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**Efficacité des techniques de stimulation corticale non-invasive dans le traitement des douleurs chroniques et apport de la neuro-imagerie à la compréhension des mécanismes d'action et la recherche de biomarqueurs pronostiques**

Hasan Hodaj

► **To cite this version:**

Hasan Hodaj. Efficacité des techniques de stimulation corticale non-invasive dans le traitement des douleurs chroniques et apport de la neuro-imagerie à la compréhension des mécanismes d'action et la recherche de biomarqueurs pronostiques. Santé. Université Grenoble Alpes [2020-..], 2022. Français. NNT : 2022GRALS044 . tel-04105202

**HAL Id: tel-04105202**

**<https://theses.hal.science/tel-04105202v1>**

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THÈSE

Pour obtenir le grade de

**DOCTEUR DE L'UNIVERSITÉ GRENOBLE ALPES**

École doctorale : ISCE - Ingénierie pour la Santé la Cognition et l'Environnement

Spécialité : BIS - Biotechnologie, instrumentation, signal et imagerie pour la biologie, la médecine et l'environnement

Unité de recherche : Grenoble Institut des Neurosciences

**Efficacité des techniques de stimulation corticale non-invasive dans le traitement des douleurs chroniques et apport de la neuro-imagerie à la compréhension des mécanismes d'action et la recherche de biomarqueurs pronostiques**

**Efficacy of non-invasive cortical stimulation techniques in the treatment of chronic pain and contribution of the neuroimaging in the understanding of the mechanisms of action and for the research of prognostic biomarkers**

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# THESE DE DOCTORAT DE L'UNIVERSITE GRENOBLE ALPES

École doctorale N° 216

École doctorale Ingénierie pour la santé, la Cognition et l'Environnement

## Thèse de doctorat par articles

*Soutenue publiquement le 12 décembre 2022 par :*

**Hasan HODAJ**

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## **Remerciements**

Je souhaite tout d'abord remercier ma directrice de thèse, Mme Chantal MARTIN-DELON, de m'avoir guidé et accompagné pendant les nombreuses étapes de ce travail de recherche.

J'adresse aussi mes profonds remerciements à mon co-directeur de thèse, Pr Jean-Pascal LEFAUCHEUR pour son expertise et sa contribution dans la réalisation de cette thèse, et de sa confiance pour partager, depuis plusieurs années, les travaux scientifiques dans le domaine passionnant de la neuromodulation.

Je remercie sincèrement Pr Jean-Paul NGUYEN et Pr Julien NIZARD d'avoir accepté d'être les rapporteurs de cette thèse et aussi Pr Mircea POLOSAN, Mme Claire ROME et Dr Laurent VERCUEIL d'avoir accepté de faire partie du jury.

J'adresse mes vifs remerciements au Pr Jean-François PAYEN, pour sa confiance, son soutien et sa contribution dans mes travaux de recherche.

Mes chaleureux remerciements s'adressent à l'ensemble de l'équipe du Centre de la Douleur pour l'investissement au quotidien, la réussite de la pluridisciplinarité et la participation dans la recherche clinique. Mes meilleures pensées s'adressent à ce qui m'ont formé au début de mon exercice autant qu'algologue, particulièrement Dr Jean-Pierre ALIBEU.

Je remercie aussi Dr Nathalie André-Obadia et Dr Luis Garcia-Larrea, équipe NeuroPain Lyon, pour leur collaboration dans mes travaux de recherche.

Je tiens à remercier la Direction Générale, la CME et la DRCI du CHU Grenoble Alpes, qui ont soutenu les projets du Centre de la Douleur, permettant ainsi le développement de la recherche clinique et des activités innovantes.

Je remercie également les équipes qui ont participé dans la réalisation de cette recherche : le Grenoble Institut des Neurosciences, le Centre d'Investigation Clinique et la plateforme IRMaGe.

Mes remerciements les plus tendres vont ensuite à toute ma famille HODAJ, source de motivation, de savoir et de progrès, tout au long de ma vie.

Je tiens à remercier affectueusement mon Frère, qui m'a toujours inspiré dans les domaines scientifiques et philosophiques.

Je remercie tendrement ma Femme pour son soutien au quotidien et autant que collaboratrice dans mes travaux de recherche.

Merci à mes proches et à mes amis : ils sont très nombreux, mais chacun et chacune à sa place personnalisée dans mes pensées.

Mes remerciements vont aussi aux Pr Christian LETOUBLON et Pr Michel BARGE, qui m'ont soutenu et ont cru en moi, tout au début de ma carrière au CHU de Grenoble (en 1992).

J'adresse aussi mes sincères remerciements à Dr Claude JACQUOT pour son soutien et sa confiance.

Et enfin, je formule mes plus profonds remerciements à tous mes enseignants, depuis le début de ma scolarité et jusqu'à la fin de mon internat à la Faculté de Médecine à Tirana : ils m'ont formé, inspiré et encouragé à apprendre et toujours apprendre ! Parmi eux, je remercie particulièrement le Pr Besim ELEZI, qui restera pour moi un modèle d'intelligence et de rigueur professionnelle.

« Temps physique et temps psychologique (vécu) se distingue par le fait que le premier, toujours concentré dans le présent, sépare deux infinies l'un de l'autre, tandis que le temps psychologique mélange au sein même du présent un peu du passé récent et un peu de l'avenir proche...Mais il y a des exceptions à cette règle, par exemple, lorsque nous éprouvons une souffrance physique durable qui s'exprime comme une impossibilité de se détacher de l'instant présent...

Il y a dans la souffrance, l'absence insupportable de tout refuge par rapport au temps. »

Étienne Klein. Grand dictionnaire de la philosophie, 2003

C'est la mission du médecin algologue de soulager les douleurs chroniques, en particulier les formes rebelles, d'accompagner les patients avec empathie et savoir-faire, afin qu'ils puissent retrouver le goût de la vie et revivre l'instant présent. Parmi de nombreuses approches, les techniques récentes de neuromodulation non invasive, objet de cette recherche, contribuent dans la prise en charge des syndromes douloureux chroniques réfractaires.

Dr Hasan HODAJ

## Résumé

Les techniques de la stimulation cérébrale non invasives, principalement la stimulation magnétique transcrânienne répétitive (rTMS) et la stimulation transcrânienne par courant continu (tDCS), constituent des alternatives nouvelles et intéressantes dans le traitement des douleurs chroniques réfractaires. Leur intérêt réside dans leur innocuité et leur bonne tolérance.

Nombreuses études confirment l'efficacité de la rTMS et de la tDCS dans les douleurs chroniques. L'analyse de la littérature montre que la stimulation du cortex moteur par la rTMS à haute fréquence  $\geq 5\text{Hz}$ , apporte un effet antalgique de plus de 30% chez 46% à 62% des patients souffrant de douleurs neuropathiques. Cependant, la plupart des études sont de courte durée. Seulement quelques études récentes ont rapporté l'utilisation et l'efficacité des techniques de la stimulation non invasive pour soulager les douleurs chroniques à long terme, par la pratique des séances de maintien pendant plusieurs mois (principalement la rTMS).

Les techniques de neuromodulation agissent sur la douleur par différents mécanismes. En raison de leurs différents mécanismes d'action, la rTMS et la tDCS peuvent avoir des indications sélectives dans le traitement de la douleur. Pour cette raison, il paraît intéressant de comparer l'effet antalgique entre la rTMS et la tDCS et de déterminer si ces stimulations ont une incidence sur la cartographie sensori-motrice cérébrale en imagerie par résonance magnétique fonctionnelle (IRMf), afin de mieux comprendre leurs mécanismes d'action.

L'application de la rTMS et de la tDCS sur le cortex moteur pour soulager les douleurs chroniques est basée sur les résultats obtenus par la stimulation invasive du cortex moteur épidual, depuis le début des années 90, dans le traitement des douleurs chroniques réfractaires.

Compte tenu des effets bénéfiques qui peuvent être obtenus dans le traitement des douleurs chroniques réfractaires par les techniques de stimulation corticale ou médullaire utilisant des électrodes implantées chirurgicalement, il apparaît licite d'étudier les effets antalgiques à long terme que pourraient produire les techniques de stimulation non-invasive du cortex et de la moelle.

Dans cette thèse doctorale, nous étudierons l'utilisation des techniques de neuromodulation non-invasive dans le traitement des syndromes douloureux chroniques suivants :

- Douleurs neuropathiques chroniques réfractaires ;
- Algoneurodystrophies des membres ;
- Migraines chroniques.



La thèse comporte un volet clinique et un volet neuro-imagerie.

### *Volet clinique*

- I. Evaluation de l'effet antalgique de la tDCS et de la rTMS dans les douleurs neuropathiques chroniques pharmaco-résistantes (étude randomisée en groupes croisés).
- II. Comparaison de l'effet antalgique de la stimulation non invasive du cortex moteur (tDCS et rTMS) et de la stimulation trans-spinale (tsDCS) dans l'algoneurodystrophie des membres (étude randomisée en groupes parallèles).
- III. Evaluation de l'efficacité prophylactique de la tDCS dans les migraines chroniques (étude randomisée en double aveugle, contrôlée versus placebo).
- IV. Etude de l'effet antalgique de la rTMS à long terme chez les patients souffrant de douleurs neuropathiques chroniques, en fonction de leur profil clinique.

### *Volet neuro-imagerie*

- I. Analyse, au moyen de l'IRMf, des modifications éventuelles des cartes corticales sensori-motrices induites par la rTMS ou la tDCS à court terme (J5) et comparaison entre les deux techniques.
- II. Analyse, au moyen de l'IRMf, des modifications éventuelles de la cartographie cérébrale induites par la rTMS à long terme et corrélation entre ces modifications et l'effet antalgique de la stimulation corticale.
- III. Etude des modifications centrales de la perfusion cérébrale qui pourraient être en lien avec les douleurs neuropathiques chroniques (séquence non invasive grâce à pCASL : plateforme IRMaGe, IRM Achieva 3.0T dStream, Philips).
- IV. Utilisation de l'imagerie cérébrale pour améliorer le ciblage de la zone corticale à stimuler par la rTMS.

**Mots-clés :** douleur chronique, rTMS, tDCS, tsDCS, cortex moteur primaire, IRM fonctionnelle et de perfusion

## **Summary**

The techniques of non-invasive brain stimulation, mainly the repetitive transcranial magnetic stimulation (rTMS) and the transcranial direct current stimulation (tDCS) are new and promising alternatives in the treatment of refractory chronic pain. Their interest resides in their safety and good tolerance. Numerous studies about the use of rTMS or tDCS demonstrated significant analgesic effects in patients suffering from chronic pain. In the literature, motor cortex rTMS at high frequency  $\geq 5\text{Hz}$  shows an analgesic effect of more than 30% in 46% to 62% of treated patients with chronic neuropathic pain. However, reported results are usually of short duration. Only a few recent studies have reported the use and efficacy of non-invasive stimulation techniques (mainly for rTMS), to relieve chronic pain in the long term, by maintenance therapy with repeated sessions for several months.

The neuromodulation techniques may act on pain by different mechanisms. Because of their different mechanisms of action, rTMS and tDCS may have selective indications in pain therapy. Therefore, it seems interesting to compare the antalgic effect between rTMS and tDCS and to determine if these stimulations have any difference in the cortical sensory-motor map of the brain in functional Magnetic Resonance Imaging (fMRI), in order to better understand their mechanisms of action.

The application of rTMS and tDCS over the motor cortex for chronic pain relief is based on the results provided by invasive epidural motor cortex stimulation, in the treatment of refractory chronic pain, since the beginning of the nineties. Based on the beneficial effects that can be obtained in the treatment of refractory chronic pain by cortical or medullary stimulation techniques using surgically implanted electrodes, it seems licit to study the long-term analgesic effects that could be produced by non-invasive stimulation techniques of the cortex and the spinal cord.

In this doctoral thesis, we will study the use of non-invasive neuromodulation techniques in the treatment of the following chronic pain syndromes:

- Chronic refractory neuropathic pain;
- Algoneurodystrophy of limbs;
- Chronic migraines.

The thesis includes a clinical and a neuroimaging component.

### ***Clinical component***

- I. Evaluation of the analgesic effects of rTMS versus tDCS in patients suffering from chronic neuropathic pharmacoresistant pain: à randomized crossover study.
- II. Comparison of the analgesic effect between the motor cortex stimulation (tDCS and rTMS) and the trans-spinal stimulation (tsDCS) in the algoneurodystrophy of members: a randomised clinical study in parallel groups.
- III. Evaluation of the prophylactic efficacy of tDCS in chronic migraines: a randomized double-blind placebo controlled study.
- IV. Long-term maintenance of rTMS analgesic effects in patients suffering from chronic neuropathic pain, according to their clinical profile.

### *Neuroimaging component*

- I. Analysis, by means of fMRI, of the modifications of cerebral cartography induced by rTMS or tDCS in short term (D5) and comparison between the two techniques.
- II. Analysis, by means of fMRI, of the possible modifications in brain mapping induced by rTMS in long term (D180) and correlation between these modifications and the analgesic effect of cortical stimulation.
- III. Study of central modifications of cerebral perfusion that may be related to chronic neuropathic pain (non-invasive sequence thanks to pCASL: plateforme IRMaGe, IRM Achieva 3.0T dStream, Philips).
- IV. Using of brain imaging to improve targeting of the cortical area stimulated by the rTMS.

**Keywords:** Chronic pain, rTMS, tDCS, tsDCS, primary motor cortex, functional and perfusion MRI

## **Abréviations**

**IRMf** : Imagerie par résonance magnétique fonctionnelle

**rTMS** : Stimulation magnétique transcrânienne répétitive

**tDCS** : Stimulation transcrânienne par courant continu

**tsDCS** : Stimulation trans-spinale par courant continu

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# 1. INTRODUCTION

Dans le rapport de l'Enquête Santé Protection Sociale de l'IRDES de 2011 [1], la prévalence de la douleur chronique sévère, définie par une douleur très fréquente et intense, est évaluée à 11 % chez l'adulte. L'efficacité des traitements médicamenteux disponibles à ce jour reste limitée.

En cas d'échec des traitements médicamenteux, la stimulation invasive des voies cordinales postérieures de la moelle (colonnes dorsales) a été proposée comme approche thérapeutique dès la fin des années 60. Puis, l'intérêt de cibles cérébrales profondes de stimulation (thalamus, substance grise périaqueducale) a été évalué, avant que la stimulation du cortex moteur voie le jour au début des années 90. Ces techniques de neuromodulation invasive pour le traitement de la douleur chronique sont réalisées au moyen d'électrodes implantées chirurgicalement. La mise en œuvre des techniques de neuromodulation invasive pose cependant plusieurs problèmes en pratique quotidienne : elle nécessite l'intervention d'une équipe spécialisée en milieu hospitalier et elle peut être refusée par les patients, s'agissant d'une implantation d'électrodes à moyen ou long terme. Dans ce contexte clinique, ces techniques ont leur place seulement dans les cas les plus réfractaires. Ainsi, le nombre de patients bénéficiant de ces approches invasives reste limité.

Parmi les techniques de stimulation cérébrale non-invasives, la stimulation magnétique transcrânienne répétitive (rTMS) ainsi que la stimulation par courant continu (tDCS), constituent depuis plus de 25 ans (rTMS) ou près de 20 ans (tDCS) des alternatives nouvelles et prometteuses dans le traitement des douleurs.

La stimulation magnétique transcrânienne a été utilisée initialement comme outil d'investigation neurophysiologique pour étudier la conduction nerveuse motrice centrale sur les voies pyramidales et comme technique d'étude de l'excitabilité corticale et de cartographie cérébrale [2]. Par la suite, des appareils ont permis de délivrer des stimulations en séquences rapides (stimulation « répétitive » : **la rTMS**), capables de modifier l'excitabilité et les fonctions des régions corticales stimulées. Au milieu des années 90, la rTMS a été utilisée dans le traitement de la dépression et ensuite dans plusieurs domaines : psychiatrie, neurologie, rééducation fonctionnelle, douleurs chroniques, ORL.

Le principe de cette technique repose sur les relations entre l'électricité et le magnétisme, selon les lois de l'induction électro-magnétique découvertes par Faraday en 1831. Un courant électrique de haute intensité passant dans une bobine de fil de cuivre génère un champ

magnétique. Si ce champ magnétique est délivré par cette bobine placée sur le scalp, il induit dans le milieu conducteur sous-jacent qu'est le cerveau un courant électrique ayant une certaine direction et pénétrant à une profondeur de 2 à 3 cm. Les mécanismes d'action de la rTMS sont variés et repose sur ses propriétés neuromodulatrices de l'excitabilité corticale. L'effet antalgique de la rTMS délivrée au niveau du cortex moteur primaire se produit par le recrutement de circuits neuronaux représentés dans cette région corticale, qui sont impliqués dans différentes grandes fonctions sensorielles, cognitives, et émotionnelles, et se projettent potentiellement très à distance de la zone de stimulation [3]. La stimulation corticale pourrait notamment réduire l'hyperactivité de certains relais thalamiques impliqués dans la transmission des stimuli douloureux [4]. Concernant l'implication des neuromédiateurs, l'effet antalgique pourrait se produire par la modulation des contrôles endogènes opioïdes [5,6] ou la restauration de l'inhibition gabaergique intra-corticale [7].

**La tDCS** apparaît comme une simplification majeure de la technique de stimulation cérébrale par rapport à la rTMS, permettant de moduler l'activité neuronale grâce à l'induction d'un faible courant électrique continu généré habituellement par deux larges électrodes posées sur le scalp. Les mécanismes d'action de la tDCS ne sont pas encore entièrement connus. Une stimulation anodique sur le cortex moteur produit a priori un effet excitateur, tandis qu'une stimulation cathodique a un effet inhibiteur. La stimulation anodique provoque la dépolarisation de la membrane, entraînant un déplacement du potentiel de la membrane au repos vers des valeurs moins négatives, tandis que la stimulation cathodique hyperpolarise la membrane [8]. Probablement la tDCS joue un rôle neuromodulateur dans différents systèmes de neurotransmission gabaergique, dopaminergique, sérotoninergique, ou cholinergique [9]. En ce qui concerne les effets neuro-métaboliques de la tDCS, la majorité des études ont été effectués à l'aide de la tDCS anodique placée sur le M1 gauche et ont montré la tendance d'une diminution de la concentration de GABA après stimulation [10]. Il est établi que les effets immédiats de la tDCS sont la conséquence des modifications du potentiel de membrane induit par l'anode ou la cathode, ce qui a pour conséquence une modification de l'excitabilité nerveuse [11]. Les effets à moyen terme, auraient un lien avec la mise en jeu des récepteurs NMDA, récepteurs activés par le glutamate et impliqués dans la mémoire cellulaire [12].

Récemment a été développée une approche de neuromodulation non-invasive de la moelle épinière, la stimulation transcutanée à courant continu (**la tsDCS**), en analogie avec la stimulation médullaire électrique implantée et ciblant les mêmes structures. Plusieurs études, ont fourni la preuve que la tsDCS était capable d'interférer avec les structures nerveuses de la



moelle pour moduler la conduction dans les voies lemniscales et spino-thalamiques ou d'induire des changements persistants dans les propriétés transsynaptiques des neurones spinaux [13,14,15,16]. Les études cliniques sur l'efficacité antalgique de la tsDCS sont peu nombreuses et explorent principalement des réponses physiologiques chez les sujets sains.

Compte tenu des effets bénéfiques obtenus dans le traitement des douleurs pharmaco-résistantes par les techniques invasives, il nous a paru licite d'étudier les effets antalgiques que pourraient produire dans le même contexte clinique, des techniques de stimulation non-invasive du cortex et de la moelle.

Dans cette thèse doctorale, nous étudierons l'utilisation des techniques de neuromodulation non-invasive dans le traitement des syndromes douloureux chroniques suivants :

- Douleur neuropathique chronique réfractaire ;
- Syndrome douloureux régional complexe (algoneurodystrophie) des membres ;
- Migraine chronique.

L'objectif de la thèse est l'étude de l'efficacité des techniques de stimulation corticale non-invasive dans le traitement des douleurs chroniques et de l'apport de l'IRMf à la compréhension des mécanismes d'action et la recherche de biomarqueurs pronostiques.

La thèse comporte un volet clinique et un volet neuro-imagerie.

**Le volet clinique** réside sur :

1. Les protocoles expérimentaux du Centre de la Douleur du CHU de Grenoble (Promoteur : CHU de Grenoble Alpes) :

**Doloris** : « *Evaluation de la rTMS versus stimulation par courant continu dans le traitement des douleurs neuropathiques chroniques. Analyse des modifications cérébrales induites, au moyen de l'IRMf* ». L'étude a été approuvée par le CPP du Sud-Est V Grenoble (N° 6705), et a été enregistrée auprès de clinicaltrials.gov (NCT02854332).

**Medis** : « *Evaluation de l'efficacité prophylactique de la stimulation transcrânienne à courant continu dans la migraine chronique. Etude randomisée et contrôlée versus placebo, en double aveugle* ». L'étude a été approuvée par le CPP du Sud-Est V Grenoble (N° 6705), et a été enregistrée auprès de clinicaltrials.gov (NCT02120326).

**Algostim** : « *Comparaison de l'effet antalgique de la stimulation non-invasive du cortex moteur (tDCS et rTMS) et de la stimulation trans-spinale (tsDCS) dans l'algoneurodystrophie des*

*membres* ». L'étude a été approuvée par le CPP du Sud-Est V Grenoble (N° 6705), et a été enregistrée auprès de clinicaltrials.gov (NCT02817880).

**Neurostim** : « *Etude randomisée en double aveugle de l'effet antalgique de la rTMS dans le traitement des douleurs neuropathiques chroniques : stimulation du cortex moteur superficielle, profonde et placebo. Analyse des modifications cérébrales induites, au moyen de l'IRMf* ». L'étude a été approuvée par le CPP du Sud Méditerranée III Nimes, et a été enregistrée auprès de clinicaltrials.gov (NCT04936646).

2. L'étude rétrospective observationnelle de l'effet antalgique de la rTMS à long terme chez les patients souffrant de douleurs neuropathiques chroniques : années 2014-2018.

**Le volet neuro-imagerie** comporte :

1. L'analyse, au moyen de l'IRMf, dans le cadre des protocoles de recherches Doloris, Algostim et Neurostim :
  - *des modifications éventuelles des cartes corticales sensori-motrices induites par la rTMS ou la tDCS à court terme (J5) et par la rTMS à long terme (J60, J180) ;*
  - *des modifications centrales de la perfusion cérébrale qui pourraient être en lien avec les douleurs neuropathiques chroniques.*
  - *des modifications de la connectivité fonctionnelle.*
2. La détermination avec plus de précision de la zone à stimuler *au moyen de l'IRM 3D (structurelle) et de l'IRMf (fonctionnelle).*

## 2. ETAT DE L'ART

Les protocoles utilisés dans les études de recherche clinique et thérapeutique des techniques de neuromodulation non-invasive (rTMS, tDCS et tsDCS) et les avancées scientifiques dans la compréhension de leur mode d'action par notamment l'apport de la neuro-imagerie, ont été analysés dans les articles respectifs composant cette thèse.

Concernant la place de ces techniques dans l'arsenal thérapeutique de la prise en charge des syndromes douloureux chroniques, les données de la littérature sont encore insuffisantes ou controversées.

Cependant l'efficacité de la rTMS paraît actuellement mieux établie que la tDCS. Dans les recommandations françaises et internationales pour l'utilisation de la rTMS, les experts ont retenu un niveau de preuve A concernant l'effet antalgique de la rTMS (fréquence  $\geq 5\text{Hz}$ ) dans les douleurs neuropathiques chroniques et un effet antalgique de plus de 30% a été observé chez 46 à 62% des patients [17,18]. D'autre part, la rTMS est conseillée comme traitement de 3eme ligne dans les recommandations françaises pour la prise en charge des douleurs neuropathiques chroniques [19].

Cependant, des effectifs hétérogènes de patients et des protocoles variés quant aux paramètres de stimulation et à la durée du traitement ne permettent pas toujours de transposer facilement l'utilisation de la rTMS en pratique clinique courante.

En effet, les études rapportent des paramètres de stimulation très variables selon le type de bobine utilisée, l'orientation de la bobine, le site de stimulation, l'intensité de stimulation, la fréquence de stimulation, la durée de la stimulation (train), l'intervalle entre les stimulations (inter-train), le nombre de chocs par séance, la durée de la séance, le rythme des séances.

D'autre part, le progrès de la neuroimagerie permet à présent de mieux définir la région cible grâce à l'IRM anatomique et/ou fonctionnelle individuelle intégrée dans un système de neuronavigation [20]. La neuronavigation guidée par l'IRM s'avère utile pour déterminer avec précision la cible à stimuler par la rTMS, pour rendre en compte des variabilités anatomiques inter-sujets, pour améliorer la reproductibilité des stimulations, pour suivre sur l'écran en temps réel la position et l'orientation de la bobine au cours d'une séance, et pour améliorer la fiabilité du placement de la bobine entre les sessions. Cependant, les études montrant l'intérêt de l'utilisation d'un système de neuronavigation pour améliorer l'efficacité clinique de la rTMS manquent encore. Par ailleurs, la correction des mouvements de la tête du

patient au cours des séances de stimulation peut être effectuée par l'utilisation combinée d'un bras robotisé et d'un système de neuronavigation. Il est important de souligner à ce stade que la rTMS nécessite un équipement lourd ayant un coût non négligeable (particulièrement si elle est guidée par la neuronavigation IRM et un bras robotisé).

**La tDCS**, du fait de son innocuité, de son faible coût et de sa simplicité d'utilisation, apparaît dans un tel contexte comme une alternative potentiellement intéressante. Le développement récent de l'utilisation de la tDCS à domicile constitue une solution encore moins onéreuse, évitant notamment des coûts de transport des patients. L'utilisation de la tDCS comme thérapeutique antalgique a fourni des résultats encourageants chez des patients souffrant de syndrome douloureux chronique [21,22,23]. Cependant, les données actuelles de la littérature, ne permettent pas d'affirmer, avec un niveau de preuve satisfaisant, l'efficacité du traitement au long cours par tDCS dans les douleurs chroniques [24,25]. A noter que les protocoles de tDCS sont variés, mais globalement moins complexes que ceux de la rTMS et diffèrent principalement selon l'intensité et le site de la stimulation, le montage et la polarité (anode ou cathode) des électrodes, et la durée et le rythme des séances. Le montage le plus fréquemment utilisé consiste au positionnement de l'anode en regard du cortex moteur et la cathode au niveau sus orbitaire controlatéral pour le traitement de la douleur [20].

Concernant **la tsDCS**, il y a très peu d'études cliniques évaluant son efficacité antalgique. La tsDCS a été récemment utilisée chez les patients souffrant de lésion médullaire comme une thérapeutique de rééducation ou pour réduire les spasmes musculaires [26,27]. Seulement deux études récentes ont rapporté l'effet antalgique de la tsDCS [28,29]. Une étude de modélisation a démontré que l'emplacement des électrodes en position longitudinale le long du rachis cervical ou lombaire, était le plus pertinent en regard de la distribution du champ électrique de la tsDCS dans moelle épinière [30]. En pratique clinique, ce montage est très simple à mettre en place, ouvrant des perspectives intéressantes pour son éventuelle utilisation future à domicile.

Cependant, la plupart des études sont de courte durée. La propriété principale de la rTMS s'appuie sur la persistance de ses effets antalgiques par rémanence au-delà de la période de stimulation. Mais les effets antalgiques d'une seule séance sont de courte durée et leur répétition est indispensable pour obtenir un soulagement durable par un effet cumulatif [31]. La nécessité de la répétition des séances, pour les mêmes raisons, concerne également la tDCS [32]. Seulement quelques études décrivent l'utilisation et l'efficacité antalgique à long terme de la rTMS [33,34,35,36,37] et de la tDCS [32,38].

D'autre part, étant donné que les mécanismes d'action des techniques de neuromodulation non-invasive sont différentes, leur place dans l'arsenal thérapeutique reste à définir, particulièrement l'utilisation de la tDCS ou de la tsDCS en cas d'échec de la rTMS. Dans ce cadre, la comparaison de l'effet antalgique des techniques de neuromodulation non-invasive est une piste très intéressante, sachant que l'analyse de la littérature retrouvent très peu d'études comparant l'effet antalgique de la rTMS et de la tDCS [39,40] et aucune étude comparative pour la tsDCS.

### **3. PROBLEMATIQUES, BUTS ET OBJECTIFS DE L'ETUDE**

#### **3.1. Volet clinique**

##### **3.1.1. La stimulation magnétique transcrânienne répétitive (rTMS)**

Dans les recommandations françaises et internationales, les experts ont retenu un niveau de preuve A concernant l'effet antalgique de la rTMS dans les douleurs neuropathiques chroniques [17].

#### **Problématiques**

En général, les protocoles sont de courte durée. Les études concernent des populations hétérogènes et des paramètres de stimulations variés. Par ailleurs, quelques méta-analyses ont rapporté un faible niveau de preuve des études contrôlées versus placebo.

Dans ce cadre, les experts recommandent :

- La nécessité de nouvelles études contrôlées versus placebo ;
- Le ciblage précis et reproductible ;
- L'utilisation de la neuronavigation ;
- Le développement de nouvelles formes de bobines ;
- L'explorations par la neuro-imagerie ;
- L'évaluation de l'effet antalgique de la rTMS à long terme.

#### **Objectifs**

Nos objectifs se réfèrent aux recommandations sus-citées des experts :

- a. Etudes sur l'efficacité antalgique à long terme de la rTMS en pratique clinique : protocoles homogènes et indications bien définies.
- b. Nouvelle cible de stimulation en pratique clinique : cortex moteur bilatéral (dans les névralgies pudendales).
- c. Utilisation d'une nouvelle bobine angulaire stimulant plus profondément (B70).
- d. Comparaison de l'effet antalgique de la stimulation superficielle (B65) versus une stimulation plus profonde (B70).
- e. Comparaison de protocoles de stimulations rTMS vraies versus placebo.

### **3.1.2. La stimulation transcrânienne par courant continu (tDCS)**

L'utilisation de la tDCS comme thérapeutique antalgique dans la douleur chronique a fourni des résultats encourageants. La tDCS constitue une éventuelle alternative à la rTMS, séduisante par sa simplicité d'utilisation, son innocuité, son faible coût et les perspectives de développement d'un appareil utilisable à domicile.

#### **Problématiques**

Les données actuelles de la littérature, ne permettent pas d'affirmer, avec un niveau de preuve satisfaisant, l'efficacité de la tDCS dans les douleurs chroniques. Dans la littérature il y a très peu d'études comparant l'efficacité de la tDCS versus rTMS.

#### **Objectifs**

Etudes contrôlées versus placebo pour évaluer l'efficacité de la tDCS à long terme.

Etudes comparatives de l'efficacité des deux techniques (tDCS et rTMS).

### **3.1.3. La stimulation trans-spineale par courant continu (tsDCS)**

La stimulation médullaire électrique implantée est utilisée depuis plus de 40 ans pour traiter une variété de syndromes douloureux. Par analogie, une approche de neuromodulation non-invasive a été récemment développée : la tsDCS. Cette technique pourrait être particulièrement appliquée dans la prise en charge des douleurs chroniques neuropathiques périphériques.

#### **Problématiques**

A ce jour, les études cliniques sur l'efficacité antalgique de la tsDCS sont peu nombreuses et explorent principalement les modifications physiologiques générées chez des sujets sains.

#### **Objectifs**

Etudes de l'effet antalgique de la tsDCS et comparaison avec les méthodes de référence de stimulation non-invasive du cortex moteur : la rTMS et la tDCS.

### **3.1.4. Implication des dysautonomies dans les syndromes douloureux chroniques**

Depuis quelques années, les mécanismes de certains syndromes douloureux chroniques se précisent et un intérêt particulier est porté aux dysfonctionnements rapportés aux petites fibres nerveuses A-delta et C. Ces fibres sont peu ou pas myélinisées et jouent un rôle primordial dans

la transmission de la sensibilité thermo-algique et dans le fonctionnement du système nerveux autonome. Leurs dysfonctionnements peuvent s'intégrer dans le cadre d'une neuropathie des petites fibres et leur exploration ouvre de nouvelles perspectives tant pour la compréhension que pour le traitement de ces phénomènes de douleurs périphériques.

### **Problématiques**

La biopsie cutanée est aujourd'hui l'un des piliers du diagnostic de la neuropathie des petites fibres. Cette technique n'est cependant pas disponible à grande échelle et est invasive ne peut donc pas être réalisée systématiquement pour un suivi longitudinal. D'autre part la biopsie explore principalement les anomalies structurelles (perte en fibres) mais non fonctionnelles des petites fibres.

### **Objectifs**

Evaluer l'atteinte du système autonome sympathique et de la neuropathie des petites fibres par la technique de Sudoscan<sup>®</sup> de mesure des conductances électrochimiques cutanées, qui est simple, rapide, non-invasive et reproductible.

Evaluer notamment la dysfonction sympathique des membres dans le cadre du syndrome douloureux régional complexe (algoneurodystrophie) et son rapport avec la présence de douleurs neuropathiques chroniques latéralisées. Etudier l'évolution de ces anomalies chez des patients traités par des techniques de neuromodulation non-invasive.

## **3.2. Volet neuroimagerie**

L'IRM s'avère comme un outil très intéressant dans l'exploration de la douleur chronique permettant l'étude des modifications de la plasticité cérébrale et des réseaux impliqués dans la douleur chronique.

### **Problématiques**

Les mécanismes d'action de la rTMS et de la tDCS ne sont pas bien connus, particulièrement leurs modifications induites au niveau cérébral. A notre connaissance, il n'y a aucune étude IRMf sur les modifications de plasticité ou de perfusion cérébrale induite à long terme par les techniques de neuromodulation non-invasive.



Concernant la cible corticale à stimuler : sa détermination est praticien-dépendant, même en utilisant l'IRM anatomique (3D), et les modifications de la plasticité cérébrale (post-AVC, etc.) peuvent être sources d'imprécision.

### **Objectifs**

- a. Etudier et comparer, au moyen de l'IRMf, les modifications de cartographie sensori-motrice éventuellement induites par la tDCS et par la rTMS à court terme et par la rTMS à long terme.
- b. Explorer les modifications centrales de perfusion cérébrale à l'état basal (en pré-cure rTMS) qui pourraient être en lien avec les douleurs neuropathiques et en post-cure rTMS.
- c. Déterminer avec précision la zone corticale à stimuler au moyen de l'IRM 3D (anatomique) et de l'IRMf (fonctionnelle).
- d. Etude des éventuelles modifications cérébrales (IRMf) et de la conductance cutanée (Sudoscans<sup>®</sup>) induites par la rTMS et leurs corrélations.

## 4. RECAPITULATIF DE THEMATIQUES ET RESULTATS

### PUBLICATIONS

#### *I. Volet RTMS, tDCS et tsDCS*

##### *A. Etudes sur l'efficacité antalgique à long terme de la rTMS en pratique clinique*

**Article 1** : Hodaj H, Payen JF, Dumolard A, Delon-Martin Ch, Lefaucheur JF. Treatment of pudendal neuralgia by high-frequency rTMS of the medial wall of motor cortex bilaterally using an angled figure-of-eight coil. **Brain Stimulation**, 2020; 13:1412-1413.

**Article 2** : Hodaj H, Payen JF, Hodaj E, Dumolard A, Maindet C, Cracowski JL, Delon-Martin Ch, Lefaucheur JP. Long-term treatment of chronic orofacial, pudendal, and central neuropathic limb pain with repetitive transcranial magnetic stimulation of the motor cortex. **Clinical Neurophysiology**, 2020 ; 131 :1423-1432.

##### *B. Comparaison de l'effet antalgique de la stimulation du cortex moteur par la rTMS versus tDCS : protocole de recherche « Doloris »*

**Article 3** : André-Obadia N, Hodaj H, Hodaj E, Simon E, Delon-Martin C, Garcia-Larrea L. Better fields or currents? A head-to-head comparison of Transcranial Magnetic (rTMS) versus Direct Current Stimulation (tDCS). **Neurotherapeutics** 2022; doi: 10.1007/s13311-022-01303.

