitantly to clinical improvements (Maihofner et al., 2004, Marinus et al., 2011, Sorel et al., 2018).

Cerebral Plasticity and Noninvasive Neurostimulation

Noninvasive neurostimulation can influence cerebral plasticity and reverse maladaptive neural changes (Bolognini et al., 2009, Engineer et al., 2011, Massé-Alarie and Schneider, 2011, Massé-Alarie and Schneider, 2016, Naro et al., 2016); thus, these techniques can be potentially implemented into interdisciplinary approaches that precisely aimed at promoting the central reorganization at the origin of the pain condition improvement. Compared to other invasive treatments, neurostimulation techniques offer multiple advantage. They are painless, particularly with the use of magnetic stimulation (rTMS, rPMS) and do not have side-effects (or limited ones such as transient headaches for rTMS and tDCS). Especially, they can be used as adds-on of rehabilitation exercises. Indeed, neurostimulation can normalize the maladaptive brain plasticity in few chronic pain pathologies (Massé-Alarie et al., 2017), which primes and potentiates the effects of the task-oriented rehabilitation, thus making it possible to go beyond the gains already reached and plateaued. It is hypothesized that neurostimulation would do the same in chronic CRPS. It is known furthermore that patients with CRPS often experience kinesiophobia or fear of movement (Marinus et al., 2013). This said, rPMS that mimics the contraction / relaxation mechanisms and triggers movements of the CRPS limb with any pain (base on other population with pain) could help reduce kinesiophobia and all the psychological stress surrounding the attempt to move, thus easing at the end the compliance to therapy and its success.

Perspective

Future work is warranted to foster the evidence of the efficacy of noninvasive neurostimulation in CRPS, alone or combined to other treatments, and understand if there are responders and non-responders to one or all techniques, what could be the predicting factors and if they are specific to a technique. Beyond, due to high variability of CRPS

profiles, and to the fact that not all people respond to treatment or with the same extent, it will be crucial to customize the individual approach in neurostimulation. Precisely, the integrity of corticospinal pathways and neural status (brain changes) will have to be documented in order to customize individualized protocols of neurostimulation adapted to each case.

CONCLUSION

Knowledge of CRPS physiopathology has evolved rapidly in the last decades, with more evidence of neural changes involvement in the chronicization, the symptoms and the resistance to conventional treatment. Despite some promising data, literature on neurostimulation trials in CRPS remains scarce. Insights from other pain conditions suggest however that noninvasive neurostimulation techniques can substantially decrease pain intensity, improve the other symptoms and influence the maladaptive neural plasticity, which could sustain the changes in the long term. The current review lays the stress on the fact that noninvasive neurostimulation of brain or of nerve / muscles / spinal roots, alone or in combination with conventional therapy, represents a fertile ground for further investigations with a view of developing more efficient approaches for pain management in CRPS.

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Figure 1. Brain Changes in People with a Complex Regional Pain Syndrome (CRPS)

This figure illustrates the main data reported in Table 2 owing to the increase or decrease of grey matter volume (GMV), connectivity, activity and metabolism and the alteration of maps related to hand sensorimotor function.

Table 1. The "Budapest Criteria" for Complex Regional Pain Syndrome (CRPS) Diagnosis*

1. Continuing pain, which is disproportionate to any inciting event

2. Must report at least one symptom on three of the four following categories (clinical diagnosis) OR in all four (research purpose):

   Sensory hyperesthesia and/or allodynia

   Vasomotor: temperature asymmetry and/or skin colour changes and/or skin colour asymmetry

   Sudomotor/oedema: oedema and/or sweating changes and/or sweating asymmetry

   Motor/trophic: decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

3. Must display at least one sign at the time of evaluation in 2 or more of the following categories (clinical criteria and research purpose):

   Sensory: evidence of hyperalgesia (to pinpricks) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)

   Vasomotor: evidence of temperature asymmetry (>1°C) and/or skin colour changes and/or asymmetry

   Sudomotor/oedema: evidence of oedema and/or sweating changes and/or sweating asymmetry

   Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

4. There is no other diagnosis that better explains the signs and symptoms

*(Harden et al., 2010). *Diagnosis of CRPS requires to meet all four criteria.*

Table 2. Brain Changes Reported in Complex Regional Pain Syndrome (CRPS).

Changes of Volumes and Maps *(decrease ↓ or increase ↑)*
↓ grey matter volume in right anterior insula, OFC, right ventral PFC, CC, inferior PL, SMA, nucleus accumbens, putamen (Azqueta-Gavaldon et al., 2020; Barad et al., 2014; Geha et al., 2008; Shokouhi et al., 2018)
↑ grey matter volume in the M1 contralateral to CRPS hand, dorso-medial PFC, right hypothalamus, bilateral dorsal putamen, choroid plexus (Barad et al., 2014; Zhou et al., 2015)
= or ↓ extent of CRPS hand maps in the contralateral S1 and in M1 (Di Pietro et al., 2013; Juottonen et al., 2002; Maihofner et al., 2003; Mancini et al., 2019; Pfannmoller et al., 2019; Pleger et al., 2004; Vartiainen et al., 2008; Krause et al., 2006)
↑ shifting of CRPS hand map in the contralateral S1 (Maihofner et al., 2003)
Changes of Connectivity, Activation, Metabolism
Alteration or decrease (↓) or no change (=)
↓ default mode network (Bolwerk et al., 2013; Kucyi et al., 2014; Zang et al., 2014).
↓ connectivity to sensorimotor cortices (Shokouhi et al., 2018)
↓ metabolism in the M1 and dorsal PFC (Shiraishi et al., 2006)
↓ connectivity between M1 and SLP in the hemisphere contralateral to CRPS side (Shokouhi et al., 2018)
↓ connectivity between ventro-medial PFC and basal ganglia (Geha et al., 2008)
↓ thalamic perfusion (Fukui, 2003; Fukumoto et al., 1999)
↓ connectivity between putamen and cerebellum (Azqueta-Gavaldon et al., 2020)
↓ opercular activation during painful stimulation (Freund et al., 2010)
↓ pain and sensory threshold via sensitisation of N-methyl-D-aspartate (glutamate) receptors (Puchalski and Zyluk, 2016)
Increase (↑) *or no change* (=)
↑ activation of M1 and SMA during movement (Maihofner et al., 2007)
↑ activation of M1 and SMA at rest (Shokouhi et al., 2018)
↑ metabolism bilaterally in S2, mid-anterior and posterior CC, PC, PPC, cerebellum, right posterior insula and thalamus (Shiraishi et al., 2006)
= or ↑ amplitude and frequency of SSEP in the contralateral S1 hand area in response to stimulation on the CRPS side (Juottonen et al., 2002) (Mancini et al., 2019)
↓ suppression of SSEP by paired-evoked paradigm bilaterally (Galea, 2012; Lenz et al., 2011)
= peak latency of SSEP (Juottonen et al., 2002; Maihofner et al., 2003; Pleger et al., 2004; Vartiainen et al., 2008)
= peak strength of SSEP (Galea, 2012; Pleger et al., 2004)
↑ connectivity between ventro-medial PFC and insula (Geha et al., 2008)

↑ connectivity between putamen and pre-postcentral gyri (Azqueta-Gavaldon et al., 2020)
↑ activation of PPC during painful stimulation (Freund et al., 2010)
Changes of Neurophysiological Outcomes *(decrease ↓ or no change = or increase ↑)*
↓ reactivity of M1-related 20-Hz rhythm to tactile stimulation (Juottonen et al., 2002; Kirveskari et al., 2010)
↓ SICI (Eisenberg et al., 2005; Pfannmoller et al., 2019; Schwenkreis et al., 2003)
↓ LAI (Morgante et al., 2017)
= SAI (Morgante et al., 2017; Turton et al., 2007)
= PAS (Morgante et al., 2017)
= Cortical silent period (P. Krause et al., 2005; Morgante et al., 2017)
= RMT (Krause et al., 2004; Morgante et al., 2017; Schwenkreis et al., 2003; van Velzen et al., 2015).
= or ↓ MEP amplitude (Krause et al., 2004, 2005; Morgante et al., 2017; Schwenkreis et al., 2003; van Velzen et al., 2015).
= or ↑ ICF (Morgante et al., 2017; Schwenkreis et al., 2003)
↑ I-wave facilitation (Eisenberg et al., 2005)

Acronyms of neurophysiological outcomes*. SICI: short-interval intracortical inhibition; LAI, SAI: long / short-afferent inhibition; PAS: paired associative stimulation; RMT: resting motor threshold; ICF: intracortical facilitation; I-wave: indirect wave corresponding to indirect activation of corticospinal cells (at the cell body, not directly at the axons) by transcranial magnetic stimulation*

Acronyms for structures*. OFC: orbitofrontal cortex; PFC, prefrontal cortex; CC: cingulate cortex; PL: parietal lobule; SMA: supplementary motor area; M1, S1: primary motor and somatosensory cortex, respectively; SPL: superior parietal lobe; S2: secondary somatosensory cortex; PC: parietal cortex; PPC: post-parietal cortex; SSEP: somatosensory-evoked potential*

Table 3. Studies with Noninvasive Neurostimulation in Complex Regional Pain Syndrome (CRPS).

References	Study type	Population	Intervention						
			Stimulation protocol	Control	Number of sessions	Site	Parameters	Scales and time of testing	Outcomes reported
Bilgili et al., 2016	Double-blinded, placebo-controlled, randomized trial	CRPS type I (N = 30) Exp = 15 Sham = 15	TENS + standard physical therapy	Sham stimulation + standard physical therapy	15 sessions, frequency/week not reported	Active electrode on the dorsal aspect of the forearm, passive electrode on the dorsal aspect of hand	100-Hz TENS (50–100 ms pulse duration) at intensity below the discomfort threshold, 20 min	VAS, LANSS, DN-4, ROM, edema size, functional capacity with hand dynamometer and DHI;	Reduction of pain, edema and fingers ROM
Bodenheim & Bennett, 1983	Case report	SA Exp = 1	TENS	na	24 sessions (3 sessions/week, 8 weeks)	Acupuncture points	20-Hz TENS at intensity adjusted to patient tolerance (100-μs pulse width), 60 min	Clinical evaluation of pain and physical outcomes	Reduction of pain, recovery of ankle ROM, increase of bone stock and reversal of atrophy
Gaertner et al., 2018	Open-label and nonrandomized study	CRPS type I and II (N = 21) Exp = 6 Exp = 15	iTBS + rTMS iTBS + rTMS	na na	1 session 5 sessions (1 session/day, 5 days)	Contralateral M1 Contralateral M1	iTBS at 70% RMT (5-Hz bursts of 3 pulses at 50 Hz, 2 sec ON / 8 sec OFF, total = 600 pulses) followed immediately by 10-Hz rTMS at 80% RMT (10-sec trains, 30-sec inter-train interval; total = 2000 pulses). Total = 2600 pulses per session	VAS, at baseline, then after the single or the 5 sessions and 2 weeks after	Significant pain reduction after one session and one-week posttreatment; however, no group differences were present
Houde et al., 2020	Case report	CRPS type I Exp = 1	Anodal tDCS Anodal tDCS + TENS	na na	5 sessions (1 session/day, 5 days) 10 sessions (1 session/day, 5 days, repeated after 6 months)	tDCS on contralateral M1, TENS over painful area	2-mA tDCS and 3-Hz TENS (400 μs), 25 min	VAS; at baseline, after 15 min of each intervantion, after 6 months from tDCS + TENS only	tDCS + TENS slightly reduced pain intensity and unpleasantness
Kesler et al., 1988	Cohort study	RSD (N = 10) Exp = 10	TENS + home-based physical therapy	na	Various depending on the patient (4 sessions/day, multiple days)	Over vascular supply of affected extremity	Intensity adjusted to comfort, 60 min. No other information provided	Clinical evaluation of pain and physical outcomes	N=7 with complete remission within two months
Krause et al., 2005	Cohort study	CRPS type I (N = 22) Exp = 12 Control = 10	rPMS	Healthy subjects	1 session	Over C7/C8	20-Hz rPMS at 120% RMT; 10 trains of 10 sec each, inter-train interval not reported; Total = 2000 pulses over ~10 min	Cortical and spinal MEP, contra-and-ipsilateral cortical silent period; pre/post-rPMS testing	Less effective input to the motor cortical system
Lagueux et al., 2018	Randomized parallel single blind study	CRPS type I (N = 22) Exp = 11 Control = 11	Anodal tDCS + graded motor imagery	Sham stimulation + graded motor imagery	14 sessions (1 session/day, 5 days/week for 2 weeks, 1 day/week for 4 weeks)	Contralateral M1	2-mA tDCS of 20 min	Pain perception, quality of life, kinesiophobia, pain catastrophizing, anxiety, mood; at baseline, at 6 weeks of treatment and 1 month after th end of treatment	No added value of tDCS combined with GMI for reducing pain
Leo at al., 1983	Case report	RSD Exp = 1	TENS	na	2 sessions (1 session/day, 22 days apart)	Bilaterally at acupuncture points	4-Hz TENS at intensity below pain threhsold, 30 sec for each point	Pain and right upper extremity ROM; at baseline and after each session	Reduction of pain and increased ROM at painful, improvements still present at 3 months
Picarelli et al. 2010	Double-blind, placebo-controlled, 2-arm, randomized trial	CRPS type I (N = 23) Exp = 12 Sham = 11	rTMS + best medical treatment	Sham stimulation	10 sessions (1 session/day, 5 days/week, 2 weeks)	Contralateral M1	10-Hz rTMS at 100% RMT; 25 trains of 10 sec each, 60-sec inter-train interval; total = 2500 pulses over ~29 min	VAS, MPQ, SF-36, HDRS; at baseline, then daily during the 10 sessions and 1 week/3 months after the last session	Reduction of pain and improvement of affective aspects only during the period of stimulation

Pleger et al., 2004	Cohort study	CRPS type I Exp = 10	rTMS	Sham stimulation	1 session	Contralateral M1	10-Hz rTMS at 110% RMT; 10 trains of 1.2 sec each, 10-sec inter-train interval; total = 120 pulses over ~2 min	VAS; baseline, 30 sec after, then 15/45/90 min after the stimulation	Pain reduction at 30 sec with lowest VAS score at 15 min
Richlin et al., 1978	Case report	RSD Exp = 1	TENS	na	30 sessions (3 sessions/day, 10 days)	Proximal electrode over the right femoral triangle, distal electrode over the dorsum of the right foot	40-Hz TENS at intensity below discomfort threshold, 80-μs pulse width, 30 min	Pain, ROM, thermography, skin temperature; at baseline, five days after the beginning of treatment, two days later, and four weeks from the beginning	Reduction of hyperalgesia, increased ROM, complete pain relief after the treatment
Robaina et al., 1989	Cohort study	RSD Exp = 26	TENS	na	Various depending on the patient (2-5 sessions/day, multiple days)	Painful area or proximal area next to painful area or nerve trunk	80-120-Hz TENS at intensity at parasthesia threshold (50-200 μs pulse width), 30 to 60 min depending on the patient	VAS, MPQ; at baseline and follow-up over 10 to 36 months	N= 20 / 29 with good/excellent pain reduction
Schmid et al., 2011	Case report	CRPS type not specified Exp = 1	Anodal tDCS + sensorimotor hand training	Sham stimulation	1 session	Contralateral M1	Anodal tDCS for 20 min. No other information provided	Specific sensorymotor hand training, VAS; pre-post-tDCS testing	Pain reduction and improved performance on ST
Stilz et al., 1977	Case report	RSD Exp = 1	TENS	na	2 weeks, number of sessions not reported	Proximal electrode over the right femoral triangle, distal electrode over the right foot dorsum	50-Hz TENS at 3.5 mA, no other information provided	Clinical evaluation of pain and physical outcomes	Reduction of pain, hyperesthesia, edema and cyanosis. Pain was still absent after one month

Acronyms of population.

   RSD: Reflex Sympathetic Dystrophy; SA: Sudeck's Atrophy; CRPS: Complex Regional Pain Syndrome

Acronyms of intervention.

   TENS: transcutaneous electric current stimulation; tDCS: transcutaneous direct current stimulation; rTMS: repetitive transcranial magnetic stimulation; iTBS: intermittent theta burst stimulation

Acronyms of scales and outcomes.

   ROM: range of motion; VAS: visual analogue scale; MPQ: McGill Pain Questionnaire; SF-36: 36-Item Short Form Survey; HDRS: Hamilton Rating Scale for Depression;
   ST: sensorimotor hand training; Clinical evaluation: therapist judgement without scales

na: not available

FIGURE 1. Brain Changes in People with a Complex Regional Pain Syndrome

● GMV increase	○ GMV decrease
— Connectivity increase	--- Connectivity decrease
● Activation increase	▲ Metabolism increase
⊙ Alteration of cortical hand maps	▽ Metabolism decrease
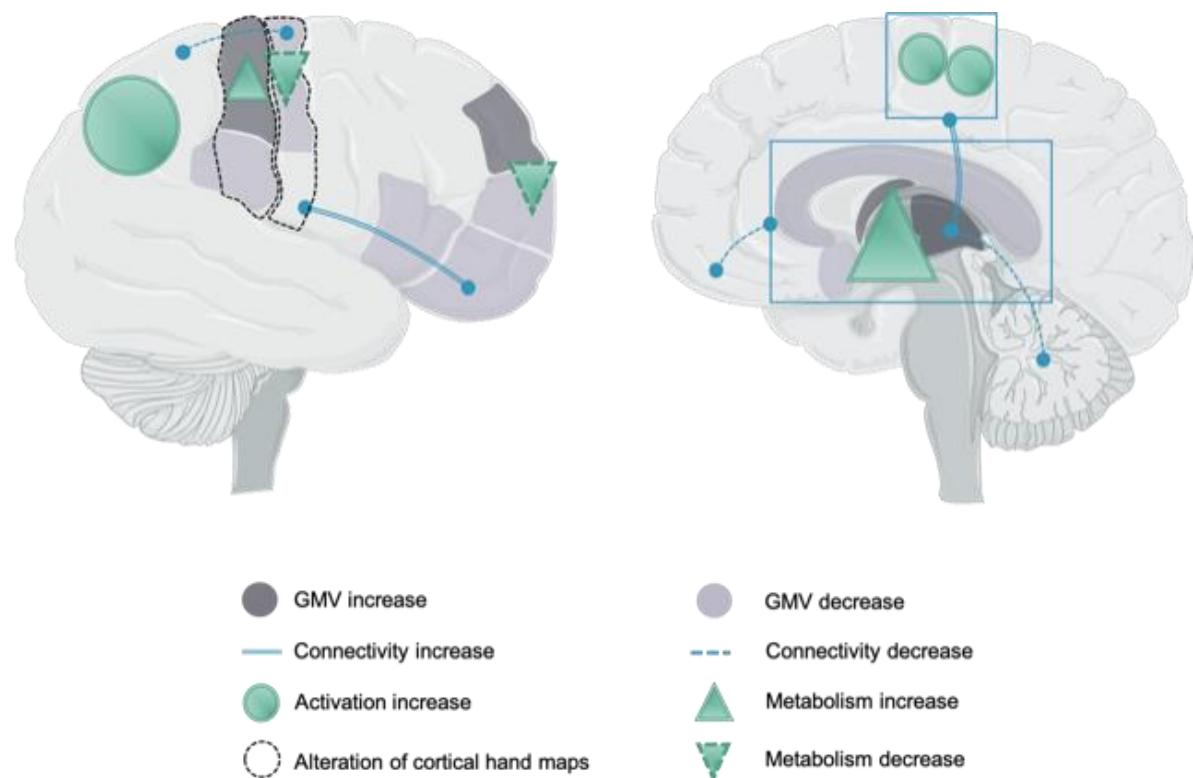
SECTION 2 : HYPOTHÈSES ET OBJECTIFS DU PROJET DE MAÎTRISE

Rationnel du projet suivant les recommandations de la revue de littérature

Étant donné :

- que le SDRC induit des changements au niveau des cortex moteur primaire (M1) des deux hémisphères pour le contrôle des membres atteint et non-atteint (Allen Demers et al., in preparation);

- que cette réorganisation centrale pourrait expliquer le maintien dans le temps des incapacités résiduelles liées au SDRC;

- que malgré les traitements conventionnels : 62% sont encore restreints dans la réalisation de leurs activités de la vie quotidienne trois à neuf ans après le début du SDRC (Geertzen et al., 1998), plus de la moitié des gens diagnostiqués avec un SDRC présente encore des déficiences (comme une diminution de force ou de la raideur) un an après le début du syndrome (Bean et al., 2014) et la majorité ne sont pas en mesure de retourner à leur occupation, ont besoin d'adaptations sur leur lieu de travail ou sont déclarés officiellement invalides (Borchers and Gershwin, 2014).

- qu'il devient impératif de développer des méthodes d'interventions moins coûteuses, moins douloureuses, moins invasives et plus efficaces pour traiter les personnes atteintes de SDRC résistant aux traitements conventionnels (Bruehl 2010);

- que les changements dans le fonctionnement des M1 rapportés dans la littérature ne sont pas tous cohérents entre eux (Allen Demers et al., in preparation);

- qu'il est possible de tester le fonctionnement du M1 et de la *voie corticospinale** (par stimulations magnétiques transcrâniennes (TMS, de l'anglais « transcranial magnetic stimulations », Beaulieu et al. 2017a; Beaulieu et al. 2017c; Malcolm et al. 2006);

> **Le système corticospinal ou voie corticospinale inclut les neurones et interneurones du cortex moteur, soit les cellules corticospinales ou pyramidales qui envoient les commandes motrices aux motoneurones alpha de la moelle épinière qui innervent les fibres musculaires.*

- que les stimulations magnétiques répétées en périphérie (rPMS des muscles, de l'anglais « repetitive peripheral magnetic stimulations ») génèrent un flux massif d'informations sensorielles (non-douloureuses et cohérentes avec le mouvement produit) qui atteignent

le cerveau par les voies somatosensorielles via le thalamus (Beaulieu & Schneider 2015; Beaulieu et al. 2017b);

- que ce flux d'informations somatosensorielles permettrait d'influencer la plasticité des circuits sensorimoteurs du cortex fronto-pariétal (possiblement par des mécanismes de potentialisation à long terme impliquant les récepteurs glutamatergiques N-methyl-D-aspartate ou NMDA) et permettent, dans les cas de douleur chronique lombaire, d'influencer les M1, dont leur excitabilité motrice corticale (Massé-Alarie et al. 2013);

- que, dans ces cas, les rPMS permettent de diminuer les douleurs vécues (Massé-Alarie et al. 2013);

- que les rPMS n'ont pas encore été testées avec les gens souffrant de SDRC :

Il est raisonnable de tenter de :

- tester le fonctionnement des M1 (notamment l'excitabilité motrice corticale et corticospinale) grâce aux TMS de M1 chez des adultes vivant avec un SDRC au membre supérieur (étude 1)

- influencer le fonctionnement des M1 avec des rPMS au niveau des *muscles de la zone douloureuse** et par le fait même, de diminuer la douleur et améliorer la fonction manuelle (étude 2).

> **Le fléchisseur superficiel des doigts (FDS, du latin « Flexor Digitorum Superficialis ») a été choisi comme muscle cible au traitement puisque le SDRC est plus prévalent au membre supérieur qu'inférieur (Bruehl, 2015), qu'on retrouve fréquemment une diminution d'amplitude articulaire de flexion des doigts et du poignet chez les patients atteints d'un SDRC au membre supérieur et que l'amélioration de son contrôle permettrait par la même occasion l'amélioration de plusieurs tâches fonctionnelles (notamment celles impliquant la fermeture de la main).*

Hypothèses de travail

Il sera possible de mesurer des changements de fonctionnement d'un ou des M1 chez les participants adultes avec SDRC au membre supérieur par rapport à des participants sans douleur (étude 1).

Une session de rPMS sur le muscle FDS du côté atteint permettra de diminuer la douleur et sera accompagné d'une réduction des différences de fonctionnement du/des M1, soit des mesures se rapprochant de celles d'un groupe d'adultes sans douleur (étude 2).

Objectifs principaux

À la suite du premier article de revue de littérature (en SDRC et neurostimulation) qui compose l'introduction et soutient le rationnel de la maîtrise, ce mémoire présente deux études expérimentales développées pour tester les hypothèses de travail et adresser les objectifs suivants :

L'objectif principal de la **première étude** était de tester le fonctionnement des M1 chez un groupe d'adultes vivant avec un SDRC au membre supérieur par rapport à celle d'un groupe d'adultes sans douleur. L'objectif principal de la **seconde étude** était de tester, chez les adultes avec SDRC, si une seule séance de rPMS permettait de diminuer la douleur et si cela était en relation avec une normalisation des différences de fonctionnement du/des M1, en comparaison avec le groupe de participants sans douleur.

Spécifiquement, chez une population adulte vivant avec un SDRC au membre supérieur, les objectifs étaient :

Pour l'étude 1, par rapport à un groupe d'adultes sans douleur :

1) déterminer les différences de fonctionnement des zones motrices corticales du *muscle premier interosseux dorsal* (FDI)* par TMS du M1 et enregistrement

*Le fonctionnement du M1 (en pré et post-rPMS du muscle FDS) a été testé par TMS de la zone motrice corticale contrôlant le muscle FDI, puisque sa stimulation par TMS autant que sa captation par EMG de surface est plus précise que celle du FDS (l'EMG de surface captent les muscles voisins/superposés qui sont nombreux dans le cas du FDS), qu'il est grandement étudié dans la littérature, parce que la mesure de la zone motrice du FDI est un bon indicateur du fonctionnement de la zone motrice du FDS (bien que précises, les zones motrices se chevauchent afin d'améliorer la précision des gestes moteurs complexes en groupes de muscles synergiques) (Gagné & Schneider 2007, 2008; Melgari et al. 2008) et parce que la zone douloureuse en SDRC est souvent grande et non limité à un seul muscle.

d'électromyographie (EMG) de surface des réponses du muscle FDI, en évaluant notamment l'excitabilité motrice corticale et corticospinale via le seuil moteur de repos (RMT, de l'anglais « resting motor threshold ») et d'autres variables décrites dans la section 1.6 Mesures neurophysiologiques;

2) mesurer la fonction manuelle des deux mains via les mesures d'amplitude articulaire active des doigts, de force musculaire de préhension, de proprioception des membres supérieurs et de sensibilité au toucher léger;

3) quantifier, via des questionnaires, les symptômes vécus;

4) déterminer s'il existe des corrélations entre mesures de fonction manuelle ou symptômes et mesures TMS de fonctionnement du M1.