##### *C. Recherche fondamentale sur la tDCS : stimulation vraie versus placebo. Protocole de recherche Medis.*

**Article 4** : Hodaj H, Payen JF, Mick G, Vercueil L, Hodaj E, Dumolard A, Noëlle B, Delon-Martin C, Lefaucheur JF. Long-term Prophylactic Efficacy of Transcranial Direct Current Stimulation in Chronic Migraine. A randomised, patient-assessor blinded, sham-controlled trial. **Brain Stimulation**, 2022; 15: 441-553

##### *D. Comparaison de l'effet antalgique de la stimulation trans-spinale (tsDCS) et de la stimulation non invasive du cortex moteur (rTMS et tDCS) : protocole de recherche « Algostim ».*

**Article 5** : Hodaj H, Payen JF, Hodaj E, Sorel M, Dumolard A, Vercueil L, Delon-Martin C, Lefaucheur JP. Long-term analgesic effect of trans-spinal direct current stimulation (tsDCS) compared to non-invasive motor cortex stimulation (rTMS and tDCS) in complex regional pain syndrome. A randomized, controlled study. **Article soumis**, octobre 2022

#### *II- Volet neuro-imagerie*

**A. Ciblage du cortex moteur et recherche d'un algorithme de localisation des 3 cibles anatomiques (IRM 3 D) : Membre supérieur, membre inférieur, face.**

**Article 6** : Lefaucheur JP, Nguyen JP, Delmas A, Croci C, Luc Bredoux L, Hodaj H. Targeting lower limb, upper limb, and face representation in the primary motor cortex for the practice of neuronavigated TMS. **Article soumis**, decembre 2022.

**B. Analyse, au moyen de l'IRMf, des modifications éventuelles cérébrales induites par la rTMS à long terme.**

**Article 7**: Delon-Martin Ch, Lefaucheur JP, Hodaj E, Sorel M, Dumolard A, Payen JF, Hodaj H. Role of S1 in pain-autonomic coupling and the analgesic effect of motor cortex rTMS in complex regional pain syndrome (CRPS). **Article soumis**, decembre 2022.

**PROJET DE RECHERCHE EN COURS**

**I. Recherche fondamentale sur la rTMS : Protocole « Neurostim »**

Etude randomisée en double aveugle de l'effet antalgique de la rTMS dans le traitement des douleurs neuropathiques chroniques : stimulation du cortex moteur superficielle, profonde et placebo. Analyse des modifications cérébrales induites, au moyen de l'IRMf.

**II. Etude préliminaires des données de l'IRMf pré-cure.**

## 5. PUBLICATIONS

### 5.1. Long-term treatment of chronic orofacial, pudendal, and central neuropathic limb pain with repetitive transcranial magnetic stimulation of the motor cortex.



Clinical Neurophysiology  
Volume 131, Issue 7, July 2020, Pages 1423-1432



## Long-term treatment of chronic orofacial, pudendal, and central neuropathic limb pain with repetitive transcranial magnetic stimulation of the motor cortex

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Accepted 6 March 2020, Available online 10 April 2020, Version of Record 6 May 2020.

**Long-term treatment of chronic orofacial, pudendal, and central neuropathic limb pain with repetitive transcranial magnetic stimulation of the motor cortex**

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**Running title:** *Long-term rTMS treatment of chronic pain*

## **Abstract**

*Objective:* To assess the long-term analgesic effects of high-frequency repetitive transcranial magnetic stimulation (rTMS) of the motor cortex in patients with chronic pain syndrome.

*Methods:* The study included 57 patients (orofacial pain, n=26, pudendal neuralgia, n=18, and neuropathic limb pain, n=13) with an "induction phase" of 12 daily rTMS sessions for 3 weeks, followed by a "maintenance phase" of bi-monthly sessions for the next five months.

*Results:* All pain measures significantly decreased from baseline to the end of the induction phase. Analgesic response, defined as pain intensity decrease  $\geq 30\%$  compared to baseline, was observed in 39 patients (68%), who could be differentiated from non-responders from the 7th rTMS session. At the end of the maintenance phase (D180), 27 patients (47%) were still responders. Anxio-depressive symptoms and quality of life also improved. The analgesic response at the end of the induction phase was associated with lower pain score at baseline, and the response at the end of the maintenance phase was associated with lower anxio-depressive score at baseline.

*Conclusion:* The analgesic efficacy of motor cortex rTMS can be maintained in the long term in various chronic pain conditions. Patients with high pain level and severe anxio-depressive symptoms may have a less favorable profile to respond to the procedure.

*Significance:* The overall impact of rTMS treatment on daily life requires a multidimensional evaluation that goes beyond the analgesic effect that can be achieved.

**Keywords:** chronic pain; facial pain; long-term; neuropathic pain; predictive factor; pudendal neuralgia; rTMS treatment.

## **1. Introduction**

Repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex (M1) is increasingly used to treat various types of chronic refractory pain. Meta-analyses of the literature argued for the efficacy of rTMS of M1 at high frequency ( $\geq 5$  Hz), especially in neuropathic pain (Jin et al., 2015; Cruccu et al., 2016; Baptista et al., 2019). The main neuromodulatory property of rTMS relies on its prolonged effects lasting beyond the stimulation period, but rTMS sessions need to be repeated to achieve sufficient pain relief consistent with therapeutic use in clinical practice (Lefaucheur et al., 2004a). However, most published studies are short-term and only 4 studies reported the results of motor cortex rTMS therapy performed for at least 6 months. These studies included 80 patients with central neuropathic pain of various origins (Pommier et al., 2016; Quesada et al., 2018), 55 patients with facial pain (Hodaj et al., 2015), 20 patients with fibromyalgia (Mhalla et al., 2011), and 18 patients with central poststroke pain (Kobayashi et al., 2015) who received verum rTMS. Overall, motor cortex rTMS was found to be beneficial in these patients with refractory chronic pain syndrome.

The objective of this work was to reappraise the long-term efficacy of rTMS therapy in clinical settings for three types of chronic pain syndrome, i.e. orofacial pain, pudendal neuralgia, and neuropathic limb pain. We studied the analgesic effects of rTMS during an initial induction phase and the maintenance of its efficacy in responders by means of bi-monthly sessions for 6 months. In addition, using multidimensional assessment tools, we looked for predictive factors that could influence the therapeutic response to rTMS in the short and long term.

## **2. Methods**

### ***2.1. Patients***

This observational study included 57 consecutive patients (21 men and 36 women) treated by rTMS between March 2014 and April 2018 in the Pain Center of Grenoble University Hospital, France. The patients were classified into three groups according to the type of pain: orofacial pain (26 patients), pudendal neuralgia (18 patients), and central neuropathic limb pain (13 patients). All patients had chronic pain refractory to conventional therapies for more than a year. At the time of inclusion, current analgesic medication included anticonvulsants (68% of patients), antidepressants (77%), and opioids (58%).

Orofacial pain was related to a definite lesion of the trigeminal nerve or nucleus in 8 patients, secondary to a neurosurgical procedure (Gasser's ganglion thermocoagulation (n=2), microvascular decompression (n=2), neurinoma surgery (n=1)) or an infectious or

inflammatory process (herpes zoster (n=2), multiple sclerosis (n=1)). In 12 patients, orofacial pain was of undetermined cause, including 6 patients with persistent idiopathic facial pain (PIFP), in a context of dental intervention (n=5) and facial trauma (n=1), and 6 patients with burning mouth syndrome (BMS), according to the most recent International Classification of Headache Disorders (Headache Classification Committee of the International Headache Society (IHS), 2018). In patients with orofacial pain, the analgesic response was further analyzed into two subgroups: facial pain and BMS, given the specificities of this syndrome (Ariyawardana et al., 2019).

Pudendal neuralgia was diagnosed in 18 patients according to validated clinical criteria (Labat et al., 2008), confirmed by positive anesthetic pudendal nerve block in 14 patients. In 7 of these patients, pain was persistent despite previous surgical decompression of the pudendal nerve.

Central limb neuropathic pain was secondary to a definite lesion of the brain in 5 patients (brain surgery (n=2), trauma (n=1), stroke (n=1), multiple sclerosis (n=1)) or the spinal cord in 5 patients (spinal stroke (n=4), syringomyelia (n=1)). In two patients, upper limb pain was secondary to brachial plexus avulsion. The last patient had lower limb pain secondary to amputation (phantom limb pain).

## ***2.2. rTMS procedure***

Stimulation was performed using a MagPro stimulator (MagVenture (distr. Mag2Health), Farum, Denmark) using either a flat B65 coil (MagVenture) in patients with orofacial, upper limb or hemibody pain or an angled B70 figure-of-eight coil (MagVenture) in patients with lower limb or pudendal pain.

First, the resting motor threshold (rMT) was determined as the minimum stimulus intensity that produced a motor evoked potential (MEP) of about 50  $\mu$ V in at least 5 of 10 trials (Rossini et al., 2015). For this measurement, the MEP monitor amplifier of the MagPro stimulator was used. When a B65 coil was applied, the MEPs were recorded in all cases on the abductor pollicis brevis (APB) muscle with the coil oriented perpendicular to the central sulcus. When a B70 coil was applied, the MEPs were recorded on the tibialis anterior (TA) muscle with the coil aligned to the interhemispheric fissure. However, if no MEPs could be obtained on the TA muscle, then they were recorded on the APB muscle, still with the B70 coil.

For therapeutic stimulation, the motor cortical representation of the painful region was targeted with the coil held in posteroanterior orientation. In patients with orofacial pain, upper limb or hemibody pain, a flat B65 figure-of-eight coil was used and the site of cortical stimulation was determined using a TMS Navigator system, integrating individual brain magnetic resonance



imaging (MRI) data (Localite, Sankt Augustin, Germany). Targeting was performed according to the previously described functional anatomy of the precentral gyrus (Ayache et al., 2016). For hemibody pain, the hand area was targeted.

In patients with pudendal neuralgia or lower limb pain, an angled B70 figure-of-eight coil was used (Hodaj et al., 2018) and the site of cortical stimulation was fixed at the vertex (Cz in the International 10–20 system). Compared to flat figure-of-eight coils, the B70 coil is more powerful, leading to lower the resting motor threshold (rMT) by 10 to 33% (Kammer et al., 2001). In addition, the B70 stimulates deeper and larger, able to bilaterally activate the motor cortex corresponding to pelvic-perineal and lower limb muscles when placed at the vertex due to its angle of 150°, without requiring an image-guided navigation system for targeting.

Stimulation was performed at 10 Hz with an intensity set at 80% of the rMT. Each rTMS session consisted of 40 trains of 5-sec duration with intertrain interval of 25 sec for a total of 2,000 pulses in 20 minutes. This protocol is in conformity with the expert recommendations for safety (Rossi et al., 2009; Lefaucheur et al., 2011). In all cases, the rTMS treatment protocol was initiated after the agreement of a multidisciplinary team meeting and the informed consent of the patient.

### ***2.3. Clinical evaluation***

The rTMS protocol consisted of an induction phase of one session per day for five days during two consecutive weeks (weeks 1 and 2), then 2 sessions in the next week (week 3) for a total of 12 sessions. Average daily permanent pain and paroxysmal pain intensities were scored on a 0-10 visual numerical scale (VNS) and the number of painful paroxysms was recorded before rTMS therapy (D0), and the day after each session up to the end of the induction phase (D21). Then, in patients with analgesic response, defined as a decrease in the VNS score of permanent pain  $\geq 30\%$  compared to baseline, a maintenance therapy was undertaken, consisting of one rTMS session in week 4 and then bi-monthly sessions for the next five months, for a total of 11 sessions. During the maintenance phase, pain scores were recorded on a VNS the day after each session and the rTMS therapy was stopped if pain score reduction became  $<30\%$  compared to baseline.

In patients who completed the study, a multidimensional assessment was performed in addition to pain scores at the end of the maintenance phase (D180), including the Neuropathic Pain Symptom Inventory (NPSI) total score and subscores (Bouhassira et al., 2004) assessing the symptomatic pain profile (used in this study for both neuropathic and non-neuropathic pain, although "non-validated" in the latter indication), the Hospital Anxiety and Depression (HAD)

scale (Zigmond and Snaith, 1983) assessing anxiety and depression, and the Physical and Mental Component Summaries (PCS, MCS) of the Short Form (36) Health Survey (SF-36) (Ware and Sherbourne, 1992) assessing the quality of life, scored with the RAND 36-Item Health Survey 1.0 (Hays et al., 1993). Finally, patients self-assessed the global effect of rTMS therapy at D180 on the Clinical Global Impression (CGI) scale (Busner and Targum, 2007).

#### ***2.4. Statistical analysis***

Data are presented as mean  $\pm$  standard deviation (SD). The significance level of p value was set at 0.05. Statistical analyses were performed using the Stata 13.0 software (StataCorp, College Station, Texas, USA). Parametric or non-parametric tests were used depending on whether the data had a normal distribution or not, as shown by the Shapiro–Wilk test.

First, analyses on baseline data were performed according to the origin of pain: orofacial pain, limb neuropathic pain, and pudendal neuralgia. Kruskal-Wallis or one-way ANOVA test was used for quantitative variables (age, pain syndrome duration, VNS scores of permanent and paroxysmal pain, daily number of pain paroxysms, and NPSI, HAD, and SF-36 PCS and MCS scores) and Fisher's exact test for categorical variables (gender, medications).

Second, the effect of rTMS on pain scores (VNS scores of permanent and paroxysmal pain and daily number of pain paroxysms) was studied in the entire series of patients using repeated-measures ANOVA with Bonferroni's post-hoc test for comparisons to baseline. In addition, the scores measured at the end of the induction phase (D21) were compared to baseline in the entire series of patients and each of the three subgroups defined by the origin of pain using the Wilcoxon matched-pairs test.

According to the percentage of reduction of the VNS score of permanent pain, patients were classified into four groups (Hodaj et al., 2015): very good response (for pain reduction  $\geq 70\%$  on VNS score), good response (pain reduction from 50% to 69%), moderate response (pain reduction from 30% to 49%), and poor or no response (pain reduction  $< 30\%$ ). Overall, responders were defined by a decrease in this pain score  $\geq 30\%$  compared to baseline. The groups of responders and non-responders were compared using unpaired t test or Mann-Whitney-Wilcoxon rank-sum test (quantitative variables) or Fisher's exact test (categorical variables) regarding the following variables: age, gender, pain syndrome duration, pain origin, location (face, perineum, upper or lower limb) or side (bihemispheric, right- or left-sided) of the stimulated cortical target, rMT, current analgesic medication (anticonvulsants or not, and antidepressants or not, and opioids or not), the various clinical scores measured at baseline (VNS, NPSI, HAD, and SF-36 scores) and the VNS scores at the end of the induction phase.

From the VNS scores of permanent pain recorded after each of session of the induction phase, repeated-measures ANOVA was performed, which was based on an interaction model between responders/non-responders and time. The objective of this analysis was to determine whether the time course of pain scores differed between responders and non-responders, and if so from which time point.

Third, in the patients who completed the study, excluding the patients who relapsed during the maintenance phase, the effect of rTMS on pain scores (VNS scores of permanent and paroxysmal pain and daily number of pain paroxysms) was studied using repeated-measures ANOVA. In addition, the pain scores (VNS scores of permanent and paroxysmal pain and daily number of pain paroxysms) measured at the end of the maintenance phase (D180) were compared to those measured at the end of the induction phase (D21) and to baseline using the Wilcoxon matched-pairs test in the entire series of patients and in each of the three subgroups defined by the origin of pain. The other clinical scores (NPSI, HAD, and SF-36 scores) measured at D180 were compared to baseline also using the Wilcoxon matched-pairs test in the entire series of patients.

The groups of responders and relapsing patients were compared using unpaired t test or Mann-Whitney-Wilcoxon rank-sum test (quantitative variables) or Fisher's exact test (categorical variables) regarding the same demographic and clinical variables as between responders and non-responders at the end of the induction phase. Finally, the association between patients' CGI and status in terms of responders or non-responders was studied using the Fisher's exact test.

### **3. Results**

#### ***3.1. Differences in baseline characteristics between groups according to pain origin***

Demographic and baseline data are presented in Table 1. The mean ( $\pm$  SD) age of the patients was  $62.2 \pm 15.0$  years and did not differ between groups, as well as mean pain syndrome duration. Conversely, there were gender differences between groups: a majority of women was found in the cases of pudendal neuralgia and orofacial pain (72-73%), but not in the case of neuropathic limb pain (31%). In terms of treatment, the groups differed on opioid intake, which was less frequent in orofacial pain (42%) than in pudendal neuralgia and neuropathic limb pain (67-77%). In terms of clinical scores, the groups differed on physical functioning (SF36), which was lower in neuropathic limb pain ( $35.6 \pm 30.2$ ) than in orofacial pain ( $66.8 \pm 27.5$ ) and pudendal neuralgia ( $61.6 \pm 17.7$ ). No other significant differences between groups according to pain origin were found.

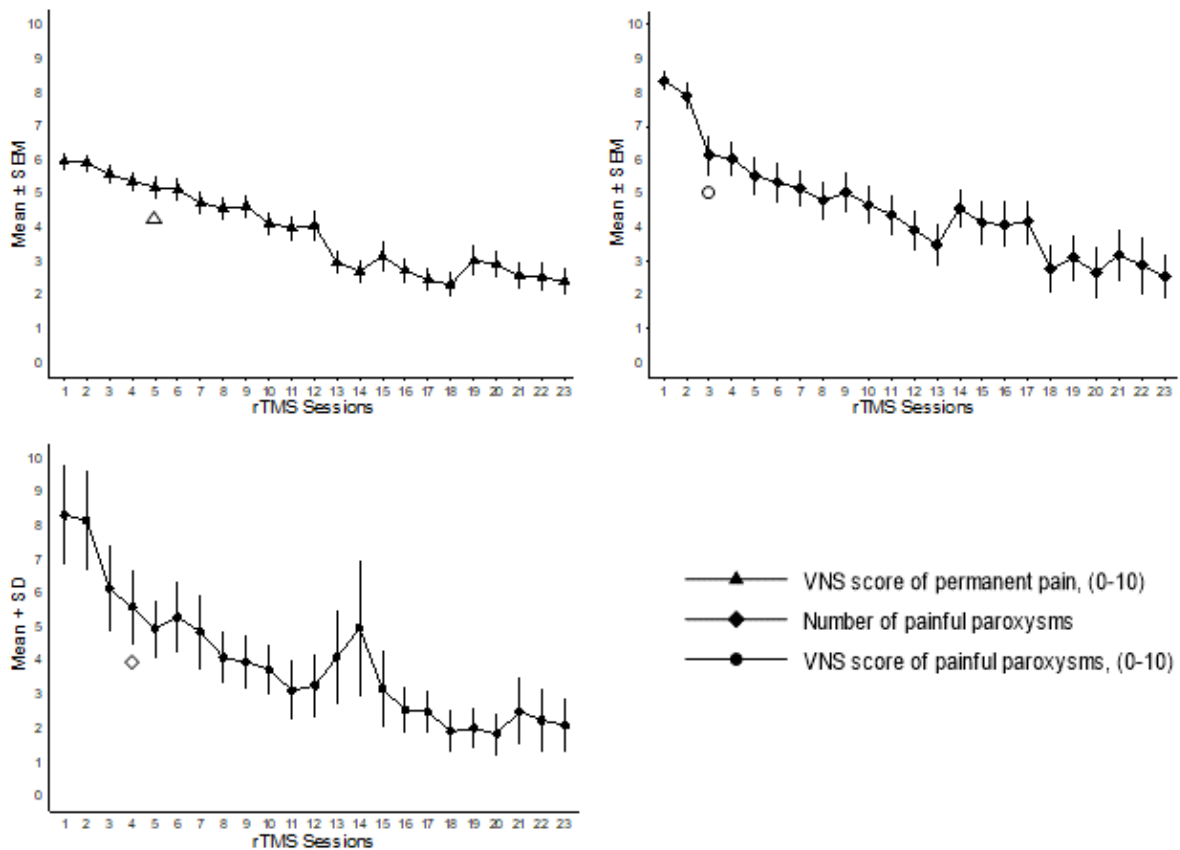
**Table 1.** Demographic and baseline data according to pain origin and in the entire series of patients

	Orofacial pain (n=26)	Neuropathic limb pain (n=13)	Pudendal neuralgia (n=18)	P	All patients (n=57)
Age, years	65.8 ± 14.0	57.7 ± 15.1	60.4 ± 15.9	0.237 <sup>¥</sup>	62.2 ± 15.0
Sex, women n (%)	19 (73.1)	4 (30.8)	13 (72.2)	0.028 <sup>†</sup>	36 (63.2)
Pain syndrome duration, months	87.5 ± 72.1	116.8 ± 166.5	94 ± 64.7	0.716 <sup>§</sup>	96.2 ± 98.3
Prior interventional gesture, Yes n (%)	9 (34.6)	2 (15.4)	15 (83.3)	0.000 <sup>†</sup>	26 (45.6)
Anticonvulsants, Yes n (%)	20 (76.9)	8 (61.5)	11 (61.1)	0.468 <sup>†</sup>	39 (68.4)
Antidepressants, Yes n (%)	23 (88.5)	10 (76.9)	11 (61.1)	0.112 <sup>†</sup>	44 (77.2)
Opioids, Yes n (%)	11 (42.3)	10 (76.9)	12 (66.7)	0.009 <sup>†</sup>	33 (57.9)
Permanent pain, VNS score (0-10)	6.0 ± 2.0	6.6 ± 2.0	5.4 ± 1.7	0.270 <sup>¥</sup>	6.0 ± 1.9
Painful paroxysms, number of patients	13	4	12		29
Painful paroxysms, number per day	7.3 ± 4.9	19.6 ± 15.7	5.7 ± 2.8	0.311 <sup>§</sup>	8.3 ± 7.9
Painful paroxysms, VNS score (0-10)	8.6 ± 1.4	8.6 ± 0.5	8.0 ± 1.6	0.448 <sup>§</sup>	8.4 ± 1.4
NPSI – Total score (/100)	32.9 ± 18.2	39.7 ± 16.8	42.4 ± 23.7	0.373 <sup>¥</sup>	36.5 ± 19.3
NPSI – Burning spontaneous pain (/10)	5.3 ± 3.3	6.0 ± 3.1	4.7 ± 3.4	0.692 <sup>¥</sup>	5.3 ± 3.2
NPSI – Pressing spontaneous pain (/10)	2.6 ± 3.1	4.1 ± 2.8	4.7 ± 2.7	0.119 <sup>¥</sup>	3.4 ± 3.1
NPSI – Paroxysmal pain (/10)	3.6 ± 2.8	3.7 ± 3.1	4.5 ± 3.6	0.718 <sup>¥</sup>	3.9 ± 3.0
NPSI – Evoked pain (/10)	3.9 ± 2.5	3.9 ± 3.7	4.8 ± 3.3	0.709 <sup>¥</sup>	4.1 ± 2.9
NPSI – Paresthesia/dysesthesia (/10)	2.5 ± 2.7	3.1 ± 3.3	4.7 ± 4.0	0.199 <sup>¥</sup>	3.1 ± 3.2
HAD – Total score (/42)	15.2 ± 8.8	18.1 ± 10.3	18.7 ± 5.5	0.344 <sup>¥</sup>	17.0 ± 8.2
HAD – Anxiety (/21)	7.9 ± 4.8	8.7 ± 5.1	10.3 ± 3.2	0.205 <sup>¥</sup>	8.9 ± 4.5
HAD – Depression (/21)	7.3 ± 4.9	9.4 ± 6.0	8.3 ± 3.5	0.464 <sup>¥</sup>	8.0 ± 4.7
SF-36 – Physical component score (/100)	41.1 ± 17.4	29.6 ± 18.9	34.8 ± 5.4	0.057 <sup>§</sup>	37.3 ± 15.8
SF-36 – Mental component score (/100)	45.7 ± 23.1	45.7 ± 24.4	40.4 ± 24.1	0.853 <sup>§</sup>	44.3 ± 23.2
SF-36 – Physical functioning (/100)	66.8 ± 27.5	35.6 ± 30.2	61.6 ± 17.7	0.039 <sup>§</sup>	59.9 ± 27.7
SF-36 – Role physical (/100)	24.0 ± 31.8	15.6 ± 35.2	12.5 ± 19.9	0.548 <sup>§</sup>	19.4 ± 29.6
SF-36 – Bodily pain (/100)	23.8 ± 23.1	16.5 ± 16.2	16.3 ± 10.9	0.765 <sup>§</sup>	20.5 ± 19.4
SF-36 – General health (/100)	49.7 ± 7.5	50.5 ± 9.8	48.6 ± 7.2	0.751 <sup>§</sup>	49.5 ± 7.7
SF-36 – Vitality (/100)	34.8 ± 19.1	31.9 ± 25.2	32.8 ± 24.7	0.821 <sup>§</sup>	33.7 ± 21.3
SF-36 – Social functioning (/100)	54.0 ± 26.7	51.6 ± 27.9	49.0 ± 34.3	0.976 <sup>§</sup>	52.2 ± 28.5
SF-36 – Role emotional (/100)	38.7 ± 42.7	45.8 ± 46.9	30.3 ± 37.9	0.820 <sup>§</sup>	37.9 ± 41.7
SF-36 – Mental health (/100)	55.2 ± 23.4	53.5 ± 20.2	51.8 ± 25.4	0.946 <sup>§</sup>	54.0 ± 22.9

NPSI: Neuropathic Pain Symptom Inventory, HAD: Hospital Anxiety and Depression scale, SF-36: Short Form (36) Health Survey. Quantitative variables are presented as mean±SD. ¥ one-way ANOVA; §: Kruskal-Wallis test; †: Fisher's exact test

### 3.2. Analgesic effect at the end of the induction phase

The rTMS protocol was well tolerated by all patients, without any report of serious adverse events. All pain measures significantly decreased over time during the induction phase ( $p < 0.0001$ , repeated-measures ANOVA) (Figure 1).



**Figure 1.** Time course of the effect of rTMS therapy on the various pain scores during the induction phase in the entire series of patients. Mean values (with standard error bars),  $P < 0.005$ , Bonferroni's post-hoc test compared to baseline:  $\Delta$  from the 5th session for the VNS score of permanent pain,  $\circ$  from the 3rd session for the VNS score of painful paroxysms,  $\diamond$  from the 4th session for the daily number of painful paroxysms.

Compared to baseline, all scores significantly improved at D21 ( $p < 0.0001$ , Wilcoxon matched-pairs or paired t-test): (i) the VNS score of permanent pain (from  $6.0 \pm 1.9$  to  $4.1 \pm 2.9$ ); (ii) the number of painful paroxysms per day (from  $8.3 \pm 7.8$  to  $3.3 \pm 4.5$ ); (iii) the VNS score of painful paroxysms (from  $8.4 \pm 1.4$  to  $3.9 \pm 2.7$ ). Regarding the type of pain, the VNS score of permanent pain significantly decreased from baseline to the end of the induction phase for orofacial pain (from  $6.0 \pm 2.0$  to  $3.7 \pm 2.9$ ,  $p < 0.0001$ , paired t-test), limb neuropathic pain (from  $7.0 \pm 1.6$  to  $5.3 \pm 2.8$ ,  $p = 0.013$ ), and pudendal neuralgia (from  $5.4 \pm 1.9$  to  $3.7 \pm 3.0$ ,  $p = 0.013$ ).

According to the percentage of reduction of the VNS score of permanent pain, analgesic response was considered very good in 12 patients (21%), good in 8 patients (14%), moderate in 19 patients (33%), and poor in 18 patients (32%) (Table 2a).

**Table 2.** Response rate according to the origin of pain

a) At the end of the induction					
	Responders			Non-responders	
	Very good response	Good response	Moderate response		
Orofacial pain (n = 26)	6	7	5		8
Facial pain (n = 20)	6	6	4		4
Burning mouth syndrome (n =6)	0	1	1		4
Neuropathic limb pain (n = 13)	2	1	6		4
Pudendal neuralgia (n = 18)	4	0	8		6
Entire series of patients (n = 57)	12	8	19		18
b) At the end of the maintenance phase					
	Responders			Relapsing patients	Lost to follow-up
	Very good response	Good response	Moderate response		
Orofacial pain (n = 18)	8	3	4	2	1
Facial pain (n = 16)	8	2	3	2	1
Burning mouth syndrome (n =2)	0	1	1	0	0
Neuropathic limb pain (n = 9)	1	2	3	3	0
Pudendal neuralgia (n = 12)	1	3	2	5	1
Entire series of responders at the end of induction phase (n = 37)	10	8	9	10	2

Very good response: pain reduction  $\geq 70\%$ ; good response: pain reduction from 50% to 69%; moderate response: pain reduction from 30% to 49%; poor or no response: pain reduction  $< 30\%$ .

Thus, a total of 39 responders (68%) vs. 18 non-responders (32%) was found. Obviously, the VNS score of permanent pain at D21 was extremely different between these two groups ( $2.9 \pm 2.3$  vs.  $7.6 \pm 1.5$ ,  $p < 0.0001$ , unpaired t-test), as well as the VNS score of painful paroxysms ( $4.0 \pm 2.7$  vs.  $8.7 \pm 1.3$ ,  $p = 0.008$ , Mann-Whitney-Wilcoxon test), but not the number of painful paroxysms per day ( $3.4 \pm 4.5$  vs.  $4.5 \pm 2.2$ ,  $p = 0.217$ ).

No difference in terms of analgesic response at the end of the induction phase was found according to age, sex, symptom duration, location or side of the stimulated cortical target, rMT, current analgesic medication, or paroxysmal pain features, and NPSI (total score and 4/5 subscores), HAD, or SF-36 scores at baseline (Table 3). Conversely, there was an influence of the VNS score of permanent pain at baseline, which was significantly lower in responders than

in non-responders ( $5.5 \pm 1.9$  vs.  $7.0 \pm 1.4$ ,  $p=0.005$ ) as well as the NPSI subscore concerning the "burning spontaneous pain" ( $4.3 \pm 3.2$  vs.  $7.5 \pm 1.8$ ,  $p=0.002$ ) (Table 3).

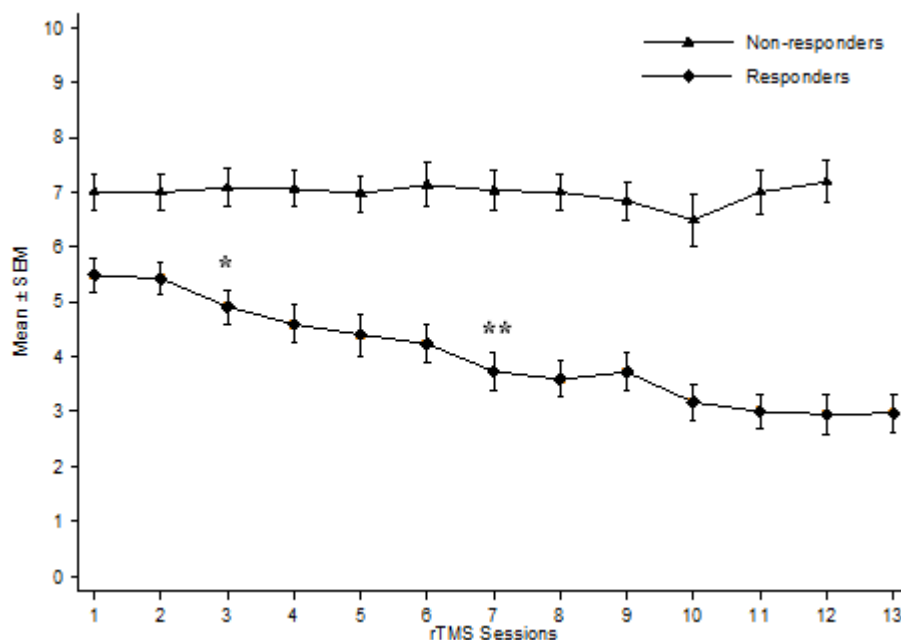
**Table 3.** Demographic and baseline data according to rTMS outcome at the end of the induction phase.

	<b>Responders (n=39)</b>	<b>Non-responders (n=18)</b>	<b>P</b>
Age, years	61.4 ± 15.6	64.1 ± 13.8	0.540 <sup>¥</sup>
Sex, women n (%)	23 (59.0)	13 (72.2)	0.389 <sup>†</sup>
Pain syndrome duration, months	101.4 ± 111.1	85 ± 63.8	0.823 <sup>§</sup>
<i>Pain origin, n (%)</i>			0.981 <sup>†</sup>
Orofacial pain	18 (69.2)	8 (30.8)	
Neuropathic limb pain	9 (69.2)	4 (30.8)	
Pudendal neuralgia	12 (66.7)	6 (33.3)	
<i>Motor cortex target, n (%)</i>			0.835 <sup>†</sup>
Face area	18 (46.1)	8 (44.4)	
Hand area	5 (12.8)	1 (5.6)	
Leg area	4 (10.3)	3 (16.7)	
Perineal area	12 (30.8)	6 (33.3)	
<i>Stimulation side, n (%)</i>			0.973 <sup>†</sup>
Bi-hemispherical	14 (35.9)	7 (38.9)	
Right hemisphere	14 (35.9)	6 (33.3)	
Left hemisphere	11 (28.2)	5 (27.8)	
rMT (%)	51.0 ± 9.8	48.3 ± 7.6	0.307 <sup>¥</sup>
Anticonvulsants, Yes n (%)	29 (74.4)	10 (55.6)	0.156 <sup>†</sup>
Antidepressants, Yes n (%)	28 (71.8)	16 (88.9)	0.191 <sup>†</sup>
Opioids, Yes n (%)	24 (61.5)	9 (50.0)	0.412 <sup>†</sup>
Permanent pain, VNS score (0-10)	5.5 ± 1.9	7.0 ± 1.4	0.005 <sup>¥</sup>
Painful paroxysms, number of patients	25	4	
Painful paroxysms, number per day	8.9 ± 8.3	4.4 ± 2.2	0.427 <sup>§</sup>
Painful paroxysms, VNS score (0-10)	8.4 ± 1.5	8.1 ± 0.7	0.676 <sup>§</sup>
NPSI – Total score (/100)	35.1 ± 19.0	39.7 ± 20.5	0.484 <sup>¥</sup>
NPSI – Burning spontaneous pain (/10)	4.3 ± 3.2	7.5 ± 1.8	0.002 <sup>¥</sup>
NPSI – Pressing spontaneous pain (/10)	3.3 ± 2.9	3.7 ± 3.4	0.680 <sup>¥</sup>
NPSI – Paroxysmal pain (/10)	4.1 ± 2.8	3.2 ± 3.5	0.345 <sup>¥</sup>
NPSI – Evoked pain (/10)	4.2 ± 2.8	3.8 ± 3.3	0.672 <sup>¥</sup>
NPSI – Paresthesia/dysesthesia (/10)	2.9 ± 3.1	3.5 ± 3.4	0.587 <sup>¥</sup>
HAD – Total score (/42)	16.7 ± 8.5	17.3 ± 7.9	0.799 <sup>¥</sup>
HAD – Anxiety (/21)	8.8 ± 4.5	9.1 ± 4.5	0.785 <sup>¥</sup>
HAD – Depression (/21)	8.0 ± 5.0	8.2 ± 4.4	0.852 <sup>¥</sup>
SF-36 – Physical component score (/100)	37.1 ± 14.6	37.8 ± 18.9	0.797 <sup>§</sup>
SF-36 – Mental component score (/100)	45.8 ± 24.9	40.9 ± 19.2	0.455 <sup>§</sup>

NPSI: Neuropathic Pain Symptom Inventory, HAD: Hospital Anxiety and Depression scale, SF-36: Short Form (36) Health Survey. Quantitative variables are presented as mean±SD. ¥ unpaired t-test, § Mann-Whitney-Wilcoxon rank-sum test, † Fisher's exact test

Regarding the type of pain, a lower rate of responders was observed in the patients with BMS (33%) than in patients with other facial pain (80%), limb neuropathic pain (69%), or pudendal neuralgia (67%) (Table 2a).

Finally, repeated-measures ANOVA showed a significant interaction between patient's status (responders vs. non-responders) and time. The post-hoc analyses showed a significant decrease of permanent pain intensity over time only in responder group ( $p < 0.0001$ ). In this group, the analgesic response was found to be significant from after the 7th session according to our interaction model between responders/non-responders and time. In addition, this response met the 'Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials' (IMMPACT) criteria of "clinically meaningful" treatment (Dworkin et al., 2008) with a mean decrease  $\geq 30\%$  and reduction  $\geq 2$  points on the VNS score of permanent pain compared to baseline (Figure 2).



**Figure 2.** Differential time course of the effect of rTMS therapy on permanent pain score during the induction phase according to the patient's status (responders vs. non-responders). Mean values (with standard error bars), \*  $p < 0.0001$  from 3<sup>rd</sup> session, \*\* the analgesic response became clinically significant in responders from the 7<sup>th</sup> session with a decrease  $\geq 30\%$  and a reduction of at least 2 points on VNS score of permanent pain [24].

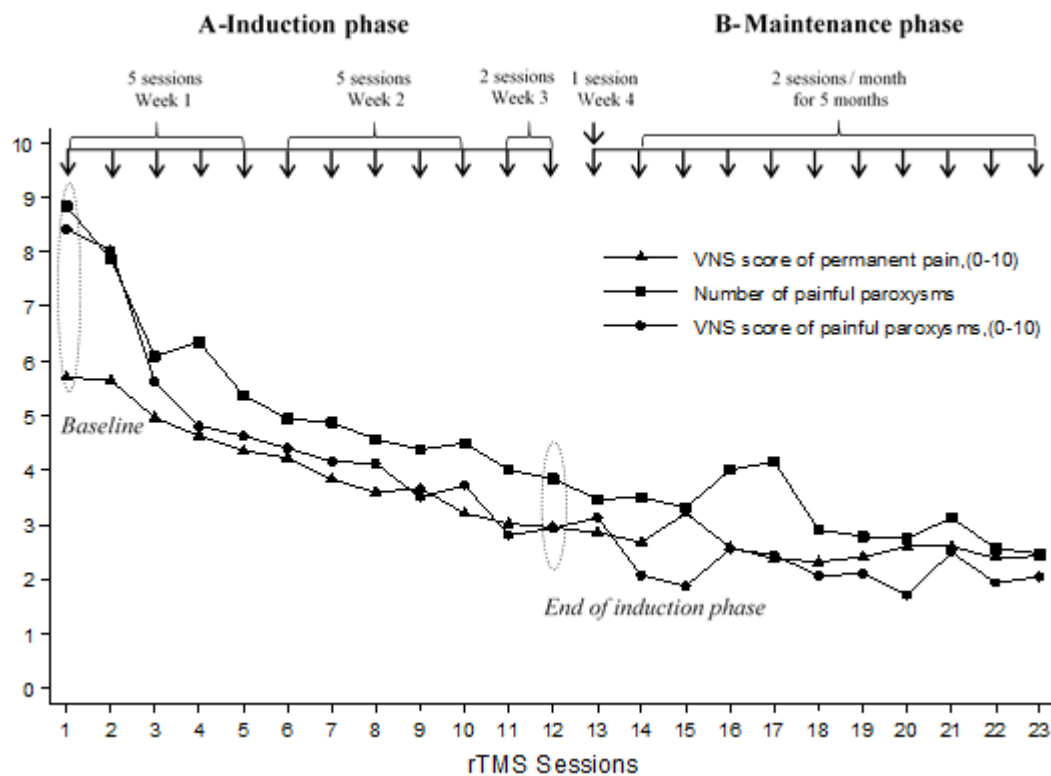
### 3.3. Analgesic effect at the end of the maintenance phase

Among the 39 patients who were responders at the end of the induction phase, 27 patients (47% of the initial series of patients) continued to be responders and to benefit from rTMS therapy until the end of the maintenance phase (D180). In 10 patients, rTMS was stopped because of reoccurrence of significant pain, which was defined as permanent pain score reduction  $< 30\%$  compared to baseline. Withdrawal occurred before the end of the 2nd month for 4 patients, 4th

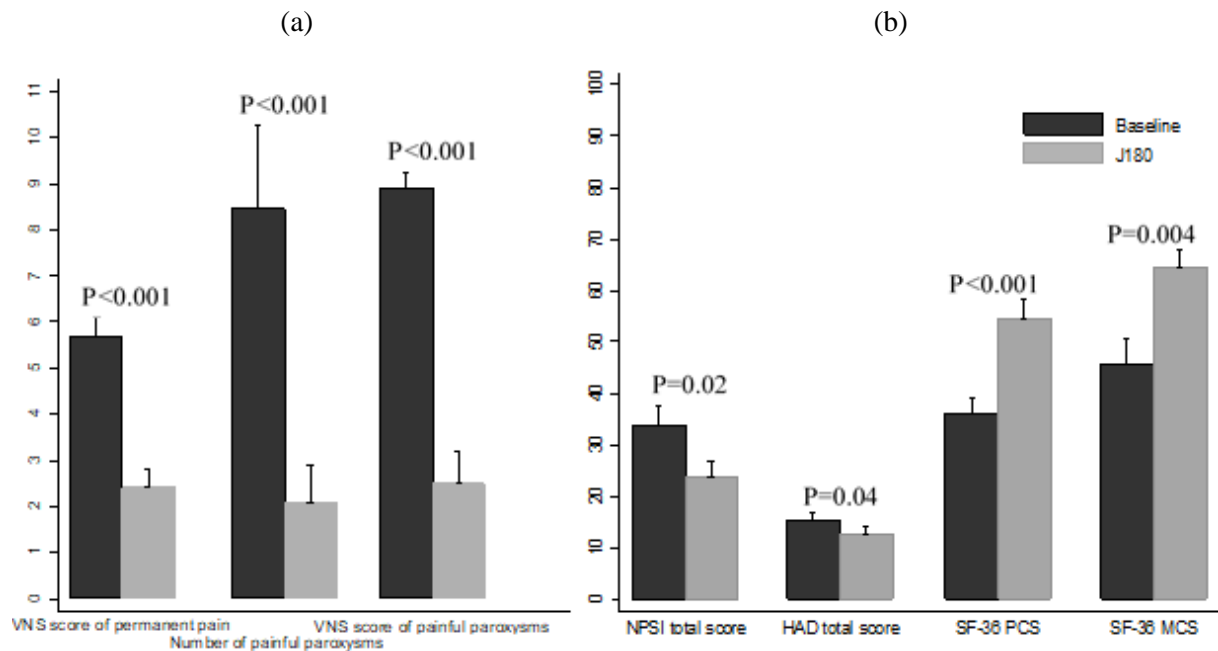


month for 4 patients, and 5th or 6th month for two patients. On the other hand, 2 patients were lost to follow-up.

In the 27 final responders, repeated-measures ANOVA showed non-significant variation of pain measures over time during the maintenance phase (Figure 3). However, compared to the end of the induction phase, the VNS score of permanent pain tended to further decrease at the end of the maintenance phase (from  $2.9 \pm 2.3$  to  $2.4 \pm 2.0$ ,  $p=0.059$ , Wilcoxon matched-pairs test), as well as the VNS score of painful paroxysms (from  $3.8 \pm 2.8$  to  $2.5 \pm 2.7$ ,  $p=0.044$ ), but not the number of painful paroxysms per day (from  $2.9 \pm 4.1$  to  $2.0 \pm 3.3$ ,  $p=0.463$ ). Compared to baseline, all scores were significantly improved at D180 ( $p<0.001$ , Wilcoxon matched-pairs test): (i) the VNS score of permanent pain (from  $5.7 \pm 2.0$  to  $2.4 \pm 2.0$ ); (ii) the number of painful paroxysms per day (from  $8.8 \pm 1.3$  to  $2.5 \pm 2.7$ ); (iii) the VNS score of painful paroxysms (from  $8.4 \pm 7.2$  to  $2.0 \pm 3.3$ ) (Figure 4a).



**Figure 3.** Time course of the effect of rTMS therapy on the various pain scores during the rTMS sessions in the 27 responders. 3A- All pain measures significantly decreased over time during induction phase ( $p<0.0001$ , repeated measures ANOVA). 3B- Pain scores assessed after the last session of the induction phase (session 12) and after the 11 sessions of the maintenance phase. P values of repeated-measures ANOVA are:  $p=0.163$  for VNS score of permanent pain,  $p=0.494$  for Number of painful paroxysms,  $p=0.132$  for VNS score of painful paroxysms.



**Figure 4.** Assessment of pain scores (4a) and multidimensional assessment (4b) at D0 and D180 in the 27 responders who completed the study (mean values with standard error bars). VNS: 0-10 visual numerical scale, NPSI: Neuropathic Pain Symptom Inventory (0-100), HAD: Hospital Anxiety (0-21) and Depression scale (0-21), SF-36 PCS and MCS: Physical and Mental Component Summaries of the Short Form (36) Health Survey (0-100).

The change in the VNS score of permanent pain from the end of the induction phase (D21) to that of the maintenance phase (D180) showed a significant decrease only for patients with orofacial pain (from  $2.6 \pm 2.0$  to  $1.9 \pm 1.8$ ,  $p=0.041$ ), but not for neuropathic limb pain ( $3.7 \pm 2.8$  vs.  $3.5 \pm 1.9$ ,  $p=0.833$ ) and pudendal neuralgia ( $2.9 \pm 3.0$  vs.  $2.7 \pm 2.3$ ,  $p=0.750$ ).

Concerning the multidimensional assessment performed at D0 and D180 in the responders who completed the study, a significant improvement was observed for the NPSI total score, the HAD total score and the PCS and MCS scores of the SF-36 (Figure 4b). Regarding the NPSI subscores, a significant improvement was observed for burning spontaneous pain ( $4.7 \pm 3.2$  vs.  $2.5 \pm 2.3$ ,  $p=0.004$ ), paroxysmal pain ( $4.3 \pm 2.7$  vs.  $2.1 \pm 2.2$ ,  $p=0.002$ ), and evoked pain ( $4.1 \pm 2.8$  vs.  $2.6 \pm 1.9$ ,  $p=0.014$ ), but not for pressing spontaneous pain ( $2.9 \pm 3.0$  vs.  $2.1 \pm 2.4$ ,  $p=0.14$ ) and paresthesia/dysesthesia subscores ( $2.7 \pm 2.7$  vs.  $2.6 \pm 2.2$ ,  $p=0.818$ ).

According to the percentage of reduction of the VNS score of permanent pain in the 27 responder patients, analgesic response was considered very good in 10 patients (37%), good in 8 patients (30%), moderate in 9 patients (33%) (Table 2b). According to the CGI scale, 8 patients (30%) were found to very much improved, 15 patients (55%) to be much improved, and 4 patients (15%) to be minimally improved. The patients' impression was significantly associated with the patients' response regarding the percentage of reduction of the VNS score of permanent pain ( $p=0.001$ , Fisher's exact test).

No difference between responders and relapsing patients during the maintenance phase was found according to age, sex, symptom duration, pain origin, location or side of the stimulated cortical target, rMT, current analgesic medication, pain, NPSI total score and subscores, and SF-36 scores at baseline (Table 4)

Conversely, the HAD total score at baseline was lower in responders than in patients who relapsed ( $14.9 \pm 8.1$  vs.  $21.2 \pm 7.8$ ,  $p=0.049$ ) (Table 4).

**Table 4.** Demographic and baseline data according to rTMS outcome at the end of the maintenance phase

	<b>Responders (n=27)</b>	<b>Relapsing patients (n=10)</b>	<b>P</b>
Age, years	59.2 ± 12.8	68.3 ± 18.5	0.100 <sup>¥</sup>
Sex, women n (%)	19 (70.4)	4 (40.0)	0.132 <sup>†</sup>
Pain syndrome duration, months	106.4 ± 127.8	90 ± 65.3	0.631 <sup>§</sup>
<i>Pain origin, n (%)</i>			0.134 <sup>†</sup>
Orofacial pain	15 (88.2)	2 (11.8)	
Neuropathic limb pain	6 (66.7)	3 (33.3)	
Pudendal neuralgia	6 (54.6)	5 (45.4)	
<i>Motor cortex target, n (%)</i>			
Face area	15 (55.6)	2 (20.0)	0.168 <sup>†</sup>
Hand area	3 (11.1)	2 (20.0)	
Leg area	3 (11.1)	1 (10.0)	
Perineal area	6 (22.2)	5 (50.0)	
<i>Stimulation side, n (%)</i>			
Bi-hemispherical	8 (29.6)	5 (50.0)	0.583 <sup>†</sup>
Right hemisphere	11 (40.7)	3 (30.0)	
Left hemisphere	8 (29.6)	2 (20.0)	
rMT (%)	50.3 ± 9.1	53.8 ± 12.2	0.355 <sup>¥</sup>
Prior interventional gesture, Yes n (%)	11 (40.7)	5 (50.0)	0.716 <sup>†</sup>
Anticonvulsants, Yes n (%)	8 (80.0)	19 (70.4)	0.694 <sup>†</sup>
Antidepressants, Yes n (%)	20 (74.1)	7 (70.0)	0.999 <sup>†</sup>
Opioids, Yes n (%)	16 (59.3)	6 (60.0)	0.999 <sup>†</sup>
Permanent pain, VNS score (0-10)	2.9 ± 2.3	2.7 ± 2.0	0.918 <sup>¥</sup>
Painful paroxysms, number of patients	16	7	
Painful paroxysms, number per day	2.9 ± 4.1	4.5 ± 6.0	0.437 <sup>§</sup>
Painful paroxysms, VNS score (0-10)	3.8 ± 2.8	3.9 ± 2.4	0.892 <sup>§</sup>
NPSI – Total score (/100)	33.7 ± 17.8	32.7 ± 17.2	0.800 <sup>¥</sup>
NPSI – Burning spontaneous pain (/10)	4.7 ± 3.2	2.5 ± 3.2	0.156 <sup>¥</sup>
NPSI – Pressing spontaneous pain (/10)	2.9 ± 3.0	3.7 ± 2.5	0.557 <sup>¥</sup>
NPSI – Paroxysmal pain (/10)	4.3 ± 2.7	3.1 ± 2.7	0.332 <sup>¥</sup>
NPSI – Evoked pain (/10)	4.1 ± 3.0	3.6 ± 2.1	0.718 <sup>¥</sup>
NPSI – Paresthesia/dysesthesia (/10)	2.7 ± 2.7	2.9 ± 3.6	0.868 <sup>¥</sup>
HAD – Total score (/42)	14.9 ± 8.1	21.2 ± 7.8	0.049 <sup>¥</sup>
HAD – Anxiety (/21)	7.8 ± 4.2	10.8 ± 4.1	0.077 <sup>¥</sup>
HAD – Depression (/21)	7.1 ± 5.0	10.4 ± 4.2	0.078 <sup>¥</sup>
SF-36 – Physical component score (/100)	36.0 ± 15.9	41.9 ± 10.3	0.439 <sup>§</sup>
SF-36 – Mental component score (/100)	45.7 ± 23.8	49.8 ± 28.1	0.737 <sup>§</sup>

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NPSI: Neuropathic Pain Symptom Inventory, HAD: Hospital Anxiety and Depression scale, SF-36: Short Form (36) Health Survey. Quantitative variables are presented as mean $\pm$ SD. ¥ unpaired t-test, § Mann-Whitney-Wilcoxon rank-sum test, † Fisher's exact test

Regarding the influence of remaining pain symptoms at the end of the induction phase (D21), no difference was found between responders and relapsing patients for the VNS score of permanent pain ( $2.9 \pm 2.3$  vs.  $2.7 \pm 2.0$ ,  $p=0.818$ , t-test), the number of painful paroxysms per day ( $2.9 \pm 4.1$  vs.  $4.5 \pm 6.0$ ,  $p=0.437$ , Mann-Whitney-Wilcoxon test), and the VNS score of painful paroxysms ( $3.8 \pm 2.8$  vs.  $3.9 \pm 2.4$ ,  $p=0.892$ ).

Overall, among the 27 responders, there were 13 patients with facial pain (orofacial pain excluding BMS): 65% of this group at baseline and 81% of this group at the beginning of the maintenance phase; 6 patients with neuropathic limb pain: 46% of this group at baseline and 67% of this group at the beginning of the maintenance phase; and 6 patients with pudendal neuralgia: 33% of this group at baseline and 50% of this group at the beginning of the maintenance phase. Although non-significant, facial pain may be a more favorable condition to rTMS therapy, especially in the long term.

Finally, analgesic medication has been able to be reduced or discontinued in 20 of the 27 responders (74%) at the end of the maintenance phase, but in none of the non-responders. Among these patients, 16 had anticonvulsants, which were reduced in all cases (100%), 15 had antidepressants, which were reduced in 10 patients (67%), and 9 had opioids, which were reduced in 4 patients (44%). Among the 12 patients on drug combinations, at least two drugs were reduced in 10 patients (83%).

#### **4. Discussion**

This study showed a significant pain relief at the end of the induction phase in the entire series of patients, including 68% of responders, defined by a decrease in pain VNS score  $\geq 30\%$  compared to baseline. Such a change meets the IMMPACT criteria of “clinically meaningful” treatment (Dworkin et al., 2008). The rate of responders in this study is slightly above the range of values usually reported, i.e. 46 to 62% (Lefaucheur et al., 2014). In our study, only one factor was associated with the clinical response at short-term (D21), i.e. the intensity of pain at baseline, which was lower in responders than in non-responders. The fact that patients who did not respond to rTMS was, on average, more painful than the responders should be considered in the indication of rTMS therapy, which might be more cautious in patients with the highest levels of pain.

Conversely, we did not find that pain duration, origin, and location were relevant prognosis factors. Previous studies reported that pain location at the face was a relevant predictor of good outcome (Lefaucheur et al., 2004b, 2006; Hodaj et al., 2015). In the present study, orofacial pain other than BMS may be the most favorable condition to rTMS therapy, but BMS was clearly the least favorable. This could reflect the fact that patients with BMS had higher permanent pain intensity and anxiety score at baseline compared to the other groups (data not shown). Since BMS only represented a small subgroup in our series, further studies should be performed to confirm this observation.

One original finding of this study lies in the long-term treatment of pudendal neuralgia by motor cortex rTMS and the use of the B70 coil, more adapted than the conventional flat figure-of-eight coils to stimulate the bi-hemispheric cortical representation of the pelvis. Only a few studies describe the use of rTMS in chronic pelvic pain: in patients with endometriosis (Pinot-Monange et al., 2019), bladder pain syndrome (Cervigni et al., 2018; Nizard et al., 2018) or as a predictive test of the analgesic efficacy of cortical implantation (Nizard et al., 2015). In our series, the therapeutic response in pudendal neuralgia at the end of the induction phase was good (67% of responders), but during the maintenance phase, pain relapse tended to be more frequent than in case of orofacial pain (50% vs. 20% of relapses in these two groups, respectively). It is worth mentioning that although not significant, HAD anxiety score at baseline also tended to be higher in patients with pudendal neuralgia than orofacial pain (mean HAD anxiety score: 10.3 vs. 6.7) (Table 1), reinforcing our hypothesis on the implication of anxiety in the recurrence of pain during the maintenance phase.

Concerning the site of cortical stimulation, we targeted the anatomical representation to the motor cortex of the pain zone. Conversely, in most studies, the hand cortical area contralateral to pain side is targeted regardless of pain location. Indeed, the somatotopic effect of rTMS-induced analgesia has not been demonstrated (Lefaucheur et al., 2006; Ayache et al., 2016; André-Obadia et al., 2018). In this study, face or upper limb motor targeting was based on individual MRI-guided navigation, while less focal stimulation using the B70 coil was delivered over perineal or lower limb motor cortical representation. No significant difference between these two approaches was found in terms of outcome. Thus, according to the few previous studies that addressed this issue (Hodaj et al., 2015; Ayache et al., 2016), our results cannot help in determining whether MRI-guided rTMS of M1 is more efficient or not to relieve pain than a non-navigated procedure.

Another original finding of this study concerns the comparison of the evolution of pain scores on VNS over time between patients who were classified as responders or non-responders at the

end of the induction phase. This analysis showed that the difference became significant only from the 7th session. Thus, the level of pain relief after 7 sessions could predict the effect of rTMS in the longer term. However, depending on the various limitations of the study, it is premature to make it a reliable indicator to determine whether a patient suffering from pain is "responder" or "non-responder" to rTMS therapy and eligible for maintenance sessions after only 7 sessions. This deserves further specific study. Another group recently showed that the analgesic efficacy of motor cortex rTMS reached significance after just 4 sessions in central neuropathic pain, but with consecutive sessions, each separated by 3-4 weeks (Quesada et al., 2018). In any case, a few rTMS sessions are probably required to determine whether a patient is responder or not to the procedure and no prolonged protocols of "induction" are needed for this objective.

In the maintenance phase, regarding the 27 responders who completed the study, pain scores were stabilized or tended to further decrease between D21 and D180, including 23 patients who declared to be much or very much improved. Compared to baseline, all other clinical scores (NPSI, HAD, and SF-36) were improved at D180 in the patients who completed the study. However, the rTMS therapy was stopped in 10 patients who showed pain reoccurrence. The only variable differentiating these 10 patients from the 27 final responders was the HAD total score at baseline, which was higher in patients who relapsed.

As mentioned in the introduction, only 4 studies previously reported the long-term efficacy of rTMS over at least a 6-month period (Mhalla et al., 2011; Hodaj et al., 2015; Kobayashi et al., 2015; Pommier et al., 2016; Quesada et al., 2018). In the present study, 47% of the patients who initiated rTMS therapy were still responders with a clinically meaningful improvement at 6 months, including a significant improvement in pain perception, anxiety-depression, and quality of life. This result observed on multidimensional assessment well correlates with patients' impression of global improvement showing 23 of the 27 responders who felt much or very much improved. Thus, it appears important to evaluate the effect of rTMS in chronic pain patients in terms of daily functioning and quality of life and not only on pain scores.

In addition, during the maintenance phase, rTMS treatment made it possible to reduce or stop analgesic drug consumption in 74% of responders. Given the classes of the drugs used (anticonvulsants, antidepressants, and opioids) that are known to carry many side effects, reducing the daily dose might provide clinical benefit in daily life beyond the impact on economic aspects and cost savings. Reduction of side effects in patients who discontinued analgesics has not been specifically evaluated in this study, but it would be worth investigating these aspects in future studies.

Our study also confirms that repeating rTMS sessions for several weeks or months might be able to maintain or enhance rTMS-induced analgesia (Lefaucheur, 2008). However, in the present series of 57 patients with various chronic pain syndromes, the percentage of responders dropped from 68% at the end of the induction phase to 47% (-21%) at the end of the maintenance phase, but this drop was smaller in the subgroup of 20 patients with facial pain (excluding BMS), from 80% to 65% of responders at 6 months (-15%). In our previous study of 55 patients with facial pain (Hodaj et al., 2015), this reduction was twice as important, from 73% to 40% of responders at 6 months (-33%). The fact that the maintenance phase consisted of bi-monthly sessions in the present study vs. monthly sessions in our previous study may explain these differential results.

Another original finding of our study lies in the investigation of factors that can influence the long-term therapeutic outcome. We found that relapsed patients during the maintenance phase had more severe anxio-depressive symptoms at baseline than patients with consistent rTMS efficacy over time. This finding may prove useful in clinical practice. It can be assumed that psychological support and appropriate treatment of anxio-depressive symptoms may reduce the number of relapses in the long term.

Finally, we have to acknowledge some study limitations. First, the absence of control group cannot rule out a placebo effect. However, it is difficult to consider long-term sham-controlled study in patients with refractory pain, according to the benefit already demonstrated of rTMS in clinical practice. Second, it is an observational study over 4 years with heterogeneity of pain site and origin. An empirical choice of periodicity of maintenance sessions should also be noted, which was based primarily on the few long-term studies published in this domain.

## **5. Conclusion**

Our study confirms the cumulative analgesic efficacy of high-frequency rTMS of M1 by the repetition of sessions in the treatment of various chronic refractory pain syndromes. The advantage of rTMS lies in its safety and good tolerance. In responders, rTMS can reduce drug treatments thus avoiding side effects of medication. On the other hand, this technique suffers from various constraints, such as the cost of the equipment (especially regarding a system coupled with neuronavigation), the requirement for a specific training, and an incompressible medical or technician time because of the need to repeat sessions. Medico-economic studies will be essential to determine the role of rTMS in the therapeutic armamentarium and the interest of its use for the treatment of refractory pain in clinical practice. In this regard, studies with long-term maintenance therapy and assessment are needed.

On the other hand, rTMS studies require multidimensional assessment, since chronic pain has frequent and possibly serious effects on mood and quality of life. The improvement of these associated symptoms can contribute to the overall satisfaction of the patient even in the absence of reduction of pain intensity (Hodaj et al., 2018). In addition, with regard to the proper analgesic effect, it seems important to study paroxysmal pain or provoked pain if it exists, and not just the ongoing average permanent pain.

Pain is a complex perception and the goal is to obtain overall improvement of the patient beyond analgesic effects. Multidimensional evaluation, the search for predictive factors of therapeutic response, protocol harmonization and personalization are avenues to explore and integrate into our strategy. Although various double-blind controlled studies already demonstrated the efficacy of rTMS, the protocols were rather heterogeneous with short-term assessment, ultimately lacking relevance for current practice. Naturalistic observational studies are valuable to present long-term results and to define the place of the technique in the daily treatment of chronic pain syndromes. However, multicenter controlled studies are still needed to confirm the validity of this approach.

### **Conflict of interest statement**

The authors have no relationship or financial interest related to this work that may have influenced or biased this article.

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## 5.2. Treatment of pudendal neuralgia by high-frequency rTMS of the medial wall of motor cortex bilaterally using an angled figure-of-eight coil.



Brain Stimulation

Volume 13, Issue 5, September–October 2020, Pages 1412–1413



# Treatment of pudendal neuralgia by high-frequency rTMS of the medial wall of motor cortex bilaterally using an angled figure-of-eight coil

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Received 9 July 2020, Accepted 18 July 2020, Available online 23 July 2020, Version of Record 7 August 2020.

## **Treatment of pudendal neuralgia by high-frequency rTMS of the medial wall of motor cortex bilaterally using an angled figure-of-eight coil**

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**Running title:** *rTMS treatment of pudendal neuralgia*

Dear Editor,

High-frequency repetitive transcranial magnetic stimulation (HF-rTMS) of the motor cortex was shown effective in treating chronic pain, in particular neuropathic pain [1]. A flat figure-of-8 coil is classically used, focusing cortical stimulation in the superficial layers of the motor cortex [2]. Deeper brain structures can be stimulated by other types of coils (e.g., double-cone or H-coil), but their value to modulate pain perception remains controversial [3]. In fact, these coils stimulate more deeply but also more broadly the brain. On the other hand, the B70 coil, which is an angled figure-of-8 coil consisting of two partially overlapping coils making an angle of 150°, stimulates deeply, while remaining focal [4]. To our knowledge, the B70 coil was only used to treat neuropathic pain in the lower limbs in a single case [5]. Compared to a flat figure-of-8 coil, the B70 coil more easily reaches the medial wall of the motor cortex bilaterally, where the pelvic muscles are represented, corresponding to the anterior extension of the paracentral lobule towards the supplementary motor area [6].

In the Pain Center of Grenoble University Hospital, HF-rTMS is used for several years in clinical practice to treat various chronic pain syndromes [7,8]. From our last study [8], we would like to focus on the interest of applying HF-rTMS with a B70 coil in a series of 18 patients suffering from perineal pain due to pudendal nerve entrapment syndrome (13 women and 5 men, age (mean  $\pm$  sd): 60.4  $\pm$  15.9 years, pain duration: 94  $\pm$  64.7 months).

The rTMS procedure was performed using a MagPro stimulator (MagVenture, Farum, Denmark); each 10Hz-rTMS session consisted of delivering 2,000 pulses in 20 minutes (40 trains of 5 sec with intertrain interval of 25 sec); the intensity of stimulation was set at 80% of the resting motor threshold; the B70 coil was held in posteranterior orientation, centred on the vertex (Cz), without using neuronavigation for targeting. The therapeutic protocol included an induction phase: one rTMS session per day for five days during two consecutive weeks, followed by two sessions the next week (12 sessions). In patients who responded to rTMS (reduction in average daily pain intensity  $\geq 30\%$  on a 0-10 numerical rating scale), a maintenance phase of bi-monthly sessions for five months was undertaken (11 sessions).

Compared to the baseline, a significant decrease was found at the end of the induction phase (D21) regarding the average intensity of ongoing daily pain (from  $5.4 \pm 1.9$  to  $3.7 \pm 3.0$ ,  $p=0.006$ , Wilcoxon signed-rank test) and paroxysmal daily pain (from  $8.0 \pm 1.8$  to  $3.8 \pm 3.0$ ,  $p=0.005$ ). The average number of painful paroxysms was also reduced (from  $5.7 \pm 3.1$  to  $2.4 \pm 2.5$ ,  $p=0.006$ ). Regarding individual responses, pain reduction was  $\geq 70\%$  in 4 patients, between 30% and 49% in 8 patients, and  $<30\%$  in 6 patients. The 12 responders (67%) entered in the maintenance phase.

Six patients (33% of the initial series and 50% of the responders to the induction phase) completed the study to the end of maintenance phase (D180). They had pain reduction  $\geq 70\%$  ( $n=1$ ) or ranging between 50% and 69% ( $n=3$ ) or between 30% and 49% ( $n=2$ ). Overall, the average intensity of ongoing and paroxysmal daily pain intensity remained stable between D21 and D180 ( $2.9 \pm 3.0$  vs.  $2.8 \pm 2.3$ ,  $p=0.75$  and  $3.8 \pm 3.1$  vs.  $3.7 \pm 3.1$ ,  $p=0.90$ , respectively). The average number of painful paroxysms was also stable ( $2.3 \pm 3.0$  vs.  $2.9 \pm 3.7$ ,  $p=0.16$ ). In addition, compared to baseline, these patients showed a significant improvement of the Physical (but not Mental) Component Summary of the Short Form (36) Health Survey (from  $33.8 \pm 5.6$  to  $55.0 \pm 15.7$ ,  $p=0.04$ ).

Regarding the other 6 patients who entered the maintenance phase, 5 patients stopped the study because of pain recurrence and one patient was lost to follow-up.

A careful review of the literature only retrieved 5 articles on the use of rTMS to relieve pelvic or perineal pain, including two series of patients treated by repeated sessions [9, 10]. In 12 patients with endometriosis [10], 5 sessions of HF-rTMS were applied over the left motor cortex with a flat figure-of-eight coil, leading to an average of 1-point reduction in pain intensity (from 5.1 to 4.1/10). In 13 patients with bladder pain syndrome [9], 10 sessions of HF-rTMS were applied over the whole motor cortex with an H-coil, leading to a more marked reduction in pain

intensity (from 7.9 to 6.2/10). However, there was no previous study based on repeated sessions of HF-rTMS of the motor cortex for the treatment of pudendal neuralgia.

This study shows that repeated sessions of HF-rTMS applied to the vertex using a B70 coil could produce effective and sustained pain relief in some patients with refractory pudendal neuralgia. The average reduction in ongoing pain intensity (-1.7/10 at the end of the induction phase) was similar to that previously reported with a deep H-coil [9] and possibly higher than using a flat figure-of-eight coil [10], although it is difficult to make comparisons between these studies. If confirmed, it could mean that perineal pain can be relieved more effectively by a stimulation more appropriate to reach the medial wall of the motor cortex bilaterally in the depth of the interhemispheric fissure. Regarding the mechanisms of action, this result is in favor of specifically targeting HF-rTMS on the cortical motor zone corresponding to the painful region, although unilateral focal stimulation of the motor cortex can also be effective for diffuse pain, especially non-neuropathic pain [1].

From a practical point of view, the use of a “deep coil” (B70, double-cone, or H-coil) facilitates rTMS application by avoiding the need for neuronavigation. Finally, the value of such “deep coils” for treating perineal pain could be extended for pain in the lower limbs, of which cortical representation also locates in the medial wall of the motor cortex in the depth of the interhemispheric fissure [6]. Some of our results support this hypothesis [5,8].

### **Conflict of interest statement**

The authors have no conflicts of interest to declare.

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### 5.3. Long-term Prophylactic Efficacy of Transcranial Direct Current Stimulation in Chronic Migraine. A randomised, patient-assessor blinded, sham-controlled trial.



## Brain Stimulation

Volume 15, Issue 2, March–April 2022, Pages 441–453



# Long-term prophylactic efficacy of transcranial direct current stimulation in chronic migraine. A randomised, patient-assessor blinded, sham-controlled trial

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**Long-term Prophylactic Efficacy of Transcranial Direct Current Stimulation in Chronic Migraine. A randomised, patient-assessor blinded, sham-controlled trial.**

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**Running title:** Prophylactic Efficacy of tDCS in Chronic Migraine.

## **Abstract**

*Objective:* To assess the prophylactic effect of anodal tDCS of the left motor cortex in patients with resistant chronic migraine (CM) and its long-term maintenance.

*Methods:* In a patient-assessor blinded, sham-controlled trial, 36 patients were randomized to receive anodal tDCS (active group, n=18) or sham tDCS (sham group, n=18). The studied population was characterized by a previous failure of at least 3 classes of preventive drugs and a mean duration of migraine history of 26 years. The tDCS procedure consisted of an induction phase of 5 consecutive daily sessions (week 1) followed by a maintenance phase of 1 weekly session during the next 4 weeks and two bimonthly sessions in the next month, for a total of 11 sessions during 2 months. Anodal tDCS was delivered at 2 mA intensity for 20 min over the left motor cortex. The primary endpoint was the reduction in the monthly number of migraine attacks from baseline to each period of follow-up (months 1, 2, 3, 5) between the active and sham groups.

*Results:* The monthly number of migraine attacks expressed as the percentage of reduction from baseline was significantly reduced in the active versus the sham group, from the end of first month (-21%  $\pm$ 22 vs. -2%  $\pm$ 25, p=0.019) to the end of follow-up (3-month post-treatment) (-32%  $\pm$ 33 vs. -6%  $\pm$ 39, p=0.011). At this time, the rate of responders, defined as a reduction of the monthly number of migraine attacks  $\geq$ 30% from baseline, was significantly higher in the active group than in the sham group (50% vs. 14%, p=0.043).

*Conclusion:* Our results show a marked prophylactic effect of anodal tDCS of the left motor cortex in resistant CM extending several months after the stimulation period, and suggest that this neuromodulatory approach may be part of the prophylactic alternatives available for CM.

**Keywords:** chronic migraine; neuromodulation; prophylactic treatment; resistant migraine; transcranial direct current stimulation.

**Abbreviations:** CM = Chronic migraine; tDCS = transcranial direct current stimulation; a-tDCS = anodal tDCS; rTMS = repetitive transcranial magnetic stimulation; HIT-6 = Headache Impact Test-6; MIDAS = Migraine Disability Assessment Scale; SF-12 = 12-item Short-Form Health Survey questionnaire; HADS = Hospital Anxiety and Depression Scale; CGI-I = Clinical Global Impression Improvement; rmANOVA = repeated measures analyses of variance; LMM = linear mixed-effect model.

## **1. Introduction**

Migraine is considered chronic when people “have 15 or more headache days per month for more than 3 months, with at least 8 of those days meeting criteria for migraine” (International Classification of Headache Disorders, 2018) [1]. Chronic migraine (CM) is the most common form of chronic daily headache and affects approximately 2% of the adult population in Western countries [2]. The severe reduction of life quality due to CM is directly correlated with the frequency of migraine attacks and the resistance to prophylactic treatments for migraine. Since CM may result in absenteeism from work and exclusion from daily, family and social activities, its impact in terms of direct and indirect costs at the individual and societal level is substantial [3].

In CM, central sensitization or long-term changes in brain plasticity may alter the modulatory systems of nociception [4-10]. These alterations have led to develop, for prophylactic purpose, invasive and non-invasive neuromodulation techniques such as occipital nerve stimulation (ONS), repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) [11-17]. ONS involves a surgical implantation of electrodes and pulse generator by a specialized team, while rTMS requires costly equipment and iterative hospital sessions for the patients. Compared to these two techniques, tDCS is a low-cost, easy-to-perform and well tolerated non-invasive technique that can be implemented at home. In practice, tDCS corresponds to the delivery of a weak electric direct current to the cerebral cortex, usually performed by means of two large electrodes (anode and cathode) placed on the scalp. In the context of chronic pain, the usual target of cortical stimulation since the early 90s is the motor (precentral) cortex [18], either of the hemisphere contralateral to pain in case of focal or lateralized pain or of the left (dominant) hemisphere in case of more diffuse or non-lateralized pain. Using anodal tDCS (a-tDCS) delivered to this motor (precentral) cortical target, significant analgesic effects have been demonstrated in various chronic pain conditions [19-21], in particular fibromyalgia [22] and neuropathic pain secondary to spinal cord injury [23] or multiple sclerosis [24], although the clinical benefit was considered controversial [25,26].

The mechanisms of action of tDCS are not yet fully understood [27]. Based on tDCS-induced changes in motor cortex excitability [28], anodal stimulation was initially thought to produce an excitatory effect through membrane depolarization, while an inhibitory effect could be produced by cathodal stimulation through membrane hyperpolarization. However, tDCS effects on brain circuitry are more complex, depending on the direction of current flow (tangential or

radial) and the neuronal compartment impacted (somatodendritic axis or distal axon terminals) [29], and therefore on polarity, size, or placement of the electrodes, on the targeted cortical site or the duration of stimulation [27]. Moreover, it is now assumed that tDCS can play a neuromodulatory role in the central nervous system by acting on various systems of neurotransmission, e.g., GABAergic, glutamatergic, dopaminergic, serotonergic, or cholinergic, leading to its potential clinical effect [30]. As acknowledged in a recent review [31], a majority of studies exploring the impact of tDCS on synaptic neurotransmission have been performed using a-tDCS of the left motor cortex and investigated GABA changes. These studies suggested decreased GABAergic activities at the origin of plastic changes following a-tDCS. However, after-effects of a-tDCS of the left motor cortex were rather found to be related to long-term potentiation of glutamatergic synaptic transmission via NMDA receptors [32]. In migraine, changes in cortical excitability were associated with alteration of glutamatergic neurotransmission and homeostatic plasticity [33]. Therefore, there is a rationale to propose a-tDCS of the left motor cortex as a therapeutic approach in migraine. Some encouraging results have been published [12,16,34-36]. However, the current level of evidence of the therapeutic effect of tDCS protocols in migraine remains low [19]. Most of these studies were based on short-term follow-up, small and heterogeneous populations and various stimulation protocols. Notably, only a few controlled studies have investigated the use of tDCS in patients with CM [8,37,38], while patients with CM and episodic migraine were mixed in other studies [39,40]. Also, the primary objective of our randomized sham-controlled study was to assess the long-term prophylactic effect of a-tDCS delivered to the left motor cortex on the frequency of migraine attacks in a homogeneous population of patients with long-lasting resistant CM.