Pour l'étude 2, entre les temps de mesure pré- et post-rPMS

5) mesurer l'effet immédiat (en aigu) d'une seule session de rPMS du muscle FDS du membre supérieur atteint sur :

    6.1) la douleur (variable principale) et ses interférences (autres symptômes vécus);

    6.2) le fonctionnement (dont l'excitabilité avec la mesure du RMT) des zones motrices corticales du FDI par TMS;

    6.3) la fonction manuelle des deux mains via les mesures d'amplitude articulaire active des doigts, de force musculaire de préhension et de sensibilité au toucher léger;

6) déterminer la présence de facteurs prédictifs du succès de l'intervention parmi les mesures initiales, les caractéristiques descriptives ou les relations entre changements de variables, afin d'identifier les meilleurs répondants et donc mieux cibler la population qui bénéficierait du traitement expérimental rPMS.

Approches méthodologiques

Tester les hypothèses de travail et atteindre les objectifs de la maîtrise a demandé le recrutement d'adultes avec SDRC. La clientèle en phase chronique (soit ayant atteint un plateau clinique avec les traitements conventionnels) a été choisie pour tester l'effet net des rPMS et non pas celui des traitements conventionnels. Il a été choisi de recruter des participants avec un diagnostic initial de SDRC type I (sans lésion nerveuse) puisque pour envoyer les informations somatosensorielles au cerveau et permettre la plasticité cérébrale

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recherchée, les rPMS doivent stimuler un muscle qui a un réseau nerveux intact. Étant en phase chronique, les participants ayant reçu initialement un diagnostic de SDRC type I (parce qu'ils répondaient alors à tous les critères diagnostiques) correspondaient davantage à des type NOS (qui n'est pas mieux expliqué par tout autre condition, de l'anglais « not otherwise specified ») lors de leur participation à l'étude, c'est-à-dire qu'ils ne répondaient plus à l'ensemble des critères diagnostiques puisque certains symptômes étaient alors résolus (l'œdème et les changements sudomoteurs étaient notamment réglés). Les participants du groupe Sans-douleur ont été recrutés en les appariant, autant que possible, au sexe et à l'âge du groupe SDRC pour permettre la comparaison des variables mesurées.

Ces expérimentations ont permis la rédaction de deux articles. Le premier article porte sur les différences de fonctionnement des M1 (débalancement interhémisphérique d'excitabilité) et de fonction manuelle entre un groupe d'adultes vivant avec un SDRC et un groupe Sans-douleur (chapitre 2). Le second article traite des effets de l'ajout des rPMS chez la clientèle avec SDRC sur le fonctionnement du M1 (plasticité induite), la fonction manuelle et les symptômes (chapitre 3).

La méthodologie qui a permis de tester les participants et de rédiger les deux articles est exposée dans le chapitre suivant (chapitre 1). Chaque personne a participé à une seule session en laboratoire et les données ont permis les deux études : le premier article porte sur les mesures avant traitement (comparaison des participants avec SDRC avec les personnes sans douleur) et le deuxième article porte sur la comparaison pré/post-traitement expérimental chez les participants avec SDRC, soit la réduction des écarts (entre les mesures des participants avec SDRC et les valeurs normatives des participants sans douleur) en post-rPMS de ceux mesurés en pré-rPMS.

CHAPITRE 1 : MÉTHODOLOGIE

1.1 CARACTÉRISTIQUES DES PARTICIPANTS

Groupe avec SDRC

Huit adultes souffrant de SDRC type I au membre supérieur ayant atteint un plateau clinique (aucun changement de leur condition minimalement trois mois précédant la participation à l'étude et ayant terminé leur suivi en traitement conventionnel) ont été recrutés par liste de diffusion ou directement au Centre d'expertise en gestion de la douleur chronique du CHU de Québec – Université Laval (pavillon CHUL). Le groupe SDRC (six femmes et deux hommes) était âgé en moyenne de 52 ans (étendu : 35 à 65 ans). Deux des participants avait le membre supérieur non-dominant atteint (les autres ayant le membre supérieur dominant atteint). Un seul des participants était gaucher, les 7 autres droitiers. Le temps depuis l'apparition du SDRC (7 à 168 mois, moyenne de 55.9 mois), l'intensité de leur douleur (38 ± 20mm sur l'échelle visuelle analogue, EVA) et l'intensité du SDRC (2 à 12 au questionnaire « CRPS Severity Score », Annexe 1) variaient d'un participant à l'autre en début d'étude. L'ensemble des caractéristiques générales des participants sont présentées dans le Tableau 1.

Groupe Sans-douleur

Huit adultes sans douleur (appariés pour l'âge) ont été recrutés à des fin de comparaison des mesures cliniques et neurophysiologiques. Le groupe Sans-douleur (quatre femmes et quatre hommes) était âgé en moyenne de 50,8 ans (étendu : 40 à 61 ans). Un seul des participants était gaucher, les 7 autres droitiers.

Tableau 1: Caractéristiques générales des participants avec SDRC et sans douleur		
	Groupe avec SDRC	**Groupe Sans-douleur**
Participants (N)	8	8
Âge (années) : moyenne ±écart-type (étendue)	52.0 ± 11.3 (35-65)	50.8 ± 6.9 (40-61)
Dominance (droitier/gaucher)	7/1	7/1
Sexe (femmes/hommes)	6/2	4/4
Détails du SDRC		
Intensité (Questionnaire « CRPS Severity score » /17)	9 ±3	--
Côté atteint (droit/gauche)	6/2	--
Évènement précipitant (fracture de : main/avant-bras/bras)	4/3/1	--
Temps depuis son développement (mois) : moyenne ±écart-type (étendue)	55,9 ± 66,8 (7-168)	--
Intensité de la douleur (EVA en mm) : moyenne ±écart-type *Présente*	38 ± 20	--
Semaine dernière	51 ± 22	--

1.2 RECRUTEMENT

Taille de l'échantillon

En tant qu'étude exploratoire, le projet de recherche visait à recruter douze adultes par groupe pour vérifier l'hypothèse de travail. Toutefois, seulement huit participants avec SDRC (et donc huit participants sans douleur pour appariement) ont été testés (recrutement difficile des participants avec SDRC étant donné la rareté de la condition). Dépendant des variables testées, la puissance statistique calculée à postériori varie de 80% à 88% (G*Power software).

Méthode de recrutement

Le recrutement des participants s'est fait de façon non probabiliste volontaire à la suite d'un appel de participation à l'étude via : 1) les listes de diffusion de l'Université Laval, 2) une annonce affichée au Centre d'expertise de gestion de la douleur chronique du CHU de Québec – Université Laval (pavillon CHUL), 3) la proposition directe aux clients de ce centre

par le médecin traitant. Les personnes intéressées par le projet contactaient l'étudiante-physiothérapeute en charge qui (après leur avoir résumé le projet de recherche), validait avec eux les critères de participation (Tableau 2), puis leur envoyait le formulaire d'information et de consentement (FIFC). Les participants devaient signer et faire signer l'annexe du FIFC par leur médecin (pour valider l'éligibilité), puis une rencontre au laboratoire était planifiée.

Tableau 2 : Critères d'inclusion et d'exclusion du projet de recherche	
Groupe SDRC	**Groupe Sans-douleur**
Critères d'inclusion	
Avoir un diagnostic de SDRC type I selon les critères de Budapest, confirmé par le médecin traitant ou de famille et avoir terminé leur suivi en traitement conventionnel (aucun changement depuis 3 mois dans leur condition);	Ne pas avoir souffert d'une problématique de douleur dans le dernier mois ni avoir d'histoire de douleur chronique;
Être âgé de 18 ans et plus.	
Critères d'exclusion (liés à la santé générale)	
Atteintes cognitives interférant avec la compréhension et la réalisation des tâches de l'étude;	
Dénervation facettaire, thermocoagulation, chirurgie vertébrale (autre que parascopie) ou rhizotomie;	
Troubles neurologiques (AVC*, TDAH*, commotion cérébrale / TCC*, DMC*, sténose / lésion spinale / maladie affectant la moelle épinière, sclérose en plaques / latérale amyotrophique, tremblements atypiques, maladie de Parkinson ou d'Alzheimer).	
Critères d'exclusion (liés aux TMS)*	
ATCD* ou présence de tumeur cérébrale;	
ATCD* ou présence d'infection cérébrale;	
Système de dérivation du liquide céphalo-rachidien tel que rencontré dans l'hydrocéphalie à pression normale;	
Pompe viscérale / cardiaque ou stimulateur cardiaque;	
Stimulateur implanté (intracérébral, épidural, subdural);	
Grossesse;	
Toute forme d'épilepsie non contrôlée par médication;	
Syncopes récurrentes;	
Tout médicament qui abaisse significativement le seuil de convulsion (ex : antidépresseurs connus pour abaisser le seuil de convulsion)	
Chirurgie intracrânienne, clips intracrâniens (ex : clips d'anévrisme);	
Présence d'implant à la tête incluant un implant cochléaire;	
Plaque métallique au crâne, à la mâchoire ou au membre atteint;	
Fracture non consolidée ou autre contre-indication au mouvement du membre atteint.	

*AVC : accident vasculaire cérébral; TDAH : trouble du déficit de l'attention avec ou sans hyperactivité; TCC : traumatisme crânio-cérébral; DMC : déficience motrice cérébrale; TMS : stimulations magnétiques transcrâniennes ; ATCD : antécédent(s).

1.3 DEVIS EXPÉRIMENTAL

Le protocole de l'étude (accepté par le comité d'éthique de la recherche du CHU de Québec – Université Laval) consistait en une séance au laboratoire de recherche avec des prises de mesures avant et dix minutes après le traitement expérimental (pour le groupe SDRC) ou en une seule prise de mesures (pour le groupe Sans-douleur). Le choix des questionnaires et des mesures cliniques a été fait en se basant sur la pratique clinique actuelle en physiothérapie, en se rapprochant des données probantes, mais il n'y a actuellement aucun consensus dans les écrits scientifiques sur un ensemble de mesures à préconiser avec la population SDRC (Grieve et al., 2016). Le choix d'attendre dix minutes après les rPMS avant la deuxième prise de mesures (post-rPMS) se base sur des études fondamentales en stimulations magnétiques centrales utilisant la même fréquence (Huang et al., 2005) et a pour objectif de mesurer l'effet possible de ceux-ci au meilleur moment.

Préalablement et après l'expérimentation, les participants devaient être évalués par leur médecin, entre autres pour confirmer l'admissibilité au projet. Puis, chronologiquement (Figure 1) : le FIFC était lu, les questions du participant répondues, le FIFC signé par le participant et par l'étudiante-physiothérapeute en charge du projet, les questionnaires remplis (incluant les caractéristiques descriptives du participant, voir détails au point 1.4) et une physiothérapeute assistée d'un étudiant du laboratoire réalisaient la prise de mesures cliniques et neurophysiologiques (détaillées aux points 1.5 et 1.6) avant et dix minutes après l'application du traitement expérimental (détaillé au point 1.7). Puis, les participants étaient rappelés une semaine après le traitement expérimental pour quantifier la douleur vécue pendant la semaine.

Figure 1. Devis expérimental
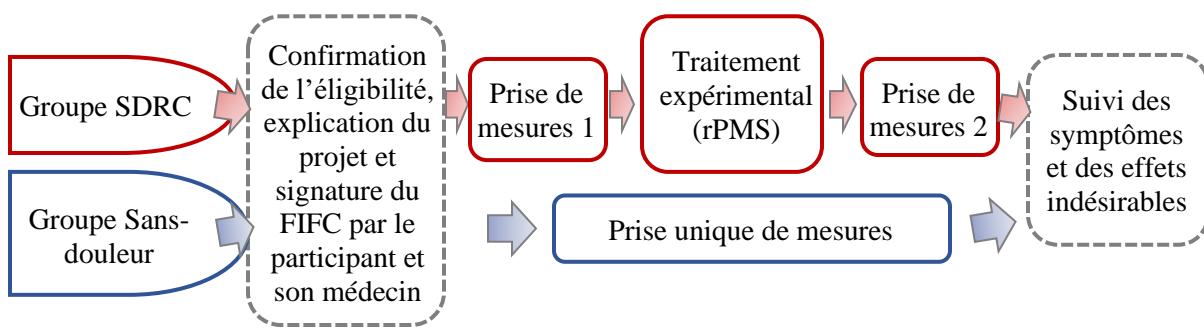
1.4 QUESTIONNAIRES

Les questionnaires, les mesures cliniques et neurophysiologiques sont résumées dans le Tableau 2.

Au début de la séance au laboratoire, un questionnaire consignant les *renseignements généraux* étaient remplis par les participants avec SDRC et sans douleur. On y recueillait pour les deux groupes : l'âge, le sexe, la dominance manuelle, les particularités pouvant affecter la fonction sensorielle, manuelle ou l'excitabilité corticale (emploi, sport, passe-temps, prise de médication, blessures musculosquelettiques antérieures, conditions médicales associées, naissance prématurée, etc.) et pour le groupe SDRC : le côté atteint, le temps depuis le SDRC et l'histoire médicale reliée au SDRC.

Figure 2. Échelle visuelle analogue
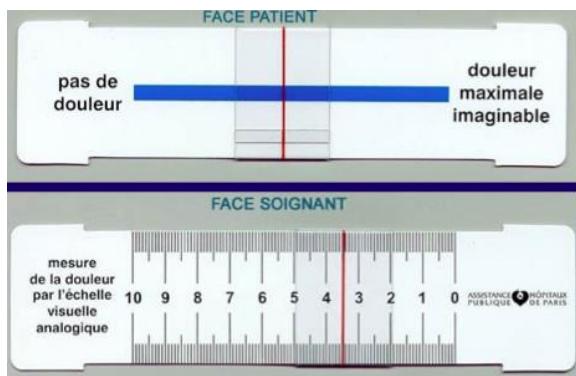
L'échelle visuelle analogue (EVA) a été utilisée pour quantifier l'intensité de la douleur vécue par chacun des participants. L'EVA est constituée d'une bande à 2 faces (Figure 2) : l'une sur lequel le participant indique à l'aide d'un curseur l'endroit représentant l'intensité de sa douleur soit entre deux extrêmes nommés « pas de douleur » à « douleur maximale imaginable ». Sur l'autre face graduée de 0 à 100 mm et cachée au participant, l'évaluateur peut lire l'intensité de la douleur quantifiée par le participant en millimètre. Il a été demandé aux participants du groupe SDRC de quantifier leur douleur ressentie au moment de l'évaluation (douleur présente), avant et après le traitement expérimental, et de quantifier la douleur vécue en moyenne dans la semaine précédant leur participation et dans la semaine suivant le traitement expérimental (douleur de la semaine). Aucune valeur de changement minimal cliniquement significatif pour l'EVA chez la population avec un SDRC n'a été trouvé dans les écrits scientifiques et comme une revue systématique pour la population en douleur aiguë propose des valeurs de changement minimal cliniquement significatif très variable d'une étude à l'autre (de 8 à 44mm, Olsen et

al., 2017), il sera nécessaire d'évaluer avec précaution les changements de douleur rapportés par les participants.

Le *« CRPS Severity Score »* (Annexe 1) a été utilisé pour pouvoir quantifier l'intensité du SDRC chez chacun des participants avec SDRC. Cet outil comprend deux parties : une première remplie par le participant lui-même qui indique si oui ou non chacun des symptômes sur la liste a été vécu dans la dernière semaine et une seconde partie remplie par un physiothérapeute qui cote si chacun des signes décrits est présent lors de l'évaluation du membre atteint. Un point est alloué par symptôme ou signe présent pour un maximum de 17 (8 symptômes et 9 signes). Ce questionnaire est suffisamment précis pour discriminer les patients ayant un SDRC de ceux n'en ayant pas, son score global est fortement associé dichotomiquement au diagnostic de SDRC établi selon les critères de recherche de Budapest et un score élevé est associé significativement à plus de limitations fonctionnelles reliées à la santé physique et au fonctionnement social, à une intensité plus grande de douleur et à un seuil de perception de la chaleur plus important du côté atteint (Harden *et al.*, 2010).

L'échelle de perturbation de la perception du schéma corporel de Bath pour les patients atteints du SDRC (Annexe 2) a été utilisée pour connaître comment les participants représentaient et se sentaient par rapport à leur membre atteint. C'est un questionnaire auto-administré comprenant sept questions dont deux avec des sous-questions. Au total, cinq des questions étaient répondues sur une échelle de 0 à 10, deux par des réponses oui/non et une réponse devait être dessinée.

1.5 MESURES CLINIQUES

Fonction sensitive

La fonction sensitive du membre supérieur a été évaluée par le seuil de perception de la pression et par la proprioception.

Le seuil de perception de la pression a été mesuré par le **test au monofilament** de Semmes et Weinstein. Ce test consiste à appliquer une pression sur la peau avec des fils de diamètre croissant (Figure 3). La force appliquée est celle la plus faible permettant de créer une déformation dans le fil. Le participant garde les yeux fermés durant le test et doit mentionner lorsqu'il ressent une pression et à quel endroit. Trois points sur chacun des membres supérieurs étaient testés chez les participants afin d'évaluer la main et l'avant-bras : à la moitié du 3ème métacarpe (face palmaire), à la moitié du 3ème métacarpe (face dorsale) et à deux centimètres (cm) en distal du pli du coude (au niveau de la ligne médiane de la face antérieure de l'avant-bras).

Figure 3. Test au monofilament de Semmes et Weinstein

La proprioception quant à elle est la capacité de percevoir la position de notre corps dans l'espace. Elle a été évaluée en suivant les directives décrites par Le Métayer pour mesurer la **proprioception « directe » et « brouillée »** du membre supérieur (Le Métayer, 2007). Brièvement, les participants étaient assis, dos appuyé sur une chaise sans appui-bras, genou à 90°, pieds au sol et mains déposées sur les cuisses (position initiale). Une cible était placée devant eux (Annexe 3). On leur demandait de toucher la cible avec le bout de l'index et de revenir en position initiale, et ce, à trois reprises avec les yeux ouverts (mouvement de pratique). Ensuite, ils devaient fermer les yeux et essayer de toucher à la cible où l'on marquait la localisation du doigt (proprioception directe). Après quoi, ils devaient refaire les trois mouvements de pratique avec les yeux ouverts en reprenant la position initiale entre

chaque mouvement. Puis, yeux fermés, leur membre supérieur évalué était déplacé par l'évaluateur en s'assurant de faire bouger l'épaule dans différentes directions, puis leur main était redéposée sur leur cuisse dans la position initiale. Sans ouvrir les yeux, ils devaient essayer de toucher à la cible et on marquait l'endroit où le doigt était placé (proprioception brouillée). La plus courte distance entre la position du doigt et le centre de la cible était ensuite mesurée et représentait leur proprioception pour chacune des conditions (directe ou brouillée); plus la distance est petite et plus la proprioception est élevée.

Fonction motrice

La fonction motrice a été évaluée par l'amplitude articulaire active des doigts et la force musculaire de préhension.

L'**amplitude articulaire active** a été mesurée en flexion pour chaque main à l'aide d'un goniomètre manuel à doigts (Figure 4) au niveau des articulations métacarpo-phalangiennes (en rouge) et interphalangiennes proximales (en bleu) **des 1er, 2ème et « pire » doigts**. Le « pire » doigt (entre le 3ème, 4ème et 5ème) a été choisi par chacun des participants en fonction du doigt qu'il avait le plus de difficulté à bouger (douleur ou restriction de mouvement). Les

Figure 4. Goniomètre manuel à doigt et articulations mesurées
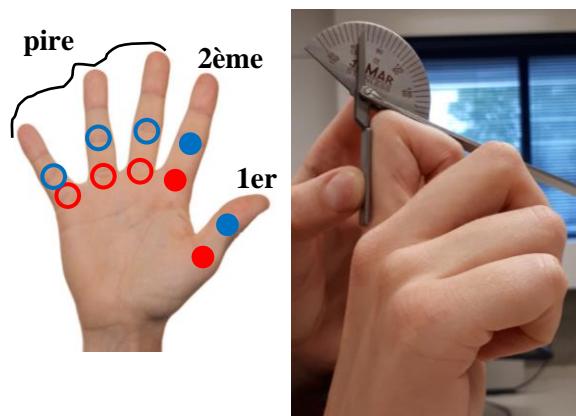
cinq doigts non pas été mesurés pour ne pas allonger la séance de prise de mesures et éviter la fatigue, particulièrement chez les participants avec SDRC. Pour le groupe sans douleur, le 1er, 2ème et 5ème doigt ont été mesurés. Pour la mesure des amplitudes articulaires du 1er doigt, le participant était assis avec l'avant-bras en appui sur une table d'évaluation (seule la main évaluée en dépassant) avec l'épaule et le poignet en position neutre et le coude à 90° de flexion. Pour la mesure des amplitudes articulaires des autres doigts, le coude était appuyé sur la table d'évaluation, épaule légèrement fléchie et poignet au neutre. Les mesures des articulations interphalangiennes proximales étaient prises avec les articulations

métacarpophalangiennes en position neutre (main en griffe). Il était demandé aux participants de plier leurs doigts au maximum tolérable.

Figure 5. Dynamomètre JAMAR
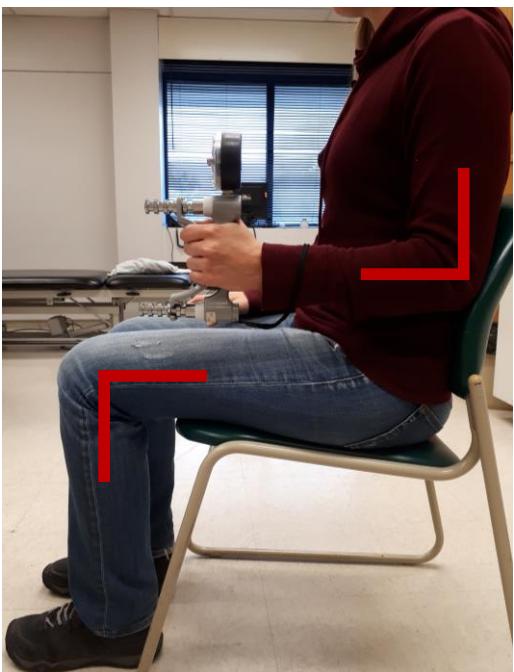
La **force musculaire de préhension** a été mesurée avec un dynamomètre hydraulique de type JAMAR (Figure 5). La moyenne de trois essais par main a été utilisée pour représenter la force musculaire maximale de préhension de chaque participant. Le participant était assis, bras le long du corps avec l'épaule et le coude à 90° de flexion et le poignet à 0°. La poignée du dynamomètre a été positionnée selon les instruction de Mathiowetz (Mathiowetz et al., 1984) dans sa seconde position et permettait sa localisation chez tous les participants au niveau de leur phalange proximale (lorsque main ouverte). Des encouragements standardisés leur étaient donnés (« Forcez fort, fort, fort, maximum, maximum maximum et relâchez. ») sur huit secondes de contraction maintenue pour favoriser l'obtention d'une valeur fiable (Buckinx et al., 2017).

1.6 MESURES NEUROPHYSIOLOGIQUES

Configuration et installation

Le fonctionnement de M1 a été testé bilatéralement, soit à l'hémisphère controlatéral (HC) au membre avec SDRC et à l'hémisphère ipsilatéral (HI) au membre avec SDRC. Comme le système corticospinal est croisé, l'HC contrôle la main avec SDRC et l'HI la main sans SDRC (Purves et al., 2011). Les TMS de la zone du M1 qui contrôle le muscle FDI (muscle impliqué dans la pince pouce-index, Figure 6) ont été utilisées pour mesurer les variables décrites plus bas.

Figure 6. Muscle premier interosseux dorsal de la main

Lors de la prise de mesures par TMS, le participant était assis confortablement dans un fauteuil inclinable et ajustable avec les hanches et les genoux légèrement fléchis, les bras au repos sur des appuis-bras. Les TMS ont été administrées à l'aide du stimulateur électromagnétique MagStim 200² (The MagStim Company limited, Whitland, UK, Figure 7) qui produit des pulsations monophasiques simples. Une bobine de stimulation en forme de 8 a été utilisée pour une stimulation plus focale, donc plus précise (par rapport à une bobine circulaire standard, Cohen *et al.*, 1990; Beaulieu *et al.*, 2015). Elle était positionnée sur le crâne dans un angle de 45° avec la ligne médiane pour induire un courant électrique à l'intérieur du M1 dans le sens postéro-antérieur (Sakai et al., 1997). Pour mesurer les potentiels moteurs évoqués dans le muscle (MEP, de l'anglais « motor evoked potentials ») par la TMS de M1, l'activité musculaire du FDI a été enregistrée par EMG de surface. Les recommandations SENIAM (de l'anglais « surface electromyography for the non-invasive assessment of muscles ») ont été utilisées pour limiter la variabilité des mesures (nettoyage de la peau, grandeur des électrodes, etc.; excepté pour le positionnement des électrodes d'EMG, puisque la description

Figure 7. Stimulateur électro-magnétique Mag Stim 200 et bobine de stimulation en forme de 8

du positionnement sur le muscle FDI n'est pas décrit dans leurs recommandations) (Hermens et al., 2000). Des repères anatomiques et la contraction musculaire ont permis d'assurer un positionnement consistant entre participants (et les électrodes n'ont pas été déplacées entre les temps de mesure pré et post traitement expérimental).

Électromyographie de surface

Les électrodes d'enregistrement EMG de surface (enregistrement de l'activité globale du muscle, Delsys Inc.) utilisées dans ce projet ont été collées au niveau des ventres musculaires des FDI droit et gauche avec des adhésifs double-face hypoallergènes sur la peau préalablement nettoyée à l'alcool à friction pour diminuer l'impédance électrique. Les électrodes contiennent des préamplificateurs miniatures et sont connectées à une unité préamplificatrice portable isolée électriquement (Figure 8).

Figure 8. Électrode d'EMG de surface, collant double-face et unité préamplificatrice

Une électrode de référence était collée sur le processus olécrânien de l'ulna pour avoir une zone neutre de référence sans activité électrique et obtenir des enregistrements plus propres. Le signal myoélectrique filtré (20-450 Hz) et échantillonné à 2kHz a été enregistré sur un ordinateur pour visionnement en cours d'expérimentation et analyses ultérieures.

Détermination de la zone du M1 qui contrôle le muscle visé

Le positionnement de la bobine TMS est important. Le site de stimulation retenu était le point optimal (appelé « **hotspot** ») qui, lorsque stimulé par TMS, permet d'obtenir les MEP de plus grande amplitude dans le muscle FDI controlatéral au M1 investigué. En début d'expérimentation, l'utilisation du système international d'électroencéphalographie 10-20 (Figure 9, Klem et al. 1999) a permis de cibler la région d'intérêt du M1 à l'aide de repères anatomiques sur le crâne : il est connu que les aires de représentation du membre supérieur

dans le M1 se situent autour de C3/C4. La bobine TMS a été apposée sur le crâne dans la région anatomiquement identifiée et la position finale

Figure 9. Système international d'électroencéphalographie 10-20

a été précisée par les premiers tests de stimulation. Une fois ce « hotspot » localisé, il a été marqué au niveau du cuir chevelu avec un crayon chirurgical avec encre effaçable comme référence visuelle pour permettre la reproductibilité du positionnement de la bobine TMS au cours de la séance (Wolf et al., 2004).
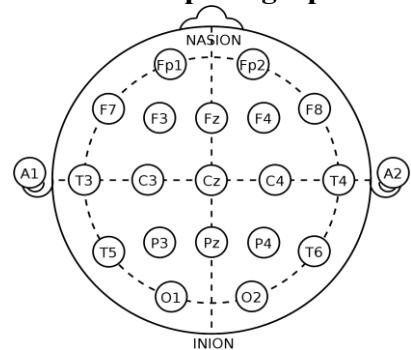
Mesure du seuil moteur de repos

Le **seuil moteur de repos** (RMT) correspond à l'intensité TMS la plus faible pour obtenir un MEP dont l'amplitude pic à pic est égale ou plus grande à 50 µV pour 5 essais sur 10 (Rossini et al., 2015). Il est exprimé en pourcentage de l'intensité maximale du stimulateur (MSO, de l'anglais « maximal stimulator output »). Cette mesure est utilisée pour représenter l'excitabilité motrice corticale de M1, où plus l'intensité de la stimulation pouvant dépolariser les neurones du M1 contrôlant le muscle enregistré est petite (RMT faible) et plus l'excitabilité motrice corticale est grande. L'excitabilité motrice corticale des deux hémisphères est normalement similaire et une différence de 7% MSO et plus correspond à un déséquilibre clinique significatif (Beaulieu et al., 2017).

Amplitude et latence des MEP

Les MEP dits tests ont été obtenus avec une intensité TMS de 120% du RMT. Par exemple, si le RMT était de 50% MSO, les TMS utilisées pour les MEP tests étaient de 70% MSO.

La latence du MEP (en ms) est le temps entre la TMS et le début du MEP ou réponse EMG dans le muscle, en d'autres mots c'est le temps de conduction de l'influx nerveux jusqu'au muscle. Pour permettre la comparaison entre participants et éliminer les différences reliées au temps de transmission de l'influx nerveux en périphérie, la moyenne individuelle des latences de MEP a été exprimée en pourcentage de la taille du participant. La latence reflète la synchronisation des cellules de M1 par TMS et la synchronicité des vollées descendantes (le long des axones corticospinaux) qui permet la dépolarisation (synchrone) des

motoneurones alpha de la moelle épinière (Kobayashi & Pascual-Leone, 2003; Groppa et al., 2012).

L'amplitude du MEP (mV) est l'amplitude de la réponse biphasique mesurée pic à pic. Elle reflète le volume des cellules de M1 activé par la TMS (c'est-à-dire les neurones corticospinaux et les interneurones associés), mais également l'excitabilité des motoneurones et la synchronicité des vollées descendantes pour une réponse synchrone des motoneurones et des fibres musculaires innervées (Kobayashi & Pascual-Leone, 2003; Rossini et al., 2015).

Il est à noter que le RMT ainsi que la latence des MEP sont les mesures TMS avec les meilleures propriétés métrologiques chez des participants en santé ou avec lésion du système nerveux central (Beaulieu et al., 2017a.c; Malcolm et al., 2006). On peut donc dire avec assurance qu'un changement (significatif et supérieur à l'erreur de mesure) dans les valeurs de ces mesures, reflèterait un réel changement d'excitabilité du M1 ou de synchronicité des volées corticospinales.

Mécanismes d'inhibition et de facilitation intracorticale - MEP conditionnés
Les paradigmes de double TMS ont été utilisés pour tester les mécanismes d'inhibition et de facilitation de M1 (Figure 10) à l'aide d'une bobine TMS reliée à deux stimulateurs MagStim 200^2. Plus précisément, ces paradigmes testent le niveau d'excitabilité des circuits neuronaux de M1, régis soit par les récepteurs GABA_A pour les circuits inhibiteurs (inhibition intracorticale de court-intervalle, SICI, de l'anglais « short-interval intracortical inhibition ») soit par les récepteurs glutamatergiques NMDA et AMPA (α-amino-3-hydroxy-5-méthylisoazol-4-propionate) pour les circuits excitateurs (facilitation intracorticale, ICF, de l'anglais « intracortical facilitation » et facilitation intracorticale de court intervalle, SICF, de l'anglais « short-interval intracortical facilitation ») (résumés au Tableau 3.) (Nielsen et al., 2007; Gracies 2005; Rogasch et al., 2014).

Figure 10. Mécanismes d'inhibition et de facilitation

En bleu, tracée EMG obtenu avec un MEP test.

En rouge, tracée EMG obtenu avec un MEP conditionné en inhibition ou facilitation : donc MEP conditionné plus petit en inhibition (SICI) ou plus grand en facilitation (ICF ou SICF) comparé au MEP test.
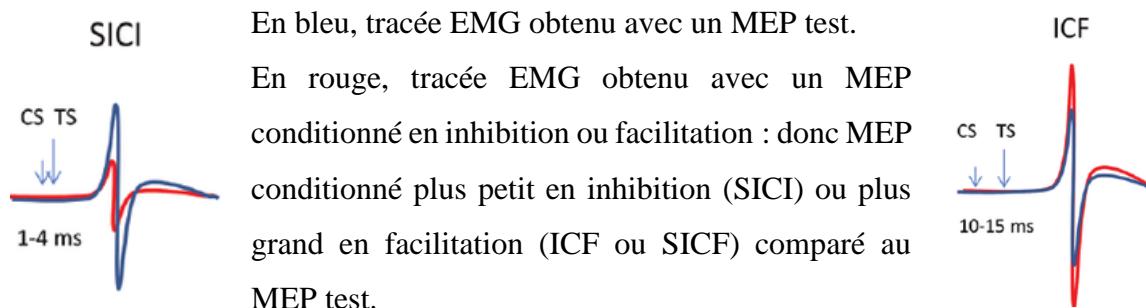
SICI : de l'anglais « short-interval intracortical inhibition »); CS : TMS conditionnante; TS : TMS test; ms : millisecondes; ICF de l'anglais « intracortical facilitation » (Rogasch, Daskalakis, and Fitzgerald 2014)

Pour tester ces circuits, une TMS dite conditionnante est envoyée avant la TMS test (SICI, ICF) ou après la TMS test (SICF). La TMS conditionnante a une intensité inférieure au RMT : utilisée seule elle ne permet pas de dépolariser assez de cellules corticospinales pour déclencher une réponse MEP, mais elle est suffisante pour activer les interneurones de M1 (cellules inhibitrices ou facilitatrices) au voisinage des corps cellulaires des cellules corticospinales. En double TMS, lorsque la TMS test dépolarise les cellules corticospinales, celles-ci sont déjà en partie inhibées (paradigme SICI) ou facilitées (paradigme ICF) par la TMS conditionnante. Dans des conditions normales (sujets en santé et sans douleur), le MEP conditionné en SICI a une amplitude inférieure à celle du MEP test et le MEP conditionné en ICF ou SICF a une amplitude plus grande. Les paramètres des paradigmes SICI, ICF et SICF sont détaillés dans le Tableau 3 ci-après. Ces paramètres ont été testés dans de nombreuses études TMS et pharmacologiques et ils dépendent notamment de la nature des récepteurs et neuromédiateurs impliqués et de la distance des interneurones par rapport aux corps cellulaires des cellules corticospinales (Rossini et al., 2015).

L'intensité des TMS tests a été ajustée en post-intervention dans l'étude 2 pour que les amplitudes des MEP tests soient comparables avec celles prises en pré-intervention et que la comparaison pré/post-intervention des amplitudes des MEP conditionnés soit valide (Beaulieu et al. 2017a). Des moyennes de douze MEP tests et de douze MEP conditionnés

ont été prises par participant, par paradigme TMS afin de contrôler pour la variabilité des MEP mesurés (Nielsen et al., 2007; Arya et al., 2011).

Tableau 3 : Paramètres des paradigmes de doubles TMS utilisés			
	SICI	**ICF**	**SICF**
Intensité TMS conditionnante	80% RMT	80% RMT	90% RMT
Intensité TMS test	120% RMT	120% RMT	100% RMT
Intervalle de temps pour TMS conditionnante	3 ms <u>avant</u> la TMS test	15 ms <u>avant</u> la TMS test	1 ms <u>après</u> la TMS test
Amplitude MEP conditionné	< MEP test	> MEP test	> MEP test
Exprimé en % de :	MEP test (120% RMT)	MEP test (120% RMT)	MEP test (100% du RMT)

TMS : stimulations magnétiques transcrâniennes, de l'anglais « transcranial magnetic stimulations »; SICI : inhibition intracorticale avec conditionnement à courte latence, de l'anglais « short-interval intracortical inhibition »; ICF : facilitation intracorticale, de l'anglais « intracortical facilitation »; SICF : facilitation intracorticale avec conditionnement à courte latence, de l'anglais « short-interval intracortical facilitation »; RMT : seuil moteur de repos, de l'anglais « resting motor threshold »; MEP : potentiel moteur évoqué dans le muscle, de l'anglais « motor evoked potentials ».

TABLEAU 4. Résumé des variables et mesures des deux études

QUESTIONNAIRES

a) **Renseignements généraux du participant** (questionnaire auto-administré recueillant les données descriptives, facteurs confondants ou potentiellement prédictifs de la réussite du traitement);

b) **Intensité de la douleur présente** et la moyenne de la douleur vécue **dans la dernière semaine** (échelle visuelle analogue);

c) **Intensité des signes et symptômes du SDRC** (« CRPS Severity Score »);

d) **Représentation du schéma corporel** (échelle de perturbation de la perception du schéma corporel de Bath pour les patients atteints du SDRC).

MESURES CLINIQUES

Fonction sensorielle

a) **Seuil de perception de la pression** (test au monofilament de Semmes et Weinstein)

b) **Proprioception directe et brouillée** (cible à atteindre, Le Métayer 2007)

Fonction motrice

a) **Amplitude articulaire active des doigts** (goniomètre à doigt);

b) **Force musculaire de préhension** (dynamomètre hydraulique JAMAR).

MESURES NEUROPHYSIOLOGIQUES

a) **Seuil moteur de repos** (RMT, TMS* simple)

b) **Amplitude des MEP à 120% du RMT** (TMS* simple)

c) **Latence des MEP à 120% du RMT** (TMS* simple)

d) **MEP conditionné testant la SICI** (en % MEP test à 120% du RMT, TMS* double)

e) **MEP conditionné testant la ICF** (en % MEP test à 120% du RMT, TMS* double)

f) **MEP conditionné testant la SICF** (en % MEP test à 100% du RMT, TMS* double)

***TMS de la zone M1 du muscle FDI mesuré par EMG de surface**

SDRC : syndrome douloureux régional complexe; MEP : potentiel moteur évoqué dans le muscle, de l'anglais « motor evoked potentials »; RMT : seuil moteur de repos, de l'anglais « resting motor threshold »; TMS : stimulations magnétiques transcrâniennes, de l'anglais « transcranial magnetic stimulations »; SICI : inhibition intracorticale avec conditionnement à courte latence, de l'anglais « short-interval intracortical inhibition »; ICF : facilitation intracorticale, de l'anglais « intracortical facilitation »; SICF : facilitation intracorticale avec conditionnement à courte latence, de l'anglais « short-interval intracortical facilitation ».

1.7 TRAITEMENT EXPÉRIMENTAL

Le traitement expérimental non invasif et indolore consiste en un paradigme rPMS de blocs de stimulations intermittentes de fréquence thêta (iTBS, de l'anglais « intermittent Theta-Burst stimulation »), c'est-à-dire des trains de 3 TMS pulsés à 5 Hz (chaque 200 ms) dans lequel les stimulations sont générés à 50 Hz (chaque 20 ms), le tout selon un mode intermittent (2 sec ON et 8 sec OFF) pendant 200 secondes (3 min 20 sec) pour un total de 600 stimulations. Ce paradigme mime une contraction volontaire en produisant un processus d'activation/relaxation du muscle stimulé, ce qui génère des informations proprioceptives cohérentes avec le contrôle du mouvement dans le but d'influencer positivement la plasticité cérébrale des cortex sensoriels et moteurs. En effet, le contrôle moteur s'ajuste en fonction des sensations reçues avec le mouvement. Une sensibilité ou proprioception perturbée nuit donc au contrôle moteur et, à l'inverse, l'amélioration ou l'envoi d'informations proprioceptives améliore la planification du mouvement et la transmission de commandes motrices est plus précise. Le meilleur exemple de ce phénomène est la difficulté qu'on a à bouger un membre engourdi lorsqu'il a été comprimé durant longtemps parce que la sensation est altérée.

Les rPMS étaient administrées au niveau du ventre musculaire du muscle FDS du membre supérieur atteint à l'aide d'une bobine en forme de 8, de 70 mm de diamètre interne (Figure 11), connectée au stimulateur Magstim Rapid-Rate^2 (Figure 12). L'intensité utilisée a été celle maximale du stimulateur pour ce paradigme intermittent (42% MSO), ce qui est supraliminaire, c'est-à-dire qu'elle était suffisamment forte pour obtenir une contraction musculaire et un mouvement visible de flexion au niveau du 2ème au 5ème doigts du membre supérieur atteint. Comme le muscle FDS est voisin des muscles fléchisseurs du poignet (fléchisseur radial et ulnaire du carpe) et que son

Figure 11. Bobine de stimulation avec ventilateur intégré appliquée sur le FDS

action secondaire est la flexion du poignet, il n'était pas rare de voir également une flexion du poignet conjointe au mouvement de flexion des doigts lors des rPMS. L'avantage des stimulations magnétiques sur les stimulations électriques est qu'il est possible d'utiliser cette intensité supraliminaire sans créer de douleur, alors qu'en stimulation électrique, l'intensité est limitée par la dépolarisation des fibres nociceptives (générant donc de la douleur). Les rPMS permettent donc d'envoyer des afférences proprioceptives plus « pures » aux cortex sensorimoteurs que les stimulations électriques (Beaulieu & Schneider, 2013, 2015; Beaulieu et al., 2017b)

Figure 12. Stimulateur Magstim Rapid-Rate[2]

1.8 RÉSUMÉ DES RÉDUCTIONS DE DONNÉES ET ANALYSES STATISTIQUES

Six variables cliniques ont été mesurées avant rPMS (données utilisées dans les deux études) et cinq après rPMS (étude 2 seulement) :

- l'intensité de la **douleur présente** au moment de son évaluation;
- la moyenne de l'intensité de la **douleur de la semaine précédente**;

Et pour les deux mains :

- l'**amplitude articulaire active** de flexion des articulations métacarpo-phalangiennes et interphalangiennes proximales des 1er, 2ème et « pire » doigts;
- la **force musculaire** de préhension (exprimé en % de normes tenant compte du sexe et de l'âge des participants (Mathiowetz et al. 1985);
- la **proprioception** « directe » et « brouillée »;
- le **seuil de perception de la pression** *(testé uniquement en pré-rPMS).*

Six variables TMS par hémisphère (mesures neurophysiologiques) ont été mesurées avant et 10 minutes après l'application des rPMS pour tester le fonctionnement et la plasticité du M1 :

- le **RMT** reflétant l'excitabilité de base du M1 (exprimé en % MSO ou en % du RMT pré-traitement du M1 contralatéral au côté atteint);

- la moyenne de l'**amplitude pic-à-pic** des MEP test obtenus à 120% RMT (en mV) et leur **latence moyenne** (en % de la taille), le tout reflétant la quantité de tissu de M1 répondant aux TMS et la synchronicité des vollées descendantes au niveau des motoneurones alpha spinaux;

- la moyenne de l'**amplitude pic-à-pic des MEP conditionnés** pour les mesures des mécanismes moteurs intracorticaux de **SICI**, **ICF** et **SICF**.

Le programme de statistiques Jamovi a permis de tester les données et leur significativité ($p<0.05$). Des statistiques descriptives (moyennes et écart-types) ont permis de comparer les groupes aux différents temps de prise de mesures. Dépendant des études (1 ou 2) et des variables, les analyses de variance (ANOVA) ont été appliquées avec les facteurs GROUPE (groupe SDRC vs groupe Sans-douleur) X CÔTÉ (HC vs HI, ou main atteinte vs non-atteinte ou vs moyenne des mains/hémisphères du groupe Sans-douleur) ou CÔTÉ X TEMPS (pré- vs post-rPMS). Les analyses post-hoc bilatérales et plans de comparaison ont permis de tester l'origine des interactions détectées. Pour les variables où il n'y avait pas de côté à tester ni de données pour le groupe Sans-douleur, comme pour l'intensité de la douleur, le test t de Student pairé bilatéral a été utilisé entre les temps pré et post-rPMS. Les matrices de corrélation de Pearson ont été utilisées pour tester les liens entre les variables présentant des changements statistiquement significatifs post-rPMS et pour détecter l'existence de facteurs prédictifs de l'efficacité du traitement, soit la présence d'un lien entre les changements mesurés chez certains participants et la valeur de leurs variables en ligne de base (avant traitement).

**CHAPITRE 2 : ARTICLE 2 « *Living with a Complex Regional Pain Syndrome (CRPS):*
Clinical and Corticomotor Changes as Compared to Pain-Free People »**

**« Vivre avec un syndrome douloureux régional complexe (SDRC): changements
cliniques et corticomoteurs par rapport aux personnes sans douleur »**

Cet article décrit les différences mesurées entre les participants adultes vivant avec un SDRC
de type I au membre supérieur en stade chronique et les participants sans douleur.

Les participants avec SDRC ont présenté une force de préhension et une amplitude articulaire
active inférieures du côté avec SDRC comparativement au côté sans SDRC ou au groupe
Sans-douleur et une altération de la différence normale entre les deux côtés du corps de la
sensibilité à la pression et de la proprioception. En parallèle, le débalancement d'excitabilité
motrice corticale était significativement plus important chez les participants avec SDRC que
chez le groupe Sans-douleur. Le sens du débalancement (hémisphère contralatéral ou
ipsilatéral au SDRC) variait d'un participant à l'autre, indépendamment du côté atteint. Ceux
avec l'hémisphère ipsilatéral moins excitable étaient ceux avec le moins d'amplitudes
articulaires, mais le moins de douleur également.

Ces résultats originaux ouvrent la voie à la nécessité de comprendre les changements
individuels de fonctionnement moteur cortical en lien avec la fonction sensorimotrice chez
des participants avec SDRC pour personnaliser l'approche en neurostimulation et influencer
la plasticité cérébrale qui pourrait permettre l'amélioration de leur condition (voir Chapitre
3 : Article 3).

En préparation pour soumission au journal PAIN

TITLE: LIVING WITH A COMPLEX REGIONAL PAIN SYNDROME (CRPS):
CLINICAL AND CORTICOMOTOR CHANGES AS COMPARED TO PAIN-FREE
PEOPLE

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RÉSUMÉ

Contexte : Le syndrome douloureux régional complexe de type I (SDRC, sans lésion nerveuse) se caractérise par des changements dans le traitement et l'organisation sensorimotrice corticale et sa pauvre réponse aux traitements. Les changements corticaux et leur association à la douleur ou aux troubles moteurs ne sont pas encore complètement compris rendant le développement d'interventions efficaces difficile.

Objectifs : Cette étude a exploré l'excitabilité des deux cortex moteurs primaires (M1) liée au muscle premier interosseux dorsal de la main (FDI) en association à des mesures de fonction manuelle sensorielle et motrice bilatérale chez des personnes avec SDRC de type 1 et des participants sans douleur.

Méthodologie : Huit adultes avec SDRC ont été comparés à huit adultes sans douleur. Les variables cliniques mesurées étaient l'intensité de la douleur et bilatéralement : la proprioception (PP), la sensibilité à la pression (SP), l'amplitude articulaire active des doigts (ROM) et la force musculaire de préhension (FP). Des stimulations magnétiques transcrâniennes (TMS) simples et doubles ont testé l'intégrité fonctionnelle des M1 du muscle FDI.

Résultats : Une altération de la différence normale entre les deux côtés du corps de la SP et de la PP a été détectée en SDRC et la diminution de ROM des doigts et de FP a été confirmée. Un débalancement interhémisphérique d'excitabilité du M1 a été identifié en SDRC avec une association avec la douleur et le trouble de ROM.

Conclusion : La prise de mesures TMS et cliniques simultanées en SDRC a fourni des données originales sur le débalancement d'excitabilité du M1 en association avec les troubles sensorimoteurs de la main. Les études futures devront considérer ces biomarqueurs spécifiques de plasticité cérébrale et de troubles moteurs pour guider le développement d'interventions individualisées et faciliter la pratique clinique en SDRC.

Mots-clés : Syndrome douloureux régional complexe, SDRC, TMS, cortex moteur primaire, intégration sensorielle, amplitude articulaire (ROM), force de préhension, homéostasie, plasticité, fonction manuelle

ABSTRACT

Background: The type-1 complex regional pain syndrome (CRPS, no nerve damage) presents with changes cortical sensorimotor processing and organization, and poor response to treatment. Brain changes and the association with pain and motor disorders are not yet clearly understood thus precluding any efficient intervention.

Objectives: This study explored the excitability of both primary motor cortices (M1) related to the first dorsal interosseus (FDI) in association with bilateral sensory and motor assessment of hand function in people with type-1 CRPS and in pain-free subjects.

Methods: Eight adults with CRPS were compared to eight pain-free adults. Clinical outcomes were pain intensity, and bilaterally: proprioception (PP), tactile sensitivity to pressure (TSP), fingers active range of motion (ROM) and grip strength (GS). Single and paired-pulse transcranial magnetic stimulation (TMS) tested the functional integrity of both M1 of the FDI.

Results: An alteration in the normal difference between the two sides of the body of TSP and PP has been detected in CRPS and the reduction of fingers ROM and GS was confirmed. Between-hemisphere imbalance of M1 excitability was identified in CRPS with an association to pain and ROM disorders.

Conclusion: Concurrent TMS and clinical testing in CRPS provided original data on FDI M1 imbalanced excitability in association with hand sensorimotor disorders. Future studies will have to consider these specific biomarkers of brain plasticity and motor disorders, to guide the development of individualized interventions and ease clinical practice in CRPS.

Keywords: Complex regional pain syndrome, CRPS, TMS, primary motor cortex, sensory processing, ROM, grip strength, homeostasis, plasticity, hand function

INTRODUCTION

Complex Regional Pain Syndrome (CRPS), formerly known among others as reflex sympathetic dystrophy or algoneurodystrophy, is a rare chronic pain condition. It is characterized by pain to one (unilateral CRPS) or more limbs (bilateral or generalized) which is disproportionate to the inciting focal event (fracture, sprain, surgery, or no traumatism identified) combined with trophic changes and sensory, motor and autonomic disorders (Borchers & Gershwin, 2014; Marinus et al., 2011). The upper limb is affected in almost 60% of cases (Bruehl, 2015) and kinesiophobia, i.e. the fear of movement, is responsible for learned non-use of the CRPS hand at the chronic stage, which worsens the condition due to reduced proprioceptive information for motor control (Marinus et al., 2013). CRPS is divided in two main categories, based on the absence (type I, 90% of all CRPS cases) or presence (type II) of nerve lesion at the periphery (Borchers & Gershwin, 2014). The therapeutic approach is multidisciplinary, including medical interventions (medications, infiltrations, etc.), rehabilitation (physical and/or occupational therapies), psychology and clinical guidelines to follow-up treatment progression. However, after discharge from pain clinics and in the long term, pain and severe impairments of daily life activities persist in almost 20% of people and 31% remain unable to be back at work two years after the onset of symptoms (Bean et al., 2014; Geertzen et al., 1998; de Mos et al., 2007; O'Connell et al., 2013; Rodham et al., 2015).

It is possible to think that refractoriness to treatment, chronicization of symptoms and generalization to other limbs than the one with the inciting event could be due to central changes not wholly understood yet and not appropriately treated. Indeed, the etiology remains unclear but the physiopathology is acknowledged as multifactorial (Bruehl, 2010) with peripheral changes and sensitization, dysregulation of the sympathetic nervous system and plastic changes within the central nervous system (Allen Demers et al., review in preparation; Borchers & Gershwin, 2014; Goh et al., 2017). Our recent comprehensive review on the topic, among others, denoted that functional limitations (beyond ankylosis or kinesiophobia) could be related to brain changes (Allen Demers et al., in preparation).

Neuroimaging and transcranial magnetic stimulation (TMS of M1) studies have contributed to knowledge of changes of volumes, connectivity, activation and excitability of different parts of the brain in CRPS, especially the primary sensory (S1) and motor (M1) cortices with clinical significance in pain control, perception and motor planning (Allen Demers et al., review in preparation; Barad et al., 2014; Geha et al., 2008; Kim et al., 2013; Kirveskari et al., 2010; Maihöfner et al., 2003; Pleger et al., 2006; Schwenkreis et al., 2009; Vartiainen et al., 2008; Walton et al., 2010; Zhou et al., 2015). The alteration of the homeostasis of M1 excitability between hemispheres (referred to as imbalanced hemispheric activity) has also been widely associated with pain and motor disorders in CRPS of the hand (Barad et al., 2014; Eisenberg et al., 2005; Kirveskari et al., 2010; Krause et al., 2006; Maihöfner et al., 2007, 2003; Di Pietro et al., 2013; Schwenkreis et al., 2003). However, the direction of imbalance remains controversial at the chronic stage (Di Pietro et al. 2013a), i.e. hyper- or hypoexcitability of M1 contralateral to the CRPS hand as compared to M1 ipsilateral. It is thus crucial to understand if imbalanced hemispheric activity is actually different between people with CRPS and if the direction of imbalance is related to the severity of the symptoms, including pain intensity and sensorimotor disorders. This will encourage the development of an individual approach in CRPS relying on M1 imbalance direction and its normalization to improve the symptoms.

Therefore, the present study aimed at investigating in people with hand CRPS type 1 (no nerve lesion) the between-hemisphere differences of corticospinal and intracortical excitability related to M1, by means of TMS of M1, concurrently with each hand function assessed by means of standardized sensory and motor testing (pain intensity, proprioception, tactile sensitivity, fingers active range of flexion, grip strength). Both the CRPS and non-CRPS sides will be compared, and the CRPS group will be compared to a group of pain-free participants.