## **2. Material and Methods**

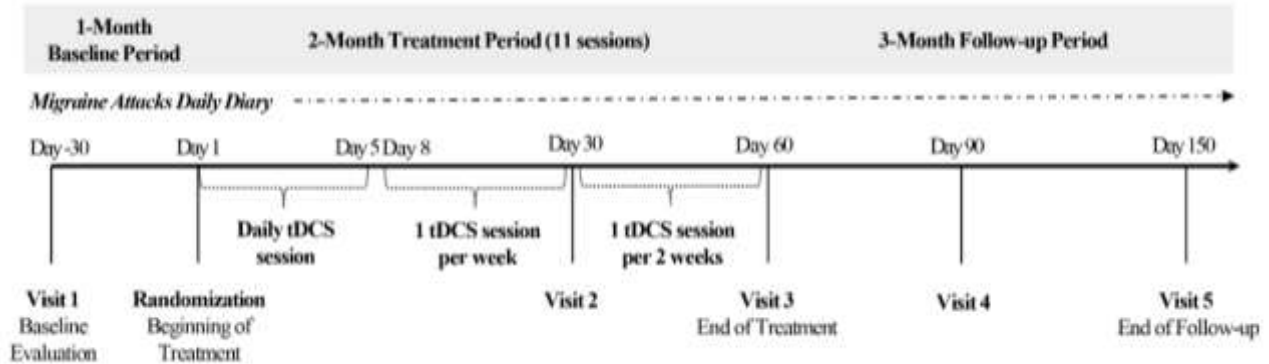
### *2.1. Study design*

The study was approved on December 14, 2013 by the Institutional Review Board of Sud-Est V, Grenoble, France (N° 6705). Written informed consent was obtained from all participants prior to enrolment. The study was registered with clinicaltrials.gov (NCT02120326).

This patient-assessor blinded, randomized sham-controlled trial with two parallel arms (active versus sham a-tDCS) was conducted between May 5, 2014 and December 18, 2019 at the Pain Centre of the Grenoble Alpes University Hospital. The study consisted of 3 phases (Figure 1): an assessment of the frequency of migraine attacks for one month before treatment with a-tDCS (Baseline); after randomisation, a 2-month period of active or sham a-tDCS, including an

induction phase and a maintenance phase for a total of 11 sessions (Month 1, 2); a 3-month follow-up post-treatment phase (Month 3, 4, 5).

Patients were evaluated at 5 scheduled visits: at one month before treatment (Day -30), at the end of the first month of treatment (Day 30), at the end of the two months of treatment (Day 60), at one month post-treatment (Day 90), and at 3 months post treatment (Day 150).



**Figure 1.** Protocol design: interventions and assessment time points. Assessments at each visit: Headache Impact Test (HIT-6); Migraine Disability Assessment (MIDAS); Patient Clinical Global Impression (CGI); the short form 12-health survey questionnaire (SF-12); Hospital Anxiety and Depression Scale (HADS).

### 2.1. Study population

Patients with CM were included if they met the following criteria: age between 18 and 85 years; diagnosis of CM [1]; disease duration  $\geq 12$  months;  $\geq 8$  migraine attacks in the past month; absence of improvement by at least 3 different well-conducted prophylactic treatments [41], which corresponds to a “resistant migraine” according to a recent international consensus [42]; no change in drug treatments during the last month; no introduction of other prophylactic treatment for migraine until the end of the follow-up study.

Patients were not included if they were pregnant or breastfeeding women, or if they had intracranial ferromagnetic material or implanted device, a history of drug addiction, epilepsy, or neuropsychiatric comorbidities, which could interfere with outcome assessments.

A total of 36 patients were included in the study and randomized to a tDCS treatment condition.

### 2.1. Randomization

After the baseline period, patients were randomly allocated in a 1:1 ratio into two groups using a secure Web-based random number generator (Research Electronic Data Capture system) to select permuted blocks, with a random block size. Patients and assessors were blinded to the

allocated group. The investigator who performed the tDCS sessions had no access to the assessments.

### *2.1. tDCS procedure*

The tDCS protocol consisted of an induction phase of 5 consecutive daily sessions during the first week (week 1) followed by a maintenance phase of 1 weekly session during the next 4 weeks and two bimonthly sessions in the next month, for a total of 11 sessions.

Stimulation was performed using a Starstim neurostimulator (Neuroelectronics, Barcelona, Spain) with saline-soaked surface sponge electrodes (35 cm<sup>2</sup>). The site of stimulation was determined according to the International 10-20 EEG System. The anode was placed on C3 to target the hand area in the left motor cortex and the cathode was placed on FP2, i.e. the right supraorbital area. A constant current of 2 mA intensity was applied for 20 min.

For the sham stimulation, the electrodes were similarly placed but the current was stopped 30 seconds thereafter: the subject felt the initial itching sensation but no stimulation was continued. This sham procedure was applied in most previous tDCS studies [28,43] and considered the most usual placebo approach in a technical guide of tDCS [44].

### *2.1. Clinical Outcomes/Endpoints*

From the baseline (Day -30) to the last follow-up assessment (Day 150), patients used a diary at home to record the following information about migraine attacks: date, duration, pain intensity using a 0-10 numerical rating scale (0 = no pain to 10 = worst pain imaginable), and use of medication. A migraine attack was defined according to the International Classification of Headache Disorders (2018) [1], including criteria of intensity (moderate or severe) and duration of attack (at least 30 min).

The primary endpoint was the reduction in the average number of migraine attacks per month from the baseline period to each period of follow-up (Month 1 to 5) between the active and sham a-tDCS groups. The number of migraine attacks was calculated on diary recordings over 30 consecutive days.

For secondary endpoints, patients completed the following self-administered questionnaires at each visit: the HIT-6 to assess the impact of headache on the overall quality of life, ranging from 36 to 78 with larger scores reflecting greater impact [45]; the MIDAS to assess the number of days of disability due to migraine, graded I-III “minimal to moderate disability” (0-20 days) or IV “severe disability” (more than >20 days) [46]; the SF-12 to assess the health-related quality of life across two dimensions (physical and mental component), using scores from 0 to

100 with a higher score indicating a better quality of life [47]; and the HADS to assess symptoms of anxiety and depression, ranging from 0 to 21 for each subscale with higher scores indicating worse symptoms [48]. The overall effect of the stimulation was estimated by the patients according to the 7-point CGI-I scale, ranging from 1 (very much improved) to 7 (very much worsened) compared to the pre-treatment baseline period [49]. An “improvement rate” was calculated as the percentage of patients improved.

Finally, we evaluated the responder rate at the end of follow-up (3-month post-treatment), according to a reduction  $\geq 30\%$  from baseline regarding the number of migraine attacks. Other secondary criteria of response were measured: a reduction  $\geq 30\%$  in the use of triptan medication; a reduction  $\geq 6$  points on the HIT-6 score or  $\geq 5$  days on the MIDAS according to the minimum clinical relevance accepted for these questionnaires [50,51].

### *2.1. Blinding integrity assessment*

The effectiveness of blinding was assessed at the end of the follow-up by asking patients to indicate which treatment they thought they had received (“active stimulation”, “sham stimulation”, or “do not know”).

### *2.1. Sample Size*

The sample size of the population was calculated on the basis of an average of  $8.2 \pm 3.7$  migraine attacks per month in CM patients [52]. Assuming a two-sided alpha risk of 0.05, a power of 80% and a correlation of 0.7 or more between repeated measurements, the enrollment of two equally sized groups (30 patients per group) could detect a 50% reduction in the number of migraine attacks per month at the end of the treatment in the active group versus 20% reduction in the sham group [53] (NQuery Advisor<sup>®</sup> 7.0).

The study was initially intended to be bicentric, but one centre failed to start the study and recruit patients. The study therefore took place in a single centre and the decision to stop the study was taken without any prior review of the data, only due to a recruitment challenge after a 5-year inclusion period. This issue reduced the sample size, but did not affect the study, which was designed to have independent recruitment and randomization for each center. Thus, a total of 36 patients were enrolled in the study.

### *2.1. Statistical analysis*

Continuous data are expressed as mean  $\pm$  standard deviation (SD) or median (25th-75th centiles), while categorical data are expressed as numbers and percentages. Comparisons were



conducted on an intention-to-treat basis by using the Chi-square or Fisher's exact test, Student's t-test or Wilcoxon-Mann-Whitney test.

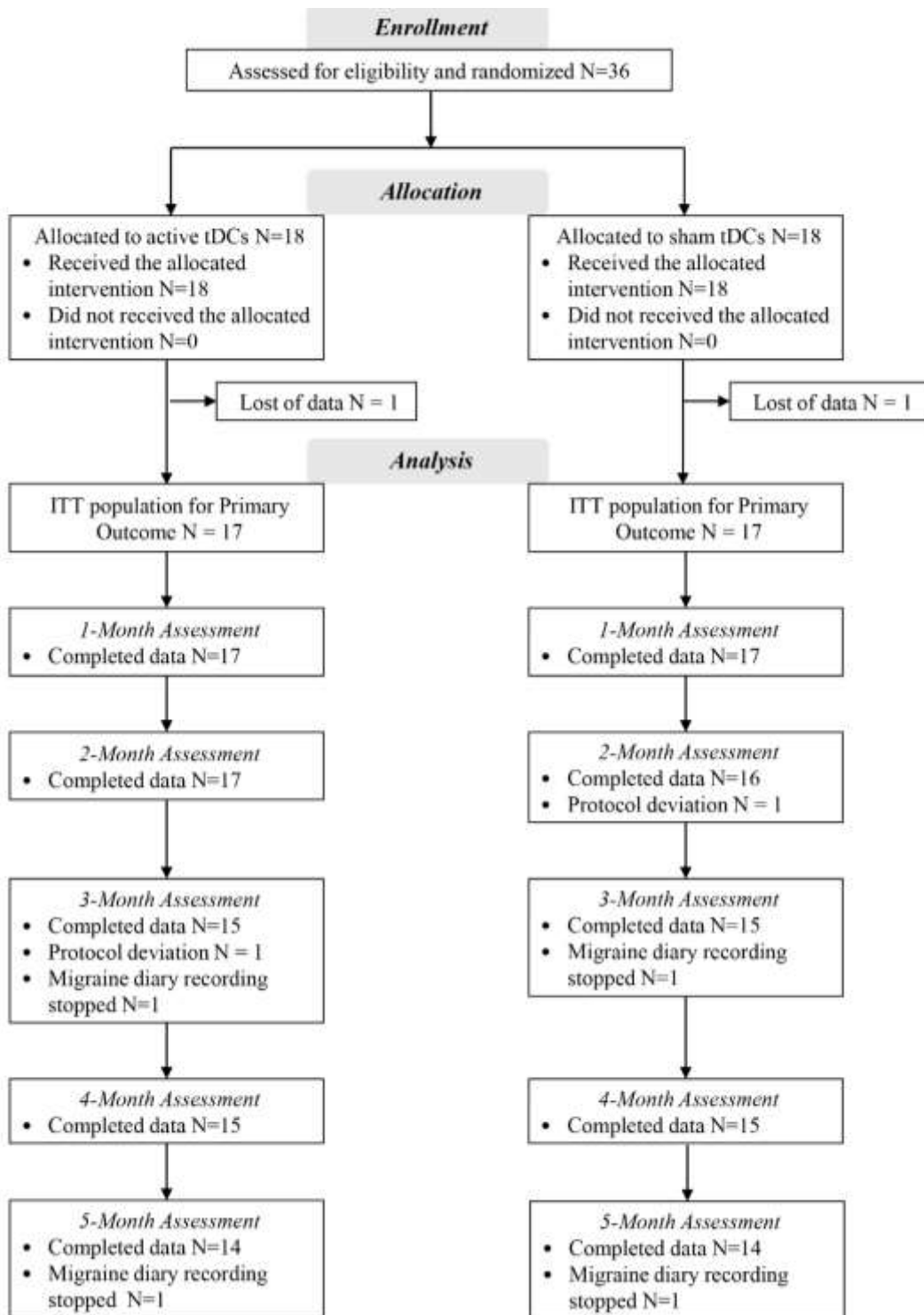
Efficacy analyses (active versus sham a-tDCS) were conducted independently for each endpoint. For continuous variables, changes from baseline to the end of the follow-up were analysed using 2-way repeated measures analyses of variance (rmANOVA) with "Time" as within-subjects factor and "Group" as between-subjects factor and the calculation of "Time-by-Group" interaction. For diary data (migraine attack frequency and analgesic medications), the factor "Time" was a 6-level variable (Baseline, Month 1, 2, 3, 4, 5); for questionnaire data (HIT-6, MIDAS, SF12 and HADS), the factor "Time" was a 5-level variable (Day -30, 30, 60, 90, 150). Bonferroni's post-hoc tests for comparisons to baseline were performed for significant main effects or interaction. Between-group differences from the baseline period to each time point of the follow-up period were compared using unpaired Student's t-test or Wilcoxon-Mann-Whitney test. Effect sizes of group differences were calculated using Cohen's *d*. A linear mixed-effect model (LMM) that accommodates missing data using missing-at-random and missing-not-at-random assumptions [54] was implemented as a sensitivity analysis to assess for heterogeneity of the factor "Group" across "Time". Models included "Time", "Group", "Time-by-Group" interaction as fixed factors and subject as random effect. Because gender, age and migraine attack number at baseline might differ between groups ( $p$ -value  $< 0.15$ ), these variables were included as fixed covariates at each of the models. The most appropriate covariance structure for the residual correlation matrix was selected. For categorical variables, we used the Chi-square or Fisher's exact test to compare between-group differences at each time point of the follow-up period.

Data were analysed using Stata 16.0 software (StatCorp, College Station, TX, USA). The statistician was blinded to the treatment groups. A two-sided  $P$  value  $< 0.05$  was considered statistically significant and no adjustments for multiple testing were performed.

### **3. Results**

#### *2.1. Flowchart of the study*

Of the 36 patients who were randomly assigned to a study group (18 in the active group and 18 in the sham group), migraine diary was lost by two patients (one in each group) (Figure 2).



**Figure 2.** Participant flow diagram. ITT (intent-to-treat) population included all randomized participants who received at least 1 session of the study treatment and recorded baseline migraine attacks.

Therefore, only 34 patients were included in the intent-to-treat (ITT) population for the primary outcome. Finally, 28 patients (14 in the active group and 14 in the sham group) completed the

5-month follow-up assessment for the primary outcome. Of these, one patient in each treatment group showed protocol deviation because they changed migraine prophylactic treatment during the study. These patients were excluded from the analysis for the period following treatment change. Two patients in each treatment group stopped completing the migraine diary and were excluded from the analysis for the period of missing data.

### 2.1. Baseline demographics and clinical characteristics

The demographics and baseline characteristics of the 36 included patients are shown in Table 1. A greater percentage of male patients and a higher age were found in the active group versus the sham group: 44% vs 11% ( $P = 0.026$ ) and  $54.5 \pm 10.6$  vs.  $46.1 \pm 14.1$  years ( $P = 0.051$ ), respectively.

**Table 1**

Baseline characteristics of patients according to the allocated group.

	Total (n = 36)	Active a-tDCS (n = 18)	Sham a-tDCS (n = 18)	p-value
Age (years), mean (SD)	50.3 (13.0)	54.5 (10.6)	46.1 (14.1)	0.051
Female, n (%)	26 (72%)	10 (56%)	16 (89%)	0.026
<b>Disease history</b>				
Time (years) since migraine onset, mean (SD)	25.9 (14.6)	27.8 (13.5)	24.1 (15.7)	0.444
History of prophylactic medication use:				
Current use, n (%)	24 (67%)	10 (56%)	14 (78%)	0.157
Number of prophylactics used, median (IQR)	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)	0.580
Type of prophylaxis used:				
Amitriptyline, n (%)	29 (81%)	14 (78%)	15 (83%)	0.999
Other antidepressant, n (%)	8 (22%)	5 (28%)	3 (17%)	0.691
Topiramate, n (%)	22 (61%)	10 (56%)	12 (67%)	0.494
Other antiepileptic, n (%)	10 (28%)	5 (28%)	5 (28%)	0.999
Oxetorone, n (%)	23 (64%)	10 (56%)	13 (72%)	0.298
Beta-blocker, n (%)	21 (58%)	12 (67%)	9 (50%)	0.310
Other antihypertensive, n (%)	7 (19%)	4 (22%)	3 (17%)	0.999
Other, n (%)	4 (11%)	3 (17%)	1 (6%)	0.603
Usual treatment of migraine attack:				
Triptan, n (%)	32 (89%)	15 (83%)	17 (94%)	0.603
Non-opioid analgesic, n (%)	33 (92%)	17 (94%)	16 (89%)	0.999
Paracetamol, n (%)	18 (50%)	11 (61%)	7 (39%)	0.182
NSAIDs, n (%)	27 (75%)	16 (89%)	11 (61%)	0.121
Weak opioid analgesic, n (%)	20 (56%)	12 (67%)	8 (44%)	0.180

**Disease characteristics during the month prior to tDCS**

Number of migraine attacks / month, mean (SD)	16.2 (7.8)	18.29 (7.9)	14.12 (7.2)	0.118
Analgesic drug consumption (number of doses):				
Triptan, median (IQR), n of patients	7.0 (4.0, 11.0) 30	5.5 (4.0, 13.0) 14	7.5 (3.5, 10.5) 16	0.662
Non-opioids, median (IQR), n of patients	10.0 (4.0, 16.0) 30	10.0 (2.0, 14.0) 15	8.0 (5.0, 19.0) 15	0.607
Weak opioids, median (IQR), n of patients	8.0 (3.0, 23.0) 19	4.0 (3.0, 36.0) 11	8.5 (0.0, 13.5) 8	0.433

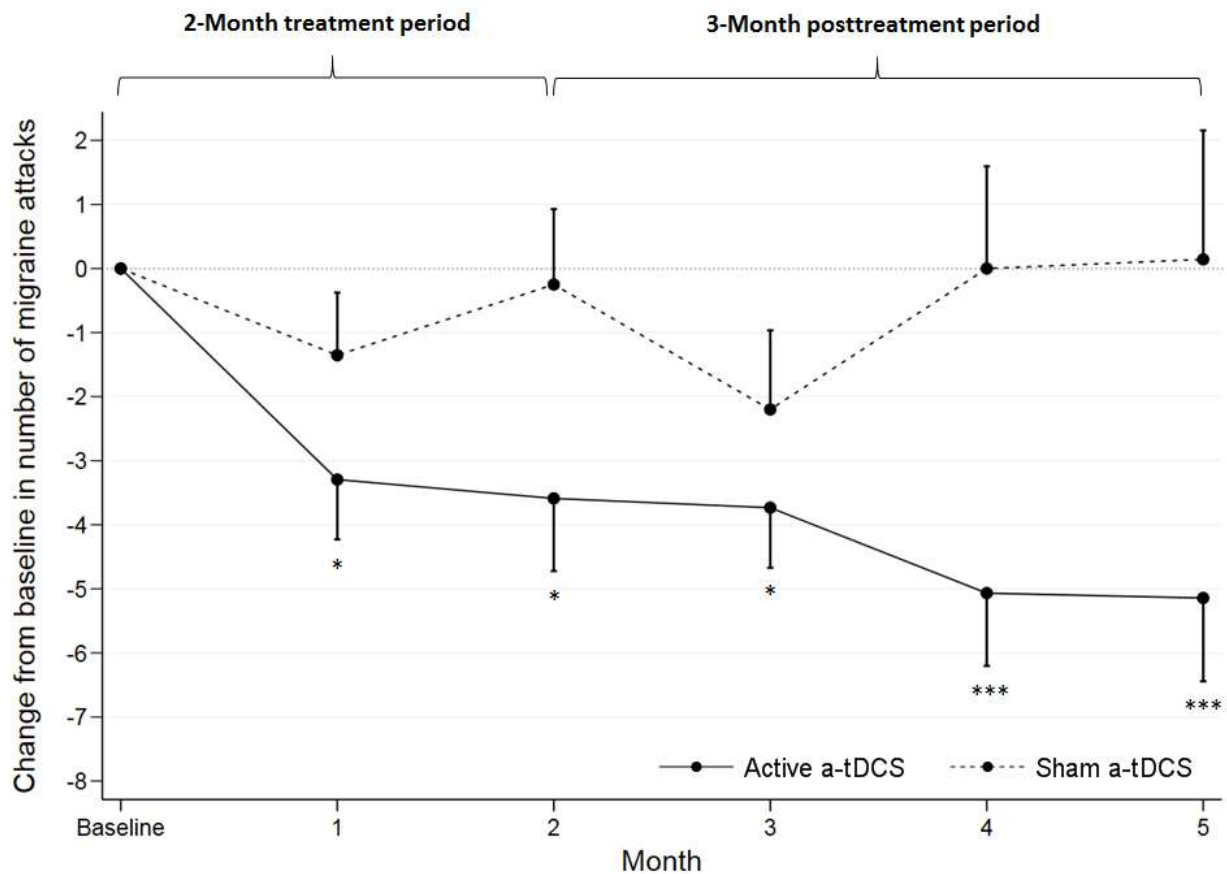
**Clinical scores at the inclusion visit, 1 month pre-tDCS**

HIT-6, mean (SD)	65.2 (4.3)	65.2 (2.9)	65.1 (5.5)	0.947
MIDAS, mean (SD)	65.8 (48.6)	68.7 (48.6)	62.6 (50.3)	0.738
SF-12 Physical component scale, mean (SD)	34.4 (9.5)	34.4 (10.0)	34.4 (9.1)	0.987
SF-12 Mental component scale, mean (SD)	36.0 (11.3)	36.9 (9.8)	34.9 (13.1)	0.625
HADS-anxiety, mean (SD)	9.7 (4.6)	9.6 (4.7)	9.9 (4.7)	0.852
HADS-depression, mean (SD)	8.7 (4.5)	9.2 (4.5)	8.2 (4.7)	0.549

Abbreviations: ITT, intention to treat; SD, standard deviation; IQR, interquartile range; NSAIDs, Non-steroidal anti-inflammatory drugs; tDCS, transcranial direct current stimulation; HIT-6, Headache Impact Test-6 (36-78); MIDAS, Migraine Disability Assessment Scale (0-270); SF-12, 12-item Short-Form Health Survey questionnaire (0-100); Physical and Mental subscales; HADS, hospital anxiety and depression scale (0-21): Anxiety and Depression subscales.

*2.1. Primary outcome: evolution of the number of migraine attacks per month*

Whether expressed as an absolute difference or as a percentage with respect to the baseline, a larger reduction in the number of migraine attacks per month was found in the active group versus the sham group throughout the follow-up (rmANOVA time-by-group interaction  $F(5,145) = 3.22$ , Greenhouse-Geisser  $P = 0.0198$ ; LMM time-by-group interaction  $F(5,146.4) = 3.29$ ,  $P = 0.008$ ). Pairwise comparisons showed a significant decrease in the number of migraine attacks per month expressed as the percentage of reduction from baseline in the active group versus the sham group from the end of the first month of treatment ( $-21.0\% \pm 21.6$  vs.  $-1.5\% \pm 24.5$ , effect size =  $-0.85$ ,  $P = 0.019$ ) to the end of follow-up (3 months post-treatment) ( $-31.9\% \pm 33.1$  vs.  $-5.6\% \pm 39.4$ , effect size =  $-1.03$ ,  $P = 0.011$ ) except at ‘Month 2’ time point (Table 2). Post-hoc tests of rmANOVA showed a significant reduction in the number of migraine attacks per month at all time points compared to baseline in the active tDCS group (Month 1:  $P = 0.034$ ; Month 2:  $P = 0.016$ ; Month 3:  $P = 0.021$ ; Month 4:  $P < 0.01$ ; Month 5:  $P < 0.03$ ) but not in the sham tDCS group (Figure 3). Overall, the tDCS sessions were very well tolerated and there were no serious side effects to report.



**Figure 3.** Change from baseline in the monthly number of migraine attacks. The line graph represents the mean values with standard errors bars on modified intention-to-treat population. Bonferroni's post-hoc tests compared to baseline: \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 10^{-3}$ .

### 2.1. Secondary outcomes: self-administered questionnaires

No significant differences between the two treatment groups were observed regarding the scores of the different questionnaires used in this study (HIT-6, MIDAS, SF-12, HAD) during or after the period of stimulation (Table 3). Regarding CGI-I, statistical results revealed no significant difference in the improvement rate between groups at all time points (data not shown).

### 2.1. Secondary outcomes: impact on treatment of migraine attacks

A significant reduction in the consumption of triptans was found in the active group versus the sham group at 'Month 4' time point (2 months post-treatment) compared to baseline ( $-2.1 \pm 3.7$  vs.  $2.5 \pm 4.7$ , effect size =  $-1.07$ ,  $P = 0.010$ ). No significant difference between groups was observed in the consumption of non-opioids or weak opioids during or after the stimulation period (Table 3).

**Table 3**

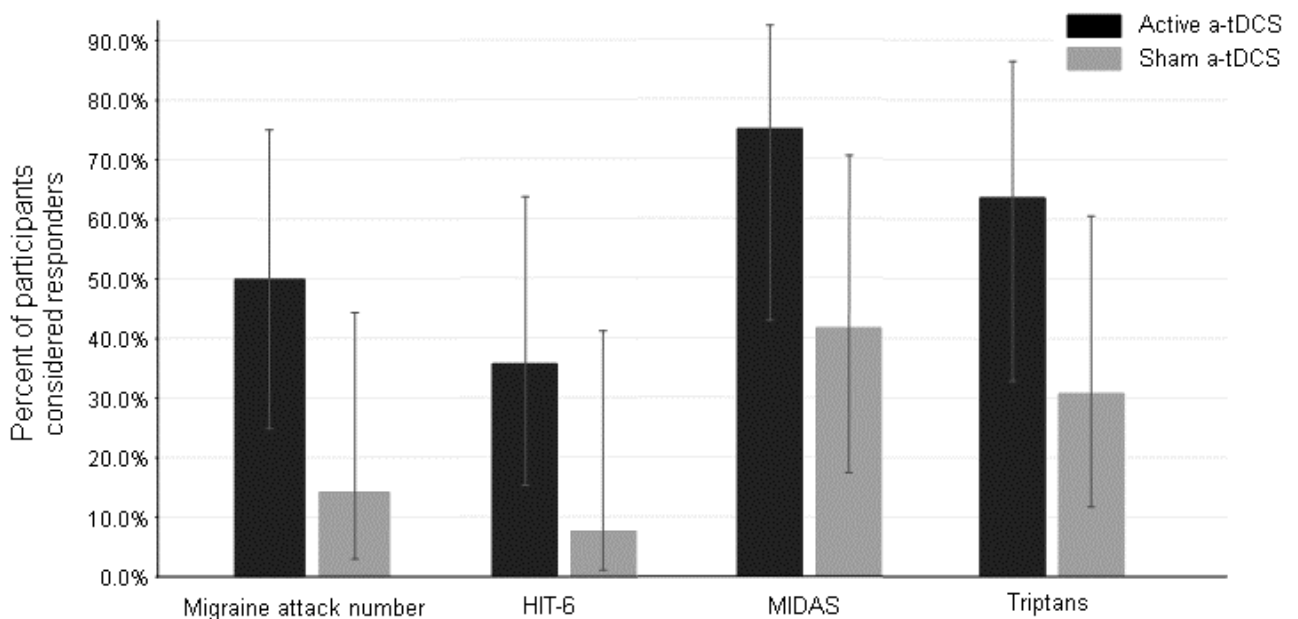
Secondary outcomes.

	Active a-tDCS	Sham a-tDCS	Between-group effect size	Between-group p-value	F (Time by Simulation)
<b>Self-administered questionnaires</b>					
<b>HIT-6</b>					
BL to D30	-2.9 (3.5)	-2.2 (5.8)	-0.13	0.747	$F_{4,109}^A = 1.60, P = 0.180$
BL to D60	-3.3 (3.7)	-1.9 (5.6)	-0.30	0.432	
BL to D90	-1.3 (2.6)	-0.9 (3.9)	-0.11	0.781	$F_{4,71.2}^L = 1.42, P = 0.236$
BL to D150	-5.1 (6.6)	-1.1 (5.4)	-0.66	0.098	
<b>MIDAS</b>					
BL to D30	-5.4 (56.3)	-20.2 (44.0)	0.29	0.507	$F_{4,93}^A = 0.55, P = 0.697$
BL to D60	-6.5 (62.5)	2.5 (46.8)	-0.16	0.691	
BL to D90	3.8 (32.7)	3.5 (52.9)	-0.01	0.989	$F_{4,94.1}^L = 0.55, P = 0.696$
BL to D150	-20.9 (44.8)	2.8 (40.3)	-0.56	0.187	
<b>SF-12 Physical component scale</b>					
BL to D30	3.6 (7.9)	2.2 (8.6)	0.17	0.661	$F_{4,108}^A = 0.58, P = 0.678$
BL to D60	4.0 (7.5)	3.2 (7.1)	0.10	0.785	
BL to D90	2.8 (7.0)	4.8 (8.4)	-0.26	0.496	$F_{4,108}^L = 0.53, P = 0.714$
BL to D150	3.4 (5.2)	2.0 (11.3)	0.17	0.668	
<b>SF-12 Mental component scale</b>					
BL to D30	-1.1 (9.0)	1.3 (8.2)	-0.27	0.485	$F_{4,108}^A = 1.23, P = 0.302$
BL to D60	4.3 (13.7)	-1.3 (9.9)	0.46	0.225	
BL to D90	2.2 (10.9)	-0.5 (10.0)	0.26	0.491	$F_{4,108.4}^L = 1.10, P = 0.361$
BL to D150	5.2 (11.1)	-0.9 (9.0)	0.60	0.141	
<b>HADS-Anxiety</b>					
BL to D30	-1.2 (3.3)	-0.8 (2.2)	-0.15	0.702	$F_{4,108}^A = 0.74, P = 0.565$
BL to D60	-1.0 (3.6)	-1.6 (2.1)	0.19	0.619	
BL to D90	-0.9 (3.5)	-2.2 (3.3)	0.37	0.332	$F_{4,107.7}^L = 0.74, P = 0.564$
BL to D150	-1.3 (3.3)	-0.7 (2.6)	-0.19	0.613	
<b>HADS-Depression</b>					
BL to D30	-0.9 (4.3)	0.0 (3.0)	-0.23	0.555	$F_{4,108}^A = 0.66, P = 0.623$
BL to D60	-2.3 (4.3)	-0.1 (4.0)	-0.54	0.173	
BL to D90	0.0 (2.6)	0.4 (4.0)	-0.12	0.761	$F_{4,108.3}^L = 0.75, P = 0.558$
BL to D150	-1.3 (3.2)	0.2 (4.1)	-0.39	0.308	
<b>Treatment of migraine attacks</b>					
<b>Triptan</b>					
BL to M1	-1.7 (3.9)	0.1 (4.5)	-0.42	0.259	$F_{5,127}^A = 1.84, P = 0.125$
BL to M2	-0.6 (5.7)	1.3 (5.2)	-0.35	0.354	
BL to M3	-1.8 (3.4)	-0.1 (3.1)	-0.52	0.185	$F_{5,126.7}^L = 1.63, P = 0.156$
BL to M4	-2.1 (3.7)	2.5 (4.7)	-1.07	0.010	
BL to M5	-1.4 (3.5)	0.5 (3.6)	-0.53	0.208	
<b>Non-opioid analgesics</b>					
BL to M1	-2.3 (5.7)	-1.0 (5.7)	-0.23	0.526	$F_{5,126}^A = 0.90, P = 0.486$
BL to M2	-3.1 (5.9)	-2.8 (5.4)	-0.06	0.870	
BL to M3	-3.1 (5.1)	-3.3 (6.8)	0.03	0.943	$F_{5,125.8}^L = 0.39, P = 0.852$
BL to M4	-4.1 (4.7)	-3.5 (6.3)	-0.12	0.751	
BL to M5	-6.8 (23.9)	-3.3 (6.8)	-0.20	0.649	
<b>Weak opioid analgesics</b>					
BL to M1	-4.9 (10.7)	-2.0 (5.7)	-0.32	0.455	$F_{5,82}^A = 0.90, P = 0.390$
BL to M2	-5.0 (10.3)	-0.8 (5.3)	-0.50	0.252	
BL to M3	-0.3 (6.5)	-2.6 (5.4)	0.38	0.439	$F_{5,61.9}^L = 0.95, P = 0.454$
BL to M4	1.1 (12.7)	0.1 (8.3)	0.09	0.847	
BL to M5	-8.1 (19.5)	-0.3 (5.8)	-0.52	0.252	

Data are expressed as absolute change from baseline (mean  $\pm$  SD). A negative change within groups means improvement except for SF-12. SD, standard deviation; BL, Baseline; D, Day; M, month; HIT-6, headache impact test-6 (36-78); MIDAS, migraine disability assessment scale (0-270); SF-12, 12-item Short-Form Health Survey questionnaire (0-100): Physical and Mental subscales; HADS, hospital anxiety and depression scale (0-21): Anxiety and Depression subscales. A Repeated measures analyses of variance. LLinear mixed-effect models.

### 2.1. Analyses in terms of responders

According to the primary criterion of response (a reduction  $\geq$  30% from baseline regarding the number of migraine attacks per month), the rate of responders was significantly higher in the active group versus the sham group at ‘Month 5’ time point (3 months post-treatment) (50 % vs. 14%, Chi2 = 4.09, P = 0.043) (Figure 4). Moreover, the rate of responders with a reduction  $\geq$  50% of the number of migraine attacks per month tended to be higher in the active group versus the sham group: 36% vs 7% respectively (Chi2 = 3.39, P = 0.065). A tendency towards a better efficacy of active versus sham a-tDCS was also observed for two secondary criteria of response: a reduction  $\geq$  6 points on the HIT-6 score (36% vs 8%, Chi2 = 3.06, P = 0.080); a reduction  $\geq$  5 days on the MIDAS (75% vs 42%, Chi2 = 2.74, P = 0.098) (Figure 4).



**Figure 4.** Responder rates at the end of the study (3 months post-treatment) from baseline. Responder status: number of migraine attacks: reduction of  $\geq$  30%; HIT-6: a score reduction of  $\geq$  6 points; MIDAS, a score reduction of  $\geq$  5 points; use of triptan: reduction of  $\geq$  30%. The errors bars represent 95% confidence intervals.

On the other hand, we did not find any significant difference between the responders and non-responders (defined on the reduction of the number of migraine attacks per month) regarding their various clinical characteristics at baseline, failing to reveal any predictive value of these characteristics (Table 4).

**Table 4**

Baseline characteristics of responders versus non-responders.

	Responders (n = 7)	Non-responders (n = 7)	p-value
Age (year), mean (SD)	55.0 (5.2)	52.9 (11.2)	0.654
Female, n (%)	4 (57%)	4 (57%)	0.999
Time (months) since migraine onset, mean	33.3 (10.7)	26.4 (15.2)	0.348
Current use of prophylactic medication, n (%)	4 (57%)	4 (57%)	0.999
Migraine attacks frequency, mean (SD)	15.7 (7.3)	22.4 (8.3)	0.135
Analgesic drug consumption (number of			
Triptan, median (IQR)	5.5 (4.0, 9.0)	4.5 (4.0, 8.0)	0.810
Non-opioids, median (IQR)	7.0 (2.0, 14.0)	12.0 (2.0, 14.0)	0.775
Weak opioids, median (IQR)	3.5 (3.0, 23.0)	28.0 (12.0, 57.0)	0.166
HIT-6, mean (SD)	64.5 (3.4)	66.0 (2.3)	0.365
MIDAS, mean (SD)	53.7 (58.7)	69.5 (38.4)	0.592
SF-12 Physical component scale, mean (SD)	39.3 (14.0)	30.7 (6.4)	0.175
SF-12 Mental component scale, mean (SD)	40.8 (9.4)	32.0 (10.4)	0.140
HADS-anxiety, mean (SD)	8.9 (2.6)	11.7 (6.4)	0.295
HADS-depression, mean (SD)	7.7 (4.7)	11.4 (4.7)	0.164

SD, standard deviation; IQR, interquartile range; HIT-6, Headache Impact Test–6 (36-78); MIDAS, Migraine Disability Assessment Scale (0-270); SF-12, 12-item Short-Form Health Survey questionnaire (0-100): Physical and Mental subscale; HADS, hospital anxiety and depression scale (0-21): Anxiety and Depression subscales.