METHODS

Participants and Procedures

Eight adults with hand type-1 CRPS (52 ±11 years old, see Table 1) were enrolled in a single session of TMS and clinical testing and they were compared to a group of eight pain-free adults (50.8 ±6.9 years old). All participants had signed the informed consent form approved by the local ethics committees. The participants with CRPS presented with a unilateral upper limb CRPS type 1 diagnosed with the Budapest clinical criteria (see Table 2) and were discharged from pain clinics follow-up. The pain-free participants did not experience pain in the last month before enrolment nor have medical history of chronic pain (pain persisting for more than three consecutive months). All participants met the exclusion criteria related to general health (absence of : spine surgery, major circulatory/respiratory/cardiac disease, other neurological condition for participants with CRPS, severe upper limb orthopaedic condition, cognitive disorder interfering with the tasks of the study) and to TMS safety guidelines (Lefaucheur et al., 2011; Rossi et al., 2011, 2009). A physician performed medical evaluation at pre- and post-enrolment to confirm eligibility and monitor adverse effects. The same physical therapist collected TMS and clinical data in both groups and data were codified post-hoc for group (CRPS vs. pain-free) until completion of analyses. After questionnaires on CRPS severity and perception, and pain evaluation (see next section), all outcomes were collected on both sides in all participants. Everyone was phoned 2 and 7 days later to document any adverse effects (Rossi et al. 2009).

Questionnaires on CRPS and Pain Intensity

CRPS severity. The Complex Regional Pain Syndrome Severity Scale (CSS) and the Bath CRPS Body Perception Disturbance Scale (Bath) were the two questionnaires used to characterize CRPS. The CSS (Harden et al., 2010) includes a section fulfilled by the participant on the presence or absence of eight symptoms and a section fulfilled by the therapist for the presence or absence of nine signs, with each symptom or sign presence counting for one point on a maximal score of 17. The CSS global score contrasts between people with and without CRPS, in strong association with the Budapest research criteria and

with, among others, the severity of physical and social limitations, pain intensity and thermal perception abnormalities (Harden et al., 2010).

Self-perception and representation of CRPS limb. The Bath CRPS Body Perception Disturbance Scale (Lewis et al., 2010) includes seven questions (two with sub-questions, five on a scale of 0-10, two with Yes/No and one drawing of the CRPS limb) and it was used to describe and quantify how the participants perceived and represented the CRPS limb.

Pain intensity. Participants' sitting position was standardized against a chair's backrest with the shoulder in neutral rotation and 0-30° abduction, elbow in 90-100° flexion, and forearm resting on a height-adjustable therapeutic table. The *visual analogue scale* (VAS, Heller et al., 2016) was used to quantify the pain intensity experienced by each participant with CRPS. The VAS consists of a two-sided band: on one side, the participant uses a cursor to rate the level of pain intensity between two extremes called "No pain" and "Maximal pain imaginable"; on the other side of VAS, hidden from the participant, a graduated scale from 0 (no pain) to 100 millimeters (maximal pain imaginable) is used by the evaluator to quantify the participant's pain intensity. VAS was used to quantify "instantaneous pain" and the mean pain in the last week.

Mean scores of CCS, Bath item 4 (the extent to which feelings regarding the CRPS limb are negative) and VAS are reported in Table 1.

(Insert Tables 1-2 near here)

Surface Electromyographic (EMG) Recordings
Painless EMG procedures were followed. After standard skin preparation (i.e. cleaning the skin with alcohol and shaving whenever necessary, Hermens et al. 2000), the parallel-bar EMG sensors with adhesive skin interfaces were installed on each participant (fixed 1cm distance between electrodes; 16-channel Bagnoli EMG System, Delsys Inc., Boston, MA). EMG sensors were placed bilaterally on the belly of the first dorsal interosseous muscle (FDI). A common ground electrode was placed on the ulna olecranon of the tested limb.

EMG signals were band-pass filtered (20-450 Hz), amplified before digitization (2 kHz) and computer-stored for offline analysis (PowerLab acquisition system, LabChart, ADInstruments, Colorado Springs-CO, US).

TMS Testing for Both Hemispheres

TMS procedures were strictly replicated for each hemisphere, following the guidelines from the International Federation of Clinical Neurophysiology (Rossini et al., 2015). Participants were comfortably in the reclining chair, arms and legs supported, hips and knees slightly bent (20° flexion).

Hotspot. Magnetic stimuli were applied over the M1 area of the FDI (index finger abductor and involved in precision grip) by a figure-of-eight coil (7-cm outer diameter each wing; Magstim Company Limited, Whitland-UK) positioned on the scalp with the long axis of the two- wing intersection pointing antero-posteriorly at a 45° angle from the medial line to active M1 cells in the postero-anterior direction (Sakai et al., 1997). The 10–20 EEG system was used to first approximate FDI M1 area (Klem, 1999). The position was then adjusted slightly to determine the 'hotspot', namely the M1 location where the MEP obtained in the contralateral FDI are of the highest amplitude at the lowest TMS intensity (Wolf et al., 2004). This hotspot was marked on the scalp (surgical pen) to ensure reliable coil positioning during the session and visual inspection of EMG recordings from both sides monitored the complete relaxation of the hands during TMS testing.

Resting Motor Threshold (RMT). RMT was determined at the TMS intensity that elicited at least five FDI MEP with an amplitude of 50 μV or higher out of ten trials. RMT has good validity and reliability (Beaulieu et al., 2017a, 2017c; Malcolm et al., 2006) and it informs on M1 basic excitability (Rossini et al., 2015; Ziemann et al., 2015) which allowed to probe the hemispheric activity balance.

MEP Amplitude and Latency. A suprathreshold test (unconditioned) TMS at an intensity of 120% RMT enabled to collect and measure the test MEP amplitude and latency. Test MEP amplitude (in mV) was measured peak-to-peak and it reflects the volume of M1 cells activated by TMS and the excitability of the corticospinal pathway (Devanne et al., 1997; Kobayashi & Pascual-Leone, 2003; Rossini et al., 2015). Test MEP latency (in % participant's height for validity of interindividual comparison) was measured from stimulation time to MEP onset and it reflects conduction time and, indirectly, the synchronicity of descending volleys to depolarize spinal motoneurons (Groppa et al., 2012; Kobayashi & Pascual-Leone, 2003).

SICI, ICF and SICF. Paired-pulse TMS (coil connected to two Magstim 200^2 monophasic stimulators) was used to test the short-interval intracortical inhibition (SICI), the intracortical facilitation (ICF) and the short-interval intracortical facilitation (SICF) (Arya et al., 2011; Ilić et al., 2002; Kujirai et al., 1993). In SICI, a subthreshold conditioning TMS (80 % RMT eliciting no MEP on its own) was delivered 3 msec before the test TMS at 120 % RMT (Kujirai et al., 1993). In ICF, the same parameters were used but at an inter-stimulus interval of 15 ms (Kujirai et al., 1993). In SICI, the conditioned MEP expressed post-hoc relative to the mean test MEP amplitude is usually of lower amplitude than the test, and in ICF it is of higher amplitude than the test (Kujirai et al., 1993). SICI probes the function of $GABA_A$ interneurons within M1 and ICF the function of oligosynaptic glutamatergic circuits (Rossini et al., 2015; Ziemann et al., 2015). In SICF, two stimuli were delivered 1 ms apart, the first TMS at 100 % RMT and the second at 90 % RMT (Ortu et al. 2008). MEP amplitude was then expressed relative to the amplitude of test MEP at 100 % RMT, which likely reflects I-waves summation following the depolarisation of M1 interneurons by TMS (Ilic et al., 2002; Rossini et al., 2015; Ziemann et al., 2015). When test MEP amplitudes were different between sides, the test TMS intensity was adjusted to match this amplitude between sides and be able to compare the conditioned MEP data between sides. Twelve test MEP and 12 conditioned MEP were collected per participant at a frequency of 0.2-0.3 Hz. Resting breaks were given on request.

Clinical Testing on Both Sides

Upper Limb Proprioception

Following Le Métayer's guidelines, the paradigm of the blurred proprioception of the upper limb was used to assess the ability to perceive limb position in space (Le Métayer, 2007). Briefly, the participants were seated, leaning against a chair without armrests, knees bent at 90° with feet flat on the floor and hands on the thighs (initial position). They had first to reach with the index a target (large red dot) on a graduated screen at gaze height and arm distance in front of them and return to the initial position and to repeat this practice three times. Then, they closed the eyes and the evaluator cautiously (without pain) moved their tested arm in the air with shoulder movements and elbow flexion / extension and put the arm back in the initial position, and the participants, without opening the eyes, had to reach back the target with the index (one trial only). The score of blurred proprioception was the distance in centimeter between the finger contact on the graduated screen (with eyes closed) and the target.

Cutaneous Pressure Threshold

This superficial tactile sensitivity was probed by means of the Semmes and Weinstein monofilaments test (Weinstein, 1993). This test consists of applying pressure on the skin at different regions of hand and forearm with wired monofilaments of increasing diameter. The participant was seated against the chair's backrest, the shoulder in neutral rotation and 0° abduction, elbow in 90-100° flexion, and forearm resting on the height-adjustable therapeutic table. With the eyes kept closed during testing, the participant had to tell where a pressure was felt. The pressure applied to the skin by the experimenter was the weakest to create the first bending of the wire. When nothing was felt, the experimenter tested the monofilament with very next higher diameter. The higher the first wire diameter felt, the higher the cutaneous pressure threshold, thus the lower the superficial tactile perception. Three points of pressure were tested on each side: at half of the third metacarpal in the palmar and on the dorsal sides of the hand and at two centimeters down to the antecubital fossae (at the midline of the forearm). The same experimenter tested all participants.

Active Range of Motion (ROM)

Active ROM in flexion was measured using a manual finger goniometer at the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the 1st and 2nd fingers and also of the "worst" finger, i.e. the finger (between the third, fourth and fifth) harder or more painful to move for each participant. For active ROM of the 1st finger, the participant was seated with the forearm positioned at rest on the table, shoulder and wrist in neutral position and the elbow flexed at 90°, and the hand protruding on the edge of the table. For active ROM of the other fingers, the elbow and shoulder were slightly bent, with the elbow at rest on the therapeutic table. The measurements of the PIP joints were taken with the wrist and MCP joints in neutral position (claw hand). Three trials were tested and averaged per MCP and PIP. Participants rested 60sec between trials.

Grip Strength

Participants were sitting with no arm support, the forearm in neutral position and the wrist between 0-30° extension and 0-15° ulnar deviation. The maximal grip strength per hand was measured using a JAMAR hydraulic hand dynamometer (Sammons Preston Rolyan, Bolingbrook-IL, USA). Following Mathiowetz's instructions (Mathiowetz et al., 1984) JAMAR dynamometer was set to the second handle position (placed in hand with help of the evaluator if needed). The average of three trials per hand was used to represent the maximum grip strength of each participant. Standardized cheers were given ("Squeeze hard, hard, hard, the hardest and release") over 8 sec s of sustained contraction to promote a reliable value (Buckinx et al., 2017). Participants rested 30s between trials.

Data Reduction and Statistical Analyses

Six TMS outcomes were collected per hemisphere per participant: RMT (expressed in % of maximal stimulator output-MSO), test MEP amplitude (mV) and latency (% participant's height), and conditioned MEP amplitudes for SICI, ICF, and SICF (% test MEP amplitude). In addition, the between-hemisphere difference of RMT was calculated for each group (D_{RMT}, % MSO).

Eleven clinical outcomes were measured per hand per participant: blurred proprioception (cm), monofilament pressure (tenth mg) for cutaneous pressure thresholds (three points: at forearm, and palmar and dorsal metacarpus sides), active ROM of MCP and PIP joints of the 1st, 2nd and worst fingers (°), and isometric muscle grip strength (%). To ensure validity of interindividual comparison, grip strength was expressed in % of grip strength norms stratified by age and sex (Mathiowetz et al., 1985).

Shapiro-Wilk's test for Normality revealed that data were normally distributed ($p>0.05$), thus parametric tests were used. Two-way analyses of variance (ANOVA, repeated measures) were applied on TMS and clinical data with factors Group (CRPS vs. Pain-free) X Hemisphere for TMS data and the factors Group X Hand for clinical outcomes. Hemispheres were defined as contralateral (CH) and ipsilateral (IH) to CRPS hand and as Dominant (D) and Non-Dominant (ND) for pain-free participants. Planned comparisons (two-sided, Tukey's post-hoc tests for multiple comparisons) were used to detect where differences lay. Bilateral unpaired Student's t-tests were applied between groups on between-hemisphere difference of RMT. Pearson's correlation matrices were produced to examine the relationships between the outcomes and especially between the primary outcome (RMT between hemispheres) and clinical outcomes (including CSS and Bath scores and pain intensity). The maximum normed residual test (Grubbs' test) helped detect an outlier from a data set approximated by normal distribution (Prism 8.0, GraphPad Software Inc, La Jolla-CA, USA): data set is analyzed and an outlier would typically be expunged when it falls beyond a critical deviation from the sample mean (chance probability to obtain the outlying value < 0.05). Significance was set at $p < 0.05$ (https://www.jamovi.org).

RESULTS

The two groups were not statistically different for age and manual dominance (one left-hander per group, $p>0.05$). A few TMS data was not collected due to head discomfort during the application of the paired-pulse TMS: out of the N=8+8 participants in the CRPS+pain-free groups, SICI is presented for 7+7 participants, ICF for 6+7 participants and SICF for 7+8 participants. Also, in the CRPS group, fingers movement were not possible for one participant (no active ROM nor grip strength collected), ROM measures were painful for another one (no ROM collected), and one was nauseous with eyes closed (no blurred proprioception nor tactile sensitivity collected); in the pain-free group, one participant was detected as outlier for the tactile sensitivity on the palmar face of the hand; thus, blurred proprioception is presented for 7+8 participants, tactile sensitivity for 7+8 on dorsal side and 7+7 on palmar side, ROM for 6+8 and grip strength for 7+8 participants. No adverse effect was reported at phone follow-ups. Table 3 presents all clinical and TMS outcomes per group.

(Insert Table 3 near here)

TMS Outcomes

Resting motor threshold. Fig 1A presents that the significant relation linking both M1 RMT in the pain-free subjects (right graph, r=0.87, p=0.005) with narrow dispersion of individual data around the perfect line. This relation was not significant in the CRPS group (r=0.62, p=0.11) and the individual data were more dispersed around the perfect line. Of note, 6/8 participants in the CRPS group presented with the hemisphere ipsilateral to CRPS hand with higher RMT as compared to the contralateral Fig. 1A). The bilateral unpaired t-test detected that the between-hemisphere difference of RMT (D_{RMT}, Fig. 1B) was close to be significantly larger in CRPS group (8±4 % MSO) than in the pain-free group (4.5 ±2.7 % MSO, *p*=0.06).

(Insert Figure 1 near here)

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Test and SICI-Conditioned MEP Amplitudes. The two-way ANOVA applied on the test MEP amplitude detected a main effect of Side ($F_{1, 14} = 4.78$; $p=0.046$) which seems to be due to the CRPS group with amplitudes close to be significantly higher in IH-hemisphere ipsilateral to CRPS hand (1.4 ±1.8 mV) than in the CH-hemisphere contralateral to CRPS hand (0.76 ±0.7 mV, $p=0.07$, Fig. 1C). The planned comparisons of the ANOVA for the conditioned MEP of the SICI detected that SICI tended to be reduced (conditioned MEP higher) in CH (59.8 ±63.0 % test) as compared to the dominant hemisphere of the pain-free participants (18 ±11 % test, $p=0.06$, Fig. 1D). The standard deviation of CH SICI mean above y=100% denotes that some participants with CRPS did not have any SICI in CH. No other between-group or between-side differences were detected in TMS outcomes.

(Insert Figure 2 near here)

Clinical Outcomes

Proprioception. The planned comparisons of the two-way ANOVA applied on the blurred proprioception detected that the distance from the target was significantly smaller for the non-dominant hand of the pain-free participants (2.9 ±1.0 cm) than the dominant (5 ±2.7 cm, $p=0.038$, Fig. 3A) with no difference between hands in the CRPS group ($p>0.05$).

Cutaneous Pressure Threshold. The ANOVA applied on forearm tactile sensitivity detected a main effect of Side ($F_{1, 13} = 6.08$; $p=0.028$) which was carried on by a smaller pressure for the non-dominant forearm of the pain-free participants (2.1 ±0.4 tenth mg) than for dominant (2.7 ±0.3 tenth mg, $p=0.011$, Fig. 3B) with no difference between forearms in the CRPS group ($p>0.05$). A main effect of Group was detected for dorsal hand tactile sensitivity ($F_{1, 13} = 4.84$, $p=0.047$) with smaller pressure for the pain-free group (Fig. 3C). A main effect of Side ($F_{1, 12} = 12.49$, $p=0.004$) was detected for palmar hand tactile sensitivity with smaller pressure on the non-CRPS hand (2.48 ±0.48 tenth mg) than on CRPS (3.07±051 tenth mg, $p=0.02$, not represented) and no hand difference in pain-free group.

Active ROM. The ANOVA applied on the 1ˢᵗ MCP joint ROM detected a main effect of Side ($F_{1, 12} = 9.01$, $p=0.011$) which was explained by lower ROM for the CRPS hand ($43.3 \pm 14.4°$)

than for non-CRPS (43.3±14.4 °, p=0.042, not represented) and no difference between sides in the pain-free group. A Group X Side interaction was found for the worst MCP joint ROM $(F_{1, 12}$ = 11.4, p=0.005) with ROM lower for CRPS hand (74.2 ±16.6°) than for non-CRPS (93.3 ±9.3°, p<0.001), than the dominant (92.5 ±7.6°, p=0.02) and the non-dominant hands (92.5 ±7.1°, p=0.02) of the pain-free group (Fig. 3D). The ANOVA applied on the worst PIP joint ROM showed a Group X Side interaction ($F_{1, 12}$ = 5.09, p=0.044) with ROM smaller for CRPS hand (94.2 ±10.2°) than for non-CRPS (102.5 ±8.83°, p=0.04), than the dominant (104.4 ±3.2°, p=0.011) and the non-dominant hands (105.0 ±4°, p=0.008) of the pain-free group (Fig. 3E).

Grip Strength. The ANOVA applied on the grip strength detected Group X Side interaction $(F_{1, 13}$ = 14.7, p=0.002) with strength lower for CRPS hand (75 ±16%) than for non-CRPS (111 ±14%, p<0.001), than the dominant (101 ±22 %, p=0.03) and the non-dominant hands (109 ±30%, p=0.008) of the pain-free group (Fig. 3F).

(Insert Figure 3 near here)

Correlations in CRPS Group

The active ROM of the first finger MCP joint was smaller among patients for the higher RMT of M1 ipsilateral to CRPS hand (IH, r = -0.76, p=0.029, Fig. 4A). In other words, MCP ROM was more limited (and below the shared area of pain-free values) in patients with IH more hypoactivated. Of note, the last week pain intensity was lower in patients with IH more hypoactivated (r = -0.46, p=0.038, Fig. 4B). Fig. 4C presents that the amount and direction of RMT imbalance between hemispheres influenced the active ROM of the worst finger PIP joint (r = 0.84 p=0.038). Precisely, ROM decreased (below values of pain-free participants) for patients with IH RMT higher than CH RMT, meaning the more IH was hypoactivated (as compared to CH), the smaller was ROM. Fig. 4D shows the positive relation between the score at the 4th item of the Bath Body Perception Disturbance scale and pain, especially instant pain (r =0.8, p=0.016), meaning that pain was scored as more intense by patients with more negative feelings regarding the CRPS hand.

(Insert Figure 4 near here)

DISCUSSION

This study provides original data on concurrent TMS-of-M1 and clinical outcomes collected on both sides in people with type-1 hand CRPS compared to pain-free subjects. An impaired lateralization of proprioception and tactile sensitivity was detected for the first time in CRPS and the reduction of fingers range of motion and grip strength was confirmed. Between-hemisphere imbalance of M1 excitability was identified in CRPS with a link to pain and hand motor disorders. The potential mechanisms involved are discussed in order to better understand the changes and guide the future development of treatment more appropriate to the individual characteristics.

Impaired Hemispheric Lateralization for Sensory Processing in CRPS

CRPS type 1 is characterized by changes in cortical processing and organization, perceptual disturbances, and poor response to conventional treatments (Allen Demers et al., review in preparation; Barad et al., 2014; Borchers & Gershwin, 2014; Geha et al., 2008; Kim et al., 2013; Kirveskari et al., 2010; Lagueux et al. 2018; Maihöfner et al., 2003; Marinus et al., 2011; McCormick et al. 2015; Pleger et al., 2006; Reinersmann et al. 2013; Schwenkreis et al., 2009; Vartiainen et al., 2008; Walton et al., 2010; Zhou et al., 2015).

There are still however no clusters of clinical measures used to describe the CRPS population (Borchers & Gershwin 2014; Grieve et al. 2016) and CRPS clinical trials use a wide range of outcome measures with different measuring tools making comparisons and meta-analyses challenging. Also, the lack of measures on the both sides of pain-free people limits the comparison of CRPS to the dominant hand.

Our data in a CRPS group at the chronic phase (> 6 months after the onset of symptoms) and compared to pain-free people confirmed the lower grip strength and the smaller active ROM of the fingers on the CRPS side, precisely at MCP and PIP joints. Testing both sides in pain-free participants rendered it possible for the first time to detect that the blurred proprioception integration and the tactile sensitivity to pressure were lateralized, with better performances on the non-dominant side. The CRPS group did not show such lateralization with equivalent values between sides. Our results in the pain-free group, though original with such testing tools, confirm that the non-dominant (most often right) hemisphere can have a leading role

in the proprioceptive feedback processing (Contu et al., 2015; Goble & Brown, 2018) by the monitoring of spino-cerebellar proprioceptive inputs for spatial orientation of the upper limb (Ferrè et al. 2015; Kirsch et al. 2018). In addition, the non-dominant hemisphere is prevalent in the perception of cutaneous sensation (Oliveri et al 1999) with stronger activation of right S1 with left-hand stimulation than on the other side (Jin et al 2020). The lack of hemispheric lateralization for sensory processing is a new result in CRPS. This could be explained in part by the alteration of thalamo-cortical activity (Walton et al., 2010) or the maladaptive reorganization of cutaneous maps (Pleger et al., 2006). Clinically, this may be associated with the difficulty of people with CRPS to contrast between the affected and non-affected hands (Moseley, 2004). Interestingly, it was reported that people with high trait anxiety did not show the left-right side difference in cutaneous pressure threshold (Naveteur & Honoré, 1995). A hypothesis could be that brain commands a generic strategy to protect the whole body, rather than a strategy specific to painful side, as already shown in the chronic patellofemoral pain syndrome (Jensen et al., 2007) where the somatosensory perception of the painless side was altered. In support, Fig. 4B showed that the last week pain intensity was related to the level of M1 excitability in the hemisphere ipsilateral to CRPS hand, i.e. the ipsi-H controlling the non-painful side. Thus, the generic strategy in our participants could have worked via a pain processing lateralized in ipsi-H, which was the right hemisphere in 7 out of 8 patients. This hypothesis could be supported by the fact that the frontal areas of the right hemisphere are more active in unilateral pain (Hsieh et al. 1996; Coghill et al. 2001; Symonds et al. 2006). More precisely, the right anterior cingulate cortex (ACC) and the right dorsolateral prefrontal cortex (rDLPFC) are overactivated, for instance by the insula (Symonds et al. 2006) and, via corticocortical linking to premotor areas, they increase the right M1 excitability (Dum & Strick 2002). Future studies should test this hypothesis in unilateral CRPS.

One exception to the loss of hemispheric lateralization of sensory processing in our CRPS group was the palmar area whose cutaneous threshold was lower for the non-CRPS hand than the CRPS (same between-side difference as pain-free, Table 3). It is questioned whether this may reflect a task-oriented plasticity of the palmar S1 area in relation to the need and the overuse of the hand palmar area in all-day activities.

Cortical Motor Changes and Relation to Pain and Sensorimotor Impairment

TMS of M1 provides outcomes that reflect the integrity of the cortical and corticospinal components of the motor systems. We thus used TMS of M1 hand area with clinical scores to better understand the abnormal control of the CRPS hand. Literature about TMS outcomes in CRPS is controversial with MEP unchanged between hemispheres or as compared to pain-free people (Krause et al., 2004; Morgante et al., 2017; Schwenkreis et al., 2003; van Velzen et al., 2015), or, for the same authors, MEP was either unchanged (Krause et al., 2004) or bilaterally decreased as compared to pain-free subjects (Krause et al., 2005). SICI was reported as reduced in both hemispheres as compared to pain-free subjects (Krause, et al., 2006) or reduced only in M1 contralateral to CRPS hand (Eisenberg et al., 2005; Lefaucheur et al., 2006; Pfannmoller et al., 2019). We did not obtain significant changes in CRPS, but only trends of MEP increase in ipsi-H and SICI decrease in M1 contralateral. One explanation could be that our CRPS group was at the chronic stage; participants were at acute stage in the previous studies and it is known that changes of TMS outcomes can resolve in the long term due to homeostatic plasticity, i.e. brain mechanisms to balance M1 activity (Manganotti et al., 2008). The trending increase of MEP could however reflect global increase of corticospinal excitability, including a larger volume of M1 cells responding to TMS and more synchronicity of descending volleys to excite the alpha-motoneurons in the spinal cord (Devanne et al., 1997, Kobayashi & Pascual-Leone, 2003, Rossini et al., 2015). The trending decrease of SICI could reflect M1 disinhibition still acting on the modification of sensorimotor maps (Ziemann et al., 2001) to learn alternate motor strategies to recover motor control in the presence of persistent pain (Massé-Alarie & Schneider, 2017). The net effects were an imbalance of M1 excitability between hemispheres, as detected by RMT.

RMT-related data are the main TMS findings of our study. RMT informs on the transsynaptic excitability of M1 tissues (Ziemann et al., 2014) and the absence of RMT correlation between hemispheres in CRPS (Fig. 1A, left graph) could reflect an alteration of interhemispheric homeostasis. Homeostasis maintains a balanced M1 excitability between hemispheres (Abraham, 2008; Abraham & Bear, 1996; Hassanzahraee et al., 2018; Hulme et al., 2013; Karabanov et al., 2015; Mansour et al., 2014; Nijs & Van Houdenhove, 2009; Ziemann & Siebner, 2008). A potential cause of homeostasis alteration could be the smudging or the

overlap of sensorimotor maps contralateral to CRPS, as already denoted (Di Pietro et al., 2013b, 2013a; Pleger et al., 2006). The modulation of excitatory influences to M1 or the changes of connectivity to M1 could have imbalanced M1 excitability between hemispheres. This is supported by the fact that S1 ipsilateral to CRPS is larger than S1 in pain-free subjects (Di Pietro et al., 2015), thus increasing the S1-M1 activation. Also, the connectivity from the prefrontal cortex to the frontal lobe is augmented in CRPS at the chronic stage (Shokouhi et al., 2018), thus potentially overactivating M1.

Correlations of Fig. 4 showed the association between the excitability of ipsi-H (right-H in 7/8 patients) and CRPS fingers ROM and pain intensity. Precisely, among patients, the higher the ipsi-H excitability, the larger the active ROM (Fig.4A,C) but the more intense the last week pain (Fig.4C). Thus, the ipsi-H excitability as compared to the contralateral seems an interesting biomarker to guide treatment. For example, any approach capable to down-regulating ipsi-H activity could decrease pain intensity. Then, rehabilitation could be painlessly administrated. However, the portrait is not that simple and the association between the item 4 of the Bath Body Perception Disturbance Scale and the intensity of pain (Fig. 4D) revealed that the more were the negative feelings regarding the CRPS limb the higher the pain intensity was. This emotional aspect of CRPS may be related to connectivity changes of the DLPFC networks including the limbic system (Shokouhi et al., 2018). In addition, kinesiophobia may have created a vicious circle that worsened the condition: the CRPS hand was less or no more used and this resulted in substantial learned non-use maladaptive changes in sensorimotor areas (Hotta et al., 2015) thus potentially enlarging and exciting further S1-M1 in ipsi-H .

Methodological Considerations
The small number of participants and missing data due to discomfort to paired-pulse TMS or clinical testing (ROM, eyes closed) precludes from any generalization of our results and the findings need to be replicated in larger samples with better effect size. The study offers the advantages of testing sensory function (proprioception, tactile sensitivity) and hand motor function (fingers ROM, grip strength) in both the CRPS and non-CRPS hand, in comparison to the both sides of pain-free participants and concurrently to TMS outcomes from both

hemispheres. This provides a valuable foundation for future work to decipher in parallel different mechanisms of action in CRPS that could be relevant to guide the appropriate therapies against refractoriness to treatment: lateralized sensory processing, hemispheric balanced activity (direction, amount), central sensitization, emotional aspects, neuroimaging and TMS investigation. psychosocial evaluation.

CONCLUSION

Concurrent TMS and clinical testing in type-1 CRPS hand provided original data on the impairment of hemispheric balanced activity of the primary motor cortex and the lateralization of sensory processing along with an association with pain and hand/finger function outcomes. Future studies will have to consider these specific biomarkers of brain plasticity and motor disorders, to guide the development of individualized interventions and ease clinical practice in CRPS.

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FIGURES CAPTIONS

FIGURE 1. Resting Motor Threshold (RMT). **A.** Relation between RMT of both hemispheres in the CRPS group (left graph) and the pain-free group (right graph). Note the significant relation in the pain-free group and the small dispersion of individual values around the perfect line (dotted line, y=x) and the non significant relation in the CRPS group with larger dispersion of individual values. **B.** Group means ± SD of the absolute difference of RMT between hemispheres (Δ_{RMT}) in each group. M1: primary motor cortex; MSO: maximal stimulator output; Contra-/ipsi-M1: M1 contralateral / ipsilateral to CRPS hand.

FIGURE 2. Test and Conditioned MEP Amplitudes. A. Group means ± SD of the test MEP amplitudes per hemisphere in each group. **B.** Group means ± SD of the conditioned MEP amplitudes related to SICI per hemisphere in each group. CH, IH: hemispheres contralateral and ipsilateral to CRPS hand; DH, NDH: dominant and non-dominant hemispheres in the pain-free group; MSO: maximal stimulator output; SICI: short-interval intracortical inhibition. # $p < 0.05$ main effect of Side

FIGURE 3. Clinical Outcomes (group means). for the CRPS hand (CH), the non-CRPS hand (NCH), and the dominant (DH) and non-dominant (NDH) hands in pain-free participants. **A**. Blurred proprioception performance (cm from the target, Le Métayer, 2007). **B-C**. Pressure (tenth mg) of first monofilament perceived for tactile sensitivity of forearm (**B**) and dorsal side of the hand (**C**). **D-E**. Worst finger range of motion (ROM, deg) at metacarpophalangeal (MCP) joint (**D**) and at proximal interphalangeal (PIP) joint (**E**). **F**. Grip strength expressed in % of the norm stratified by age and sex. The normative data (Norm) are represented by a shaded area (mean ± 1 SD) or the horizontal dotted lines. * $p < 0.05$ or ** $p < 0.01$ between sides; # $p < 0.05$ main effect of Side; @ $p < 0.05$ main effect of Group; + $p < 0.05$ CRPS hand as compared to all others (Group X Side interaction)

FIGURE 4. Group Correlations. A-B. Decreasing relation between RMT of M1 ipsilateral to CRPS hand (IH) and the first finger range of motion (ROM, deg) at metacarpophalangeal (MCP) joint on CRPS side (**A**) or the mean pain experienced over the last week (**B**). **C.** Increasing relation between the worst finger ROM at proximal interphalangeal (PIP) and the raw difference of RMT between the hemispheres contralateral (CH) and ipsilateral (IH) to CRPS hand. Note that, among patients, ROM decreased with IH hypoactivation (as compared to CH). **D.** Increasing relation between the item #4 of the Bath Body Perception Disturbance scale (negative feelings related to CRPS limb) and the instant and last week pain. M1: primary motor cortex; MSO: maximal stimulator output

TABLE 1. General Characteristics of Participants.

Characteristics	Groups	
	CRPS	**Pain-free**
Number (N)	8	8
Age (years): mean ±SD (range)	52 ±11 (35-65)	50.8 ±6.9 (40-61)
Dominance (N): *right/left*	7/1	7/1
Gender (N): *females/males*	6/2	4/4
Severity score (/17)	9 ±3	--
Bath item 4	5 ±1.5	--
Altered side (N): *right/left*	6/2	--
Inciting event: *N fracture of hand/forearm/arm*	4/3/1	--
Time since onset (months): mean ±SD (range)	55,9 ±66,8 (7-168)	--
Pain intensity (VAS, mm): mean ±SD		--
Instantaneous	38 ±20	--
Last week	51 ±22	--

CRPS: complex regional pain syndrome; SD: standard deviation; Severity score : CRPS Severity Scale (CSS); Bath: Bath CRPS Body Perception Disturbance scale, item 4 relates to the extent to which the emotions regarding the CRPS limb are negative (worst = 10/10); VAS: visual analogue scale.

TABLE 2. The "Budapest Criteria" for Complex Regional Pain Syndrome (CRPS) Diagnosis (Harden et al., 2010). Diagnosis of CRPS requires to meet all four criteria.

The "Budapest Criteria" – CRPS Diagnosis
1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom on three of the four following categories (clinical diagnosis) OR in all four (research purpose):   *Sensory hyperesthesia and/or allodynia*   *Vasomotor: temperature asymmetry and/or skin colour changes and/or skin colour asymmetry*   *Sudomotor/oedema: oedema and/or sweating changes and/or sweating asymmetry*   *Motor/trophic: decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)*
3. Must display at least one sign at the time of evaluation in 2 or more of the following categories (clinical criteria and research purpose):   *Sensory: evidence of hyperalgesia (to pinpricks) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)*   *Vasomotor: evidence of temperature asymmetry (>1°C) and/or skin colour changes and/or asymmetry*   *Sudomotor/oedema: evidence of oedema and/or sweating changes and/or sweating asymmetry*   *Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)*
4. There is no other diagnosis that better explains the signs and symptoms

TABLE 3. Raw Clinical and TMS Data in CRPS and Pain-Free Groups.

Clinical Outcomes	CRPS Group (mean ±SD)		Pain-free Group (mean ±SD)
B-proprioception (cm)	C-hand: 4.7 ±2.7 NC-hand: 4.2 ±1.7		D-hand: 5 ±2.7 * ND-hand: 2.9 ±1.0
Tactile sensitivity - forearm (tenth mg)	C-hand: 2.6 ±0.6 NC-hand: 2.5 ±0.7	#	D-hand: 2.7±0.3 * ND-hand: 2.1 ±0.4
Tactile sensitivity - dorsal (tenth mg)	C-hand: 2.71 ±0.67 NC-hand: 2.52 ±0.22	@	D-hand : 2.4 ±0.3 ND-hand: 2.2 ±0.3
Tactile sensitivity - palmar (tenth mg)	C-hand: 3.07 ±0.51 * NC-hand: 2.48 ±0.48	#	D-hand : 2.9 ±0.6 ND-hand: 2.6 ±0.2
1st MCP (°)	C-hand: 43.3 ±14.4 * NC-hand: 51.7 ±14.7	#	D-hand: 53.8 ±14.3 ND-hand: 60.0 ±12.5
1st PIP (°)	C-hand: 65.8 ±16.3 NC-hand: 73.3 ±19.1		D-hand: 72.5 ±17.3 ND-hand: 75.6 ±10.2
2nd MCP (°)	C-hand: 77.5 ±11.3 NC-hand: 84.2 ±8.6		D-hand: 86.9 ±3.7 ND-hand: 88.1 ±6.5
2nd PIP (°)	C-hand: 101.7 ±6.1 NC-hand: 104.2 ±7.4		D-hand: 104.4 ±4.2 ND-hand: 104.4 ±6.2
Worst MCP (°)	C-hand: 74.2 ±16.6 ** NC-hand: 93.3 ±9.3 +		D-hand: 92.5 ±7.6 ND-hand: 92.5 ±7.1
Worst PIP (°)	C-hand: 94.2 ±10.2 * NC-hand: 102.5 ±8.8 +		D-hand: 104.4 ±3.2 ND-hand: 105.0 ±4.6
Grip strength (%)	C-hand: 75 ±16 ** NC-hand: 111 ±14 +		D-hand: 101 ±22 ND-hand: 109 ±30
TMS Outcomes	**CRPS Group (mean±SD)**		**Pain-free Group (mean±SD)**
RMT (% MSO)	CH: 52.1 ±11.4 IH: 54.4 ±8.7 Δ (abs): 8 ±4		DH: 59.8 ±10.3 NDH: 58.3 ±10.4 Δ (abs): 4.5 ±2.7
MEP amplitude (mV)	CH: 0.76 ±0.7 IH: 1.4 ±1.8	#	DH: 0.4 ±0.4 NDH: 0.8±0.6
MEP latency (%height)	CH: 15.3 ±1.1 IH: 15.1 ±0.9		DH: 15.0 ±1.0 NDH: 15.1 ±1.1
Conditioned MEP - SICI (%test)	CH: 59.8 ±63.0 IH: 30.5 ±17.2		DH: 24.8 ±20.9 NDH: 29.3 ±25.7
Conditioned MEP - ICF (%test)	CH: 176.7 ±139.0 IH: 148.2 ±106.4		DH: 132.9 ±87.4 NDH: 125.6 ±57.9
Conditioned MEP - SICF (%test)	CH: 542.7 ±539.8 IH: 557.8 ±802.5		DH: 1084.6 ±2339.6 NDH: 1010.2 ±778.8

C-hand, NC-hand: CRPS and non-CRPS hands; D-hand, ND-hand: dominant and non-dominant hands; CH, IH: hemispheres contralateral and ipsilateral to CRPS hand; DH, NDH: dominant and non-dominant hemispheres; VAS: visual analogue scale; N/A: non applicable; 1st, 2nd: first and second fingers; worst: the finger the harder or more painful to move out of the 3rd,4th or 5th; MCP: metacarpophalangeal joint active range of motion (ROM); PIP: proximal interphalangeal joint ROM; B-proprioception: blurred proprioception; TMS: transcranial magnetic stimulation; RMT: resting motor threshold; MSO: maximal stimulator output; CH / IH: hemisphere contralateral / ipsilateral to the CRPS hand; Δ: interhemispheric difference; abs: absolute value; MEP: motor evoked responds; SICI: short-interval intracortical motor inhibition; ICF: intracortical motor facilitation; SICF: Short-interval intracortical motor facilitation. * p<0.05 or ** p<0.01 between sides; # p<0.05 main effect of Side; @ p<0.05 main effect of Group; + p<0.05 Group X Side interaction

FIGURE 1. Resting Motor Threshold (RMT).
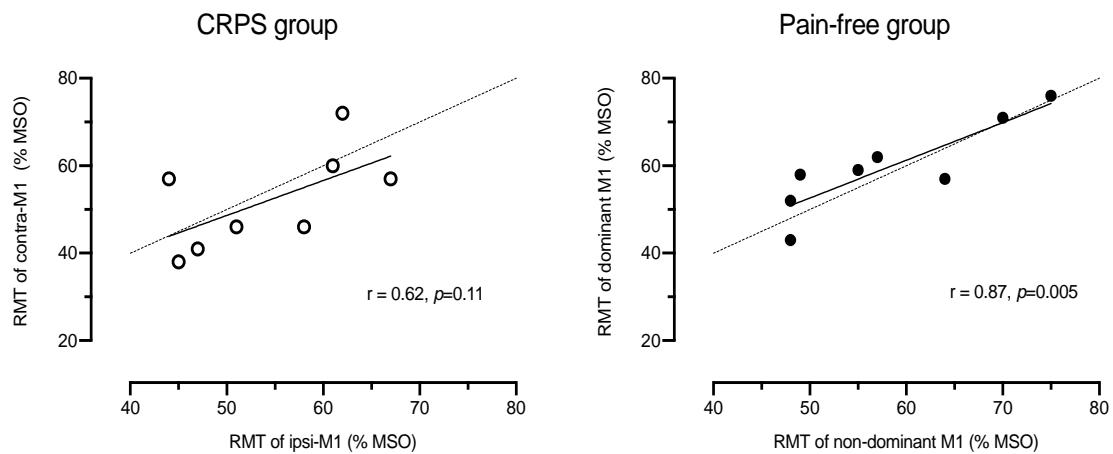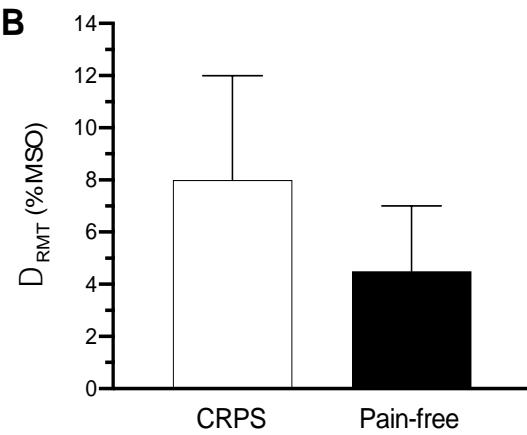
FIGURE 2. Test and Conditioned MEP Amplitudes.
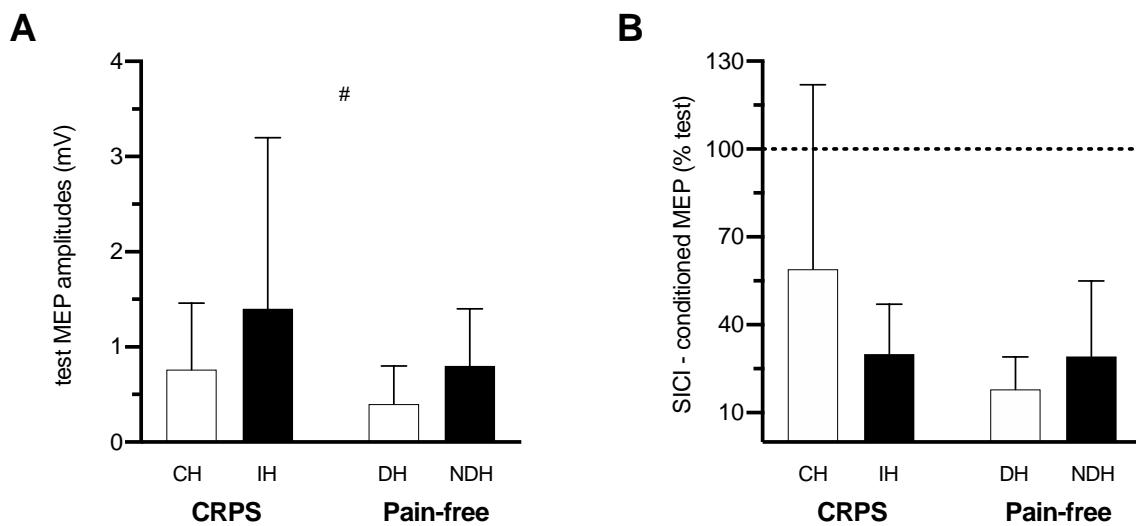
FIGURE 3. Clinical Outcomes (group means).
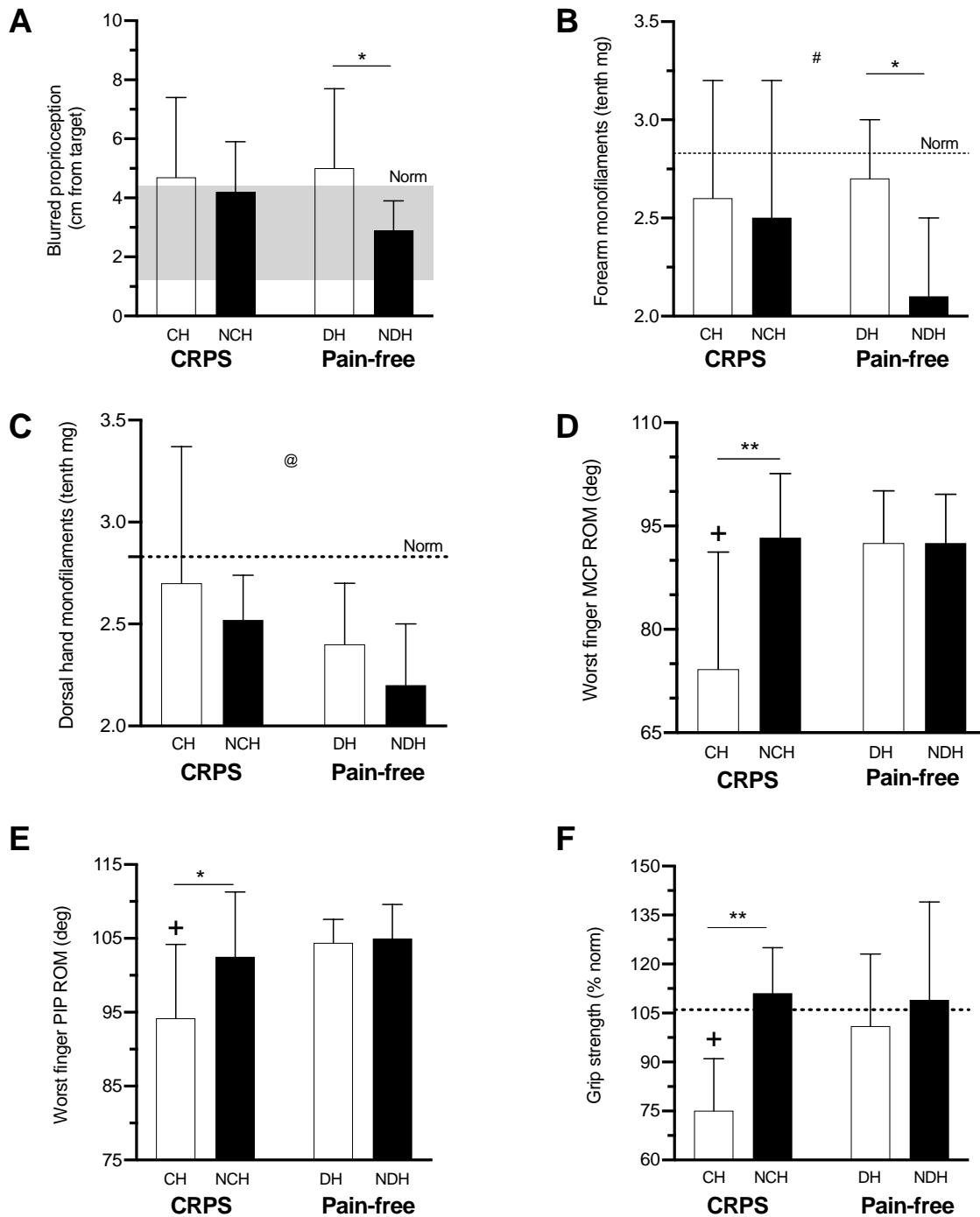
FIGURE 4. Group Correlations.
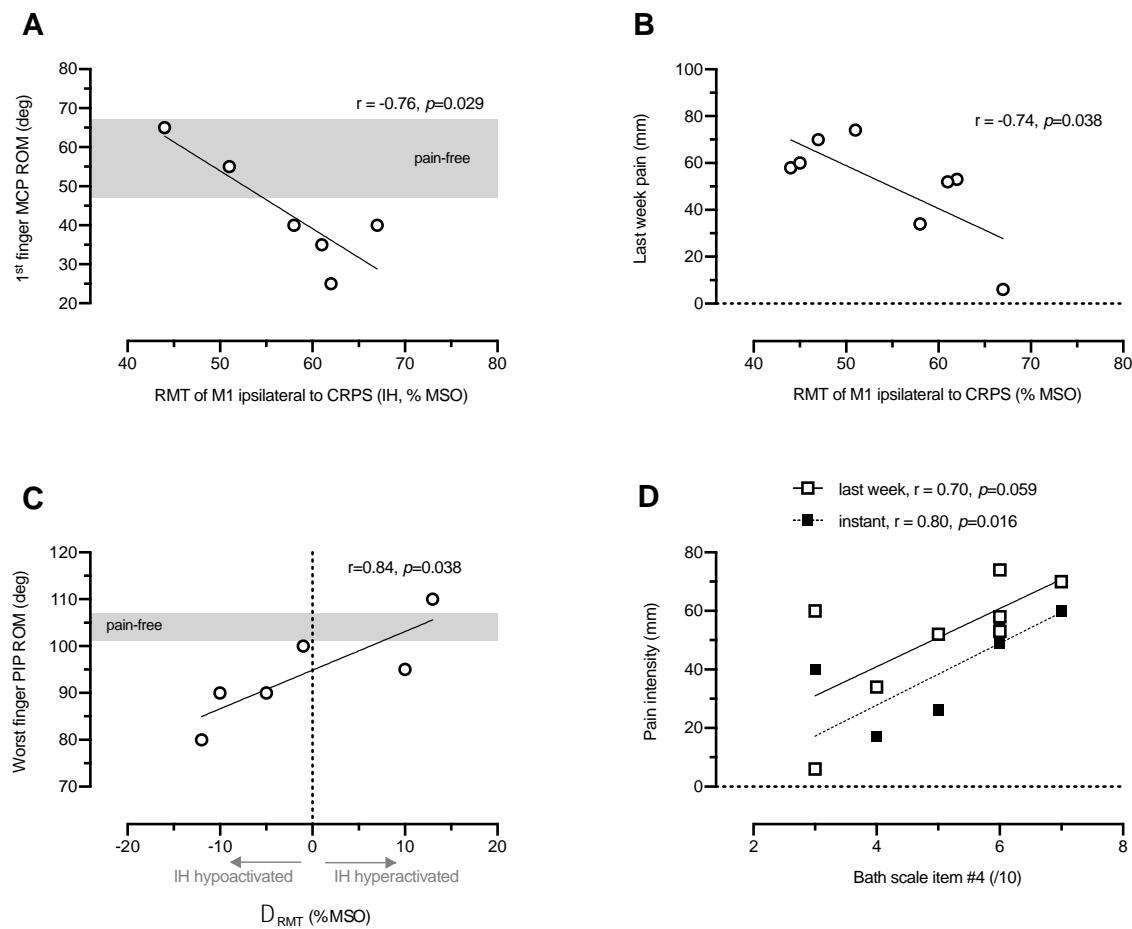
CHAPITRE 3 : ARTICLE 3 « *Theta Burst Stimulation Over Forearm Muscles in Complex Regional Pain Syndrome (CRPS): Influence on Brain and Clinical Outcomes* »

« Stimulations magnétiques intermittentes de fréquence thêta sur les muscles de l'avant-bras en syndrome douloureux régional complexe (SDRC)- Son influence sur les résultats cliniques et neurophysiologiques »

L'étude expérimentale 1 (Chapitre 2 : Article 2) a permis de montrer une altération de la fonction sensorimotrice chez les participants avec SDRC de type I au membre supérieur et le besoin de considérer la présence d'un débalancement d'excitabilité motrice corticale et le sens de ce débalancement. Comme il est connu que les rPMS peuvent influencer positivement la plasticité cérébrale, l'étude expérimentale 2 (article 3) a testé l'apport d'une séance de rPMS sur la douleur, la fonction et l'excitabilité motrice corticale en SDRC.

Il a été possible de mesurer des changements à la suite d'une seule séance de rPMS : une diminution du débalancement d'excitabilité motrice corticale, une diminution de l'intensité de la douleur, une amélioration d'amplitude articulaire active des doigts et de proprioception du membre supérieur, ainsi qu'une levée d'inhibition et une augmentation de facilitation motrices corticales (signes de plasticité induite).

Ces résultats originaux supportent l'efficacité et la faisabilité des rPMS en SDRC et le lien entre rebalancement interhémisphérique d'excitabilité motrice corticale et baisse de la douleur. Ceci renforce le besoin de mieux comprendre les changements du fonctionnement sensorimoteur cortical pour personnaliser les traitements de neurostimulation en SDRC.

THETA BURST STIMULATION OVER FOREARM MUSCLES IN COMPLEX REGIONAL PAIN SYNDROME (CRPS): INFLUENCE ON BRAIN AND CLINICAL OUTCOMES.

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RÉSUMÉ

Contexte et objectifs : Le syndrome douloureux régional complexe (SDRC) est caractérisé par des changements cérébraux qui ne sont actuellement que peu adressés par les traitements conventionnels. Les stimulations magnétiques répétées en périphérie (rPMS des muscles) sont indolores et non invasives et peuvent influencer ces changements (induire une plasticité cérébrale) pour réduire la douleur et améliorer la motricité. Cette étude originale a testé leurs effets immédiats en SDRC sur l'intensité de la douleur, le contrôle sensorimoteur du membre supérieur et les changements d'excitabilité du cortex moteur primaire (M1).

Méthodologie : Quatorze adultes ont été recrutés (six avec un SDRC, huit sans douleur). Le groupe avec SDRC a été testé en pré- et post-rPMS du muscle fléchisseur superficiel des doigts atteint et comparé aux valeurs normatives du groupe Sans-douleur (sans rPMS). Les variables cliniques mesurées étaient : l'intensité de la douleur, la proprioception, l'amplitude articulaire active et la force musculaire de préhension. L'excitabilité du M1 a été testée par stimulations magnétiques transcrâniennes (TMS) simple et double du M1.