### 2.1. Blinding integrity

At the end of the follow-up period, most patients were not able to indicate which treatment they had received: “active stimulation”, “sham stimulation” or “do not know” was the response given by 3, 2, and 9 patients, respectively, in the active group and by 5, 4, and 6 patients, respectively, in the sham group ( $\chi^2=1.73$ ,  $P = 0.42$ ). The responses to the blinding integrity questionnaire showed the reliability of blinding in both groups.

## 4. Discussion

This study assessed the prophylactic efficacy of a-tDCS of the left motor cortex in patients with resistant CM and its long-term maintenance. The strengths of this study were the design of the study (sham-controlled trial and blinded assessors and patients) and the homogeneity of the



patient population (resistance to at least 3 different prophylactic treatments and long disease duration  $\geq 12$  months, 25.9 years on average).

To our knowledge, this is the first sham-controlled study evaluating the long-term reduction in the frequency of migraine attacks using a-tDCS of the left motor cortex in the context of well-defined resistant CM with a very long disease duration. In designing this study with an induction phase and a maintenance phase, we were inspired by the protocols using rTMS in the long-term treatment of chronic pain [55] and our observations in this domain [56,57]. In the present study, a significant decrease in the number of migraine attacks per month was observed from one month of treatment in the active group. This positive effect was even more pronounced at the end of follow-up (3 months post-treatment). Post-hoc tests of rmANOVA also showed a significant reduction in the number of migraine attacks per month at all time points compared to baseline in the active group, but not in the sham group. Thus, a significant prophylactic effect of a-tDCS treatment was observed, including early and long-lasting beneficial effects.

Finally, the rate of responders ( $\geq 30\%$  reduction) at 5 month follow-up (3 months post-treatment) was significantly higher in the active group versus the sham group regarding the number of migraine attacks per month and tended to be higher regarding two secondary outcome measures: the HIT-6 and the MIDAS.

### *2.1. Prophylactic treatments of CM*

The first-line prophylactic treatments of CM are based on medications [58-62]. The anticonvulsant topiramate has been recently recommended as the first-line prophylactic treatment for CM in French guidelines [59], because of the highest level of evidence of efficacy, notably based on a large, multicenter, controlled clinical trial [63]. In this benchmark study, the efficacy of topiramate (100 mg/day) was compared with placebo for the treatment of 306 patients with CM. Topiramate intake resulted in a significant reduction by 11% at 3 month follow-up in the mean number of migraine attacks or migrainous headache days per month from baseline compared to placebo ( $-37.1\% \pm 34.8$  vs  $-26.0\% \pm 40.8$ ,  $P = 0.012$ ). In the present study, a significant reduction in the monthly number of migraine attacks at 5 month follow-up in the active group versus the sham group was also found, but this reduction was of 26.4% ( $-31.9\% \pm 33.1$  vs.  $-5.6\% \pm 39.4$ ,  $P = 0.011$ ). Although the sample population studied was small, our findings indicate that a-tDCS of the left motor cortex may be a prophylactic treatment for CM. In chronic pain, it is recommended to report the percentage of patients responding with a reduction  $\geq 30\%$  on a pain measure, as reflecting a clinically important (at least moderate) difference in a pain treatment trial [64]. In the present study, the response to treatment was

defined as a reduction  $\geq 30\%$  from baseline regarding the number of migraine attacks per month. At the end of follow-up (3-month post-treatment), the rate of responders was significantly higher following active versus sham a-tDCS (50.0% vs. 14.3%). For comparison, in the large, multicenter, controlled clinical trial on the efficacy of topiramate mentioned above, this criterion of response (set at  $\geq 25\%$  reduction rather than  $\geq 30\%$ ) was met by 68.6% vs 51.6% in the active and placebo groups, respectively [65]. We have no explanation for the fact that the placebo response is much lower in our study than in the previous study with topiramate, but it appears not to be due to a break in blinding integrity (referring to our assessment of the reliability of blinding). Thus, the efficacy of a-tDCS of the left motor cortex seems to be comparable to topiramate used as first-line prophylactic treatment in CM. The efficacy of a-tDCS observed in the present study is also comparable to that recently reported in studies considering the impact of botulinum toxin type A (BTA) or monoclonal antibodies against CGRP (mAbs) on the number of headache days as primary endpoint, reporting an effect size and responder rate of 50% [62,66-69]. Thus, the efficacy of a-tDCS of the left motor cortex seems to be at least similar to all medications currently used as prophylactic treatment for CM and also for resistant CM, an observation that must to be confirmed by larger studies.

### *2.1. Previous tDCS studies in migraine*

Previously published studies aimed at treating headache by using tDCS are very heterogeneous in terms of stimulation setup, patient clinical profile, sample size, and follow-up duration [13,35]. In the literature, we found 14 sham-controlled tDCS studies performed in migraine patients. Six studies were based on cathodal tDCS of the occipital cortex [70-75] and 5 studies were based on anodal tDCS of the left motor cortex or the motor cortex contralateral to the most frequent migraine side [8,37,39,76,77]. Other studies included the cathodal tDCS of the right sensorimotor cortex [40,78], the cathodal tDCS of a scalp region identified by thermographic examination [38], or the stimulation of the dorsolateral prefrontal cortex [37,74]. The majority of these tDCS studies concerned patients with episodic migraine. Two publications addressed chronic medication overuse headache [74,77]. Finally, typical CM was only addressed in 5 studies. In two of these studies, patients with CM were mixed with patients with episodic migraine without any distinction in the results provided [39,40]. Therefore, only 3 studies were specifically conducted in patients with typical CM. In one study, the tDCS protocol was based on the cathodal stimulation of a scalp region identified by thermographic examination without any further detail on the corresponding cortical anatomical area [38]. In a second study, only 6 patients received active stimulation (anodal tDCS of the motor cortex) for a total of 12 sessions,

with no follow-up after treatment [37]. Finally, only one study can be compared to the present study. In that study, only 8 patients with CM received active anodal tDCS over the motor cortex region contralateral to the dominant pain side for a total of 10 sessions within 4 weeks [8]. In the present study, 17 patients with CM received active anodal tDCS over the left motor cortex for a total of 11 sessions within 8 weeks, with a follow-up of 3 months post-treatment. In the study of DaSilva et al., 2012 [8], the results obtained with a-tDCS of the motor cortex were compared to a sham group of only 5 patients and showed only a trend for significant reduction of pain intensity of the migraine attacks at the end of the a-tDCS protocol. At a delayed follow-up of 3 months, the reduction in the intensity of pain and the duration of migraine episodes was significant. This could be considered as a preliminary study with no reported data on the effect of a-tDCS on the number of migraine days. The present study goes much further and shows the significant therapeutic beneficial effects on the number of migraine attacks in resistant CM. Other studies found a significant reduction in the number of headache/migraine days from one to 6 months following 3 to 20 sessions of a-tDCS of the motor cortex in episodic migraine or chronic medication overuse headache [39,76,77]. Interestingly, one study showed that a prolonged treatment of 22 sessions (over 10 weeks) of monopolar cathodal tDCS of the right motor cortex (with the anode on the left arm) could also reduce the number of migraine attacks for a very long period, up to 12 months, compared to a sham protocol [40]. In contrast, a shorter protocol of 5 sessions of anodal or cathodal tDCS of the right motor cortex was ineffective to improve the long-term efficacy of an acute withdrawal protocol in patients with chronic medication overuse headache [78].

### *2.1. Duration and prediction of effects*

As with rTMS, the analgesic effects of a single session of tDCS are short-lived and session repetition is essential to achieve lasting relief through a cumulative effect. A recent meta-analysis showed that treatment with tDCS repeated over several days for a period  $\geq 4$  weeks could be effective in reducing the intensity and duration of migraine attacks [35]. Sustained and repeated tDCS sessions can thus induce cumulative and lasting neuroplastic changes in the cerebral cortex [79].

Regarding the duration of efficacy, a problem to be solved is the potential synergistic effect with drug treatments. For example, one study supported an add-on prophylactic effect of cathodal tDCS delivered to various cortical targets as an adjunct to topiramate, with a marked reduction in the frequency of migraine attacks in patients treated for CM [38]. In the present study, there was no difference between responders and non-responders regarding the

concomitant use of prophylactic drugs, as well as in the consumption (number of doses) of analgesic drug to treat attacks. However, the synergistic effects between tDCS and drugs have not been well studied. In any case, the potential prophylactic long-term effect of preventing migraine attacks by tDCS appears encouraging in terms of routine clinical application, although intriguing compared to the rather less prolonged therapeutic effects of tDCS reported in other pathological conditions [19].

Unfortunately, the analysis of responder profile in the present study did not reveal any predictor of therapeutic response (cf Table 4), possibly due to a lack of statistical power due to the small sizes of patient subgroups.

### *2.1. Mechanisms of action*

The article of DaSilva et al., 2012 [8], included a modeling study which supports a diffuse effect of anodal tDCS from the motor cortex site of stimulation to various deeper structures of the pain neuromatrix, such as cingulate gyrus, insular cortex, thalamic nuclei, and brainstem. Neuroimaging investigations of CM-induced brain plasticity, although sparse, have shown various types of changes, including a bihemispheric increase in the regional cerebral blood flow in the primary somatosensory cortex, which was positively correlated with headache attack frequency [80]. During migraine attacks, there are also various changes in thalamo-cortical connectivity, notably involving the motor cortex [10]. Therefore, there is a rationale for the use of a-tDCS of the motor cortex as an analgesic therapy in resistant CM, as one type of chronic pain syndrome among others. Indeed, as reported in various reviews [18, 81-83], beyond a direct modulation effect on the underlying neuronal fibers running superficially in the precentral gyrus, a-tDCS of the motor cortex is also able to modulate neuronal activities in many cortical and subcortical structures distant from the site of stimulation. These structures can play an important role in the control of nociception, such as the thalamocortical pathways. Stimulation of the motor cortex can also lead to strengthening or restoring the descending inhibitory controls of nociceptive information transmission. Finally, brain structures involved in the cognitive and affective aspects of pain, such as the cingulate, prefrontal, and orbitofrontal cortices, can also be modulated, via action on various neurotransmitter systems. All these mechanisms remain to be studied regarding the specific effect of a-tDCS of the left motor cortex in patients with CM.

### *2.1. Limitations*

Several limitations should be recognized. First, the sample size was smaller than originally calculated for optimal statistical power. Therefore, some estimates may not have followed the statistical constraints necessary to show significant results. As mentioned above, this may explain the lack of any predictor of therapeutic response, possibly due to decreased statistical power.

Second, imprecision remains as to the location of the cortical region stimulated by a-tDCS. Although the placement of the anode was centered on the motor cortex, this site was defined as C3 using the International 10-20 EEG System and not by means of individual anatomical mapping using image-guided navigation, for example. In addition, since the electrode used was a disc with a radius < 3.5 cm, this means that the electrode covered the premotor region rostrally (the premotor cortex being 3-3.5 cm anterior to the “motor hotspot” [84]) and the primary somatosensory region caudally. However, as usual in the literature, this tDCS montage was described as primarily targeting the motor cortex throughout the article.

A third limitation is about the understanding of the mechanisms of action of a-tDCS of the left motor cortex on the reduction of the number of migraine attacks. As mentioned above, these mechanisms remain speculative, although the long-term lasting effects argue for a plasticity-induction protocol. However, whether plasticity was induced by an increase or a decrease of cortical excitability remains to be determined. Indeed, a-tDCS is usually considered an excitatory protocol, but this varies according to timing-dependent effects of homeostatic plasticity. For example, the behavioral effects of a-tDCS on motor learning depend whether a-tDCS is applied concurrently or prior to the motor task, reflecting the influence of homeostatic interactions on GABAergic synaptic changes due to the stimulation [85]. The polarity of the electrode also plays a role, since cathodal but not anodal tDCS was found to restore the normal facilitatory response to high-frequency rTMS in patients with migraine, counteracting homeostatic mechanisms of cortical hypo-responsivity [86].

### *2.1. Suggestions for future research*

The limitations described above should be the basis for future research to better understand and define the place of tDCS in the treatment of CM.

In a recent narrative review, it was concluded that the data on the prophylactic efficacy of tDCS in CM were conflicting [16]. This has already been discussed previously, and the positive results of the present study can be explained by the homogeneity of our population, despite the limitation of the sample size. Multicenter sham-controlled trials using the same stimulation

parameters are needed to confirm the present results, given the difficulties in performing large single-center studies.

Second, although the motor cortex appears to be a promising target, questions remain open about which hemispheric side to stimulate (left, contralateral to the dominant migraine side, or even bilateral). The value of the motor cortex also remains to be compared with alternative cortical targets, such as the occipital cortex. Finally, alongside conventional bipolar montages, multisite (multifocal) tDCS is under development and is yielding interesting results [87-89]. This targeting question is one of the most important challenges in the use of tDCS as a therapeutic strategy and relies on a better understanding of the brain networks to be stimulated and how to stimulate them to improve a pathological neurological condition.

Third, with regard to the understanding of the mechanisms of action, a major issue will be to study the effects of a-tDCS of the motor cortex on the alterations of cortical excitability which are known to exist in migraine patients [90,91]. Cortical excitability changes can be assessed in particular by neurophysiological techniques, such as non-invasive transcranial stimulation protocols, even concerning the influence of homeostatic plasticity processes [92,93]. The goal of future studies will be to determine what excitability changes are induced by tDCS of the motor cortex (especially according to the polarity of the stimulating electrode) in patients with CM and to see if these changes are correlated with clinical effects, such as the reduction of migraine attacks.

Finally, the place of tDCS alongside other neuromodulation techniques, such as transcutaneous electrical stimulation of the supra-orbital or occipital nerves, transcutaneous auricular or cervical stimulation of the vagus nerve, or high-frequency rTMS of the motor or the prefrontal cortex [13,17,94], remains to be confirmed for the prophylactic treatment of migraine. The advantage of tDCS relies also upon its safety and very good tolerance, leading to the fact that its acceptance by patients is potentially better than drugs treatments.

However, some constraints of tDCS should be mentioned, including the need for iterative sessions, although the number and timing of sessions needed to induce significant and prolonged clinical effects remain to be determined. In this context, the development of the at-home use of tDCS [75, 95] constitutes an interesting and costless alternative to be addressed.

In responders, a-tDCS of the left motor cortex may help reduce drug consumption, thereby avoiding polypharmacy and its side effects, including drug addiction and chronic medication overuse headache. This aspect also deserves future studies, as well as the interest of tDCS as a preventive tool to avoid the evolution of resistant CM towards “refractory migraine”, defined as CM not improved by at least 5 different and well-conducted prophylactic treatments.

Medico-economic studies will be also essential to assess the cost-efficacy of tDCS in a medical environment, particularly in comparison with the newly proposed prophylactic but costly treatments, such as BTA and anti-CGRP mAbs.

## **5. Conclusion**

Our study shows the prophylactic efficacy of a-tDCS of the left motor cortex in the treatment of CM, including several months of lasting effects. However, the place of tDCS remains to be evaluated in the therapeutic armamentarium of CM, in particular as an alternative or in combination with prophylactic drug treatments and not only as a last resort in severe forms of patients with CM, who already have significant impact on mood and quality of life. The use of tDCS could therefore be an interesting therapeutic strategy to prevent the evolution of CM towards a refractory form. Larger controlled trials are needed to confirm the efficacy showed in the present study, and to identify predictive factors that may influence the clinical response to tDCS.

## **Declaration of competing interest**

The authors declare no conflict of interest.

## **Acknowledgements**

The authors would like to thank Dr Jean-Pierre Alibeu, Mr Nicolas Gonnet and Mr Zaza Putkaradze for their contribution to this article.

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## 5.4. Better fields or currents? A head-to-head comparison of Transcranial Magnetic (rTMS) versus Direct Current Stimulation (tDCS) for Neuropathic Pain

Neurotherapeutics 2022

doi: 10.1007/s13311-022-01303



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**Article type:** original article

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**Running title:** rTMS versus tDCS in Neuropathic Pain.

## Summary

While high-frequency transcranial magnetic stimulation (HF-rTMS) is now included in the armamentarium to treat chronic neuropathic pain (NP), direct-current anodal stimulation (a-tDCS) to the same cortical targets may represent a valuable alternative in terms of feasibility and cost. Here we performed a head-to-head, randomized, single-blinded, cross-over comparison of HF-rTMS *versus* a-tDCS over the motor cortex in 56 patients with drug-resistant NP, who received 5 daily sessions of each procedure, with a washout of at least 4 weeks. Daily scores of pain, sleep and fatigue were obtained during 5 consecutive weeks, and functional magnetic resonance imaging (fMRI) to a motor task was performed in a subgroup of 31 patients. The percentage of responders, defined by a reduction in pain scores of >2 SDs from pre-stimulus levels, was similar to both techniques (42.0% vs 42.3%), while the magnitude of “best pain relief” was significantly skewed towards rTMS. Mean pain ratings in responders decreased by 32.6% (rTMS) and 29.6% (tDCS), with half of them being sensitive to only one technique. Movement-related fMRI showed significant activations in motor and premotor areas, which did not change after 5 days of stimulation, and did not discriminate responders from non-responders. Both HF-rTMS and a-tDCS showed efficacy at 1-month in drug-resistant NP, with magnitude of relief slightly favoring rTMS. Since a significant proportion of patients responded to one procedure only, both modalities should be tested before declaring a patient as unresponsive.

**Keywords:** rTMS; tDCS; neuropathic pain; fMRI; non-invasive stimulation.

**Abbreviations:** NP = Neuropathic Pain; HF-rTMS = High-Frequency repetitive Transcranial Magnetic Stimulation; tDCS = transcranial Direct Current Stimulation; fMRI = functional Magnetic Resonance Imaging; IASP = International Association for the Study of Pain; NRS = Numerical Rating Scale; rmANOVA = repeated measures analyses of variance.

## 1. Introduction

Shortly after the description of the neurosurgical procedure of epidural motor cortex stimulation for neuropathic pain (NP) control [1], repetitive transcranial magnetic stimulation (rTMS) was proposed as a non-invasive method to mimic epidural stimulation and predict its subsequent effectiveness. The potential value of rTMS as a pain therapy in its own right was soon recognized, and the use of rTMS as a full-fledged pain-relieving procedure has received considerable support in the last 10 years [2]. Although methodological drawbacks limited the quality of evidence of early studies due to low patients' samples, absent blinding, lack of randomization and follow-up, etc. [3,4], a number of well-conducted studies using single or double-blinded methodology, randomization and inclusion of more than 20 patients in active groups have been recently reported in chronic NP of various origins, with positive results when using stimulus frequencies of at least 10 Hz [5-11]. Accordingly, recent reviews concluded to a significant superiority over placebo of high-frequency (HF) motor cortex rTMS in chronic neuropathic pain [12-15], and clinical recommendations have now included HF-rTMS of the motor cortex as a "third line" therapeutic option, at the same level as spinal cord stimulation [16]. In the same line, a recent report of the US Department of Veterans Affairs which analysed rTMS data under a "best-evidence approach" (multisite studies, control of potential confounding factors), concluded that rTMS may reduce symptoms in NP and could be a treatment option for patients who have exhausted standard available options [12].

Transcranial direct current (galvanic) stimulation (tDCS), i.e. the non-invasive transcranial flow of electric charge that does not change direction, modulates the neuronal resting membrane state without eliciting action potentials, and has been empirically applied for medical purposes since the Roman Antiquity (Scribonius Largus ~70 AC, <https://prabook.com/web/scribonius.largus/3727651>). Modern research showed that surface anodal polarization of the cortex increases spontaneous unit discharges in rodents and felines [17,18] and enhances human motor cortical excitability with magnitude and duration comparable to those observed with rTMS [19,20]. Anodal tDCS appears therefore as a promising tool, able to emulate the analgesic effects of conventional motor cortex stimulation, with practical advantages over rTMS including its lower cost, the paucity of safety issues and the availability of home-based long-lasting protocols. However, because of the limited quality of most published reports, the level of evidence regarding tDCS effects in chronic neuropathic pain remains very low and highly conflicting, despite a large number of studies published [2,21,22].

One single study comparing the short-term effect of 3 sessions of anodal tDCS *versus* HF-rTMS in lumbosacral radiculopathy concluded to the superiority of rTMS [23], while a very recent report in 12 patients with brachial plexus injuries found similar results from both techniques [24]. Head-to-head studies directly comparing the efficacy of HF-rTMS and a-tDCS for chronic, drug-resistant NP in large patients' series are therefore warranted. In the present study we report the results of a full head-to-head, randomized, prospective, single-blinded, cross-over study comparing HF-rTMS versus anodal tDCS over the motor cortex in a large series of patients with drug-resistant NP of different etiologies. To make the results directly comparable and maximize their clinical significance, each patient could benefit consecutively from the two techniques, separated by an adequate wash out period, and daily quotations of pain and pain-related items were obtained from written diaries during the full follow-up. In addition, functional magnetic resonance imaging (fMRI) during a motor task involving the painful area was obtained before and after the procedure in a subset of patients, to investigate the possible relations between clinical efficacy of the neurostimulation techniques and changes in the activity level of task-related motor networks.

## **2. Patients and methods**

### *2.1. Study population*

This bi-centric protocol was conducted in the Neurological Hospital of the Hospices Civils de Lyon, France and in the Pain Center of the Grenoble Alpes University Hospital, France from February 2013 to December 2020. The study was approved in both centers by the Institutional Review Boards Sud-Est IV Lyon (N° 10619), and Sud-Est V Grenoble (N° 6705), France, and was registered with clinicaltrials.gov (NCT02120326, NCT02854332). All patients approved and signed an informed consent prior to entering the protocol.

Equipment, stimulation protocol and pain evaluation methods were identical in both sites, with the exception of the diameter of tDCS electrodes ( 6,2 cm soaked sponges in Grenoble, 1 cm Gel electrodes in Lyon, both by the same manufacturer Neuroelectronics®, both validated in terms of safety and without difference of effectiveness) ([25] and see results 3.3.).

Sixty-eight patients aged 18 to 80 years, suffering from lateralized pharmaco-resistant chronic neuropathic pain for more than one year, without any change in medical treatment since at least one month, were included in this study. Mean pain duration was  $5 \pm 3.8$  years. Diagnosis of neuropathic pain followed IASP NeuPSIG guidelines [26], and a level of probable to definite neuropathic pain was required for inclusion [27]. The patients were classified into five groups

according to the origin of pain: central post-stroke pain, central cancer and vascular pain, spinal cord injury, facial pain, brachial plexus injury (Table 1). They were not included if they had a history of epilepsy, drug-addiction, migraine, intracranial ferromagnetic material or implanted stimulator.

All patients (except one who had discontinued all drugs due to inefficacy before entering the study) were taking one or more analgesic treatments (anti-epileptic drugs, antidepressants and / or painkillers level 1, 2 or 3) (Table 1). Patients were asked to maintain their ongoing analgesic treatment unchanged for the duration of the protocol, but were allowed to take medication for breakthrough pain if needed.

**Table 1**

Baseline characteristics of patients according to the allocated group.

	<b>Total (n = 56)</b>	<b>rTMS then tDCS (n = 26)</b>	<b>tDCS then rTMS (n = 30)</b>	<b>P-value</b>
Age (year), mean (SD)	58.6 (13.2)	60.2 (13.7)	57.3 (12.9)	0.407
Female, n (%)	27 (48%)	12 (46%)	15 (50%)	0.774
Washout period (week), median (IQR)	10.0 (9.0, 12.1)	10.0 (9.0, 12.0)	10.7 (9.0, 12.1)	0.904
<b>Disease history</b>				
Pain syndrome duration (year), median (IQR)	5 (3, 8)	5 (3, 8)	5 (3, 7)	0.391
Pain origin, n (%):				0.569
Brachial plexus injury	4 (7%)	2 (8%)	2 (7%)	
Spinal cord injury	6 (11%)	4 (15%)	2 (7%)	
Central post-stroke pain	21 (37.5%)	7 (27%)	14 (46%)	
Brain tumor, vascular and other pain	4 (7%)	2 (8%)	2 (7%)	
Orofacial pain	21 (37.5%)	11 (42%)	10 (33%)	
<b>Summary of pharmacological treatment</b>				
Number of drugs/patient, median (IQR)	2 (2, 3)	2 (2, 3)	2 (2, 2)	0.340
Drug class, n (%):				
Antiepileptics	39 (70%)	18 (69%)	21 (70%)	0.950
Antidepressants	36 (64%)	17 (65%)	19 (63%)	0.873
Strong opioids	6 (11%)	2 (8%)	4 (13%)	0.496
Weak opioids	22 (39%)	11 (42%)	11 (37%)	0.666
Non-opioid analgesics	15 (27%)	9 (35%)	6 (20%)	0.218
<b>Clinical score<sup>a</sup> during the week pre-stimulation</b>				
Pain score, mean (SD)	6.4 (2.0)	6.0 (2.1)	6.7 (2.0)	0.180
Sleep score, mean (SD)	4.7 (2.5)	4.8 (2.6)	4.7 (2.6)	0.876
Fatigue score, mean (SD)	5.5 (2.3)	5.0 (2.4)	5.9 (2.2)	0.170

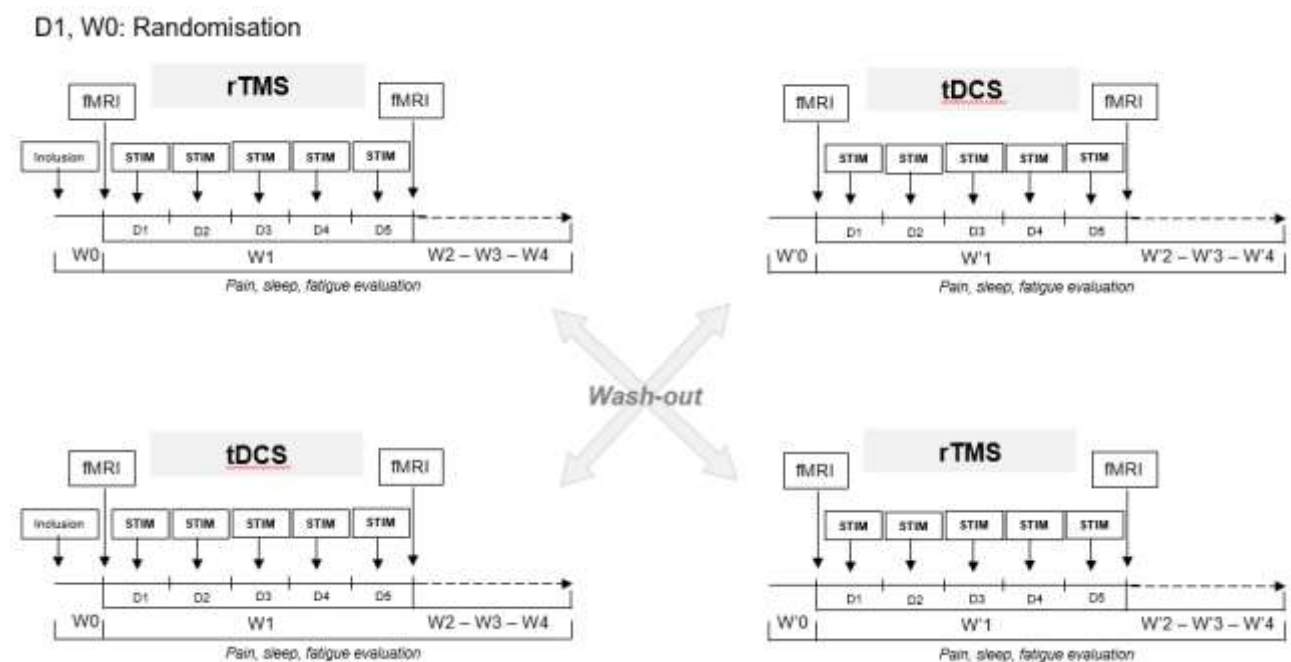
Abbreviations: *SD*, standard deviation; *IQR*, Interquartile Range. <sup>a</sup>Numerical rating scale (NRS). The NRS score ranges from 0 to 10, with 0 indicating no pain/sleep disorder/fatigue and 10 the worst imaginable pain/sleep disorder/fatigue.

## 2.2. Study design

Eligible patients were randomized 1:1 to one of the two treatment sequences: rTMS followed by tDCS (group I) or tDCS followed to rTMS (group II) through simple randomization (random numbers generated by computer). Each patient benefited from two stimulation cycles of 1-week each (rTMS and tDCS) at least 4 weeks apart, each cycle comprising 5 daily sessions of stimulation (Figure 1). Patients filled a diary evaluating pain intensity using a numerical rating scale (NRS) ranging from 0 (no pain) to 10 (the worst pain possible) every day during 5 weeks: from one week (W0) before stimulation week (W1) to 3 weeks after the end of stimulation (W2, W3 and W4). In addition, patients were also asked to provide daily ratings of sleep quality, fatigue, and “rescue” medication [28]. A minimal wash-out period of 4 weeks preceded the second phase, with identical design but different stimulus modality. At the end of the second phase, patients sent their notebook to a nurse different from the investigators and continued medical follow-up with their pain physician. Investigators did not have access to the patients’ ratings before the end of each trial.

**Figure 1.** Study design.

Abbreviations: *rTMS*, Repetitive Transcranial Magnetic Stimulation; *tDCS*, Transcranial Direct Current Stimulation; *fMRI*, Functional Magnetic Resonance Imaging; *D*, day; *W0*, baseline; *W1*, stimulation sessions; *W2-W3-W4*, follow-up period.



Chronic drug intake was maintained unchanged during the whole study period, with the exception of punctual ‘rescue’ drugs for breakthrough pain, if needed, which must be reported in the patients’ logbook. From 68 patients initially entering the study, 56 completed all 5 weeks of data for at least one mode of stimulation, and 46 completed all follow-up from both techniques (Figure 2).

The protocol included two identical magnetic resonance imaging (MRI) sessions, respectively preceding and immediately following the first week of stimulation, whatever its type. The sessions were performed on 3T Philips Achieva-TX scanners with a 32-channel head coil at both Lyon and Grenoble sites. Each session included a first morphological 3D T1-weighted sequence eventually used for neuronavigation-based treatment, and then a set of four BOLD weighted fMRI runs. The fMRI runs included each a different movement task: a right hand movement of the Vth finger, a left hand movement of the Vth finger, a right zygomatic movement of the face and a left zygomatic movement (half a smile). Each fMRI run consisted in a block design with 3 epochs of 30 seconds alternating with rest epochs of 30 seconds, for a total duration of 3 minutes and 30 seconds per run.

The complete procedure is schematized in Figure 1.

### *2.3. Stimulation parameters*

Stimulation was carried out in the University Hospital Pain Center (CETD) of the Neurological Hospital of Lyon and in the Pain Centre of the Grenoble Alpes University Hospital. rTMS and tDCS were performed using the same stimulators in both experimental centers.

rTMS (Mag-Pro X100, MagVenture<sup>®</sup>) induced biphasic magnetic pulses via an eight-shaped coil (cool-B65 butterfly shape coil MagVenture<sup>®</sup>). The motor strip was localized in each patient using T1-3D MRI, and the stimulating coil positioned perpendicular to the central sulcus, with postero-anterior orientation. The optimal position of the coil was determined using the MRI-Neuronavigation system with Visor<sup>®</sup> software (ANT<sup>®</sup>) and collecting EMG responses of the abductor digiti minimi. Motor threshold at rest was defined before each stimulation session as the lowest intensity that produced five responses with peak-to-peak amplitude of at least 50  $\mu$ V in ten consecutive trials [29]. Each 10Hz-rTMS session comprised 32 consecutive trains of 50 pulses, delivered at 90% of motor threshold, separated by inter-trains intervals of 25 s (i.e. a total of 1600 pulses during a 17 min session).

tDCS (DC stimulator NIC-Starstim<sup>®</sup>, Neuroelectrics<sup>®</sup>) was delivered in Grenoble via sponge electrodes soaked in salty solution and in Lyon via NG electrodes placed on prefixed positions on a neoprene cap with a conductive gel between the electrodes. An impedance below 5 kOhms

was required to initiate stimulation. For each tDCS session, a 2 mA anodal stimulation was applied during 20 min over the motor cortex contralateral to pain, over C3/C4 positions of the international 10-20 system. The cathode was placed over the frontal-polar region, ipsilateral to pain, over Fp1/Fp2.

#### *2.4. Outcome variables and Statistical analyses*

From the week preceding the stimulation (Day -7) to the end of the four week following the stimulation period (Day 28), patients used a diary at home to record the following information: pain intensity, quality of sleep and fatigue, using a 0-10 numerical rating scale (total 5 weeks). Daily NRS ratings were averaged week per week.

The primary outcome was the analgesic effect of each stimulation modality compared to its own baseline (week before stimulation: W0 on Figure 1). Secondary outcomes were the quality of sleep and fatigue for each stimulation modality compared to its own baseline (same analyses as for pain intensity).

To allow inter-subject comparisons, daily NRS were normalized using Z-scores [30,31]. Thus, each daily pain rating was Z-transformed using the formula  $(X_i - X_{\text{baseline}}) / SD_{\text{baseline}}$ , where  $X_i$  is the actual raw daily rating in day “i”,  $X_{\text{baseline}}$  is the average rating from the pre-stimulation week in the same individual, and  $SD_{\text{baseline}}$  the associated standard deviation of NRS values during this pre-stimulation week. Patients were considered as “responders” if their pain ratings decreased by at least 2 standard deviations (SD) from baseline, during at least one week.

Continuous data are expressed as mean  $\pm$  standard deviation (SD) or median (25th-75th centiles), and categorical data are expressed as numbers and percentages. Comparisons of baseline characteristics between allocated groups (rTMS/tDCS versus tDCS/rTMS) and responders versus non-responders to each modality were conducted by using the Chi-square or Fisher's exact tests, Student's t-test or Wilcoxon-Mann-Whitney test. Homogeneity of the two groups regarding pain ratings was tested by comparing with a two-tailed paired t-test their respective NRS during the baseline week, before initiating the stimulation periods. NRS during the week before the first and second stimulation cycles (regardless of the stimulation type) were also compared with two-tailed paired t-test to check for possible carry-over effects. In the patients who completed the entire study (n=46), normalized pain scores were compared using a 2-way repeated-measures ANOVA (time x stimulation mode). A p-value <0.05 was considered significant after Greenhouse-Geisser correction when needed. Correlation between the magnitude of the analgesic effect from rTMS and tDCS was studied using Pearson-product-moment coefficients.



Data were analyzed using GraphPad Prism. A two-sided P value  $<0.05$  was considered statistically significant.

### 2.5. *fMRI analysis*

Using SPM12 software (The Wellcome Department of Cognitive Neurology, London; <http://www.fil.ion.ucl.ac.uk/spm/>), image pre-processing was performed in each subject's referential and included motion correction, slice timing and registration to the anatomical image of the pre-treatment session. Doing so, both pre-treatment and post-treatment functional images are in the same referential. Individual statistical analysis was estimated using a linear generalized model to produce the following contrasts: (i) the individual contrasts for each task at each time point and (ii) the differential contrast for each task after *vs.* before the treatment. The anatomical image of the pre-treatment session of each subject was segmented into 6 classes of tissue (grey matter, white matter, cerebrospinal fluid, large vessels, meninges and scalp) using the tissue probability maps provided by the software. In order to transform the images in a common referential for group analysis, we computed the deformation field to be applied to each individual to match a symmetrical template, provided by the CAT12 software ([neuro.uni-jena.de/cat12-html/cat\\_versions.html](http://neuro.uni-jena.de/cat12-html/cat_versions.html)). The DARTEL method was used to achieve a clear difference between primary motor and primary sensory cortices [32]. The deformation field computed for each subject were applied to individual contrast images. Since the pain lateralization is patient-dependent, so was the stimulated hemisphere. In order to be able to pool the stimulated hemispheres and to compare them to the non-stimulated hemispheres, the individual contrast images were left-right flipped when necessary so as to obtain the stimulated hemisphere on the left side of the image and the unstimulated hemisphere on the right side of the image.