Résultats : Les rPMS ont réduit l'intensité de la douleur instantanée et de la semaine, normalisé le débalancement d'activité hémisphérique, amélioré la proprioception et l'amplitude articulaire et induit des changements plastiques que dans le M1 de l'hémisphère ipsilatéral (HI) au SDRC. Plus l'HI était hypoactivé au départ, plus la douleur était réduite.

Conclusion : Cette étude original fournit des résultats prometteurs pour l'utilisation des rPMS en SDRC en mettant l'accent sur les changements plastiques de l'HI. Des études futures devront confirmer l'existence d'une relation de cause à effet entre les variables TMS et la diminution de douleur post-rPMS pour favoriser le développement de traitements personnalisés de neurostimulation non invasive en SDRC.

Mots-clés : Syndrome douloureux régional complexe, SDRC, rPMS, TMS, douleur chronique, plasticité, neurostimulation

ABSTRACT

Background and Objective. The complex regional pain syndrome (CRPS) is characterised by brain changes that are currently only rarely addressed by conventional treatment regimens. Repetitive peripheral magnetic stimulation (rPMS of muscles) is painless and noninvasive and it can influence these changes (induction of brain plasticity) to reduce pain and improve motricity. This original study in CRPS tested rPMS after-effects in CRPS on pain intensity and sensorimotor control of the upper limb, along with changes of the primary motor cortex (M1) excitability.

Methods. Fourteen adults were enrolled (six with CRPS, eight pain-free) in a single session. The CRPS group was tested at pre- and post-rPMS over the flexor digitorum superficialis muscle on the CRPS side and was compared to normative pain-free group values (no rPMS). The clinical outcomes were pain intensity, proprioception, active range of motion, grip strength. M1 excitability was tested using single and paired-pulse transcranial magnetic stimulation (TMS) of M1.

Results. rPMS reduced instant and week pain, normalized the hemispheric activity imbalance, improved proprioception and range of motion, and induced plastic changes only in M1 ipsilateral to CRPS side (IH). The more IH was hypoactivated at baseline, the more pain was reduced.

Discussion. This original study provided promising findings for the use of rPMS in CRPS with a focus on the plastic changes of IH. Future studies should confirm the existence of a causal relationship between TMS outcomes and post-rPMS decrease of pain. This will favor the development of personalized treatments of noninvasive neurostimulation in CRPS.

Keywords: CRPS, rPMS, TMS, chronic pain, plasticity, neurostimulation

INTRODUCTION

Complex Regional Pain Syndrome (CRPS), formerly known among others as reflex sympathetic dystrophy or algoneurodystrophy, is a chronic pain condition characterized by pain to one or more limbs which is disproportionate to the inciting event (fracture, sprain, surgery, or no traumatism identified) combined with trophic changes and sensory, motor and autonomic disorders (Borchers & Gershwin, 2014; Marinus et al., 2011). All causes leading to CRPS remain unclear but evidence proposes three mechanisms explaining the symptoms: peripheral changes and sensitization, dysregulation of the sympathetic nervous system and maladaptive neuroplasticity (Allen Demers et al., in preparation, February, 2021; Borchers & Gershwin, 2014; Goh et al., 2017). Interindividual variability of the contribution of each mechanism over time makes it difficult to administer an efficient treatment for all people with CRPS.

Conventional treatments include medical interventions (medications, topical cream, injections, etc.), rehabilitation (physical and/or occupational therapies) and, ideally, psychological therapy and follow-up. But even with clinical guidelines and medical follow-up of response to treatment, there is almost no evidence to support therapies currently used in CRPS (Bruehl, 2015; Truchon, 2015; O'Connell et al., 2015). Actually, more than half of people diagnosed with CRPS still present deficiencies as diminution of strength or stiffness one year after onset (Bean et al., 2014), 62% of diagnosed people still have activities of daily living limitations 3 to 9 years after onset (Geertzen et al., 1998) and most are unable to come back to their previous occupation, need workplace adjustments or are declared officially disabled (Borchers and Gershwin, 2014).

The persistence of symptoms and refractoriness to treatment could be due to central changes that are not sufficiently influenced by conventional approaches, such as changes of volumes, connectivity, activation and excitability of different parts of the brain (Allen Demers et al., in preparation, February, 2021; Barad et al., 2014; Geha et al., 2008; Kim et al., 2013; Kirveskari et al., 2010; Maihöfner et al., 2003; Pleger et al., 2006; Schwenkreis et al., 2009; Vartiainen et al., 2008; Walton et al., 2010; Zhou et al., 2015). Among the changes, the

imbalanced hemispheric activity between motor cortices (M1) has been pointed out (Barad et al., 2014; Eisenberg et al., 2005; Kirveskari et al., 2010; Krause et al., 2006; Maihöfner et al., 2007, 2003; Di Pietro et al., 2013; Schwenkreis et al., 2003). However, the direction of the imbalance remains controversial: is the hemisphere contralateral to the CRPS hand (CH controlling the limb with CRPS) hyperexcitable or hypoexcitable as compared to the hemisphere ipsilateral (IH controlling the non-CRPS hand)? Our recent original study (Allen Demers et al., in preparation, February, 2021) tested M1 excitability of adults with CRPS type I by means of transcranial magnetic stimulation (TMS). The results showed that one size does not fit all, i.e. that pain did not influence M1 excitability in the same way between the participants, thus providing a clue for the controversy in the literature on the direction of imbalanced hemispheric activity and likely contributing to the misunderstanding of how to appropriately / efficiently adapt CRPS treatments.

One new technology currently proposed in clinical research on CRPS is noninvasive magnetic neurostimulation, which is painless and can sustainedly inhibit or excite sensorimotor areas (depending on the parameters used), thus influencing neuroplasticity related to pain and motor improvement. However, the possibility that imbalance between CH and IH excitability can be different between people with hand CRPS (Allen Demers et al., unpublished data, February, 2021) questions the rationale of studies that all administrated excitatory neurostimulation over the M1 of CH. It is indeed legitimate to think that if M1 excitability is related to CRPS pain intensity (Allen Demers et al., in preparation, February, 2021) then the protocols chosen to reduce the interhemispheric excitability imbalance and impact pain should be personalized according to the imbalance direction. Another point of importance is kinesiophobia (Marinus et al., 2013), i.e. the fear of movement in CRPS due to pain induced, thus the installation of a vicious circle of non-use of the CRPS limb that worsens further the impaired motor control due to reduced proprioceptive afferents (Allen Demers et al., unpublished data, February, 2021).

Repetitive peripheral magnetic stimulation (rPMS) is applied with a coil positioned on skin over the muscles (Struppler et al., 2003b). The intensity is suprathreshold to trigger muscle contraction and mimic the mechanisms of muscle contraction/relaxation: this generates flows

of proprioceptive information to brain from either the structures stimulated (afferents, muscle fibers, nerve terminals) and the muscles stretched by joint movement (Beaulieu & Schneider, 2013, 2015; Massé-Alarie & Schneider, 2011). rPMS in physiopathology (coil over painful area or spastic paretic muscles) have been shown to induce changes of fronto-parietal networks activity (Struppler et al., 2007) and of M1 excitability (Massé-Alarie et al., 2017; Beaulieu et al. 2015, 2017). This was reported with clinical significance, i.e. pain reduction and motor improvement in people with chronic low back pain (Massé-Alarie et al., 2013, 2017) or with brain lesion (Beaulieu et al., 2015, Beaulieu et al., 2017, Krewer et al., 2014, Struppler et al., 2003b), and enhancement of perceptual-cognitive function (Struppler et al., 2003a). It is noteworthy furthermore that electroencephalography studies have shown that suprathreshold peripheral magnetic stimulation did elicit somatosensory evoked potentials in the primary sensory areas that are of almost pure proprioceptive origin, i.e. with negligible cutaneous and nociceptive inflow as compared to electrical stimulation (Kunesch et al., 1993, Zhu & Starr, 1991). Thus, rPMS administration is painless and with minimal cutaneous contamination of the proprioceptive signals to sensorimotor areas (Beaulieu & Schneider, 2015). The mechanisms of action of rPMS could be related to long-term potentiation (LTP) and depression (LTD) which are associated with neuroplasticity (Hasselmo, 1995; Pell et al., 2011). In CRPS, these mechanisms are involved in central sensitization (Puchalski & Zyluk, 2016). Thus, rPMS in people with CRPS could potentially have a triple influence leading to reduce pain intensity and improve motor control, i.e. central desensitization (by influence on LTP/LTD), rebalance of hemispheric activity (by influence on M1 excitability), and suppliance of the reduced proprioceptive information.

Therefore, the present study aimed at testing in people with hand CRPS type 1 (no nerve lesion) if a single session of rPMS could reduce pain (primary outcome) and improve function of the affected limb. rPMS was administrated over the flexor digitorum superficialis muscle (FDS), largely involved in hand function, and the acute after-effects were assessed by means of clinical outcomes (pain intensity, fingers active range of motion, grip strength, proprioception) and TMS outcomes (M1 function, including corticospinal and intracortical excitability). Data collected before and after rPMS were compared to data of a group of pain-free participants.

MATERIALS AND METHODS

Participants and Procedures

Six adults with hand type-1 CRPS (54.3 ±10.6 years old, see Table 1) were enrolled in an open-label single session of rPMS (plus pain intensity follow-up at one week) and were compared at pre- and post-rPMS to a group of eight pain-free adults (50.8 ±6.9 years old) tested at one time point only (no rPMS). All participants had signed the informed consent form approved by the local ethics committees. The participants with CRPS presented with a unilateral upper limb CRPS type 1 diagnosed with the Budapest clinical criteria (see Table 2) and were discharged from pain clinics follow-up. The pain-free participants did not experience pain in the last month before enrolment nor have medical history of chronic pain (pain persisting for more than three consecutive months). All participants met the exclusion criteria related to general health (spine surgery, major circulatory/respiratory/cardiac disease, other neurological condition for participants with CRPS, severe upper limb orthopaedic condition, cognitive disorder interfering with the tasks of the study) and to TMS safety guidelines (Lefaucheur et al., 2011; Rossi et al., 2011, 2009). A physician performed medical evaluation at pre- and post-enrolment to confirm eligibility and monitor adverse effects. None of the participants had history of specific repetitive motor activity (as a musician or professional level athlete). The physical therapist collected clinical and TMS outcomes also applied rPMS but data were then codified for group (CRPS vs. pain-free) and time of testing (pre- vs. post-rPMS for CRPS group) until completion of analyses. The fact that the same physical therapist ensured clinical testing for all participants reduced the inter-evaluator variability. All outcomes were collected in a single 3-hour session (including rest breaks), as follows: clinical outcomes, TMS outcomes, then rPMS intervention over FDS, and 10min later TMS outcomes and clinical outcomes. All outcomes were collected on both sides (when appropriate) for all participants. Everyone was phoned 2 and 7 days later to document any adverse effect (Rossi et al. 2009). Participants with CRPS were questioned on the mean intensity of week pain at 7 days (one-week follow-up).

(Insert Tables 1-2 near here)

Intervention

Participants were comfortably seated in a reclining-adjustable chair with limb supports and the forearms in supination. rPMS was administered on CRPS side with an air-film cooled figure-of-eight coil (7 cm outer diameter per wing, biphasic waveform, 400-µs pulse width, Rapid² Magstim, Magstim Company, England) held tangentially on the skin overlying the FDS muscle belly with the long axis of coil junction perpendicular to muscle fibres orientation (for a review of parameters of rPMS application, see Beaulieu and Schneider, 2015). The FDS was the target muscle because of the decrease of fingers/wrist flexion AROM commonly reported in CRPS with functional significance, such as grasping impairment (Bean et al., 2014; Geertzen et al. 1998; de Mos et al. 2007; Rodham et al. 2015). rPMS was delivered at theta-burst frequency (5-Hz trains of three pulses at 50 Hz during 200s, 2s ON / 8s OFF, 600 pulses total). This intermittent mode of rPMS was used to elicit cyclic muscle activation/relaxation as already reported by our research group (Beaulieu et al., 2015, 2017; Flamand et al., 2012; Flamand & Schneider, 2014, Schneider et al. 2016; Massé-Alarie et al., 2013, Massé-Alarie et al., 2017). rPMS intensity was set at 42% of maximal stimulator output (the maximal possible on TBS mode with Rapid² Magstim equipment) to produce palpable FDS contractions with visible wrist/fingers flexion which was painless for the CRPS participants.

Clinical Testing

All following outcomes (except pain and proprioception) were collected on both sides (either hand for clinical or hemisphere for TMS of M1), before and ten minutes after rPMS for the CRPS group, or once for the pain-free group.

Pain Intensity. Participants' sitting position was standardized against a chair's backrest with the shoulder in neutral rotation and 0° abduction, elbow in 90-100° flexion, and forearm resting on a height-adjustable therapeutic table. The *visual analogue scale* (VAS) was used to quantify the pain intensity experienced by each participant with CRPS. The VAS consists of a two-sided band: on one side, the participant uses a cursor to rate the level of pain intensity between two extremes called "No pain" and "Maximal pain imaginable"; on the other side of VAS, hidden from the participant, a graduated scale from 0 (no pain) to 100 millimeters

(maximal pain imaginable) is used by the evaluator to quantify the participant's pain intensity. VAS was used to quantify instantaneous pain at pre- and post-rPMS and the mean pain in the last week (pre-rPMS week pain) and at follow-up one week later (post-rPMS week pain).

Active Range of Motion (ROM). Active ROM in flexion was measured using a manual finger goniometer at the proximal interphalangeal (PIP) joints of the first, second and "worst" finger, i.e. the finger (between the third, fourth and fifth) harder or more painful to move for each participant. For active ROM of the second and worst fingers PIP, the elbow was bent (±130°) at rest on the therapeutic table, the shoulder slightly bent (±45°), the wrist and metacarpophalangeal joints in the neutral position (claw hand). For active ROM of the first finger PIP, the forearm was positioned at rest on the table with the hand protruding on the edge. Three trials were tested and averaged per PIP. Participants rested 60sec between trials.

Grip Strength. Participants were sitting with no arm support, the forearm in neutral position and the wrist between 0-30° extension and 0-15° ulnar deviation. The maximal grip strength per hand was measured using a JAMAR hydraulic hand dynamometer (Sammons Preston Rolyan, Bolingbrook-IL, USA). Following Mathiowetz's instructions (Mathiowetz et al., 1984), JAMAR dynamometer was set to the second handle position (placed in hand with help of the evaluator if needed). The average of three trials per hand was used to represent the maximum grip strength of each participant. Standardized cheers were given ("Squeeze hard, hard, hard, the hardest and release") over 8 sec of sustained contraction to promote a reliable value (Buckinx et al., 2017). Participants rested 30s between trials.

Upper Limb Proprioception. Following Le Métayer's guidelines, the paradigm of the blurred proprioception of the upper limb was used to assess the ability to perceive limb position in space (Le Métayer, 2007). Briefly, the participants were seated, leaning against a chair without armrests, knees bent at 90° with feet flat on the floor and hands on the thighs (initial position). They had first to reach with the index a target (large red dot) on a graduated screen at gaze height and arm distance in front of them and return to the initial position and to repeat this practice three times. Then, they closed the eyes and the evaluator cautiously (without

pain) moved their tested arm in the air with shoulder movements and elbow flexion / extension and put the arm back in the initial position, and the participants, without opening the eyes, had to reach back the target with the index (one trial only). The score of blurred proprioception is the distance in centimeter between the finger contact on the graduated screen (with eyes closed) and the target.

Surface Electromyographic (EMG) Recordings

EMG procedures were followed without induced pain in participants with CRPS. After standard skin preparation (i.e. cleaning the skin with alcohol and shaving whenever necessary) (Hermens et al. 2000), the parallel-bar EMG sensors with adhesive skin interfaces were installed on each participant (fixed 1cm distance between electrodes; 16-channel Bagnoli EMG System, Delsys Inc., Boston, MA). EMG sensors were placed bilaterally on the belly of the first dorsal interosseous muscle (FDI). A common ground electrode was placed on the ulna olecranon of the tested limb. EMG signals were band-pass filtered (20-450 Hz), amplified before digitization (2 kHz) and computer-stored for offline analysis (PowerLab acquisition system, LabChart, ADInstruments, Colorado Springs-CO, US).

TMS Testing

M1 function at pre-rPMS and 10 min post-rPMS of FDS was tested by TMS of FDI M1 area. FDI M1 excitability is easier to test as compared to FDS and is known to be increased by upper extremity flexion owing to a proximo-distal synergy in M1 (Gagné & Schneider, 2007, 2008). TMS procedures were strictly replicated for each hemisphere pre- and post-intervention, following the guidelines from the International Federation of Clinical Neurophysiology (Rossini et al., 2015). Participants were comfortably in the reclining chair with arms and legs supported, hips and knees slightly bent (20° flexion).

Hotspot. Magnetic stimuli were applied over FDI M1 area by a figure-of-eight coil (7-cm outer diameter each wing; Magstim Company Limited, Whitland-UK) positioned on the scalp with the long axis of the two- wing intersection pointing antero-posteriorly at a 45° angle from the medial line to active M1 cells in the postero-anterior direction (Sakai et al.,

1997). The 10–20 EEG system was used to first approximate FDI M1 area (Klem, 1999). The position was then adjusted slightly to determine the 'hotspot', namely the M1 location where the MEP obtained in the contralateral FDI are of the highest amplitude at the lowest TMS intensity (Wolf et al., 2004).This hotspot was marked on the scalp (surgical pen) to ensure reliable coil positioning across time of testing (Wolf et al., 2004) and visual inspection of EMG recordings from both sides monitored the complete relaxation of the hands during TMS testing.

Resting Motor Threshold (RMT). RMT was determined at the TMS intensity that elicited at least five FDI MEP with an amplitude of 50 µV or higher out of ten trials. RMT has good validity and reliability (Beaulieu et al., 2017a, 2017c; Malcolm et al., 2006) and it informs on M1 basic excitability (Rossini et al., 2015, Ziemann et al., 2015).

MEP Amplitude and Latency. A suprathreshold test (unconditioned) TMS at an intensity of 120% RMT enabled to collect and measure the test MEP amplitude and latency. Test MEP amplitude (in mV) was measured peak-to-peak and it reflects the volume of M1 cells activated by TMS and the excitability of the corticospinal pathway (Devanne et al., 1997, Kobayashi & Pascual-Leone, 2003, Rossini et al., 2015). Test MEP latency (in % participant's height) was measured from stimulation time to MEP onset and it reflects conduction time and indirectly the synchronicity of descending volleys to depolarize spinal motoneurons (Groppa et al., 2012, Kobayashi & Pascual-Leone, 2003).

SICI, ICF and SICF. Paired-pulse TMS (coil connected to two Magstim 200^2 monophasic stimulators) was used to test the short-interval intracortical inhibition (SICI), the intracortical facilitation (ICF) and the short-interval intracortical facilitation (SICF) (Arya et al., 2011, Ilić et al., 2002, Kujirai et al., 1993). In SICI, a subthreshold conditioning TMS (80 % RMT eliciting no MEP on its own) was delivered 3 msec before the test TMS at 120 % RMT (Kujirai et al., 1993). In ICF, the same parameters were used but at an inter-stimulus interval of 15 ms (Kujirai et al., 1993). The conditioned MEP expressed post-hoc relative to the mean test MEP amplitude is usually of lower amplitude than the test in SICI and of higher amplitude in ICF (Kujirai et al., 1993). SICI probes the function of $GABA_A$ interneurons

within M1 and ICF the function of oligosynaptic glutamatergic circuits (Rossini et al., 2015; Ziemann et al., 2015). In SICF, two stimuli were delivered 1 ms apart, the first TMS at 100 % RMT and the second at 90 % RMT. MEP amplitude was then expressed relative to the amplitude of test MEP at 100 % RMT, which likely reflects I-waves summation following the depolarisation of M1 interneurons by TMS (Ilic et al., 2002; Rossini et al., 2015; Ziemann et al., 2015). The test TMS intensity was adjusted at post-rPMS to match the amplitudes of test MEP obtained at pre-rPMS for the validity of comparisons of conditioned MEP amplitudes between the two times of testing (Beaulieu et al., 2015). Twelve test MEP and 12 conditioned MEP were collected per participant at a frequency of 0.2-0.3 Hz with 10% variations between trials. Resting breaks were given on request.

Data Reduction and Statistical Analysis

Five clinical outcomes were measured at pre- and post-rPMS: instant pain (mm), week pain (mm), blurred proprioception (cm), active ROM (degree), and grip strength. To ensure validity of interindividual comparison, grip strength was expressed in percentage of grip strength norms stratified by age and sex (Mathiowetz et al., 1985). Pain at post-rPMS was also expressed in % pre-rPMS. Six TMS outcomes were collected at pre- and post-rPMS: RMT (% of maximal stimulator output) also expressed in % of RMT at pre-rPMS, between-hemisphere difference of RMT (% MSO), test MEP amplitude (mV), MEP latency (% participant's height), and conditioned MEP amplitudes for SICI, ICF, and SICF (% respective test MEP amplitude).

Shapiro-Wilk's test for Normality revealed that data were normally distributed, thus parametric tests were used. Bilateral paired Student's t-tests between pre- and post-rPMS values were applied to instant and week pain, blurred proprioception and the between-hemisphere difference of RMT. The clinical and TMS outcomes were averaged between sides in the pain-free group ($p > 0.05$). One-way analysis of variance (Fisher's ANOVA) was applied to all outcomes (except pain) between CRPS side (hand or hemisphere), non-CRPS side and the mean of the pain-free group. In the CRPS group, two-way ANOVA with repeated measures were applied with factors Time (pre- vs. post-rPMS) X Hand (CRPS vs. non-CRPS) to all clinical outcomes (except pain and proprioception) and with factors Time

X Hemisphere (Contralateral-CH vs. Ipsilateral-IH) to all TMS outcome (except between-hemisphere difference of RMT). Planned comparisons (two-sided, Tukey's post-hoc tests for multiple comparisons) were used to detect where differences detected by ANOVA lay. Pearson's correlation matrices were produced to examine the relationships between the change of primary outcome (pain intensity) and the amount of change or baseline values of other variables. The maximum normed residual test (Grubbs' test) helped detect an outlier from a data set approximated by normal distribution (Prism 8.0, GraphPad Software Inc, La Jolla-CA, USA): data set is analyzed and an outlier would typically be expunged when it falls beyond a critical deviation from the sample mean (chance probability to obtain the outlying value < 0.05). Significance was set at $p < 0.05$. Statistical analysis was conducted with Jamovi (https://www.jamovi.org).

RESULTS

TMS testing was truncated for one participant per group due to head discomfort during the application of the paired-pulse TMS for SICI and ICF in both hemispheres, and another in the CRPS group for CH. Thus, SICI and ICF data in IH are presented for N=5 participants with CRPS and 7 pain-free subjects and in CH for N=4 participants with CRPS and 7 pain-free subjects. All other outcomes under study were collected with no problem and no adverse effect was reported at follow-ups. Table 3 presents all clinical and TMS outcomes per group.

(Insert Table 3 near here)

Clinical Outcomes

Four participants with CRPS (out of six) reported instant pain reduction after rPMS (mean decrease of 8 mm on the VAS corresponding to 26% reduction, range of 20-100% reduction) and all but one did report week pain reduction at the one-week follow-up (mean decrease of 8 mm on the VAS corresponding to 17% reduction, range of 15-25%, see Fig. 1A, left graph). Pre- vs. post-rPMS reduction of instant pain was close to significance (t-test p=0.06) whereas week pain reduction was significant (p=0.03, Fig. 1A right graph with post-rPMS pain expressed as % pre-rPMS).

Blurred proprioception of the CRPS upper limb was improved in all participants but one (group mean of 2 cm closer to the target, Fig. 1B, left graph). The one participant with no improvement was already better than the pain-free participants (shaded area). Pre- vs. post-rPMS improvement of blurred proprioception on the CRPS side was on the edge of significance (p=0.05, Fig. 1B, right graph).

The Side X Time ANOVA applied on the active ROM did not detect any effect. The one-way ANOVA (comparison to pain-free subjects) was significant for the worst finger PIP ROM at pre-rPMS ($F_{2, 17}$ = 3.61, p=0.049, Fig. 1C, right graph) and not significant at post-rPMS ($F_{2, 16}$ = 0.61, p= 0.56). Post-hoc test denoted that at pre-rPMS values of the CRPS hand (95.0 ±5.0 degrees) were smaller than in pain-free subjects (104.7 ±3.1, p=0.045).

Individual data (Fig. 1C, left graph) showed that only two participants had post-rPMS increase of the worst PIP ROM.

The Side X Time ANOVA applied on the grip strength detected a main effect of SIDE ($F_{1,5}$ = 18.2, p=0.008), but no effect of rPMS, with the CRPS side weaker than the non CRPS at pre-rPMS (p=0.023) and at post-rPMS (p=0.027, see Table 3). The one-way ANOVA was significant ($F_{2,17}$ = 5.51, p=0.014) with the grip strength higher in pain-free subjects than on the CRPS side (p=0.034, see Table 3).

(Insert Fig. 1 near here)

TMS Outcomes

Individual CRPS data of Fig. 2A shows that at pre-rPMS the RMT of IH (M1 ipsilateral to CRPS hand) was higher than RMT of CH (lower M1 excitability in IH) in four participants and lower in two participants (higher M1 excitability in IH). The absolute value of this imbalance was higher than 7% MSO at pre-rPMS for four participants and for only two at post-rPMS. The bilateral paired t-test applied on the absolute difference of RMT between hemispheres (whatever the direction of difference) detected a close to significant decrease of imbalance at post-rPMS (5.0 ±4.3 MSO) as compared to pre-rPMS (8.5 ±4.6 MSO, p=0.06, Fig. 2B). Of note, at post-rPMS, the mean of hemispheric difference of RMT of the CRPS group is within values of the pain-free group (shaded area).

The Side X Time ANOVA applied to MEP latency detected a main effect of TIME ($F_{1,5}$ = 6.81, p=0.048, Fig. 3A) with longer latencies at post-rPMS, significantly for IH (p=0.028).

The Side X Time ANOVA applied on the conditioned MEP (SICI, ICF, SICF) did not detect any effect. However, for SICI (Fig. 3B), the one-way ANOVA revealed that, as compared to pain-free participants (27.0 ±11.9 % test MEP), the conditioned MEP amplitudes were significantly higher in IH at post-rPMS (159.7 ±245.2 % test MEP, p=0.03). In CH, they were close to be significantly higher than in pain-free group at pre-rPMS (67.2 ±65.5, p=0.051). The conditioned MEP for ICF (Fig. 3C) were higher in IH at post-rPMS (564.9

±795.8 % test MEP) as compared to pain-free group (129.2 ±53.5 % test MEP, *p*=0.02). No other between-side or between-time or between-group differences were detected (*p*>0.05).

Correlations

Fig. 4 presents the negative relationship (r = -0.84, *p*=0.04) between the amount of post-rPMS instant pain reduction (in % pre-rPMS) and the RMT at baseline (pre-rPMS) of IH (expressed in % of CH). In other words, instant pain was more reduced after rPMS in patients with IH RMT higher (lower M1 excitability) than in CH at baseline. More precisely, the more CH was hyperactivated as compared to IH (larger imbalance), the larger was pain decrease after rPMS.

(Insert Figs. 2-3-4 near here)

DISCUSSION

This original CRPS study provides new evidence of one single rPMS session influence on pain and hand sensorimotor function with dynamic changes of M1 excitability. The potential mechanisms involved are discussed in order to better understand rPMS-driven changes.

Reduction of Pain and Improvement of Function

Only one study used rPMS in literature in CRPS but collected only TMS outcomes with no clinical data and did not report any significant effect in patients (Krause et al. 2005). The authors used a single session as we did but rPMS was applied over the cervical spine (C7-C8) at 20 Hz for a total of 2000 pulses over 10 min whereas we used iTBS (50 Hz) over the FDS on the painful side for a total of 600 pulses over 3min 20 sec. The protocols are thus not comparable. However, iTBS over muscles has already been used successively by our research group to decrease pain and improve posture-motor control in people with other pain conditions, such as chronic low back pain (Massé-Alarie et al., 2013). Our present results of a decrease of instant pain at post-rPMS and persistence over one week denotes the promising potential of rPMS in CRPS. Pain changes obtained in one single session of rPMS in parallel with improvement of worst finger PIP active range of motion as compared to pain-free participants resemble changes reported in studies having used TENS (transcutaneous electrical neurostimulation) but in 15 to 30 sessions (Bilgili et al., 2016, Bodenheim & Bennett, 1983, Kesler et al., 1988, Richlin et al., 1978) or in 5 sessions of TENS combined with brain stimulation (Houde et al., 2020). However, rPMS increased the proprioceptive signals to brain with minimal contamination of proprioceptive-motor transduction by cutaneous responses, unlike with TENS (Beaulieu & Schneider, 2015; Kunesch et al., 1993, Zhu & Starr, 1991). The improvement of performance after rPMS in the blurred proprioception paradigm (Le Métayer, 2007) provided first ever evidence that rPMS-induced flows of ascending signals could promote proprioceptive integration and sensorimotor control in CRPS and could have changed the perception of the CRPS upper limb in space. This was first suggested by the rPMS-induced and PET-scanned activation of the frontal-parietal pathways involved in perception and sensorimotor planning (Struppler et al., 2007). In further support, the decrease of week pain after rPMS could reflect an intertwined action of rPMS on sensorimotor control and pain modulation mechanisms, as already suggested in

chronic low back pain (Massé-Alarie et al., 2017). Thus, the increased availability of proprioceptive inputs following rPMS (which are decreased in CRPS due to non-use of the limb) may have contribute to the selection of more efficient strategies of pain management and motor control of the fingers.

Resting Motor Threshold in CRPS: a Predictive Factor of Responsiveness to rPMS ?
The intermittent theta-burst frequency used for rPMS and that improved proprioceptive integration in coherence with voluntary muscle contraction did likely influence sensorimotor plastic mechanisms with no spinal saturation or fatigue, as already shown in chronic low back pain and chronic stroke (Massé-Alarie et al., 2013; Beaulieu et al., 2017b). The inner mechanisms may be an action on glutamate and GABA receptors synthesis thus leading to LTP or LTD in M1 (Huang et al., 2005). It is known that these receptors influence M1 homeostasis (M1 basic excitability) which is tested by the resting motor threshold to TMS.

One new result in CRPS is the association between the imbalance of hemispheric activity at pre-rPMS (tested by RMT) and pain reduction, as shown by Fig. 4, but also by individual data in Fig. 1A. Precisely, the higher the RMT was in M1 ipsilateral to CRPS hand at baseline, i.e. IH hypoactivated (or CH hyperactivated) at pre-rPMS as compared to the other side, the larger was pain decrease at post-rPMS. We thus question whether people with CRPS who will benefit more from rPMS after-effects present with a suboptimal function of IH (hemispheric imbalance in the direction of an hypoactivation of M1 ipsilateral to painful side).

Also, pain decrease at post-rPMS concurred with the reduction of RMT hemispheric difference from values that were at pre-rPMS higher than 7% MSO, a cut-off for significant imbalance (Beaulieu et al., 2017). This rPMS-induced normalization (clinically but not significant) of imbalanced hemispheric activity in CRPS may have contributed to improve proprioceptive integration and motor planning, thus explaining further the clinical changes.

Clinical Changes Driven by Plasticity of M1 Ipsilateral to CRPS Hand ?

Unexpectedly, rPMS over the painful area did not induce any significant TMS changes in the contralateral M1 (CH). Not even the significant release from SICI reported in the literature (Krause et al., 2004, Schwenkreis et al., 2003). It is acknowledged however that in normal conditions (pain-free subjects) the massive flows of somatosensory signals mediated to brain drive M1 plasticity (Miles, 2005). Thus, the absence of TMS changes in CH questions whether one single rPMS session was sufficient and whether the after-effects in CH could have been mitigated by substantial learned non-use plastic changes of CH sensorimotor areas, though improvement of blurred proprioception performance. Of note, the higher variability of SICI in CH, as compared to IH, could be due to cortical factors such as an unstable volume of M1 cells recruited or a faulty synchronization of corticospinal cells by TMS rather than any spinal phenomena (Amassian et al., 1987).

Rather, changes of TMS outcomes were observed post-rPMS in M1 ipsilateral to CRPS hand (IH). The influence of rPMS on M1 ipsilateral to rPMS side was already reported by our research group in chronic stroke and with clinical significance (Beaulieu et al., 2017b). Our data showed in IH post-rPMS decrease of SICI (increased conditioned MEP) and increase of ICF as compared to pain-free participants (Fig. 3). M1 disinhibition (SICI release) favors the induction of plasticity by unmasking of synapses and the up-regulation of synaptic glutamatergic facilitation (Hess & Donoghue, 1994, Jacobs & Donoghue, 1991, Liepert, 2006). These ongoing synaptic changes may in turn desynchronize M1 cells response to TMS or decrease the synchronicity of the descending volleys onto alpha motoneurons. This corresponds actually to the lengthening of MEP latency that we detected in IH at post-rPMS. All these changes suggest that the hemisphere ipsilateral to CRPS hand has adapted dynamically to rPMS and was involved in the pain and sensorimotor control of this hand.

Methodological Considerations

The diagnosis of each participant with type-1 CRPS was not validated at the onset of study given resorption of some symptoms before enrolment. Thus, even if participant met the clinical criteria at the time of diagnosis, they may have been CRPS type NOS (for Not Otherwise Specified) at enrolment. This explains why the study referred to the Budapest

clinical diagnostic criteria and not the research criteria. The small number of participants affects the strength of the results, especially for TMS outcomes with missing data. However, each participant was compared to oneself (% pre-rPMS) and this could have improved data reliability. The relatively small sample size of this study did not allow the allocation of some participants to a control group, which is essential to demonstrate the effectiveness of the intervention. However, larger recruitment can be challenging given CRPS rarity. Also, in previous rPMS randomized double blind placebo controlled studies, placebo did not yield any effect on the level of pain (Beaulieu et al., 2015; Khedr et al., 2012; Massé-Alarie et al., 2013), suggesting that rPMS intervention induced a real after-effect. In support, the improvement of proprioception integration could not have been due to placebo and neither could the long-term reduction of pain (week pain post-rPMS). The experimenter applying the interventions also collected data and was not blinded to objectives and hypotheses. Thus, to avoid any bias, all pre/post-rPMS measures were strictly replicated between participants and all data were codified until completion of analyses. The study offers the advantages of testing sensory deficits (proprioception) and post-rPMS improvement, plus outcomes on both sides so that changes in IH could have been detected. Pain decrease and MEP latency lengthening in IH could have been related to the activation of descending anti-nociceptive pathways and spinal inhibition mechanisms. However, hemispheric activity balance, improvement of blurred proprioception and paired-pulse TMS paradigms rely on M1 transsynaptic mechanisms (Paulus et al., 2008, Ziemann et al., 2015).

CONCLUSION

Our study provided promising findings for the potential of rPMS to promote the condition in CRPS of the upper limb. One single rPMS session normalized the imbalanced hemispheric activity, influenced the excitability of M1 ipsilateral to the CRPS hand (IH) in parallel with clinical significance, especially pain reduction and improvement of proprioceptive system function. Importantly, pain decreased against the level of IH hypoactivity between patients. Basic studies are thus needed to explore M1 function in CRPS when IH is hypo- or hyperactivated as compared to the other hemisphere. These studies should confirm the existence of a causal relationship between TMS outcomes denoted herein and post-rPMS decrease of pain. This will favor the development of personalized treatments of noninvasive neurostimulation in CRPS.

CONFLICTS OF INTEREST. None declared.

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FIGURES CAPTIONS

FIGURE 1: Clinical Outcomes. A. Individual values (**left graph**) and group means ± SD (**right graph**) of instant and week pain at pre- and post-rPMS and expressed in percent of pain at pre-rPMS. **B**. Individual values (**left graph**) and group means ± SD (**right graph**) of blurred proprioception performance for the CRPS hand (CH) and Non-CRPS (NCH) and expressed in cm from the target (Le Métayer, 2007). **C.** Individual values (**left graph**) and group means ± SD (**right graph**) of the worst finger PIP ROM (proximal inter-phalyngeal range of motion) for the CRPS hand (CH) and Non-CRPS (NCH) and expressed in degrees. The shaded area represents the mean ± 1 SD of the pain-free group. *$p<0.05$ between pre- and post-rPMS; +$p<0.05$ with pain-free group

FIGURE 2: Resting Motor Threshold (RMT). A. Individual values of RMT at pre- and post-rPMS (empty and filled circles, respectively) in M1 contralateral to CRPS hand (CH) and M1 ipsilateral (IH) and expressed in % CH RMT at baseline (pre-rPMS). The two participants with hyperexcitability of IH (as compared to CH) are represented by greyed circles. **B.** Group means ± SD of the absolute difference of RMT between CH and IH at pre- and post-rPMS and expressed in % maximal stimulator output. The shaded area represents the mean ± 1 SD of the pain-free group.

FIGURE 3: TMS Outcomes. Group means ± SD at pre- and post-rPMS in M1 contralateral to CRPS hand (CH) and M1 ipsilateral (IH)) **A.** FDI MEP latency expressed in % of participants height. **B-C.** Amplitude of conditioned motor evoked potentials for short-interval intracortical inhibition (SICI in **B**) and intracortical facilitation (ICF in **C**) expressed in % test MEP. The shaded area represents the mean ± 1 SD of the pain-free group. *$p<0.05$ between pre- and post-rPMS; +$p<0.05$ with pain-free group

FIGURE 4: Correlation. Pain reduction (amount of change expressed in % pain at pre-rPMS) against the hemispheric balance of resting motor threshold (RMT) at pre-rPMS ($r = -0.84$, *p=0.04). Note that RMT of M1 ipsilateral to CRPS hand (IH) is expressed in % RMT of M1 contralateral, thus the more IH was hypoexcitable as compared to CH (ratio > 100) the more pain was reduced.

TABLE 1. General Characteristics of Participants.

Characteristics	Participants	
	CRPS group	**Pain-free group**
Number (N)	6	8
Age (years): mean ±SD (range)	54.3 ±10.6 (35-65)	50.8 ±6.9 (40-61)
Dominance (N: right/left)	5/1	7/1
Gender (N: females/males)	4/2	4/4
Altered side (N: right/left)	4/2	N/A
Inciting event (N: fracture of hand/forearm/arm)	2/3/1	N/A
Time since onset of CRPS (months): mean ±SD (median; range)	45.4 ±55.8 (23.5; 11-156)	N/A
Pain (VAS, mm): mean ±SD (range)	39 ±22 (6-56)	N/A

CRPS: complex regional pain syndrome; SD: standard deviation; Severity score : CRPS Severity Scale (CSS); Bath: Bath CRPS Body Perception Disturbance scale, item 4 relates to the extent to which the emotions regarding the CRPS limb are negative (worst = 10/10); VAS: visual analogue scale

TABLE 2. The "Budapest Criteria" for Complex Regional Pain Syndrome (CRPS) Diagnosis (Harden et al., 2010). Diagnosis of CRPS requires to meet all four criteria.

The "Budapest Criteria" – CRPS Diagnosis
1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom on three of the four following categories (clinical diagnosis) OR in all four (research purpose): *Sensory hyperesthesia and/or allodynia* *Vasomotor: temperature asymmetry and/or skin colour changes and/or skin colour asymmetry* *Sudomotor/oedema: oedema and/or sweating changes and/or sweating asymmetry* *Motor/trophic: decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)*
3. Must display at least one sign at the time of evaluation in 2 or more of the following categories (clinical criteria and research purpose): *Sensory: evidence of hyperalgesia (to pinpricks) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)* *Vasomotor: evidence of temperature asymmetry (>1°C) and/or skin colour changes and/or asymmetry* *Sudomotor/oedema: evidence of oedema and/or sweating changes and/or sweating asymmetry* *Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)*
4. There is no other diagnosis that better explains the signs and symptoms

TABLE 3. Raw Data in CRPS at Pre- and Post-rPMS and in Pain-free Participants.

	CRPS group		Pain-free group
Clinical Outcomes	**pre-rPMS mean ±SD**	**post-rPMS mean ±SD**	**Both hands mean ±SD**
VAS instant pain			
mm	39 ±22	31 ±23	N/A
% pre	--	(64 ±39 % pre)	
VAS week pain			
mm	46 ±23	38 ±22 *	N/A
% pre	--	(83 ±11 % pre)	
B-proprioception (cm from target)	CRPS hand: 4.8 ±2.9 Non-CPRS hand: 4.3 ±1.9	CRPS hand: 2.8 ±1.9 * Non-CPRS hand: ne	3.92 ±1.35
1st PIP ROM (°)	CRPS hand: 65.8 ±16.3 Non-CPRS hand: 73.3 ±19.1	N/E	74.1 ±13.2
2nd PIP ROM (°)	CRPS hand: 101.7 ±6.1 Non-CPRS hand:104.2 ±7.4	N/E	104.4 ±5.0
Worst finger PIP ROM (°)	CRPS hand: 95.0 ±5.0 [+] Non-CPRS hand: 98.3 ±5.8	CRPS hand: 100 ±5.0 Non-CPRS hand: 100 ±5.0	104.7 ±3.1
Grip strength (% of age/sex norm)	CRPS hand: 78 ±7 [+, @] Non-CPRS hand: 111 ±16	CRPS hand: 76 ±22 [+, @] Non-CPRS hand: 107 ±27	105 ±25
	CRPS group		Pain-free group
TMS Outcomes	**pre-rPMS mean ±SD**	**post-rPMS mean ±SD**	**Both hands mean ±SD**
RMT (% MSO)	CH: 56.3 ±9.7 IH: 57.2 ±8.3 Δ (abs): 8.5 ±4.6	CH: 55.7 ±7.1 IH: 56.3 ±6.9 Δ (abs): 5.0 ±4.3	59.0 ±10.0 Δ (abs): 4.5 ±2.7
MEP amplitude (mV)	CH: 0.6 ±0.4 IH: 0.9 ±1.0	CH: 0.6 ±0.4 IH: 0.6 ±0.6	.59 ±0.5
MEP latency (% height)	CH: 15.3 ±1.05 IH: 15.1 ±0.9	CH: 15.6 ±1.07 IH: 15.5 ± 1.1 *	15.05 ±0.99
Conditioned MEP - SICI (% test)	CH: 67.2 ±65.5 IH: 32.0 ±18.4	CH: 68.1 ±53.7 IH: 159.7 ±245.2 [+]	27.0 ±11.9
Conditioned MEP – ICF (% test)	CH: 189.8 ±151.2 IH: 152.3 ±118.4	CH: 210.7 ±96.5 IH: 564.9 ±795.8 [+]	129.2 ±53.5
Conditioned MEP - SICF (% test)	CH: 608.5 ±559.7 IH: 627.2 ±855.8	CH: 463.4 ±298.1 IH: 1951.5 ±3999.2	1047.4 ±1082.6

CRPS: complex regional pain syndrome; rPMS: repetitive peripheral magnetic stimulation; SD: standard deviation; VAS: visual analogue scale; N/A: non applicable; N/E: no evaluation; ROM: active range of motion; PIP: proximal interphalangeal joint; B-proprioception: blurred proprioception; RMT: resting motor threshold; MSO: maximal stimulator output; CH: hemisphere contralateral to the CRPS limb; IH: hemisphere ipsilateral to the CRPS limb; Δ: interhemispheric difference; MEP: motor evoked potentials; TMS: transcranial magnetic stimulation; SICI: short-interval intracortical inhibition; ICF: intracortical facilitation; SICF: short-interval intracortical facilitation.

* $p < 0.05$ between pre- and post-rPMS; + $p < 0.05$ with the pain-free group; @ $p < 0.001$ between sides.

FIGURE 1: Clinical Outcomes.
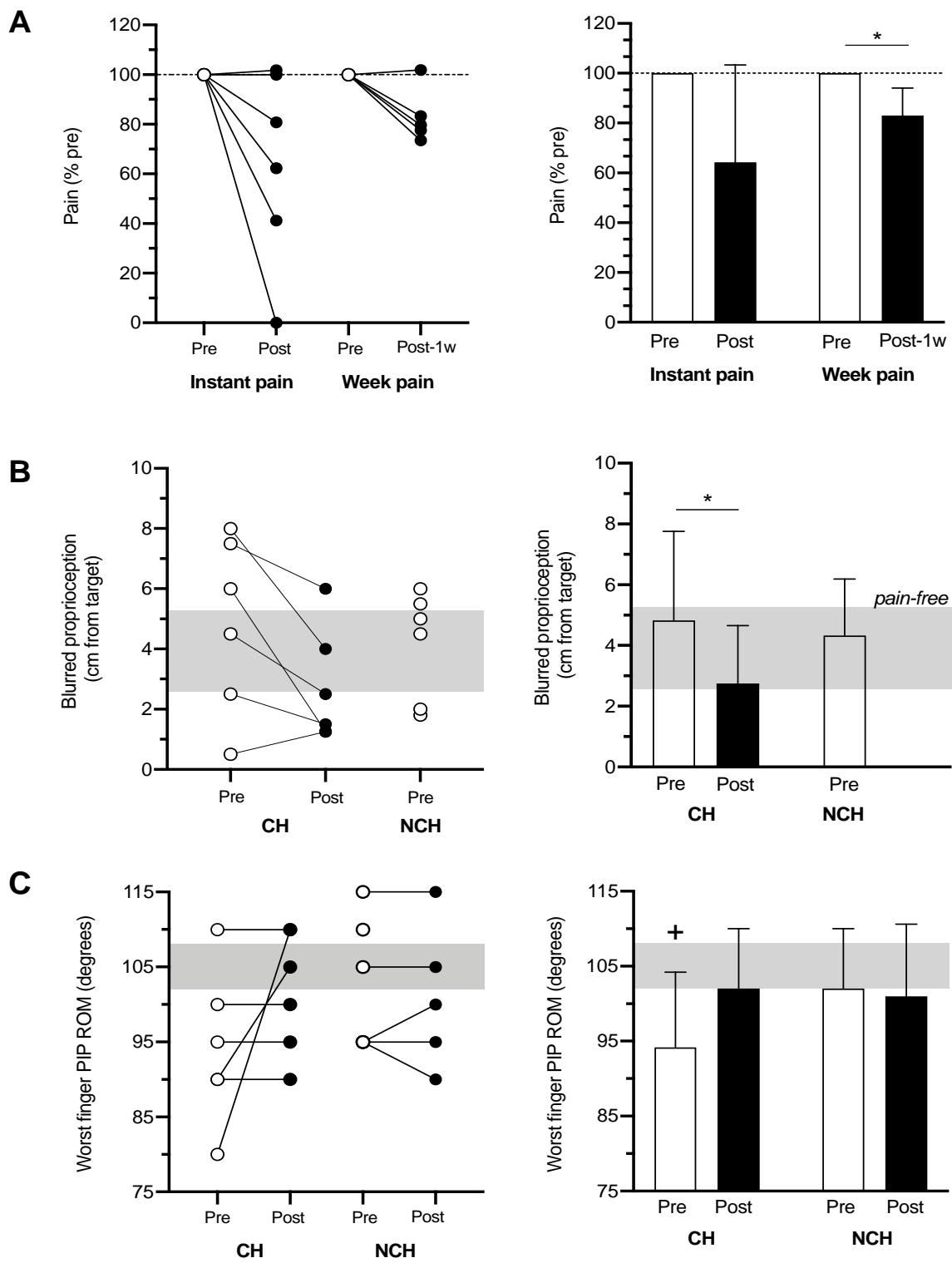
FIGURE 2: Resting Motor Threshold (RMT).
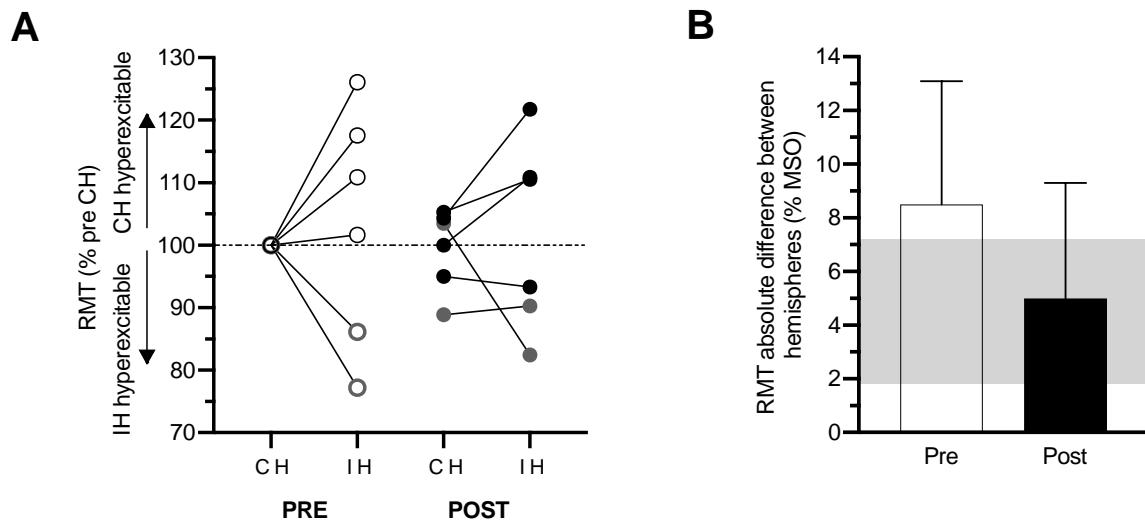
FIGURE 3: TMS Outcomes.
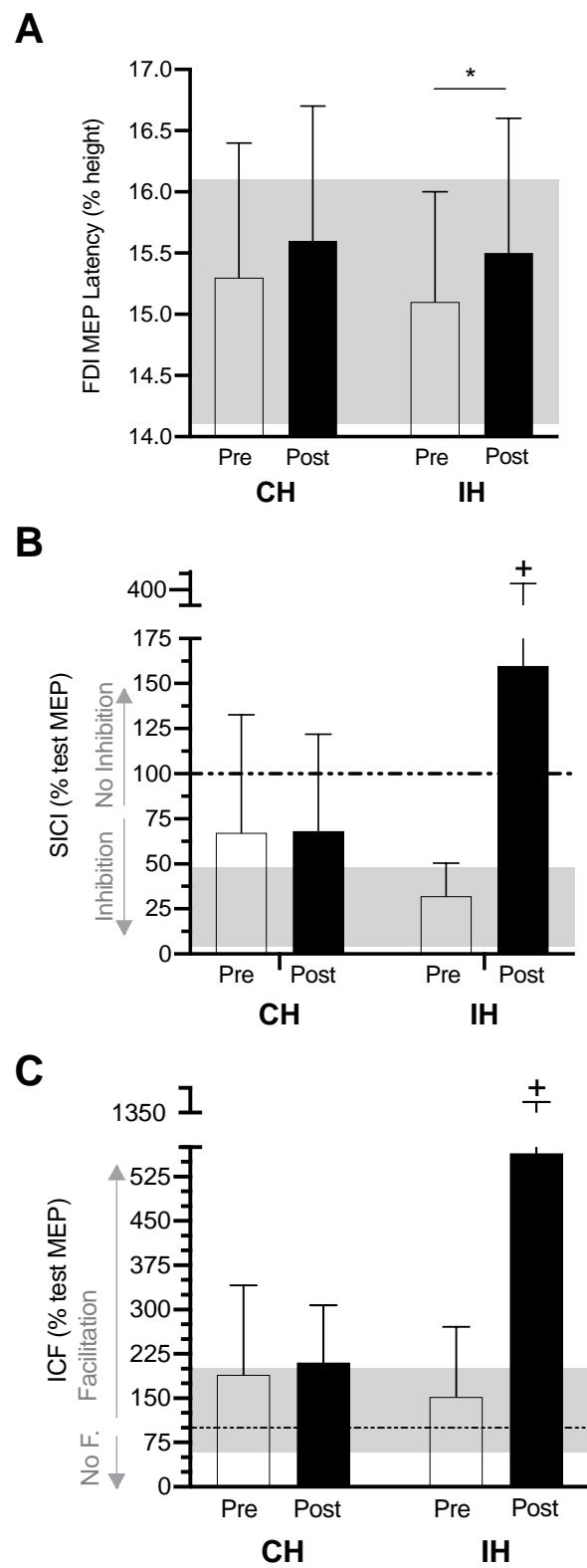
FIGURE 4: Correlation.
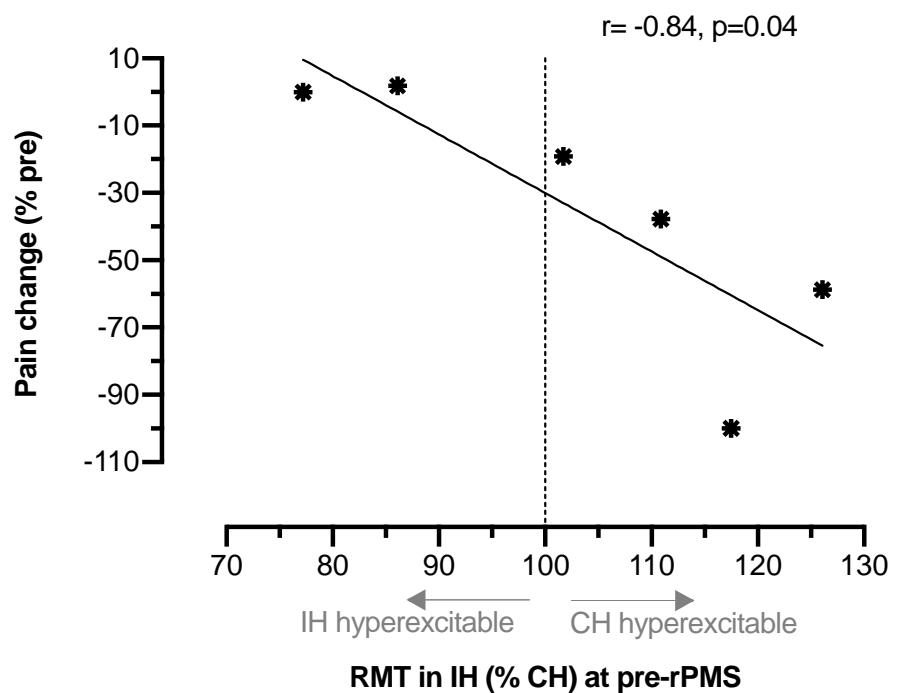
CHAPITRE 4 : DISCUSSION GÉNÉRALE

Les objectifs principaux du projet de maîtrise étaient la compréhension de la place dans la littérature de la neurostimulation non invasive en SDRC et la justification de son utilisation (revue, article 1), de comparer les évaluations cliniques et le fonctionnement des M1 (notamment les différences interhémisphériques d'excitabilité motrice corticale) en SDRC du membre supérieur par rapport à un groupe Sans-douleur (étude 1, article 2), et de tester si l'utilisation des rPMS permettait de diminuer la douleur et de normaliser cette différence d'excitabilité motrice interhémisphérique en SDRC (étude 2, article 3). Les objectifs ont été atteints et les résultats présentés dans les chapitres 2 et 3 sont discutés dans les prochains paragraphes, avec les forces et les limites du projet de maîtrise, en proposant par la suite les perspectives des études futures.