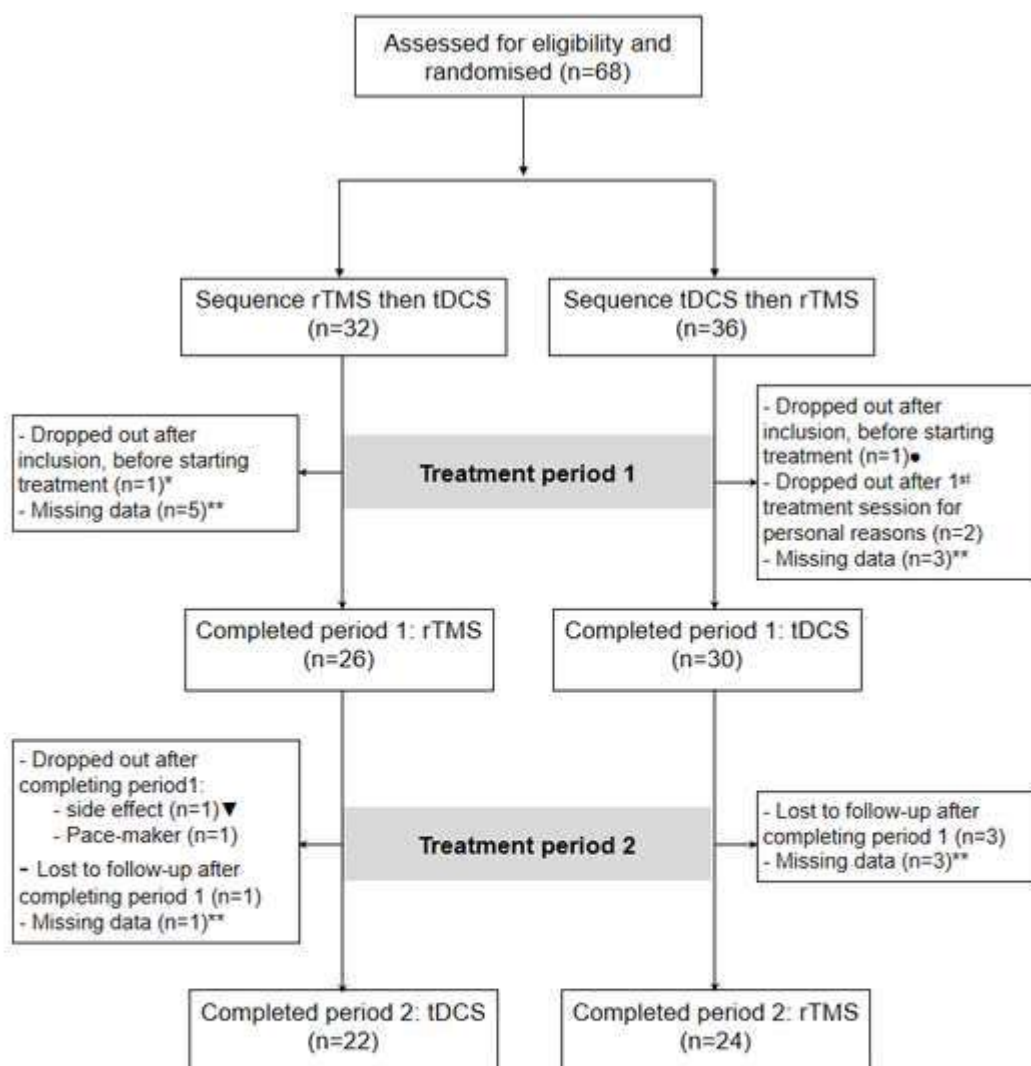
For inference at the group level, several statistical tests were performed. First, a comparison between the post- and pre-stimulation contrasts using paired t-test for the two types of treatment, each type of treatment and between type of treatment, to investigate the general effect of stimulation, the effect of each type of stimulation and the differential effect between both types of stimulation. Second, to check whether the effect of stimulation differed in responders *vs.* non-responders, a comparison between the post-stimulation and the pre-stimulation was tested between contrasts according to the responding status, using two sample t-test. Third, in order to check whether movements performed in the painful and the non-painful sides generated differential brain activation patterns, a comparison between movements in both sides previous to any treatment was tested using paired-t-test. Finally, in order to check whether the pattern

corresponding to movement in the painful side could predict the response to treatment, the contrast corresponding to movement in the painful side before treatment was compared between subgroups of responders and non-responders. Differences were considered significant when  $p < 0.05$  after correction for multiple comparisons using family-wise error at voxel level and the probability for the extent of activation cluster to be found by chance was below 0.05.

### 3. Results

#### 3.1. Flowchart of the study

**Figure 2.** Participant flow diagram.



\*post-stroke pain: no motor response at maximal energy

•interruption of the stimulation due to a technical problem

\*\*patients who benefited from the stimulation session but did not provide usable notebooks

▼noise intolerance (despite hearing protection) and headache

Figure 2 depicts the flowchart of the study participants. Sixty-eight patients were initially recruited and randomly assigned to study groups: “rTMS then tDCS” (group I) or “tDCS then rTMS” (group II). Fifty-six patients completed the first phase of the protocol (26 group I and 30 group II) and 46 patients completed both phases of study (22 group I and 24 group II). Functional imaging (fMRI) study comparing motor-evoked activations pre- and post-neurostimulation was performed in 31 of the 56 patients who completed the protocol. The MRI study could not be completed in the others for patient-dependent reasons (unavailability for the 2<sup>nd</sup> session) or organizational difficulties in connection with time-slot availability in the radiology department. Despite such difficulties, the sample presented here is to our knowledge the largest group of patients described so far with motor-related fMRI performed before and immediately after a series of motor cortical stimulation for neuropathic pain.

### 3.2. Baseline demographics and clinical characteristics

The demographics and baseline characteristics of the 56 patients who completed the 5-weeks follow-up assessment of the first phase are shown in Table 1. The mean age of the patients was  $58.6 \pm 13.2$  years. No significant differences at baseline were found between groups I and II (starting with rTMS or tDCS) according to age, sex, and origin of pain or clinical scores during the week pre-stimulation.

**Table 1**

Baseline characteristics of patients according to the allocated group.

	<b>Total (n = 56)</b>	<b>rTMS then tDCS (n = 26)</b>	<b>tDCS then rTMS (n = 30)</b>	<b>P-value</b>
Age (year), mean (SD)	58.6 (13.2)	60.2 (13.7)	57.3 (12.9)	0.407
Female, n (%)	27 (48%)	12 (46%)	15 (50%)	0.774
Washout period (week), median (IQR)	10.0 (9.0, 12.1)	10.0 (9.0, 12.0)	10.7 (9.0, 12.1)	0.904
<b>Disease history</b>				
Pain syndrome duration (year), median (IQR)	5 (3, 8)	5 (3, 8)	5 (3, 7)	0.391
Pain origin, n (%):				0.569
Brachial plexus injury	4 (7%)	2 (8%)	2 (7%)	
Spinal cord injury	6 (11%)	4 (15%)	2 (7%)	
Central post-stroke pain	21 (37.5%)	7 (27%)	14 (46%)	
Brain tumor, vascular and other pain	4 (7%)	2 (8%)	2 (7%)	
Orofacial pain	21 (37.5%)	11 (42%)	10 (33%)	
<b>Summary of pharmacological treatment</b>				
Number of drugs/patient, median (IQR)	2 (2, 3)	2 (2, 3)	2 (2, 2)	0.340
Drug class, n (%):				0.950
Antiepileptics	39 (70%)	18 (69%)	21 (70%)	

Antidepressants	36 (64%)	17 (65%)	19 (63%)	0.873
Strong opioids	6 (11%)	2 (8%)	4 (13%)	0.496
Weak opioids	22 (39%)	11 (42%)	11 (37%)	0.666
Non-opioid analgesics	15 (27%)	9 (35%)	6 (20%)	0.218
<b>Clinical score<sup>a</sup> during the week pre-stimulation</b>				
Pain score, mean (SD)	6.4 (2.0)	6.0 (2.1)	6.7 (2.0)	0.180
Sleep score, mean (SD)	4.7 (2.5)	4.8 (2.6)	4.7 (2.6)	0.876
Fatigue score, mean (SD)	5.5 (2.3)	5.0 (2.4)	5.9 (2.2)	0.170

Abbreviations: *SD*, standard deviation; *IQR*, Interquartile Range.

<sup>a</sup>Numerical rating scale (NRS). The NRS score ranges from 0 to 10, with 0 indicating no pain/sleep disorder/fatigue and 10 the worst imaginable pain/sleep disorder/fatigue.

### 3.3. Primary outcome

Patients were defined as “responders” if pain scores decreased by at least 2 SDs relative to baseline values (W0) during one week or more (see Methods), and these criteria were met by 21/50 patients (42.0%) for rTMS and 22/52 (42.3%) for tDCS, the difference being non-significant. The number of responders was also similar in the 46 patients receiving both techniques (two-sided Fisher’s exact test:  $p=0.76$ ). Of notice, almost half of these patients (21/46) responded to one modality exclusively (12 responded only to rTMS and 9 only to tDCS). We did not find any significant difference between responders and non-responders regarding their characteristics at baseline, including age, sex, origin or intensity of pain, quality of sleep and fatigue scores (Table 2).

In the 46 patients who received both stimulation modalities, a 2-way, rm-ANOVA (time x stimulation mode) on Z-normalized pain changes between W0 and W4 showed a significant effect of time ( $F(4,360)=10.98$ ;  $p<10^{-3}$ ) but no effect of stimulation mode ( $F(1,360)=0.46$ ;  $p=0.50$ ) and no interaction ( $F(4,360)=51.10$ ;  $p=0.35$ ). Figure 3 illustrates the evolution of Z-normalized pain scores during the 4 weeks post-stimulation according to response status.

The percentage of pain decrease at the “best week” (the week with most prominent changes) for each modality was significantly correlated ( $r=0.34$ ;  $p=0.005$ ). However, as illustrated in Figure 4, the slope of the regression line ( $\beta=0.34$ , 95% CI= [0.10-0.54]) was significantly biased in favor of rTMS relative to the theoretical equivalence slope ( $\beta=1$ ). No significant difference was found in the level of pain decrease according to the type of electrode used for tDCS in the two experimental sites.

**Table 2**

Baseline characteristics of responders versus non-responders.

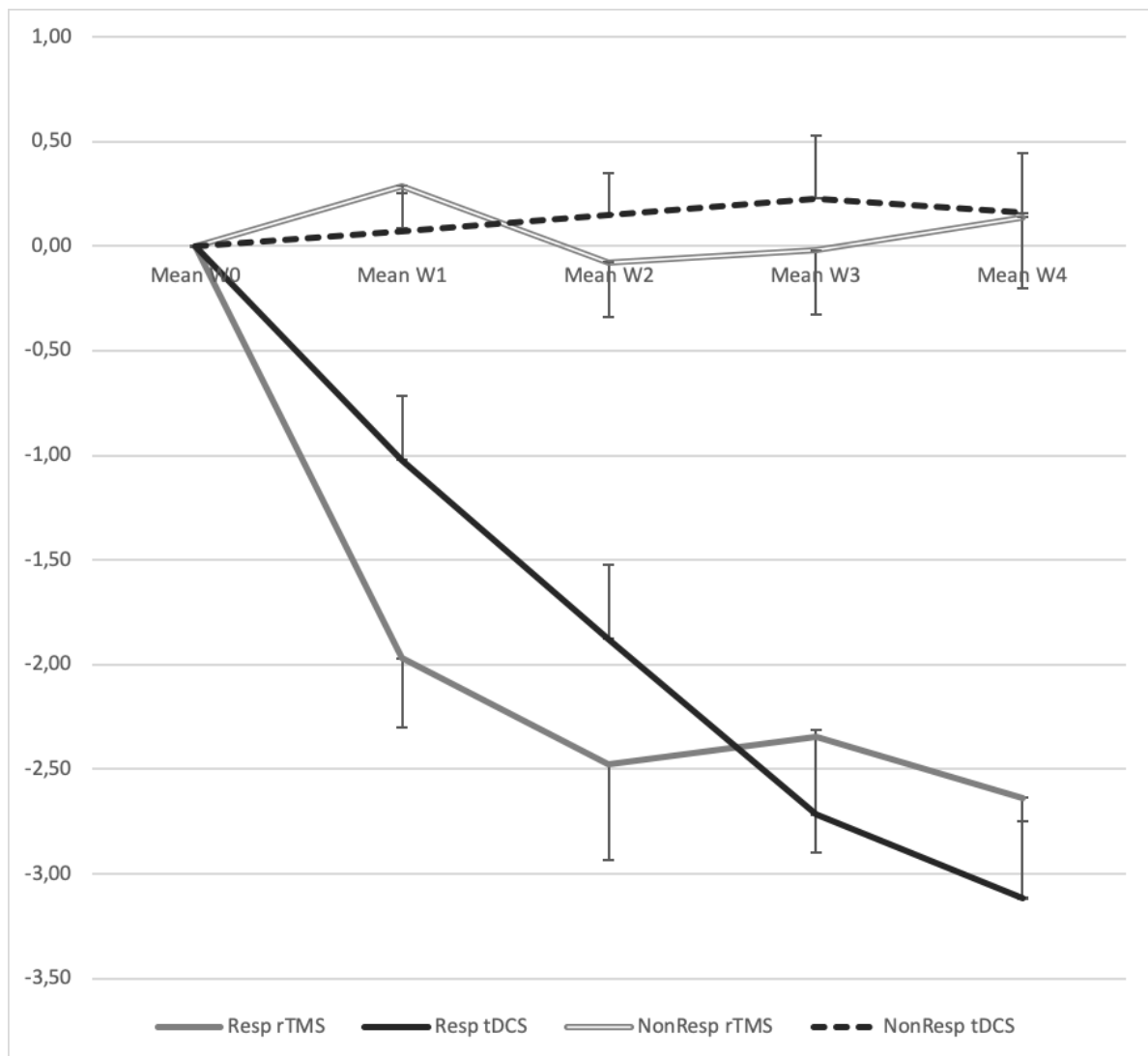
	rTMS			tDCS		
	Responders (n = 21)	Non-responders (n = 29)	<i>P-value</i>	Responders (n = 22)	Non-responders (n = 30)	<i>P-value</i>
Age (year), mean (SD)	61.1 (12.1)	57.0 (14.9)	0.299	59.5 (12.6)	58.6 (12.6)	0.817
Female, n (%)	9 (43%)	14 (48%)	0.704	12 (55%)	14 (47%)	0.575
<b>Disease history</b>						
Pain syndrome duration (year), median (IQR)	5 (3, 8)	5 (3, 7)	0.945	5 (3, 8)	5 (3, 7)	0.886
Pain origin, n (%):			0.513			0.839
Brachial plexus injury	2 (10%)	2 (7%)		1 (4.5%)	3 (10%)	
Spinal cord injury	3 (14%)	2 (7%)		2 (9%)	3 (10%)	
Central post-stroke pain	6 (29%)	11 (38%)		9 (41%)	12 (40%)	
Central cancer, vascular and other pain	3 (14%)	1 (3%)		1 (4.5%)	3 (10%)	
Facial pain	7 (33%)	13 (45%)		9 (41%)	9 (30%)	
<b>Summary of pharmacological treatment</b>						
Number of drugs/patient, median (IQR)	2 (1, 3)	2 (2, 3)	0.651	2 (1, 2)	2 (2, 3)	0.136
Drug class, n (%):						
Antiepileptics	14 (67%)	21 (72%)	0.662	13 (59%)	26 (87%)	0.023
Antidepressants	14 (67%)	17 (59%)	0.563	15 (68%)	19 (63%)	0.717
Strong opioids	3 (14%)	2 (7%)	0.390	2 (9%)	3 (10%)	0.913
Weak opioids	5 (24%)	14 (48%)	0.079	7 (32%)	12 (40%)	0.545
Non-opioid analgesics	6 (29%)	8 (28%)	0.939	4 (18%)	8 (27%)	0.473
<b>Clinical score<sup>a</sup> during the week pre-stimulation</b>						
Pain score, mean (SD)	6.7 (1.8)	6.1 (1.9)	0.297	6.7 (2.2)	5.8 (2.0)	0.144
Sleep score, mean (SD)	4.7 (2.6)	4.8 (2.3)	0.916	4.2 (2.5)	4.6 (2.7)	0.602
Fatigue score, mean (SD)	5.5 (2.2)	5.3 (2.5)	0.825	5.7 (2.1)	5.3 (2.6)	0.509

Abbreviations: *SD*, standard deviation; *IQR*, Interquartile Range<sup>a</sup>Numerical rating scale (NRS). The NRS score ranges from 0 to 10, with 0 indicating no pain/sleep disorder/fatigue and 10 the worst imaginable pain/sleep disorder/fatigue.

**Figure 3.** Evolution of Z-normalized pain scores during the 4 weeks post-stimulation.

Evolution of pain scores in responders and non-responders during the 4 weeks (W1 to W4) post-stimulation. Pain reports were normalized as z-scores relative to values during the baseline pre-stimulation week (W0; see Methods), and patients were considered as ‘responders’ if their scores decreased by more than 2SD relative to baseline. The groups of responders and non-responders were clearly differentiated since the first week post-stimulation, with no overlap.

Abbreviations: rTMS, High-Frequency repetitive Transcranial Magnetic Stimulation; tDCS, transcranial Direct Current Stimulation. Resp rTMS: responders to rTMS; Resp tDCS: responders to tDCS; NonResp rTMS: non responders to rTMS; NonResp tDCS: non responders to tDCS.

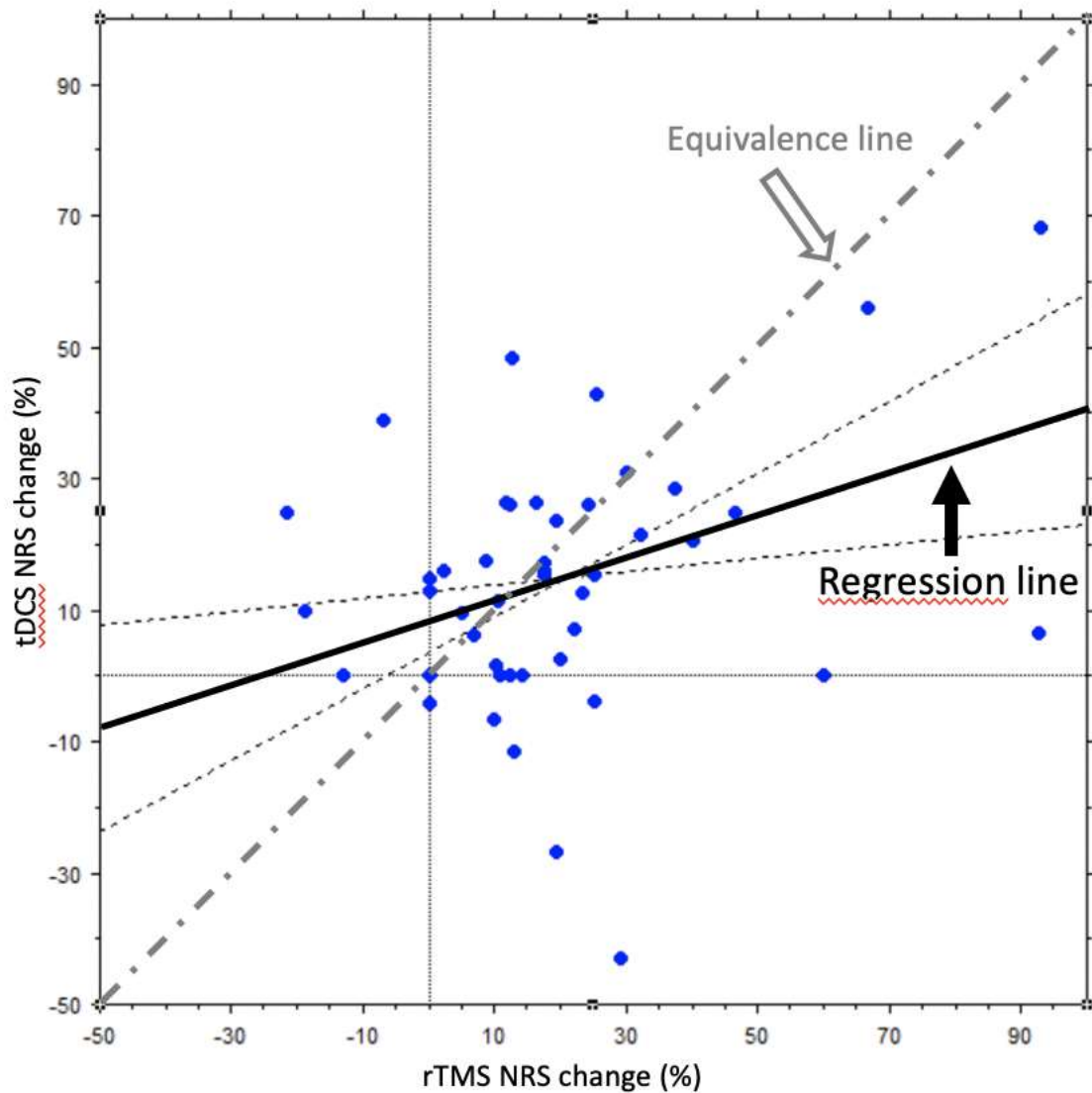


Pain scores during the baseline preceding the second stimulation session were decreased relative to those preceding the first one ( $6.4 \pm 1.9$  vs.  $5.9 \pm 2.3$ ; two-tailed paired t-test:  $p=0.03$ ) reflecting a possible carry-over effect independent of the stimulus mode. However, NRS baseline values were not significantly different when preceding rTMS or tDCS (two-tailed paired t-test:  $p=0.44$ ).

**Figure 4.** Correlation between NRS percentage changes after rTMS and tDCS.

Correlation between maximal percentage changes of numerical pain reports (NRS) after rTMS and tDCS. Although NRS changes to both techniques were correlated, the slope of the regression line was significantly skewed towards rTMS, with confidence limits (dotted lines) which did not reach the theoretical equivalence line of  $\beta=1$ .

Abbreviations: rTMS, High-Frequency repetitive Transcranial Magnetic Stimulation; tDCS, transcranial Direct Current Stimulation; NRS, Numerical Rating Scale.



### 3.4. Secondary outcomes

#### 3.4.1. Quality of sleep and fatigue

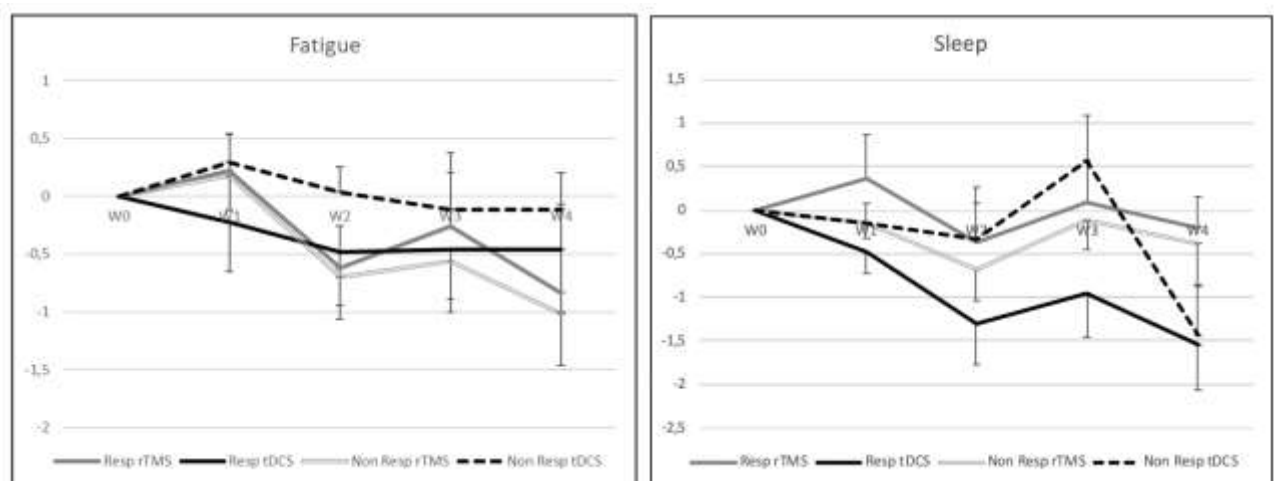
Self-assessment of sleep and fatigue changed very little during the 4 weeks post-stimulation, and no significant differences between techniques were observed (Figure 5). A 2-way, rmANOVA (time x stimulation mode) on Z-normalized fatigue changes between W0 and W4

showed a significant and favorable effect of time ( $F(4,336)=3.13$ ;  $p=0.01$ ) but no effect of stimulation mode ( $F(1,336)=0.00$ ;  $p=0.97$ ) and no interaction ( $F(4,336)=0.71$ ;  $p=0.58$ ). Comparable results were obtained for sleep changes: 2-way, rmANOVA (time x stimulation mode) on Z-normalized changes between W0 and W4 showed a significant effect of time ( $F(4,320)=6.75$ ;  $p<10^{-3}$ ) but no effect of stimulation mode ( $F(1,320)=0.11$ ;  $p=0.74$ ) and no interaction ( $F(4,320)=0.66$ ;  $p=0.62$ ).

**Figure 5.** Weekly evolution of fatigue and sleep scores in responders and non-responders during the 4 weeks (W1 to W4) post-stimulation.

A global trend to a decrease of severity with time was observed, with no significant difference either according to the stimulation modality or according to the response to treatment.

Abbreviations: rTMS, High-Frequency repetitive Transcranial Magnetic Stimulation; tDCS, transcranial Direct Current Stimulation.



### 3.4.2. Secondary outcomes: fMRI

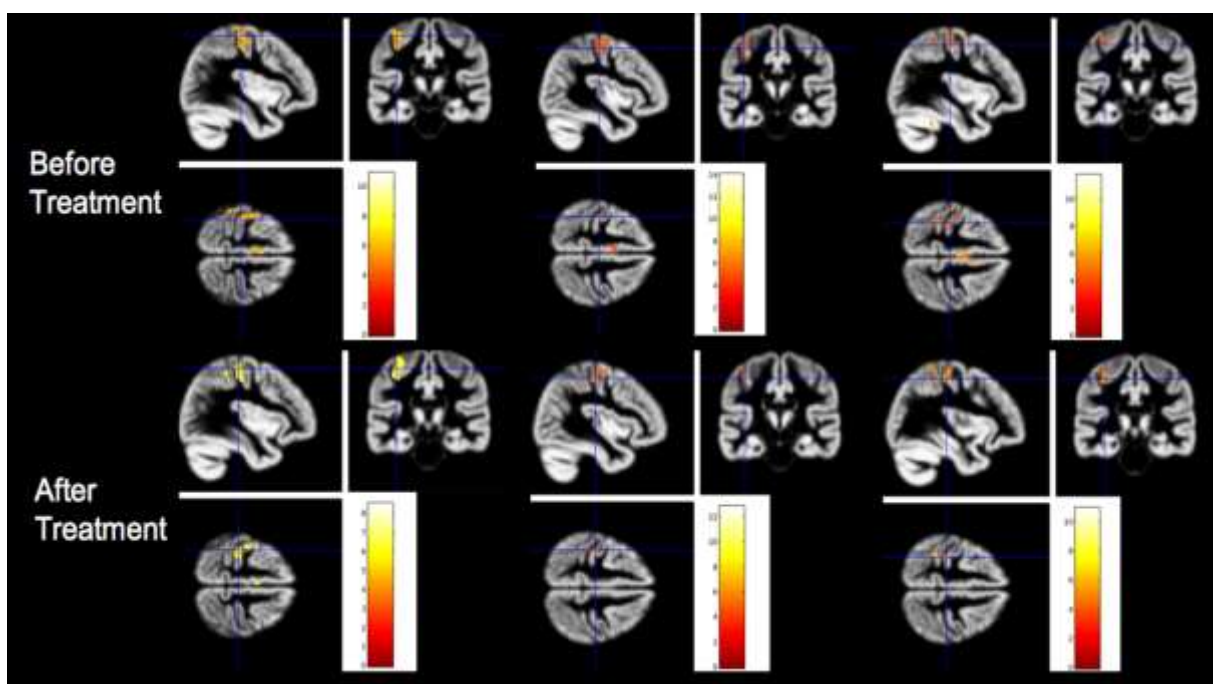
At the group-level, the activation pattern for the finger movement contralateral to the pain involved as expected the primary motor and supplementary motor areas within the motor network (Figure 6). The pattern of motor-related activation did not show statistically significant differences for the painful and the non-painful sides. This pattern was similar before and after the treatment, and not statistically different following rTMS or tDCS, nor when both treatments were pooled together. The distribution and magnitude of motor-related activation after the treatment were equivalent when compared between responders and non-responders. In order to disclose any pre-stimulation feature in motor activation that could be predictive of cortical stimulation efficacy, we checked for differences in activation patterns in responders and non-responders before treatment, but no significant differences were detected between sub-groups.



Taken together, this set of analyses showed the expected patterns of brain activation during voluntary movement, but failed to demonstrate significant differences in fMRI motor activity patterns at group level, neither between techniques nor between responders and non-responder patients.

**Figure 6.** BOLD activation patterns during the motor task.

BOLD activation patterns during the motor task, combined for both procedures (left column) or separated by type of stimulation (middle column rTMS, right column tDCS). The motor task induced significant activations in the contralateral sensori-motor cortex and the supplementary motor area (SMA), with no significant differences before (upper panel) or after one week of daily motor cortex stimulation (lower panel). See details in the text.



### 3.5. Adverse effects

No serious adverse effects were reported during or following any of the two interventions, but minor side effects were noted very occasionally. One patient complained of noise intolerance (despite wearing hearing protection) and headaches during the rTMS session and discontinued the study. One patient reported tension headache immediately after rTMS, and 3 patients complained about this symptom several days after the end of the stimulation week (1 week and 2 weeks after the end of rTMS, and 2 days after the end of tDCS). These headaches were relieved by a level-1 analgesic (paracetamol) and did not recur. Skin irritation was observed under a tDCS electrode on 3 occasions, without recurrence the following days.”

#### 4. Discussion

Both rTMS and tDCS decreased pain levels in this series of patients with pharmaco-resistant neuropathic pain. Although pain decrease was overall significant at the group level for the two interventions, individual analysis showed that only 42% of the patients achieved a significant level of pain decrease, defined as a change equal or superior to 2 SDs relative to the average ratings in the week previous to stimulation. Analysis of the consecutive weekly pain ratings showed that there was no overlap between the timelines of responders and non-responders: pain ratings in responders progressively decreased during the week of stimulation, and then during the 3 following weeks, whereas in non-responders the sequence of changes in pain ratings was virtually horizontal and around zero to either procedure (Figure 3).

Best pain decrease in responders was moderate when considering raw NRS values, about 31% of initial values in the average. This is consistent with a number of previous reviews and meta-analyses [3,4,12] and represents a significant but moderate improvement according to IMMPACT consensus statement criteria of “clinically meaningful” treatment [33]. It has been suggested that more than 5 consecutive stimulation sessions may be necessary to induce a maximal analgesic effect, both for rTMS [34] and tDCS [35], and iteration of maintenance sessions at longer intervals has proved useful to maintain or enhance the analgesic effects [5,34]. Of notice, although the changes observed here may not appear impressive, they concern patients who had previously proven to be drug-resistant to both 1<sup>st</sup> and 2<sup>nd</sup> line drugs for neuropathic pain, in many cases for more than one year. Furthermore, normalized pain ratios warranted that in any patient qualified as ‘responder’ pain had abated by at least 2 SDs relative to pre-stimulus values, and often reaching up to -3 SDs, which ensured a sizeable effect size at the individual level. Indeed, the Z-score of normalization is individually tailored and takes into account the intrinsic variability of pain reports at baseline in each patient, hence minimizing any changes in scores that do not exceed significantly such pre-stimulus variability. Z-score normalization is also the preferred method in other domains in pain research, notably when describing changes in quantitative sensory testing [28,36,37].

When tested as a group, the overall magnitude of changes in pain scores due to rTMS and tDCS did not differ significantly, and their respective levels were highly correlated. However, as illustrated in Figure 5, the regression line between the best level of pain relief in both techniques appeared skewed toward rTMS, and significantly different from the theoretical equivalence slope (45°, or  $\beta=1$ ), suggesting a slightly superior level of pain relief for rTMS at individual level, and under the conditions tested here. We cannot rule out the possibility that the number of stimulation sessions to achieve a given level of relief may be different for tDCS and rTMS.

Although there is not, to our knowledge, a direct comparison of both techniques in this respect, the number of sessions considered sufficient to obtain maximal analgesic effects was estimated as 7 for rTMS by Hodaj et al., 2020 [34], and as high as 15 for tDCS by Castillo-Saavedra et al., 2016 [35]; such disparities may have influenced the present results.

The percentage of responders to either technique was almost identical (42%), but the individual patients responding to each procedure were not the same. This is an indirect indication that the mechanisms underlying the pain-relieving effect of both techniques may differ, at least in their initial “induction” phase. In support of this view, a lack of effect of tDCS has been described in patients previously responding to rTMS [38], and conversely a patient with chronic NP not responding to rTMS could be improved in the long term by anodal tDCS [39]. A very recent report comparing these two techniques in 12 patients with brachial plexus avulsion also found that different patients may be differentially sensitive to one or the other [24]. Together with these previous reports, the present study in a larger sample of NP patients appears clinically relevant in that it highlights the possibility of using one technique if the other fails, thereby increasing the probability of a positive response, which currently tops out at about 50% for rTMS [2,3,14].

The brain activation pattern during motor tasks mainly involved as expected the primary motor and supplementary motor areas, and remained unchanged from the beginning to the end of the stimulation week, for both rTMS and tDCS. Such lack of evidence for motor-related plasticity after 1-week of stimulation might indicate that the second fMRI was conducted too early to detect possible motor-related effects triggered by the procedures, which may have occurred later. Indeed, post-intervention fMRI data were acquired at the end of the stimulation week, whereas the maximal effects on pain in responders were not obtained until one week later or more (Figure 3). If plastic changes in the cortex develop in parallel with the decrease in pain, they may have gone unnoticed in our patients because of the different temporality of recordings. Although technically challenging, future studies should consider the importance that fMRI data be acquired in close connection with changes in pain reports.

The relation of local changes in motor networks and pain relief from cortical neurostimulation remains a subject of debate, as it remains unclear whether rTMS entails sizeable changes in intracortical motor circuits under the conditions used to treat pain. Indeed, while stimulation at levels above motor threshold induced clear metabolic activation in M1, such activation was found to subside or disappear at the sub-threshold levels commonly applied for pain relief [40,41]. Also, although a correlation was initially described between intracortical motor inhibition and rTMS-induced pain relief [42], later studies in NP patients failed to reproduce

such effects [43,44], and rTMS analgesia could be blocked pharmacologically in the absence of motor excitability changes [45]. Therefore, while widespread long-distance changes in cortical and subcortical structures after rTMS/tDCS have received consistent support, the relevance of motor cortex excitability for rTMS analgesic effects remains unconfirmed.

An obvious limitation of this study is the lack of long-term follow-up beyond 5 weeks [4]. The long-term maintenance of pain relief in responding patients is a major challenge for all non-invasive stimulation methods, and different procedures are being currently tested, mostly based on the progressive spacing out of consecutive sessions [2, 46]. Future studies should consider providing assessment of pain relief during months or years if these techniques are to be accepted as routine treatments for chronic pain [12]. The head-to-head design of the study, comparing tDCS to a reference active stimulation (rTMS) instead of a placebo, also entails interpretative limitations. According to current literature, rTMS can now be considered as a validated procedure for drug-resistant neuropathic pain [2,12,14] that has been incorporated to standard guidelines for NP therapy [16] and could in our view act as a valid reference. This also made it possible to avoid subjecting patients suffering from drug-resistant pain for many years to a placebo. Although the placement of the anode tDCS was centred on the motor cortex, the size of the electrodes and the standard motor-prefrontal montages entail a current distribution covering a region much more extended than the focalised figure-of-eight rTMS coil, and could render the comparison hazardous [47]. New high-definition tDCS montages could permit more focalised current distribution around the motor cortex, but their use in neuropathic pain remains anecdotal [48]. Finally, our fMRI analysis was restricted to the activations induced by a motor task. Analysis of resting state, pain-related activity and connectivity changes before and after stimulation may prove in the future much better approaches to investigate the brain activities accompanying and/or supporting neurostimulation-related pain relief [49].

## **5. Conclusion**

In patients with drug-resistant neuropathic pain, five daily sessions of tDCS or rTMS over the motor cortex showed a similar pattern of efficacy at one month. Each technique entailed significant effects in about half of the patients, and half of them responded to one procedure only; therefore, both techniques deserve being tested before declaring a patient as unresponsive. Pain relief was not paralleled by motor-related plasticity on fMRI. Since duration of pain relief after 5 daily sessions often does not exceed some weeks (2,44), prolonging the beneficial effects of neurostimulation in responders remains a crucial issue. Potential solutions include delivering

maintenance sessions at progressively longer intervals, autonomous stimulation at home, and/or neurosurgical implanted stimulation.

### **Acknowledgments**

The authors would like to thank Dr Jean-Pierre Alibeu and Koichi Hagiwara for their contribution to the work leading to this article, the medical staff of the University Pain Centers of Lyon and Grenoble, who referred to us many of the patients treated herein, and the technical staff that provided logistic assistance.

### **Declaration of competing interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### **Funding**

This work was supported in part by the "Fondation APICIL", "Agir à Dom" and LABEX CORTEX (ANR-11-LABX-0042) of Université de Lyon, within the program "Investissements d'Avenir" (ANR-11-IDEX-0007) conducted by the French National Research Agency (ANR).

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## **5.5. Long-term analgesic effect of trans-spinal direct current stimulation (tsDCS) compared to non-invasive motor cortex stimulation (rTMS and tDCS) in complex regional pain syndrome.**

**Article soumis, Octobre 2022**

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**Running title:** *Noninvasive central neuromodulation for CRPS*

## **Abstract**

The aim of the present study was to compare the analgesic effect between high-frequency repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and transcutaneous spinal direct current stimulation (tsDCS) in patients with complex regional pain syndrome (CRPS). Thirty-three patients with CRPS were randomized to one of the three treatment groups (rTMS, n = 11; tDCS, n = 10; tsDCS, n = 12) and received a series of 12 sessions of stimulation for three weeks (induction phase) and 11 sessions for four months (maintenance therapy). The primary endpoint was the mean pain intensity assessed weekly with a visual numeric scale (VNS) during the month prior to treatment (baseline), the 5-month stimulation period and one month after the treatment. The weekly VNS pain score was significantly reduced at all time points compared to baseline in the tsDCS group, at the last two time points in the rTMS group (end of the 5-month stimulation period and one month later), but at no time point in the tDCS group. A significant pain relief was observed at the end of induction phase using tsDCS compared to rTMS ( $P = 0.008$ ) and to tDCS ( $P = 0.003$ ).

In this trial, tsDCS was more efficient to relieve pain in patients with CRPS compared to motor cortex stimulation techniques (rTMS, tDCS). This efficacy was found during the induction phase and was maintained thereafter. This study warrants further investigation to confirm the potentiality of tsDCS as a therapeutic option in CRPS.

**Keywords:** chronic pain, CRPS, direct current, magnetic stimulation, rTMS, spinal cord, tDCS, treatment, tsDCS

**Abbreviations:** CRPS = complex regional pain syndrome; rTMS = repetitive transcranial magnetic stimulation; tDCS = transcranial direct current stimulation; tsDCS = transcutaneous spinal direct current stimulation; SCS = spinal cord stimulation; VNS = visual numeric scale; SF-12 = 12-item Short-Form Health Survey questionnaire; HADS = Hospital Anxiety and Depression Scale; NPSI = Neuropathic Pain Symptom Inventory; CGI-I = Clinical Global Impression Improvement; Q-DASH = Quick Disabilities of Arm, Shoulder and Hand scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; ESC = Electrochemical skin conductance; rmANOVA = repeated measures analyses of variance; GMI = Graded Motor Imagery.

## Introduction

Complex regional pain syndrome (CRPS) is characterized by pain and autonomic signs and symptoms usually occurring in a region of trauma or other limb injury, but disproportionate in duration or sequelae. CRPS type I develops without evidence of nerve damage in the affected limb, through pathophysiological mechanisms that are partly unknown, but likely involve maladaptive neuroplasticity in the somatosensory and autonomic (sympathetic) central nervous system.

The treatment of CRPS is based on various approaches, pharmacological or non-pharmacological<sup>1</sup>. Pharmacotherapy includes a wide variety of drugs, such as steroids, nonsteroidal anti-inflammatory drugs, calcitonin, bisphosphonates, anticonvulsants, antidepressants, N-methyl-D-aspartate (NMDA) receptor antagonists, or antihypertensives. The level of evidence depends on their use in the early or late phase of the disease. Topics can also be used, as well as locoregional ‘blocks’, in particular sympathetic nerve blocks or intravenous regional anesthetic techniques. Non-pharmacological approaches include occupational or physical therapy, psychotherapy, or acupuncture, for example.

Finally, usually at the last line of the therapeutic algorithm, interventional neuromodulation, mainly based on spinal cord stimulation (SCS), can be an effective solution in chronic refractory cases<sup>2</sup>. The efficacy of surgically-implanted electrical motor cortex stimulation has also been reported<sup>3</sup>. Following the beneficial effects obtained in the treatment of CRPS by invasive cortical neuromodulation<sup>4</sup>, non-invasive techniques of cortical stimulation have been developed, such as repetitive transcranial magnetic stimulation (rTMS) and direct current stimulation (tDCS)<sup>5</sup>. The value of these techniques as alternatives for the treatment of refractory chronic pain has been demonstrated for twenty years<sup>6</sup>.

The analgesic efficacy of rTMS delivered to the motor cortex seems particularly well established. European experts have retained a level of evidence A concerning the analgesic effect of high-frequency rTMS ( $\geq 5\text{Hz}$ ) of the motor cortex in chronic neuropathic pain<sup>7</sup>. In the French recommendations for the management of chronic neuropathic pain, rTMS is recommended as a 3rd line treatment<sup>8</sup>. As for the use of rTMS in the treatment of chronic CRPS specifically, a recent analysis of the literature found only 3 controlled and short-term studies (a total of 43 patients)<sup>9</sup>.

It is important to emphasize that rTMS requires heavy equipment with significant cost (especially if guided by neuronavigation) and the constraint for the patient to come to the hospital (clinic) to be stimulated. On the contrary, tDCS, because of its low cost and ease of use (potentially performed at home), appears in such a context as a potential and interesting

alternative. Low-intensity electrical current delivered transcranially to the cerebral cortex by tDCS electrodes placed on the scalp, usually with a bipolar montage using an anode and a cathode, can modulate neural activity and induce neuroplasticity<sup>10</sup>. The use of anodal tDCS delivered to the motor cortex as an analgesic therapy has provided encouraging results in patients with chronic pain<sup>11-13</sup>. However, the current data in the literature do not allow to affirm, with a satisfactory level of evidence, the efficacy of tDCS in this context<sup>14,15</sup>.

More recently, a non-invasive neuromodulation approach to the spinal cord, transcutaneous spinal direct current stimulation (tsDCS), has been developed<sup>16,17</sup>. In the somatosensory domain, studies were mainly performed in healthy subjects, showing that tsDCS is able to interfere with spinal cord structures and to modulate conduction in the lemniscal and spinothalamic sensory pathways<sup>18,19</sup>. In contrast, clinical studies concerning the impact of tsDCS on pain are few. In fact, we found only two therapeutic studies reporting the analgesic effect of repeated sessions in tsDCS in series of patients suffering from various chronic pain syndromes affecting the limbs, notably related to multiple sclerosis<sup>20,21</sup>. In these studies, the anode was placed over the tenth thoracic vertebra and the cathode over the right shoulder<sup>20</sup> or the somatosensory cortical area<sup>21</sup>.

In the present study, our objective was to evaluate for the first time in CRPS patients the analgesic effect of tsDCS using a bipolar montage with both anode and cathode electrodes placed along the cervical or lumbar spine, and to compare this effect to that of high-frequency rTMS and anodal tDCS delivered to the motor cortex, which are more established non-invasive neuromodulation therapies for chronic pain.

Beyond the impact of these treatments on clinical questionnaires, we also assessed the possible modulation of the autonomic nervous system by recording the sympathetic-driven electrochemical skin conductance (ESC) measured with the SudoScan® device.

## **Methods**

### *Study design*

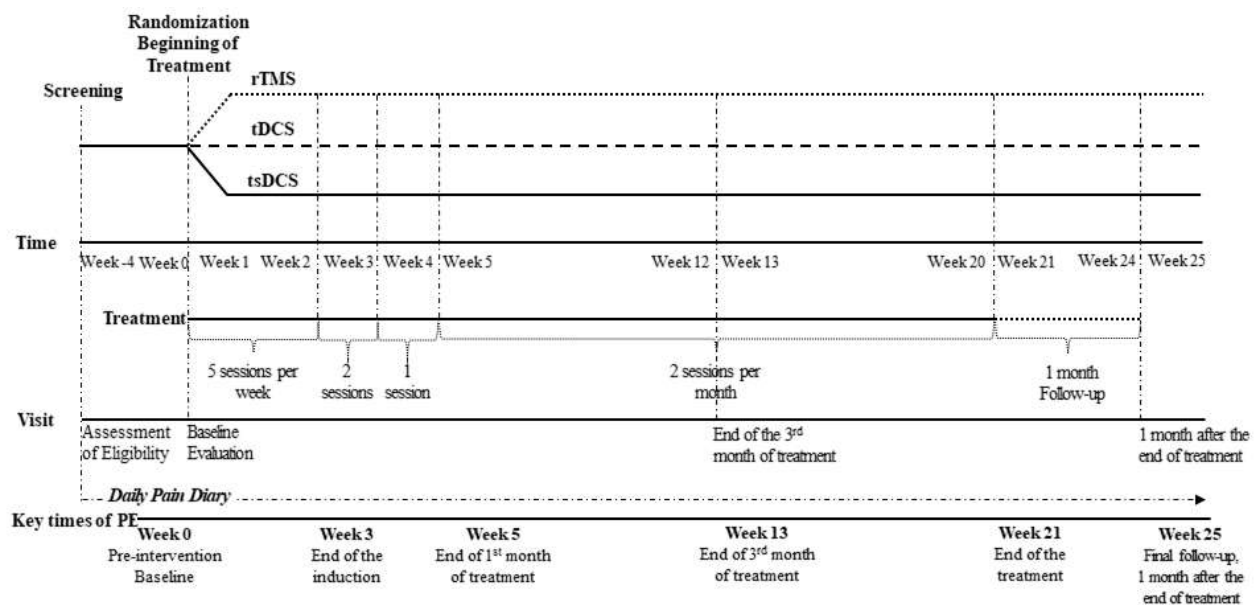
This study was a bi-centric, randomized, controlled clinical trial in three parallel arms: rTMS, tDCS and tsDCS stimulation. The study was conducted at the Pain Centre of Grenoble Alps University Hospital (Grenoble, France) and the Clinical Neurophysiology Unit of Henri Mondor University Hospital (Créteil, France) between July 25, 2016 (first visit of the first patient) and September 10, 2021 (last visit of the last patient).

The study consisted of three periods (Figure 1): (1) a 1-month pre-treatment period to assess eligibility and determine the average weekly level of pain intensity before treatment (Baseline);

(2) after randomization, a 5-month period of rTMS, tDCS or tsDCS sessions; (3) a 1-month follow-up period after treatment. Patients were evaluated at four scheduled visits: at screening to assess eligibility (Week-4), at randomization to assess baseline evaluations (Week 0), after three months of treatment (Week 13), and at 1-month post treatment (Week 25).

### Figure 1 Protocol design: interventions and assessment time points

Abbreviations: PE, Primary Endpoint; rTMS, repetitive Transcranial Magnetic Stimulation; tDCS, transcranial direct-current stimulation; tsDCS, transcutaneous spinal Direct Current Stimulation. Assessments at each visit: Patient Clinical Global Impression (CGI); the short form 12-health survey questionnaire (SF-12); Hospital Anxiety and Depression Scale (HADS); Neuropathic Pain Symptom Inventory scale (NPSI); Quick Disabilities of Arm, Shoulder and Hand (QuickDASH); Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); Sudoscan®.



The neuromodulation protocol of rTMS, tDCS or tsDCS consisted of an “induction phase” of one stimulation session per day for five consecutive days during two weeks (weeks 1 and 2), then 2 sessions in the next week (week 3) for a total of 12 sessions, and a “maintenance phase” consisting of one session in week 4 and then bi-monthly sessions for four months, for a total of 11 sessions.

The Institutional Review Board of Sud-Est V, Grenoble, France (N ° 6705), approved the study on November 13, 2015. Written informed consent was obtained from all patients prior to enrollment. The study was registered in clinicaltrials.gov (NCT02817880).

### Study population

Patients with CRPS type I were included if they met the following criteria: age between 18 and 80 years; disease duration for more than one year; a diagnosis confirmed by bone scintigraphy; pain intensity > 3/10 at screening; no change in drug treatments during the last month; lack of response to conventional treatments. Patients were not included if they were pregnant or breastfeeding women, or if they had a CRPS diagnosis with presence of a neurological lesion, an intracranial ferromagnetic material or implanted device, a history of drug addiction, epilepsy, severe traumatic brain injury or neuropsychiatric comorbidities that could interfere with the assessment of outcomes.

### *Randomization*

After the baseline period, treatment allocation was made by the physician responsible for conducting the study at each center using a secure Web-based random number generator (Research Electronic Data Capture system). Patients were randomly assigned to one of the three groups in a ratio of 1:1:1, with a random block size and stratified by two centers and affected limb (upper or lower limb).

### *rTMS procedure*

Stimulation was performed using a MagPro stimulator (MagVenture (distr. Mag2Health), Farum, Denmark) and either a flat B65 coil (MagVenture) in patients with upper limb pain or an angled B70 figure-of-eight coil (MagVenture) in patients with lower limb. Compared to flat figure-of-eight coils, the B70 coil is more powerful, leading to lower the resting motor threshold (rMT) by 10 to 33%<sup>22</sup> and stimulates deeper the motor cortex corresponding to lower limbs due to its angle of 150°<sup>23</sup>.

The motor cortical representation of the painful region was targeted using a TMS Navigator system, integrating individual brain magnetic resonance imaging (MRI) data (Localite, Sankt Augustin, Germany). Stimulation was performed at 10Hz with an intensity set at 80% of the rest motor threshold (previously determined with motor evoked potential recording) and the coil held in posteroanterior orientation. Each rTMS session consisted of 40 trains of 5-sec duration with intertrain interval of 25 sec for a total of 2000 pulses in 20 minutes. This protocol is in line with the expert recommendations for safety<sup>24,25</sup>.

### *tDCS procedure*

Stimulation was performed using a Starstim neurostimulator (Neuroelectronics®, Barcelona, Spain) with saline-soaked surface sponge electrodes (35 cm<sup>2</sup>). The site of stimulation was



determined according to the International 10-20 EEG System. The anode was placed over the motor cortex contralateral to pain, on C3/C4 in patients with upper limb pain and on C1/C2 in patients with lower limb. The cathode was placed over the supraorbital area ipsilateral to pain, on Fp1/Fp2. A constant current of 2 mA intensity was applied for 20 min.

#### *tsDCS procedure*

Stimulation was performed using the Starstim neurostimulator (Neuroelectronics<sup>®</sup>, Barcelona, Spain) and the same parameters as for the tDCS protocol, except for the placement of the stimulation electrodes. These electrodes were placed longitudinally on the cervical or lumbar spine, according to a model study which demonstrated that this configuration had a relevant impact on the distribution of the induced electric field for the efficacy of tsDCS<sup>26</sup>. In patients with upper limb pain, the anode was placed on the spinous processes of the C4-C5 vertebrae and the cathode along the column, spaced 8 cm below. In patients with lower limb pain, the anode was placed over the spinous processes of the L1-L2 vertebrae and the cathode along the column, spaced 8 cm below.

#### *Sample Size Calculation*

Assuming a mean pain intensity measured on a 0-10 visual numeric scale (VNS) of  $7 \pm 1/10$  in CRPS patients at baseline<sup>27,28</sup>, a possible reduction of  $-2/10$  at the end of the induction phase (week 4) and of  $-1/10$  at the end of the maintenance phase (week 25), and a correlation of 0.7 or more between repeated measures, the expected sample size was 20 patients for each group, providing 80% power for a two-tailed test with significance level of 0.01 (adjusting for multiple comparisons) to demonstrate differences between pairs of groups (NQuery Advisor<sup>®</sup> 7.0). Finally, only 36 patients were enrolled before recruitment stopped after a 5-year inclusion period due to a recruitment challenge and the Covid-19 pandemic.

#### *Clinical Outcomes/Endpoints*

From the screening period (Week-4) to the end of follow-up (Week 25), patients filled a diary at home to measure their daily pain intensity on a VNS ranging from 0 (no pain) to 10 (the worst pain imaginable), and also to record the use of medication.

The primary endpoint was the mean pain intensity during the week (weekly VNS pain score) measured over time (from Week-4 to Week 25).

Secondary endpoints were the following clinical scores assessed on self-administered questionnaires completed by patients at Week 0 (pre-intervention visit), Week 13 (3<sup>rd</sup> month of treatment) and Week 25 (1-month post treatment):

(1) the SF-12 questionnaire (12-item Short-Form Health Survey questionnaire) to assess the health-related quality of life across two dimensions (Physical and Mental Components) with scores ranging from 0 to 100, a higher score indicating a better quality of life<sup>29</sup>;

(2) the HADS questionnaire (hospital anxiety and depression scale) to assess symptoms of anxiety and depression, with scores ranging from 0 to 21 for each subscale, a higher score indicating worse symptoms<sup>30</sup>;

(3) the NPSI (Neuropathic Pain Symptom Inventory) to assess the characteristics and impact of neuropathic pain, with total intensity score ranging from 0 to 100 and five sub-scores corresponding to various dimensions of pain (spontaneous superficial (burning) pain, deep (pressing) pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia) ranging from 0 to 10, a higher score indicating greater symptom severity<sup>31</sup>;

(4) the *QuickDASH* (Quick Disabilities of Arm, Shoulder and Hand scale) to assess disability and symptoms affecting the upper limb, with a total intensity score ranging from 0 to 100, a higher score indicating more severe disability<sup>32</sup>;

(5) the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index for knee and hip) to assess disability and symptoms affecting the lower limb, with a total intensity score ranging from 0 to 100 (normalized for easy interpretation by multiplying total score by 100/96), a higher score indicating more severe disability<sup>33</sup>.

The overall effect of the stimulation was estimated by the patients according to the 7-point CGI-I (Clinical Global Impression – global Improvement) scale, from 1 (very much improved) to 7 (very much worsened) compared to the pre-treatment baseline period<sup>34</sup>. Illness improvement rate was calculated as the percentage of patients improved. We also evaluated the responder rate at the end of follow-up (3-month post-treatment), according to a reduction of  $\geq 30\%$  from baseline regarding the mean intensity of pain on VNS.

Finally, the self-administered CRQ questionnaire was completed at last visit (post-treatment) to assess potential side effects occurred during or after stimulation sessions (pain, tingling, burning, fatigue, nervousness, overall discomfort, sleep or concentration disturbances, alteration of visual or auditory perception, and headache)<sup>35</sup>.

*Measurement of electrochemical skin conductance (ESC)*

Beyond the clinical impact of neuromodulation on pain and disability, we also assessed the possible modulation of the autonomic nervous system, which plays a key role in CRPS pathophysiology, by recording the sympathetic-driven electrochemical skin conductance (ESC) measured with the Sudoscan® device (Impeto Medical, Paris, France). Palmar and plantar ESC values were measured (in microSiemens,  $\mu\text{S}$ ) at W0 (pre-treatment), W 13 (3<sup>rd</sup> month of treatment) and W25 (1-month post treatment). Sudoscan technology provides a quantitative assessment of small fiber neuropathy. During the test, patients were asked to stand for 2 minutes, with their palms and soles placed on large stainless-steel electrode plates. A low direct current voltage ( $<4\text{V}$ ) was applied incrementally to the electrodes, generating a current proportional to the chloride ion flow extracted from the sweat glands innervated by small fibers. The ESC value was acquired for each foot and hand. The ESC was used to assess the skin conductance of affected limb, with higher measures indicating better conductance<sup>36</sup>.

### *Statistical analysis*

Continuous data are expressed as mean  $\pm$  standard deviation (SD) or median (25th-75th centiles), and categorical data are expressed as numbers and percentages. Shapiro-Wilk test was used to assess the normality of the data. One-way ANOVA, Kruskal-Wallis Test and Fisher's exact test were used to compare outcomes at baseline across the three treatment groups.

Efficacy analyses were conducted on an intention-to-treat (ITT) basis with missing data imputed as last-observation carried forward. All patients who received at least 1 session of treatment and completed at least 1 postbaseline weekly pain measurement were included in the intent-to-treat analysis. In addition, sensitivity analyses were conducted to explore the impact of missing values by performing a secondary analysis following the per-protocol (PP) principle that concerns only patients who completed each phase of study and had measurements for all prespecified key times. We considered as key times the average of values collected in pain diary (weekly measurements) for baseline, week 3 (end of the induction phase), week 5 (after the end of 1<sup>st</sup> month of treatment), week 13 (after the end of the 3<sup>rd</sup> month of treatment), week 21 (after the end of the treatment), week 25 (final follow-up, 1 month after the end of the treatment) (Figure 1).

The primary endpoint of the study (effects of treatments on pain) was examined by the use of 2-way repeated measures analyses of variance (rmANOVA) with treatment group (rTMS, tDCS and tsDCS) as the between-subject factor, time (week before treatment, weeks 1-4 of induction phase, weeks 5-20 of maintenance phase, weeks 21-25 post treatment) as the within-subject factor and the calculation of time-by-group interaction. Change from baseline over the time was

also tested for each motor cortex neurostimulation group (rTMS and tDCS) compared with tsDCS group sequentially at a significance level of 0.017 (Bonferroni correction for three groups' pairwise comparisons). The pairwise comparisons were tested only when the time-by-group interaction of the three groups over time was considered statistically significant. A significant time-by-group interaction would indicate that the change in pain intensity over time from baseline differed among groups. Sphericity was examined for all statistical analyses and in case of non-sphericity results were corrected according to the Greenhouse Geisser method. Within-group differences from the baseline (week -1) to the follow-up periods (weeks 3, 5, 13, 21 and 25) at each group were analyzed using paired t-test. Between-group differences from the baseline period to each follow-up period were compared between the three groups using one-way ANOVA test. Bonferroni's post-hoc tests for comparisons to baseline were performed for significant main effects or interaction. Effect size was determined using Cohen's d (Cohen's criteria: small  $\leq 0.2$ ; moderate = 0.5; large  $\geq 0.8$ ) to compare the effects of the treatment group on the dependent variables. In addition, an analysis of covariance (ANCOVA) was implemented as a sensitivity analysis to compare groups at key time points, with baseline values used as covariates (Supplementary Appendix). In order to simplify the report of the results, only the values related to pairwise comparisons tsDCS vs rTMS and tsDCS vs tDCS were reported.

The same analyses were used for pre-specified secondary end points (SF-12, HADS, NPSI, Q-DASH/WOMAC and ESC affected limb) with the factor time as a 3-level variable (Figure 1): baseline (visit 2), end of the 3rd month of treatment (visit 3) and 1-month post treatment (visit 4). The Kruskal-Wallis test was used to compare the CGI-I and CRQ scale results across three treatment groups. For the responder rate, the proportion of participants in each group who demonstrated a reduction of  $\geq 30\%$  in pain from the baseline to the end of follow up was compared using the Fisher's exact test.

The statistical significance level ( $\alpha$ ) for the comparison of three groups was set to 0.05 and the significance level ( $\alpha$ ) after Bonferroni's correction for 3 groups was thus at 0.017. Analysis was conducted under blinded conditions using STATA 16.0 software (StatCorp, College Station, TX, USA).

## **Results**

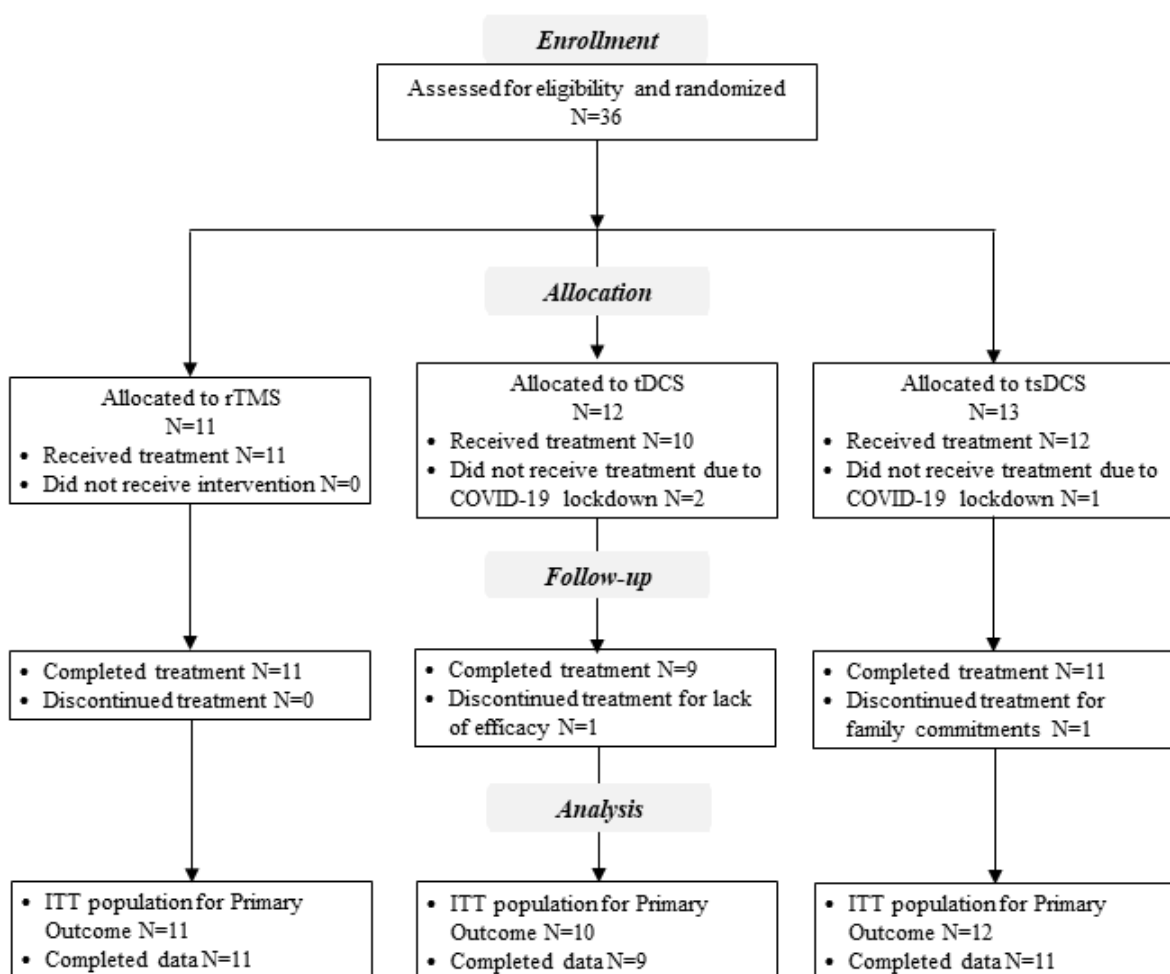
### *Flowchart of the study*

A total of 36 patients were enrolled and randomized to one of the three treatment groups (rTMS, n = 11; tDCS, n = 12; tsDCS, n = 13) (Figure 2). Three patients (2 to tDCS group and 1 to

tsDCS group) did not received treatment due to COVID-19 lockdown and therefore, only 33 patients received treatment and were included in the ITT population. Overall, 94% (31/33, 11 to rTMS, 9 to tDCS and 11 to tsDCS) completed the entire follow-up assessment for the primary outcome. Two patients discontinued treatment, one in the tDCS group for lack of efficacy and one in the tsDCS group for family commitments.

## Figure 2 Participant flow diagram

ITT (intent-to-treat) population included all randomized participants who received at least 1 session of the study treatment and recorded baseline pain.



### Baseline demographics and clinical characteristics

Baseline demographic and clinical characteristics were similar across treatment groups ( $P > 0.05$ ) (Table 1). The mean age at enrollment was 46 years, 64% of patients were women and the median duration of pain syndrome was 24 months.

**Table 1 Baseline characteristics of patients according to the allocated group**

	Total (n = 33)	rTMS (n=11)	tDCS (n = 10)	tsDCS (n = 12)
Age (years), mean (SD)	46.2 (12.2)	52.0 (9.6)	40.4 (12.5)	45.7 (12.6)
Female, n (%)	21 (64%)	6 (54.5%)	6 (60%)	9 (75%)
<b>Disease history</b>				
Pain syndrome duration (months), median (IQR)	24 (18, 34)	24 (13, 29)	22.5 (18, 38)	24 (17.5, 48)
Pain origin, n (%)				
Trauma (sprain, contusion, fracture)	14 (42.4%)	6 (54.5%)	2 (20.0%)	6 (50.0%)
Surgery	17 (51.5%)	5 (45.5%)	7 (70.0%)	5 (41.7%)
Other	2 (6.1%)	0 (0.0%)	1 (10.0%)	1 (8.3%)
Pain localization, Lower Limb, n (%)	21 (64%)	5 (45.5%)	7 (70%)	5 (42%)
Pain lateralization, Left, n (%)	18 (54.5%)	4 (36%)	8 (80%)	6 (50%)
<b>Drug treatment</b>				
Current use of background drug therapy, n (%)	28 (85)	10 (91)	8 (80)	10 (83)
Number of background therapy used, median (IQR)	2 (2, 3)	2 (2, 3)	2.5 (1, 3)	2.5 (2, 3)
Type of background therapy used, n (%):				
Non-opioid analgesics	6 (18%)	2 (18%)	1 (10%)	3 (25%)
Weak opioid analgesics	16 (48.5%)	7 (64%)	5 (50%)	4 (33%)
Antiepileptics	24 (73%)	7 (64%)	8 (80%)	9 (75%)
Antidepressants	20 (61%)	7 (64%)	5 (50%)	8 (67%)
Current use of pain crisis therapy, n (%)	29 (88%)	9 (82%)	9 (90%)	11 (92%)
Type of pain crisis therapy used, n (%):				
Non-opioid analgesics	19 (58%)	5 (45%)	6 (60%)	8 (67%)
Weak opioid analgesics	19 (58%)	6 (54.5%)	5 (50%)	8 (67%)
Strong opioid analgesics	3 (9)	0 (0%)	2 (20%)	1 (8%)
<b>Clinical assessment at baseline</b>				
VNS pain, mean (SD)	6.1 (1.8)	5.4 (1.8)	6.3 (1.6)	6.6 (1.7)
SF-12 Physical component scale, mean (SD)	30.1 (5.4)	30.7 (4.8)	28.2 (6.0)	31.2 (5.4)
SF-12 Mental component scale, mean (SD)	38.1 (11.0)	40.9 (10.1)	39.9 (14.2)	34.0 (8.1)
HADS-anxiety, mean (SD)	11.3 (4.6)	10.0 (3.6)	11.5 (5.2)	12.3 (4.8)
HADS-depression, mean (SD)	9.5 (4.6)	8.5 (3.4)	9.3 (5.9)	10.8 (4.5)
NPSI Total, mean (SD)	48.6 (22.0)	38.7 (16.6)	51.3 (26.0)	54.6 (21.4)
Q-DASH/WOMAC, mean (SD)	65.2 (14.9)	63.1 (15.8)	62.3 (14.8)	69.6 (14.4)
ESC affected limb ( $\mu$ S), mean (SD)	72.3 (16.8)	74.9 (15.3)	71.2 (19.1)	70.5 (17.6)

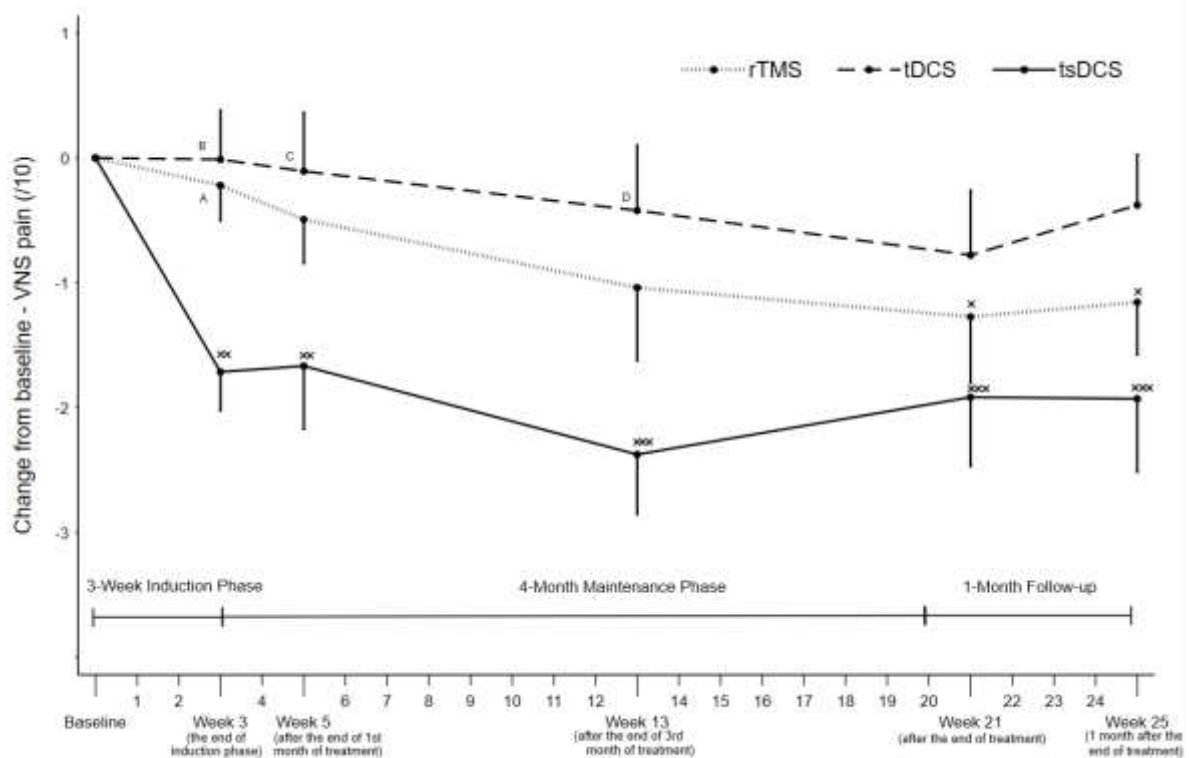
Abbreviations: SD, standard deviation; IQR, interquartile range; SNRI, Serotonin-norepinephrine reuptake inhibitor; SSRI, Selective serotonin reuptake inhibitors; NSAIDs, Non-steroidal anti-inflammatory drugs; VNS, Visual Numeric Scale (0-10); SF-12, 12-item Short-Form Health Survey questionnaire (0-100): Physical and Mental subscales; HADS, hospital anxiety and depression scale (0-21): Anxiety and Depression subscales; NPSI, Neuropathic Pain Symptom Inventory (total score 0-100, sub-scores 0-10); Q-DASH, Quick Disabilities of Arm, Shoulder and Hand scale normalized to 100 (score range 0-100); WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index for knee and hip (normalized 0-100); ESC, electrochemical sweat conductance obtained with SUDOSCAN®. Statistics: one-way ANOVA or Kruskal-Wallis test was used for continuous data and Fisher's exact test for categorical variables. All P-values are  $>0.05$ .

### Primary outcome: change in weekly VNS pain score

The primary outcome was the change in weekly VNS pain score over time from baseline (pre-treatment, Week 0) to 1-month post treatment (Week 25).

### Figure 3 Mean change over time in the visual numeric pain score according to the type of stimulation

The line graph represents the mean values with standard errors bars on intention-to-treat population. Changes from baseline in mean VNS pain score over the 25 weeks of follow-up. The two-way rmANOVA analysis revealed significant time-by-group interaction ( $P = 0.014$ , estimated by the use of rmANOVA model including stimulation group, time and the interaction of stimulation group with time), with Bonferroni's post-hoc tests compared to baseline showing VNS pain score decrease in the tsDCS group at all time points and in the rTMS group at the last two time points ( $x p < 0.05$ ,  $xx p < 0.01$ ,  $xxx p < 0.001$ ).



In Figure 3, the mean change from baseline is plotted against time for each treatment group at the various time points of assessment: Week 3 (at the end of induction phase), Week 5 (after 1 month of treatment), Week 13 (after 3 months of treatment), Week 21 (at the end of maintenance therapy), and Week 25 (final follow-up, 1 month after the end of treatment). The two-way rmANOVA analysis revealed significant time effect for rTMS group ( $F_{(25,250)} = 2.39$ ,  $P = 0.0004$ ) and tsDCS group ( $F_{(25,275)} = 2.65$ ,  $P = 0.0001$ ) but not for tDCS group ( $F_{(25,225)} =$

0.77,  $P = 0.779$ ). Post-hoc tests of rmANOVA showed a significant reduction in the weekly VNS pain score at all time points compared to baseline in the tsDCS group (Week 3:  $P = 0.001$ ; Week 5:  $P = 0.002$ ; Week 13:  $P < 10^{-3}$ ; Week 21:  $P < 10^{-3}$ ; Week 25:  $P = < 10^{-3}$ ), at the last two time points in the rTMS group (Week 21:  $P = 0.010$ ; Week 25:  $P = 0.029$ ), but at no time point in the tDCS group (Figure 3).