4.1 RETOUR SUR LES HYPOTHÈSES RELATIVES À L'ARTICLE 2

L'hypothèse de départ de l'étude expérimentale 1 (article 2) était que les participants avec un SDRC auraient une différence d'excitabilité du M1 plus grande entre leurs hémisphères que les participants sans douleur. Il a été possible de mesurer l'excitabilité du M1 chez tous les participants et l'hypothèse de départ a été validée (différence clinique mesurée). Toutefois, la douleur ne semble pas influencer le sens de ce débalancement de la même façon chez tout le monde. Ce résultat a influencé notre décision de poursuivre la mesure du débalancement dans l'étude 2 (article 3) pour comprendre si le sens du débalancement influençait la réponse au traitement.

Les résultats cliniques moteurs de l'étude expérimentale 1 (Article 2) correspondaient aux hypothèses initiales (force et amplitude articulaire active moindre pour la main avec SDRC), mais les différences des mesures cliniques sensorielles (test des monofilaments et proprioception brouillée) au membre sans SDRC par rapport au groupe Sans-douleur n'étaient pas celles attendues. Ces mesures cliniques et leurs corrélations avec l'excitabilité du M1 de l'HI sont difficiles à interpréter : est-ce qu'elles révèlent des causes et mécanismes pouvant expliquer en partie la chronicisation du SDRC (plasticité mal-adaptée du HI discutée dans l'article 2) ou peuvent-elles être dues à un petit échantillon de participants très hétérogènes. Les mesures de SICI, ICF et SICF n'ont pas permis d'améliorer l'interprétation

des changements cliniques. Les écarts-types très élevés des MEP tests et conditionnés peuvent expliquer en partie pourquoi si peu de différence a été détectée entre les groupes. Dans des études futures, la prise de davantage de MEP par condition pourrait favoriser une plus grande diminution de la variabilité des mesures TMS, ce qui concorde avec les recommandations de Beaulieu et al 2017 (Beaulieu et al. 2017c). Il est également possible que les changements de fonctionnement du M1 en SDRC impliquent d'autres variables que celles mesurées (par exemple, d'autres circuits neuronaux que ceux testés). Les études futures devront tester davantage le fonctionnement du M1 et la voie corticospinale pour éclaircir les hypothèses relevées par l'étude expérimentale 1 et, si leur puissance statistique leur permet, il serait intéressant de tester l'impact de plusieurs cofacteurs sur les mesures TMS prises en pré et post-rPMS comme le sexe des participants, leur dominance, leur côté atteint en fonction de leur dominance, etc. pour relever de possibles différences initiales entre sous-groupes et/ou des réactions différentes aux rPMS.

4.2 RETOUR SUR LES HYPOTHÈSES RELATIVES À L'ARTICLE 3

L'hypothèse de départ de l'étude exploratoire 2 (Article 3) était qu'il serait possible de mesurer des changements à la suite d'une seule séance de rPMS chez des participants avec SDRC au membre supérieur en stade chronique comparativement à leurs mesures pré-rPMS (cliniques et TMS) et que leurs mesures se rapprocheraient en post-rPMS des valeurs de celles d'un groupe Sans-douleur. Cette hypothèse a été vérifiée. Toutefois, d'autres hypothèses auraient pu être émises, entre autres à la suite de la réalisation de l'étude expérimentale 1 (Article 2), et seront discutées en lien avec les résultats de l'étude 2 (Article 3).

À la suite de l'étude 1 qui montrait un débalancement d'excitabilité du M1 avec un sens variable d'un participant à l'autre, indépendamment du côté atteint, il a été anticipé que les rPMS appliquées au membre avec SDRC auraient un impact sur un des deux sous-groupes de participants seulement : ceux avec l'HC ou l'HI plus excitable. En effet, les rPMS ont permis une diminution de la douleur présente que dans le sous-groupe avec l'HC plus excitable que l'HI (malgré une baisse de douleur à une semaine retrouvée dans les deux sous-groupes), puis plus le débalancement favorisait l'excitabilité de l'HC sur celui de l'HI en pré-

rPMS et plus la diminution de douleur était grande (article 3, Figure 4). Ces résultats devront être répliqués avant d'en tirer une conclusion définitive, mais le RMT semble donc être un bon indicateur d'efficacité au traitement (lorsque HC plus excitable).

La plus grande diminution de douleur chez les participants avec le HC plus excitable que le HI (étude 1/article 2, Figure 4B) a généré plusieurs questionnements : comme ces participants étaient également ceux avec le moins de douleur moyenne dans la semaine précédant les rPMS, la plus grande diminution de douleur était-elle donc vraiment en lien avec le sens du débalancement de RMT ou d'autres facteurs? Leur intensité de douleur moindre, la rend-elle plus difficile à réduire (car moins de possibilités de réduction de douleur) ou plus facile car moins intense? À ma connaissance, la facilité ou difficulté à réduire une douleur en fonction de son intensité n'a pas été testée en SDRC. Benedetti et al. (1997) rapportent une réduction de douleur avec une stimulation électrique transcutanée seulement chez les personnes ayant une douleur légère à modérée suite à une opération thoracique alors que ces stimulations étaient inefficaces chez les personnes dont la douleur était élevée (Benedetti et al., 1997). Il serait alors intéressant de tester et rapporter les différences d'effets des stimulations magnétiques entre différents niveaux de douleur des personnes avec SDRC. Ces études devraient avoir de plus grands échantillons, être randomisées et contrôlées et tester les stades aigus et chroniques pour décrire suffisamment bien la population et ainsi permettre de mieux personnaliser les traitements.

On aurait pu penser que seul l'HC aurait été influencé par les rPMS (retour sensoriel lemniscal croisé), mais il semble que les deux hémisphères cérébraux aient présenté des changements plastiques, ce qui suggère une communication transcallosale efficace ou des afférences sensorielles ipsilatérales pour le membre supérieur atteint de SDRC. En effet, les rPMS ont eu non seulement un impact bilatéral sur l'excitabilité des M1 (ce qui a permis de diminuer le débalancement d'excitabilité des M1), mais également sur plusieurs autres variables TMS mesurées dans l'HI. Une levée d'inhibition (diminution du mécanisme SICI), une augmentation de la facilitation (augmentation du mécanisme ICF) et une synchronisation moins bonne des volées descendantes (latence plus lente) ont été mesurées dans l'HI, le tout suggérant l'induction de mécanismes de plasticité motrice corticale. Comme discuté dans

l'article 3, ces changements sont vraisemblablement dus à la modification de la force des synapses corticospinales et à l'activation de synapses latentes (Jacobs & Donoghue 1991; Hess & Donoghue 1996; Sanes & Donoghue 2000), mais également à l'inhibition interhémisphérique (en provenance de HC) de la SICI de HI (Reis et al., 2008). Comme ces mécanismes sont reliés à la plasticité cérébrale, il est possible d'émettre l'hypothèse que les rPMS activent des mécanismes de plasticité dans l'HI ce qui permettrait, s'ils étaient utilisés avant des exercices spécifiques de réadaptation, de potentialiser les effets de la réadaptation. Les rPMS représenteraient donc potentiellement un adjuvant thérapeutique aux traitements conventionnels en réadaptation.

Les mesures de proprioception brouillée et d'amplitude articulaire active de la main avec SDRC se sont améliorées après rPMS. Ces améliorations en une seule séance rPMS de 3 minutes 20 secondes ne peuvent être dues à une diminution des restrictions mécaniques (capsule articulaire raccourcie, adhérences cicatricielles…). Il est probable que les changements dans l'HI, ainsi que la diminution du débalancement d'excitabilité des M1 ont permis d'améliorer l'intégration sensorielle et la planification motrice dans l'HC permettant l'envoi de commandes motrices plus efficaces et influençant l'amplitude articulaire active et la proprioception de la main avec SDRC. Toutefois, qu'en est-il de la main sans SDRC? Selon l'étude 1 (article 2), l'intégration sensorielle de l'HI (selon les tests de monofilaments et de proprioception) était touchée dans le groupe avec SDRC. Or, le test de monofilaments n'a été réalisé qu'en pré-rPMS et celui de proprioception de façon bilatérale en pré-rPMS, mais qu'à la main avec SDRC en post-rPMS. Il aurait été intéressant d'avoir ces résultats pour statuer si les rPMS permettaient, en parallèle des mesures de plasticité détectées dans cet hémisphère, une meilleure intégration sensorielle dans l'HI.

Deux questionnaires ont été utilisés dans les études exploratoires pour décrire la population avec SDRC ayant participé aux études. L'objectif de leur utilisation aurait pu être d'y mesurer des changements à la suite des rPMS. Or, malgré une amélioration de la fonction manuelle à la suite du traitement, très peu de modifications des scores globaux à l'échelle de sévérité du SDRC ont été mesurées à une semaine de suivi (0 à 3 points). Cela peut s'expliquer parce que l'échelle de sévérité du SDRC, contenant des questions dichotomiques plutôt que

quantitatives, est peu sensible au changement. Selon Harden et al. 2017, une différence de ≥4.9 sur l'échelle indiquerait une vraie différence dans la symptomatologie des participants (Harden et al., 2017). De la même façon, peu de changements ont été relevés sur l'échelle de perturbation de la perception du schéma corporel de Bath pour les patients atteints du SDRC, mais les participants des études (en stade chronique) y avaient en pré-rPMS noté peu de perturbations (laissant donc peu de place au changement). Ces deux questionnaires seraient possiblement plus utiles en stade aigu ou subaigu pour noter l'impact de la répétition de séances de rPMS ou l'impact des rPMS combinées à des techniques de visualisation motrice (qui influencent également la perception corporelle, Moseley, 2006).

4.3 FORCES ET LIMITES DES ÉTUDES

La portée des résultats des deux études exploratoires (articles 2 et 3) est limitée par la taille des échantillons. Toutefois, la comparaison des mesures pré/post-rPMS chez les mêmes participants augmente la force des résultats. Aussi, ces études exploratoires permettent d'émettre de nouvelles hypothèses et de soutenir la continuation d'études en SDRC, que ce soit pour mieux comprendre les changements de fonctionnement des M1 afin d'adapter les approches au débalancement fonctionnel, ou pour tester l'effet de la neurostimulation non invasive en fonction de ce débalancement et des autres variables TMS.

Le diagnostic de SDRC type I des participants n'a pas été validé au départ des études étant donné la résolution de certains de leurs symptômes avant leur participation à l'étude. Bref, même si les participants répondaient initialement aux critères diagnostiques cliniques de Budapest, ils auraient probablement été diagnostiqués SDRC de type NOS lors de leur participation. C'est pour cette raison que les critères diagnostiques de Budapest cliniques ont été utilisés plutôt que ceux de recherche.

Il est possible qu'un biais de recrutement ait influencé nos résultats. En effet, étant donné le mode de recrutement non probabiliste volontaire des participants, il est probable que ceux ayant décidé de participer aux études soient ceux qui étaient les plus motivés à s'améliorer et par le fait même les plus à risque de vivre un effet placebo. Ce qui peut s'appliquer à la majorité des études avec un même mode de recrutement. Par contre, aucun effet placebo n'a

été mesuré jusqu'à maintenant dans les études randomisées et contrôlées en rPMS en physiopathologie dans notre laboratoire (Massé-Alarie et al., 2013, 2016; Beaulieu et al., 2015). Également, un effet placebo est par définition un effet qui ne dure pas. Or, l'étude 2 montre des effets sur la douleur à une semaine post-rPMS, ce qui rassure face au risque de placebo, bien que des études randomisées contrôlées permettraient d'en écarter le risque.

Finalement, la prise des mesures cliniques a été réalisée par la même physiothérapeute pour éliminer les différences possibles reliées à la fidélité interévaluateur. Il n'était donc pas possible qu'elle soit à l'aveugle par rapport au temps de mesure (pré vs. post-rPMS) ni au groupe (SDRC vs. Sans-douleur) auquel faisait partie le participant qu'elle évaluait. Toutefois, toutes les données TMS ont été codifiées pour chacun des participants et leur analyse a donc pu être réalisée à l'aveugle des facteurs testés (groupe, temps de mesure, côté).

4.4 PERSPECTIVES CLINIQUES ET DE RECHERCHE

Les résultats obtenus dans le cadre de cette maitrise sont prometteurs et soutiennent la réalisation d'études de plus grande envergure, car plusieurs questions demeurent.

Études longitudinales

D'abord, il serait intéressant d'effectuer une étude longitudinale pour vérifier si les différences de fonctionnement du M1 sont présentes avant le SDRC et pourraient expliquer pourquoi un individu développe ce syndrome ou si, à l'inverse, elles sont la conséquence du SDRC sur le système sensorimoteur. Une meilleure connaissance des différences de fonctionnement du M1 permettrait également de mieux adapter les interventions chez la population avec SDRC pour influencer positivement la plasticité cérébrale et optimiser le fonctionnement des cortex sensorimoteurs. Le gain serait énorme pour les individus qui souffrent du SDRC, mais également sur le plan sociétal puisque le SDRC est rattaché à une restriction de participation au travail et un coût de santé important.

Répétition des séances rPMS

La réalisation d'études comprenant une répétition du nombre de séances de rPMS permettrait vraisemblablement d'optimiser et de cristalliser les gains obtenus en une seule séance. Peut-

être même que l'influence répétée sur la plasticité cérébrale des deux hémisphères permettrait de diminuer la douleur de façon équivalente entre personnes avec hyperexcitabilité de l'hémisphère controlatéral au SDRC et personnes avec hyperexcitabilité de l'hémisphère ipsilatéral.

Neurostimulation cérébrale et combinaison avec rPMS

La neurostimulation cérébrale est connue pour influencer le système sensorimoteur (telle que présenté dans la revue de l'article 1) et pourrait possiblement, lorsqu'utilisée avant les rPMS, permettre d'optimiser l'impact de ces derniers. Le projet de maitrise présenté dans ce mémoire expose les résultats qui ont servi d'assise au développement d'une étude de plus grande envergure, actuellement en cours au laboratoire, qui vise à tester ces hypothèses.

En effet, la connaissance de la présence d'un débalancement d'excitabilité du M1 de sens différent selon chaque participant (étude 1) a rendu l'application d'un même protocole de stimulation magnétique du cerveau insensée. À nos yeux, il est effectivement non logique et non éthique d'appliquer un protocole de stimulation qui augmente l'excitabilité de M1 sur un hémisphère déjà plus excitable ou un protocole inhibiteur sur un hémisphère moins excitable. Le protocole de l'étude en cours a donc été développé pour que les rPMS soient testées, dans un premier temps, seules (étude expérimentale 2) et, dans un deuxième temps, combinées à des protocoles de stimulations magnétiques centrales personnalisés au participant (selon ses propres mesures TMS de ligne de base). Les participants reçoivent alors au laboratoire sur quatre séances distinctes un protocole : excitateur sur l'hémisphère le moins excitable (pour certains sur l'HC, d'autres sur l'HI), inhibiteur sur l'hémisphère le plus excitable (HC ou HI), puis ces mêmes protocoles sont combinés aux rPMS. Ainsi, l'hémisphère stimulé est parfois le dominant ou non-dominant, le droit ou gauche, contrôlant ou non le membre avec SDRC… Un échantillon de très grande taille est donc nécessaire pour atteindre la puissance statistique suffisante pour la comparaison des différents protocoles.

Combinaison des rPMS à la réadaptation (adjuvant)

La combinaison de la neurostimulation à des exercices spécifiques de physiothérapie ou d'ergothérapie n'a pas été testée au travers des études de cette maîtrise. L'influence de la

neurostimulation sur la plasticité cérébrale permettrait vraisemblablement, lorsqu'utilisée avant des exercices, de préparer M1 et le système corticospinal pour que les exercices spécifiques aient un meilleur impact sur les circuits sensorimoteurs. Il serait donc très intéressant de développer des études combinant l'application de neurostimulation non invasive avant la pratique d'exercices spécifiques chez la population avec SDRC. Des études similaires ont été réalisées chez d'autres populations souffrant de douleur chronique et les résultats sont probants (Massé-Alarie et al. 2013, 2017; Schneider et al., en cours). Si les rPMS étaient accessibles en pratique publique et/ou privé en physiothérapie, leur applicabilité serait assez facile puisque les physiothérapeutes ont une excellente connaissance de l'anatomie (il leur serait aisé de localiser un muscle précis, positionner et maintenir la bobine sur un muscle ou groupe de muscles spécifiques et valider leur positionnement par le mouvement créé par la stimulation). Par leur formation académique, ils seraient également en mesure d'évaluer et choisir le ou les muscles dont le contrôle moteur déficient serait à améliorer par rPMS pour que de nombreuses tâches soient moins, voire non, douloureuses. Le temps de stimulation par muscle est très court (3min20sec) donc facilement intégrable même dans un contexte de soins réels avec une limite de temps par client. Par contre, d'autres évidences doivent encore être collectées et rapportées pour que de telles applications cliniques des rPMS puissent être recommandées par les ordres professionnels.

CONCLUSIONS

Les résultats des présentes études exploratoires sont novateurs, mais également très prometteurs. Les participants du groupe SDRC avaient déjà eu accès à des traitements multidisciplinaires et étaient passés au travers de l'algorithme de traitements conventionnels avec un suivi médical spécialisé d'une clinique de gestion de la douleur chronique (médication, blocs intraveineux, injections de kétamine, etc.), de l'ergothérapie (modalités actives et passives, exercices spécifiques, conseils, modalités analgésiques telle que chaleur, imagerie motrice, etc.) et un suivi psychologique. Malgré tout, comme chez 62% des participants de l'étude de Geertzen et al., ils vivaient encore avec des restrictions aux activités de la vie quotidienne et de la douleur au début de leur participation à l'étude (Geertzen et al., 1998). Il est probable que leurs difficultés résiduelles soient dues, du moins en partie, aux changements centraux qui ont pu être mesurés (notamment la différence d'excitabilité motrice corticale entre les deux hémisphères cérébraux). Or, malgré tout cela, une seule séance de rPMS de 3 minutes 20 secondes sur le muscle FDS a pu normaliser le débalancement d'excitabilité interhémisphérique et améliorer douleur et fonction.

En une seule séance rPMS, l'objectif n'était pas de résoudre complètement la douleur et les incapacités des participants, mais d'explorer l'effet des rPMS sur les symptômes de douleur, le fonctionnement de M1 et la fonction manuelle. Ces études ouvrent la porte à un grand nombre d'autres études et de perspectives de recherche et d'essais cliniques.

Comme physiothérapeute, il m'apparaît important et intéressant de contribuer aux développements de nouvelles connaissances en santé et de promouvoir la profession. Il me semble réaliste dans un proche avenir de voir les physiothérapeutes utiliser de nouvelles technologies de neurostimulation, comme les rPMS, pour continuer d'améliorer la qualité des soins et les services prodigués à la population.

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Annexe 1 – Échelle de sévérité du SDRC ou «CRPS Severity Score»

Score de sévérité du SDRC - CRPS Severity Score (CSS)

Ce questionnaire comprend 2 parties et vise à quantifier la sévérité de votre symptôme douloureux régional complexe (SDRC).

La première partie sera complétée par vous et porte sur vos symptômes ressentis dans la dernière semaine en lien avec votre SDRC.

La seconde sera complétée par le clinicien et porte sur les signes cliniques de votre SDRC présents aujourd'hui.

PARTIE 1 – Symptôme(s) rapporté(s) par le patient

Veuillez cocher la case « Présence » si vous avez vécu le symptôme décrit dans la dernière semaine et « Absence » si ce n'est pas un symptôme que vous avez vécu dans la dernière semaine.

Ce symptôme a-t-il été présent dans la dernière semaine?	Présence	Absence
1. **Allodynie OU hyperpathie** (une sensation normalement non-douloureuse vous fait ressentir de la douleur OU la sensibilité au toucher du membre atteint est augmentée ou prolongée);		
2. **Température asymétrique** (plus basse ou plus élevée) entre le membre atteint et non-atteint;		
3. **Couleur asymétrique** (plus pâle ou plus foncée) entre le membre atteint et non-atteint;		
4. **Sudation asymétrique** (plus basse ou plus élevée) entre le membre atteint et non-atteint;		
5. **Œdème asymétrique** (grosseur/volume du membre atteint différent du membre non-atteint);		
6. **Un ou des changement(s) trophique(s)** : aspects des ongles, des poils ou de la peau différente au niveau du membre atteint;		
7. **Changement(s) moteur(s)** : faiblesse musculaire OU tremblements OU dystonie (anomalies du tonus des muscles; se présente souvent par une contraction musculaire soutenue) au niveau du membre atteint;		
8. **Amplitude articulaire volontaire diminuée** au membre atteint par rapport au membre non-atteint.		
Sous-total (section symptômes) :	/8	

PARTIE 2 – Signe(s) clinique(s) objectivé(s) par le clinicien

Cocher la case « Présence » si vous observé actuellement le signe clinique décrit et « Absence » si le signe clinique n'est pas présent lors de l'évaluation.

Ce signe clinique est-t-il présent aujourd'hui?	Présence	Absence
1. **Hyperpathie à la piqûre** (sensibilité du membre atteint augmentée ou prolongée);		
2. **Allodynie** au toucher léger (brosse), au froid, à la chaleur, à la vibration ou à la pression.		
3. **Température asymétrique** (à la palpation);		
4. **Couleur asymétrique** entre le membre atteint et non-atteint;		
5. **Sudation asymétrique** entre le membre atteint et non-atteint;		
6. **Œdème** au niveau du membre atteint;		
7. **Un ou des changement(s) trophique(s)** : aspects des ongles, des poils ou de la peau différente au niveau du membre atteint;		
8. **Changement(s) moteur(s)** : faiblesse musculaire, tremblements ou dystonie au niveau du membre atteint;		
9. **Amplitude articulaire active diminuée** au membre atteint par rapport au membre non-atteint.		
Sous-total (section signes cliniques) :	/9	
Score final au CSS	/17	

Date de la passation du test : _____

Nom du patient : _____

Nom de l'évaluateur : _____

Annexe 2 - Échelle de perturbation de la perception du schéma corporel de Bath pour les patients atteints du SDRC

Échelle de perturbation de la perception du schéma corporel de Bath pour les patients atteints du SDRC

Élaborée par Jennifer S. Lewis, The Royal National Hospital for Rheumatic Diseases Bath, Angleterre, v2. ©2008. Tous droits réservés.
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Nom du patient _____   Date _____

Diagnostic _____   Date d'apparition des symptômes _____

Parties du corps atteintes :   1) _____
                       2) _____
                       3) _____

1) Sur une échelle de 0 à 10, à quel point sentez-vous que le membre atteint fait partie de votre corps?

Complètement intégré = 0__1__2__3__4__5__6__7__8__9__10 = Complètement détaché

2) Sur une échelle de 0 à 10, à quel point avez-vous conscience de la position de votre membre atteint dans l'espace?

Très conscient = 0__1__2__3__4__5__6__7__8__9__10 = Aucune conscience

3) Sur une échelle de 0 à 10, à quel point portez-vous attention à votre membre atteint? Par exemple, à quel point y pensez-vous et le regardez-vous ?

Toute mon attention = 0__1__2__3__4__5__6__7__8__9__10 = Aucune attention

4) Sur une échelle de 0 à 10, quelle est l'intensité de vos émotions à l'égard de votre membre atteint?

Fortement positive = 0__1__2__3__4__5__6__7__8__9__10 = Fortement négative

5) Remarquez-vous un écart entre l'apparence de votre membre atteint (à l'œil ou au toucher) et la manière dont vous le ressentez, en ce qui concerne

Taille	oui ☐ non ☐	Remarque _____
Température	oui ☐ non ☐	Remarque _____
Pression	oui ☐ non ☐	Remarque _____
Poids	oui ☐ non ☐	Remarque _____

6 a) Avez-vous déjà eu le désir de faire amputer le membre? Oui ☐ Non ☐

6 b) Si oui, quelle est l'intensité de ce désir en ce moment?

Nulle = 0__1__2__3__4__5__6__7__8__9__10 = Très forte

Site d'amputation désiré _____

7) Avec les yeux fermés, décrivez une image mentale de votre membre atteint et non atteint (dessiné par l'évaluateur pendant que le patient décrit, puis vérifié par le patient).

Ce dessin rend bien compte de mon image du membre atteint.

Signature _____   Date _____

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Annexe 3 – Cible utilisée pour mesurer la proprioception du membre supérieur

Cible - Mesure du sens de la position – Le Métayer 2007