The two-way rmANOVA analysis revealed significant time-by-group interaction in the three-group analysis ( $F_{(50,750)} = 1.52$ ,  $P = 0.014$ ) and the two-group analyses regarding tsDCS vs rTMS ( $F_{(25,525)} = 1.74$ ,  $P = 0.015$ ) and tsDCS vs tDCS ( $F_{(25, 525)} = 1.73$ ,  $P = 0.016$ ). Post-hoc pairwise comparisons showed a significant decrease from baseline of the VNS pain score at Week 3 (end of induction phase) regarding tsDCS vs rTMS ( $-1.7 \pm 1.1$  vs.  $-0.2 \pm 0.9$ , effect size =  $-1.5$ ,  $P = 0.008$ ) and tsDCS vs tDCS ( $-1.7 \pm 1.1$  vs.  $0.0 \pm 1.2$ , effect size =  $-1.5$ ,  $P = 0.003$ ) (Table 2). A tendency towards a better efficacy of tsDCS vs tDCS was also observed at Week 5 ( $-1.7 \pm 1.8$  vs.  $-0.1 \pm 1.5$ , effect size =  $-1.0$ ,  $P = 0.063$ ) and Week 13 ( $-2.4 \pm 1.7$  vs.  $-0.4 \pm 1.7$ , effect size =  $-1.2$ ,  $P = 0.043$ ) (Table 2).

**Table 2 Primary outcome: visual numeric pain scale**

	tsDCS	rTMS	tDCS	tsDCS vs. rTMS	tsDCS vs. tDCS
BL	6.6 (1.7)	5.4 (1.8)	6.3 (1.6)		
W3 to BL	-1.7 (1.1), $d=-1.6$	-0.2 (0.9), $d=-0.2$	0.0 (1.2), $d=0.0$	-1.5 (-2.6; -0.3), $d=-1.5$ , $P=0.008$	-1.7 (-2.9; -0.5), $d=-1.5$ , $P=0.003$
W5 to BL	-1.7 (1.8), $d=-1.0$	-0.5 (1.2), $d=-0.4$	-0.1 (1.5), $d=-0.1$	-1.2 (-2.8; 0.4), $d=-0.8$ , $P=0.210$	-1.6 (-3.2; 0.1), $d=-1.0$ , $P=0.063$
W13 to BL	-2.4 (1.7), $d=-1.5$	-1.0 (1.9), $d=-0.5$	-0.4 (1.7), $d=-0.6$	-1.3 (-3.2; 0.5), $d=-0.7$ , $P=0.234$	-2.0 (-3.9; -0.1), $d=-1.2$ , $P=0.043$
W21 to BL	-1.9 (1.9), $d=-1.0$	-1.2 (1.4), $d=-0.7$	-0.4 (1.3), $d=-0.9$	-0.6 (-2.5; 1.2), $d=-0.4$ , $P=0.999$	-1.1 (-3.1; 0.8), $d=-0.6$ , $P=0.440$
W25 to BL	-1.9 (2.0), $d=-1.0$	-1.2 (1.4), $d=-0.8$	-0.4 (1.3), $d=-0.9$	-0.8 (-2.5; 0.9), $d=-0.4$ , $P=0.796$	-1.6 (-3.3; 0.2), $d=-0.9$ , $P=0.102$

Abbreviations: *BL*, Baseline; *W*, Week; *d*, Cohen's d. effect size

Data are expressed as mean  $\pm$  SD or mean with 95%CI. A negative change within groups means improvement. Between-group differences were calculated as tsDCS group results: a negative difference favors the tsDCS group. In the right columns, pairwise comparisons were analyzed by Bonferroni post hoc tests.

In addition, the differences between groups when the means were adjusted from baseline values were in favor of tsDCS at Week 3 (difference vs rTMS:  $-1.4$ ; 95%CI:  $-2.7$  to  $-0.2$ ;  $P = 0.019$  and difference vs tDCS:  $-1.7$ ; 95%CI:  $-2.9$  to  $-0.5$ ;  $P = 0.004$ ), at Week 5 (difference vs tDCS:  $-1.5$ ; 95%CI:  $-3.1$  to  $0.1$ ;  $P = 0.077$ ) and at Week 13 (difference vs tDCS:  $-1.7$ ; 95%CI:  $-3.6$  to  $0.2$ ;  $P = 0.098$ ).

When each treatment effect was compared numerically using Cohen's d, the post treatment effect was the largest in the tsDCS group up to Week 13 (d values in the tsDCS, rTMS, tDCS



groups, respectively at Week 3: -1.6, -0.2, 0.0; Week 5: -1.0, -0.4, -0.1; Week 13: -1.5, -0.5, -0.6; Week 21: -1.0, -0.8, -0.9; Week 25: -1.0, -0.8, -0.9).

Similarly, the proportion of patients with at least 30% reduction in weekly VNS pain score from baseline (responders) was significantly higher in the tsDCS group (73%) compared to the rTMS (18%) and tDCS (11%) groups at Week 13 ( $P = 0.010$ ). On the other hand, this proportion was significantly higher in the rTMS group (54%) than in the tsDCS (27%) and tDCS (0%) groups at the end of follow-up (Week 25) ( $P = 0.035$ ).

#### *Secondary outcomes: self-administered clinical questionnaires*

For the SF-12 Mental Component score, the two-way rmANOVA analysis revealed significant time effect only for the tsDCS group ( $F_{(2,22)} = 6.05$ ,  $P = 0.012$ ) and not for rTMS group ( $F_{(2,20)} = 0.41$ ,  $P = 0.596$ ) or tDCS group ( $F_{(2,18)} = 1.87$ ,  $P = 0.195$ ). Post-hoc tests of rmANOVA showed a significant improvement only at Week 25 compared to baseline in the tsDCS group (Week 13:  $P = 0.060$ ; Week 25:  $P = 0.017$ ) but at no time points in the other groups.

For the SF-12 Physical Component score, the two-way rmANOVA analysis revealed no significant time effect.

For the HADS-anxiety score, the two-way rmANOVA analysis revealed significant time effect for the tsDCS group ( $F_{(2,22)} = 5.32$ ,  $P = 0.013$ ) and tDCS group ( $F_{(2,18)} = 7.06$ ,  $P = 0.010$ ) but not for rTMS group ( $F_{(2,20)} = 2.64$ ,  $P = 0.100$ ). Post-hoc tests of rmANOVA showed a significant reduction only at Week 25 compared to baseline in the tsDCS group ( $P = 0.007$ ) and in the tDCS group ( $P = 0.006$ ) but at no time points in the rTMS group.

For the HADS-depression score, the two-way rmANOVA analysis revealed significant time effect only for the tsDCS group ( $F_{(2,22)} = 9.38$ ,  $P = 0.003$ ) and not for rTMS group ( $F_{(2,20)} = 2.13$ ,  $P = 0.776$ ) or tDCS group ( $F_{(2,18)} = 1.38$ ,  $P = 0.276$ ). Post-hoc tests of rmANOVA showed a significant improvement at all-time points compared to baseline in the tsDCS group (Week 13:  $P = 0.007$ ; Week 25:  $P = 0.002$ ) but at no time points in the other groups.

For the NPSI score, the two-way rmANOVA analysis revealed significant time effect for the tsDCS group ( $F_{(2,22)} = 8.19$ ,  $P = 0.002$ ) and rTMS group ( $F_{(2,20)} = 7.71$ ,  $P = 0.003$ ) but not for tDCS group ( $F_{(2,18)} = 2.86$ ,  $P = 0.083$ ). Post-hoc tests of rmANOVA showed a significant reduction only at Week 25 compared to baseline in the tsDCS group ( $P = 0.002$ ) and in the rTMS group ( $P = 0.003$ ) but at no time points in the tDCS group.

For the Q-DASH/WOMAC score, the two-way rmANOVA analysis revealed significant time effect only for the tsDCS group ( $F_{(2,22)} = 3.68$ ,  $P = 0.042$ ) and not for rTMS group ( $F_{(2,20)} = 0.73$ ,  $P = 0.496$ ) or tDCS group ( $F_{(2,18)} = 0.34$ ,  $P = 0.715$ ). Post-hoc tests of rmANOVA showed a

significant improvement only at Week 25 compared to baseline in the tsDCS group ( $P = 0.050$ ) but at no time points in the other groups.

The two-way rmANOVA revealed no significant time-by-group interaction in the three-group analysis regarding any of the clinical questionnaires used in this study (SF-12, HADS, NPSI, Q-DASH/WOMAC), although a tendency towards a significant interaction was observed for SF-12 Mental Component score ( $F_{(4,60)} = 2.24$ ,  $P = 0.083$ ) (Table 3). Moreover, post-hoc pairwise comparisons showed a significant improvement of this score regarding tsDCS vs rTMS at Week 13 ( $6.8 \pm 9.0$  vs.  $-2.0 \pm 4.9$ , effect size = 1.2,  $P = 0.019$ ) and a tendency at Week 25 ( $8.3 \pm 9.8$  vs.  $-1.2 \pm 9.3$ , effect size = 1.0,  $P = 0.081$ ) (Table 3). For the other clinical variables, post-hoc pairwise comparisons only showed at Week 13 a tendency towards a better efficacy of tsDCS vs. rTMS regarding HADS-anxiety score ( $-2.0 \pm 3.0$  vs.  $0.2 \pm 1.6$ , effect size =  $-0.9$ ,  $P = 0.095$ ) and vs. tDCS regarding HADS-depression score ( $-2.4 \pm 2.9$  vs.  $0.0 \pm 2.1$ , effect size =  $-1.0$ ,  $P = 0.072$ ) (Table 3).

**Table 3 Secondary outcomes: clinical questionnaires**

	tsDCS	rTMS	tDCS	tsDCS vs rTMS	tsDCS vs tDCS
<b>SF-12 Mental Component</b> ( $F_{\text{Time} \times \text{Stimulation } 4,60} = 2.24$ ; $P = 0.083$ )					
BL	33.9 (8.0)	40.9 (10.0)	39.7 (14.2)		
W13 to BL <sup>#</sup>	6.8 (9.0), $d=0.8$	-2.0 (4.9), $d=-0.4$	1.6 (6.6), $d=0.2$	8.8 (1.2; 16.3), $d=1.2$ , $P=0.019$	5.2 (-2.6; 12.9), $d=0.6$ , $P=0.305$
W25 to BL <sup>#</sup>	8.3 (9.8)*, $d=0.8$	-1.2 (9.3), $d=-0.1$	5.7 (10.1), $d=0.6$	9.4 (-0.8; 19.7), $d=1.0$ , $P=0.081$	2.6 (-8.0; 13.1), $d=0.3$ , $P=0.999$
<b>SF-12 Physical Component</b> ( $F_{\text{Time} \times \text{Stimulation } 4,60} = 0.50$ ; $P = 0.697$ )					
BL	31.2 (5.202)	30.6 (4.9)	28.3 (6.0)		
W13 to BL	0.5 (4.2), $d=0.1$	1.5 (3.6), $d=0.4$	-0.2 (3.4), $d=-0.1$	-1.0 (-4.5; 2.4), $d=-0.3$ , $P=0.530$	0.7 (-2.8; 4.2), $d=0.2$ , $P=0.678$
W25 to BL	2.5 (5.3), $d=0.5$	3.5 (7.8), $d=0.5$	0.4 (3.2), $d=0.1$	-1.0 (-6.7; 4.7), $d=-0.2$ , $P=0.709$	2.1 (-1.9; 6.1), $d=0.5$ , $P=0.289$
<b>HADS-anxiety</b> ( $F_{\text{Time} \times \text{Stimulation } 4,60} = 1.68$ ; $P = 0.175$ )					
BL	12.3 (4.8)	10.0 (3.6)	11.5 (5.2)		
W13 to BL <sup>#</sup>	-2.0 (3.0), $d=-0.7$	0.2 (1.6), $d=0.1$	-2.0 (2.0), $d=-1.0$	-2.2 (-4.6; 0.3), $d=-0.9$ , $P=0.095$	0.0 (-2.5; 2.5), $d=0.0$ , $P=0.999$
W25 to BL	-3.4 (4.1)**, $d=-0.8$	-1.0 (2.0), $d=-0.5$	-2.8 (3.0)**, $d=-0.9$	-2.4 (-5.2; 0.4), $d=-0.8$ , $P=0.089$	-0.6 (-3.8; 2.9), $d=-0.2$ , $P=0.694$
<b>HADS-depression</b> ( $F_{\text{Time} \times \text{Stimulation } 4,60} = 2.03$ ; $P = 0.109$ )					
BL	10.7 (4.5)	8.4 (3.4)	9.3 (5.9)		
W13 to BL <sup>#</sup>	-2.4 (2.9)**, $d=-0.8$	-0.3 (2.0), $d=0.1$	0.0 (2.1), $d=0.0$	-2.1 (-4.7; 0.4), $d=-0.9$ , $P=0.116$	-2.4 (-5.0; 0.2), $d=-1.0$ , $P=0.072$
W25 to BL	-2.8 (2.5)**, $d=-1.1$	-0.45 (3.9), $d=-0.1$	-1.0 (1.9), $d=-0.5$	-2.4 (-5.2; 0.4), $d=-0.7$ , $P=0.095$	-1.8 (-3.9; 0.2), $d=-0.8$ , $P=0.075$
<b>NPSI Total</b> ( $F_{\text{Time} \times \text{Stimulation } 4,60} = 0.69$ ; $P = 0.599$ )					
BL	54.6 (21.4)	38.8 (15.8)	51.3 (26.0)		
W13 to BL	-12.0 (20.0), $d=-0.6$	-6.4 (10.2), $d=-0.6$	-6.8 (13.5), $d=-0.5$	-5.6 (-19.6; 8.3), $d=-0.4$ , $P=0.410$	-5.2 (-20.7; 10.3), $d=-0.3$ , $P=0.492$
W25 to BL	-20.0 (16.6)**, $d=-1.2$	-12.8 (11.8)**, $d=-1.1$	-10.6 (14.4), $d=-0.7$	-7.2 (-19.8; 5.4), $d=-0.5$ , $P=0.249$	-9.4 (-23.4; 4.6), $d=-0.6$ , $P=0.176$
<b>Q-DASH/WOMAC</b> ( $F_{\text{Time} \times \text{Stimulation } 4,60} = 0.72$ ; $P = 0.580$ )					
BL	69.6 (14.4)	63.1 (15.8)	62.4 (14.8)		
W13 to BL	-8.2 (15.7), $d=-0.5$	-2.3 (12.6), $d=-0.2$	-0.1 (13.0), $d=0.0$	-5.9 (-18.3; 6.5), $d=-0.4$ , $P=0.334$	-8.1 (-21.1; 4.9), $d=-0.6$ , $P=0.207$

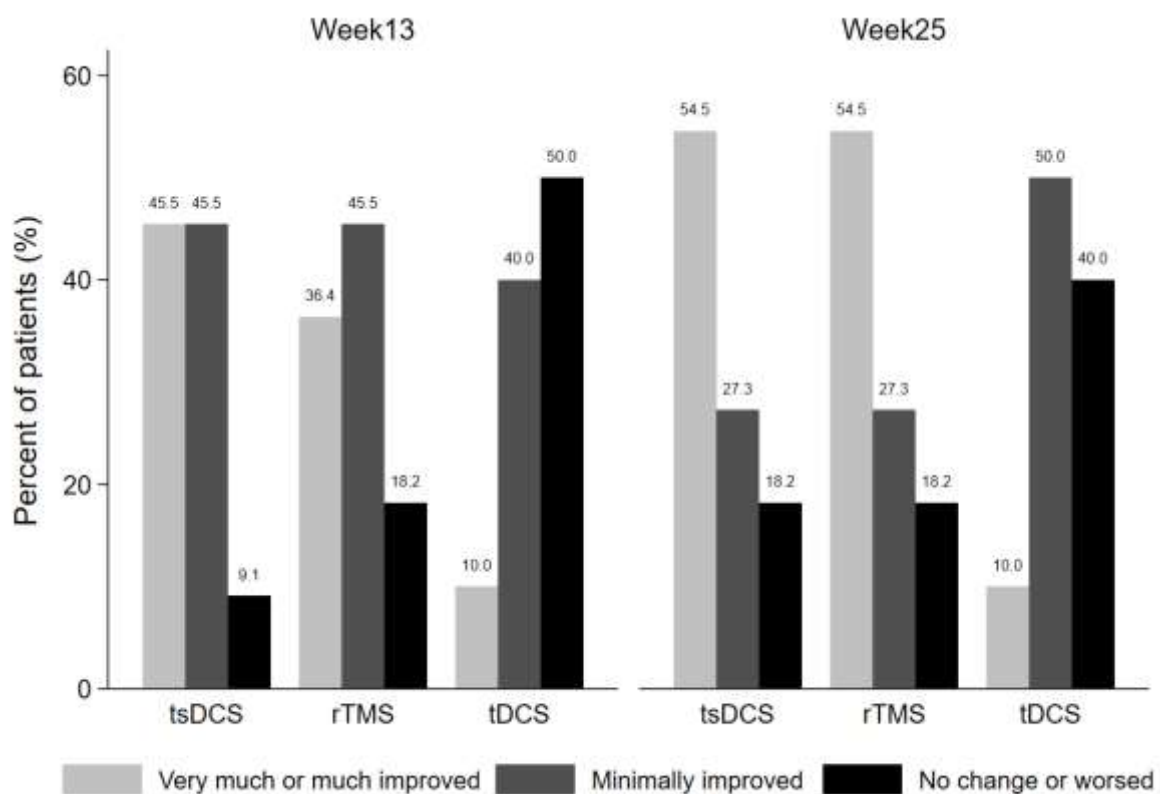
W25 to BL -10.0 (14.0), d=-0.7 -4.7 (16.2), d=-0.3 -2.7 (12.9), d=-0.2 -5.3 (-18.4; 7.8), d=-0.4, P=0.409 -7.3 (-19.4; 4.8), d=-0.5, P=0.224

Abbreviations: *BL*, Baseline; *W*, week; *d*, Cohen's d. effect size; *SF-12*, 12-item Short-Form Health Survey questionnaire (0-100): Physical and Mental subscales; *HADS*, hospital anxiety and depression scale (0-21): Anxiety and Depression subscales; *NPSI*, Neuropathic Pain Symptom Inventory, *Q-DASH*, Quick Disabilities of Arm, Shoulder and Hand scale (0-100); *WOMAC*, Western Ontario and McMaster Universities Osteoarthritis Index for knee and hip (0-100). In the right columns, pairwise comparisons were analyzed by Bonferroni post hoc tests. Data are expressed as absolute change from baseline (mean ± SD). Bonferroni's post-hoc test compared to baseline: \* P<0.05; \*\* P<0.01; \*\*\* P<0.001. # Pairwise comparisons were analyzed by Bonferroni's post hoc tests (95% CI and P) if P of difference between the three groups were ≤0.100.

*Secondary outcomes: impact on CGI-I scale*

On the CGI-I scale, a significant difference between groups was observed in the improvement rate at Week 13 (P = 0.049) but not at Week 25 (P = 0.139). The rate of patients with at least minimal improvement was higher in the tsDCS vs. tDCS group at Week 13 (P = 0.024), but not at Week 25 (P = 0.124) (Fig.4). No difference was observed between other treatment groups.

**Figure 4** The patient's CGI scale response rate



*Secondary outcomes: impact on side effects (CRQ)*

No significant difference in CRQ sum scores or any specific CRQ item was found between treatment groups (data not shown). No adverse effects were reported during or following any of the three interventions.

### *Secondary outcomes: ESC measurements*

On the ESC at the limb affected, no significant change was observed over time at Week 13 or Week 25 in any treatment groups and no difference between the groups was neither observed (data not shown). However, at baseline, ESC was reduced at the limb affected by CRPS compared to the non-affected limb (mean ( $\mu$ S)  $\pm$  SD:  $72.3 \pm 16.8$  vs.  $75.0 \pm 15.5$ ,  $P = 0.015$ ). In addition, the patients with at least 30% reduction in weekly VNS pain score at Day 90/ Week 13 from baseline (responders) had lower ESC values at the affected limb compared to the other patients (non-responders) at baseline (mean ( $\mu$ S)  $\pm$  SD:  $61.6 \pm 19.0$  vs.  $78.2 \pm 12.5$ ,  $P = 0.007$ ) and also a significant ESC increase at Day 90/ Week 13 ( $78.4 \pm 18.4$  and  $67.4 \pm 14.1$ ,  $P = 0.007$ ).

### **Discussion**

Overall, this study shows a better efficacy of spinal stimulation by means of tsDCS compared to motor cortex stimulation techniques (rTMS, tDCS) to produce an analgesic effect in patients with chronic refractory CRPS. This improved efficacy was also observed more rapidly, during the induction phase. In the longer term, rTMS also showed significant efficacy, but not tDCS. This is one of the first studies to show the efficacy of tsDCS in a chronic pain syndrome, which is also a recognized indication for implanted SCS<sup>15</sup>.

Only a few studies have been reported to date on the use of noninvasive neuromodulation in patients with CRPS, as recently reviewed<sup>37</sup>. Regarding rTMS, beyond a proof-of-principle trial based on a single session<sup>38</sup>, only two studies showed some analgesic effects of 10Hz-rTMS applied to the motor cortex in patients with CRPS<sup>28,39</sup>. First, in a sham-controlled study, Picarelli et al.<sup>28</sup> applied rTMS as an add-on intervention to standard pharmacological and rehabilitation therapy for 10 consecutive sessions in 23 patients with CRPS type I (12 active, 11 sham). Pain intensity, but also functional and affective scores were reduced during the rTMS protocol, but the effects vanished soon (less than one week) after the stimulation period. However, there was a large inter-individual variation in the response duration and one patient was completely relieved up to 3 months after rTMS. Second, in an open-label study, Gaertner et al.<sup>39</sup> investigated the effects of five daily rTMS sessions primed by a sequence of intermittent theta burst stimulation in 12 patients with CRPS of type I or II. Pain intensity score was decreased by more than 30% in 58% of the patients (7/12) at the end of the stimulation protocol. Among these seven patients, three remained improved for 3-4 weeks and two for 3-4 months beyond the rTMS protocol.

Regarding tDCS, beyond two single case reports<sup>40,41</sup>, only one randomized sham-controlled study was reported<sup>42</sup>. In a series of 22 patients with CRPS type I (11 active, 11 sham), Lagueux et al. applied anodal tDCS over the motor cortex for five consecutive days during the first two weeks of a therapy based on a technique of graded motor imagery (GMI) and once a week during four subsequent weeks of GMI therapy. No significantly greater pain reduction was observed in the group of patients receiving active tDCS vs. sham tDCS, while some differences were observed between the two groups in terms of pain catastrophizing and anxiety, but not at a clinically meaningful level<sup>42</sup>. However, the effect of a protocol of tDCS performed alone has never been assessed in the context of CRPS.

Regarding non-invasive stimulation performed on non-brain structures in patients with CRPS, there are various published studies using repetitive peripheral magnetic stimulation (rPMS) or transcutaneous electrical nerve stimulation (TENS) on neuromuscular structures (reviewed in<sup>37</sup>), but not on spinal structures. In particular, the analgesic effect of tsDCS has never been evaluated in patients with CRPS. Anodal tsDCS has mainly been applied to modulate experimentally induced pain in healthy subjects. For example, anodal tsDCS has been shown to modulate pain ratings or thresholds in response to pressure<sup>43</sup>, heavy mechanical pinprick<sup>44</sup>, or other types of nociceptive stimuli<sup>45</sup>, but without affecting hyperalgesia induced by electrical high-frequency stimulation (HFS)<sup>46</sup>. Neurophysiological correlates of these analgesic effects were also investigated, either at the segmental level of spinal nociceptive integration by assessing changes induced by tsDCS in the nociceptive withdrawal flexion reflex (NWFR)<sup>47,48</sup> or along the spinothalamic nociceptive pathways by recording laser evoked cortical potentials (LEP)<sup>19,45,49</sup>.

On the other hand, as mentioned in the introduction, we found only two clinical studies reporting the analgesic effect of repeated sessions of tsDCS in patients with chronic pain<sup>20,21</sup>. First, Guidetti et al.<sup>20</sup> applied anodal tsDCS (2.5mA) in 16 patients with chronic pain of different etiology for 5 daily sessions within a week. The anode was placed over the tenth thoracic vertebra and the cathode over the somatosensory cortex. The pain condition was related to lumbosacral radiculopathy in nine patients, herpes zoster in two patients, diabetes in two patients, or multiple sclerosis in one patient. The design of the study was a randomized, sham-controlled crossover trial. Compared to sham, anodal tsDCS decreased pain intensity and NPSI scores at 1-month after the week of stimulation, in correlation with a reduction of NWFR area. Second, Berra et al.<sup>21</sup> applied anodal tsDCS (2mA) in 33 patients with chronic neuropathic pain related to multiple sclerosis for 10 daily sessions within two weeks. The anode was placed over the tenth thoracic vertebra and the cathode over the right shoulder. The design of the study was

a randomized, sham-controlled parallel-arm trial (19 active, 14 sham). Compared to sham, anodal tsDCS decreased NPSI score from the end of the stimulation period up to one month after, while the NWFR tended to be also reduced.

Our results are consistent with these precedents, but extend the findings over the long term according to a 5-month stimulation protocol based on 23 tsDCS sessions. This point is of importance, since most rTMS and tDCS studies are of short duration, in particular the very few studies that compared the analgesic effects of rTMS versus tDCS in patients<sup>50,51</sup>. The rare studies reporting long-term analgesic efficacy of rTMS<sup>52-59</sup> and tDCS<sup>60,61</sup> have been not performed in the context of CRPS.

On the other hand, there was a striking methodological difference in our study compared to previous ones, which was the montage including the placement of both anode and cathode along the spine. Such a “spinal montage” is most relevant for focusing the induced electric field (EF) in the spinal cord as recently modeled<sup>62</sup>. Indeed, the maximum EF magnitude resulting from this montage is predicted to lie in the spinal segment comprised between the anode and the cathode in human models.

Even though the dorsal horns are probably the site most strongly modulated by tsDCS, the diffusion of EF in the transverse (horizontal) plane and the nature of the neuronal structures affected remain speculative. Modeling studies have, however, improved the understanding of the spatial distribution of the current density generated by tsDCS<sup>63,64</sup>. There is further evidence that tsDCS can induce persistent changes in the transsynaptic properties of spinal neurons<sup>64</sup>. In the context of nociceptive information processing, the neuromodulatory effect of tsDCS is primarily segmental and most likely associated with changes in the synaptic efficiency of input pathways at the level of the dorsal horn [49]. Also, long-term synaptic changes (depression or potentiation) can occur in the spinal cord in a manner dependent on the polarity of stimulation, anodal or cathodal<sup>65</sup>. Like tDCS<sup>66</sup>, tsDCS is likely to modify glutamatergic neurotransmission, notably involving N-methyl-D-aspartate (NMDA) receptors, which may have an important role in prolonging segmental changes in spinal neuronal activity in the long term. For example, it was found that the perception of provoked pain was already reduced during the application of tsDCS but became more pronounced during the 30 minutes following its discontinuation, although inter-individual variation was large<sup>47</sup>.

However, the mechanisms of action might not be strictly segmental and spinal, as tsDCS can also modulate various neural structures and neurotransmitter systems through ascending spinal pathways to the brain, including brainstem or thalamo-cortical networks. Indeed, there is evidence that the changes in excitability properties of neurons induced by tsDCS extent to

corticospinal tracts or even intracortical circuits, as revealed by TMS excitability studies<sup>67-69</sup> or fMRI of brain connectivity<sup>70</sup>. In particular, fMRI showed that anodal tsDCS resulted in a decreased connectivity between the somatosensory cortex and the posterior insula and between the thalamus and the anterior cingulate cortex, while cortico-thalamic connectivity was increased<sup>70</sup>. Regarding TMS variables, tsDCS was found to modulate resting motor cortex threshold (RMT) [68], short-interval intracortical inhibition (SICI)<sup>68</sup>, and interhemispheric functional connection (transcallosal conduction time, TCT)<sup>69</sup> in a polarity-specific manner: RMT, SICI, and TCT are increased by anodal tsDCS, while cathodal tsDCS produces rather opposite effects.

On the other hand, CRPS is characterized by various alterations in TMS parameters of cortico-spinal excitability (reviewed in<sup>71</sup>, especially a reduced SICI. These data from the literature therefore offer a pathophysiological rationale for the efficacy of anodal tsDCS, which would be to restore a deficient SICI in patients with chronic pain related to CRPS. Restoration of SICI has been the subject of several publications regarding the analgesic efficacy of neuromodulation techniques, with a proven correlation between SICI improvement and pain relief following motor cortex rTMS<sup>72</sup>, anodal tDCS<sup>73</sup>, or even rPMS<sup>74</sup>. This hypothesis merits specific investigation in future work on the analgesic role of tsDCS in patients with chronic pain.

Another interesting endpoint is the measurement of ESC, the reduction of which for the affected limb at baseline seeming to be predictive of good pain relief under treatment. Moreover, successful neuromodulation therapy was associated with a significant increase (normalization) of initially reduced ESC. This result illustrates the involvement of the sympathetic nervous system in CRPS and its “cross-talk” with somatosensory processing<sup>75</sup>. At least a subset of patients had evidence of sympathetic deficit (reduced ESC) in the affected limb and cortical or spinal neuromodulation may have corrected this central sympathetic dysfunction in association with pain relief. However, this finding was not specific to the effect of tsDCS.

Other mechanisms of action may be involved in the analgesic effect of tsDCS. Depending on the orientation and intensity of the induced EFs, a steady direct current delivered by repeated daily sessions of tDCS over 20-min duration may guide and stimulate the migration or proliferation of inflammatory or glial cells or the outgrowth of neurites by specific actions on various cytokines or neurotrophins<sup>10,76</sup>. Through the application of tsDCS, segmental modulation of inflammatory response and healing or regeneration of neural tissue may have beneficial impact on the activity and plasticity of spinal neurons. Therefore, using repeated sessions of tsDCS, pain reduction and clinical improvement may be related to various molecular

or cellular interactions beyond involving a segmental or bottom-up modulation of synaptic plasticity and neural network activities, as suggested by a recent experimental study in a rat model of chronic pain<sup>77</sup>. All of these changes can contribute to a progressive positive outcome in the long term beyond the stimulation period, as also illustrated by the impact of tsDCS procedure in the rehabilitation of motor control disorders, for example<sup>78</sup>.

As mentioned above, the potential benefit of tsDCS in CRPS echoes the fact that CRPS is a classic indication for invasive SCS<sup>15,79,80</sup>. The mechanisms of action of SCS are multiple<sup>81</sup>, probably as for tsDCS, and SCS parameters of stimulation are currently diversifying, with new modes, including broadly covering or highly focused high-frequency, burst, or paresthesia-free stimulation<sup>82</sup>. Like conventional SCS, these new modes may also be effective in treating CRPS<sup>83</sup>. On the other hand, implanted dorsal root ganglion stimulation (DRGS) has recently been shown to work even better and longer than implanted SCS to improve patients with CRPS<sup>84,85</sup>. It is unclear from modeling studies whether tsDCS can act on dorsal roots as it does on dorsal horns. Nevertheless, our study shows that a non-invasive approach to spinal stimulation could be an alternative solution to invasive SCS for the treatment of chronic pain. This is already the case for rTMS which has replaced epidural stimulation of the motor cortex in clinical practice for the treatment of neuropathic pain<sup>6</sup>. However, while rTMS and epidural MCS most likely share the same mechanisms of action for producing pain relief<sup>86</sup>, it is certain that the pulsed electrical stimuli delivered by implanted SCS or DRGS have a markedly different impact at the neuronal level compared to the constant current delivered by tsDCS. This is notably due to the fact that SCS or DRGS generate action potentials and not tsDCS<sup>10</sup>. As a non-invasive neuromodulation technique, the advantage of tsDCS, like TENS, is that it can be performed at home, without any requirement for surgically implantable devices, unlike SCS or DRGS. An intermediate solution could be the use of percutaneous direct current stimulation, currently under development<sup>87</sup>.

Although this pioneering study has various limitations (especially the absence of sham control and the relatively small sample size), these results pave the way for the use of cervical or lumbar anodal tsDCS as a therapeutic technique for providing pain relief in patients with CRPS. This is especially possible to consider given the improvement obtained in the absence of side effects and the ease of performing the technique. A future controlled study is awaited to confirm the drastic effect observed here compared to placebo stimulation. Other evaluation methods, both clinical and neurophysiological ones, should also be added to better determine the mechanisms of action of tsDCS. These mechanisms could be segmental or supraspinal, related to



modulations of sensory, nociceptive or sympathetic neuronal circuits, to neuroplasticity, or to molecular or cellular neurotrophic effects associated with longer-term improvement.

### **Acknowledgments**

The authors would like to thank Dr Jean-Pierre Alibeu, Dr Julie Bismuth, Mr Nicolas Gonnet and Mr Zaza Putkaradze for their contribution to this study.

**Declaration of interest:** The authors report no conflict of interest.

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## **5.6. Targeting lower limb, upper limb, and face representation in the primary motor cortex for the practice of neuronavigated TMS**

*Article soumis, Novembre 2022*

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## **Abstract**

The primary motor cortex (M1) is a target for therapeutic application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of chronic pain, for example. Targeting rTMS can be aided by the use of MRI-guided neuronavigation system. Mainly the M1 target corresponding to the representation of the hand (hand knob) has been precisely defined in previous neuroimaging studies in the context of rTMS navigation. However, other M1 regions can be considered as potential rTMS targets, such as the regions corresponding to the representation of the lower limb or the face. In this study, we assessed the MRI localization of the representation of the lower limb, upper limb, and face on the precentral gyrus (M1) with the aims of defining three standardized M1 targets for the practice of neuronavigated rTMS. A pointing task of these different targets was performed by three experts in motor cortex rTMS therapy for pain on a series of 44 healthy brain MRIs to assess inter-rater reliability and on two 'standard' brain MRIs that were randomly interspersed with the other MRIs to assess intra-rater reliability. First, we found a good intra-rater reliability for the three experts. Regarding inter-rater reliability, variability was greater for the antero-posterior y and superior-inferior z coordinates, especially for the face target, which also show a lower accuracy for its definite location on the precentral gyrus. However, overall the inter-rater agreement remained good according to the Bland-Altman plots, intraclass correlation coefficients, and coefficients of variation. Finally, a barycenter was calculated for each target (with x-y-z coordinates provided in normalized brain coordinate systems), as well as the geodesic distance between the scalp projection of these different targets, which ranged between 32.4 and 35.5 mm for either the lower-limb-to-upper-limb target distance or the upper-limb-to-face target distance. These results clearly show that the three motor cortex targets corresponding to the region of the lower limb, upper limb, and face, are sufficiently spaced to consider that their stimulation can act on distinct neural networks. This justifies considering that the motor cortex comprises at least three different potential targets for the application of focal rTMS and this work paves the way for the definition of these three targets in the context of MRI-guided neuronavigated rTMS.

**Key words:** Face, Limb, Motor cortex, Neuronavigation, Precentral gyrus, Therapy, Transcranial magnetic stimulation

**Running title:** Localization of different motor cortical regions for TMS targeting

## Introduction

Transcranial magnetic stimulation (TMS) is a technique allowing the non-invasive stimulation of cortical regions for diagnostic or therapeutic purposes in humans (Lefaucheur, 2019). In particular, TMS applied by repetitive trains of stimulation (rTMS) is increasingly used to produce therapeutic effects in different clinical indications (Lefaucheur et al., 2020). The therapeutic efficacy of rTMS depends on different parameters, mainly on the targeting of the stimulation on the appropriate cortical region for a given indication. The treatment of a chronic pain syndrome, for example, is a clinical indication with one of the highest levels of evidence of efficacy. In this context, rTMS is classically delivered to the primary motor cortex with a high-frequency stimulation paradigm (Lefaucheur, 2016). However, it remains unclear whether the representation of the hand in the motor cortex contralateral to the pain side (or the dominant hemisphere by default) should be targeted regardless of pain location, or if rTMS should be delivered homotopically, at the level of the motor cortical representation of the painful area (Andre-Obadia et al., 2018; Lefaucheur et al., 2006). In fact, the primary motor cortex is a narrow strip of cortex located at the posterior edge of the precentral gyrus, just anterior to the central sulcus. In this cortical strip, one can functionally define three distinct regions which correspond, in the medio-lateral axis, to the representation of the lower limb, then of the upper limb, and finally of the face (Nguyen et al., 1999), according to the traditional representation of the homunculus (Penfield and Boldrey, 1937). According to data provided by intraoperative mapping for epidural cortical electrode positioning (Lefaucheur and de Andrade, 2009), the lower limb region faces the superior frontal gyrus (F1), the upper limb region faces the middle frontal gyrus (F2), and the region of the face faces the inferior frontal gyrus (F3) (Ayache et al., 2016, Lefaucheur and Nguyen, 2019). Whatever the initial target, if a series of rTMS sessions delivered to a given M1 region does not produce satisfactory analgesic effects, it is legitimate to test the efficacy of the technique by targeting other M1 regions, as recently proposed in a standardized algorithm for the management of rTMS therapy of chronic pain (Lefaucheur and Nguyen, 2019). This approach requires or at least is greatly facilitated by the use of a neuronavigation system (Lefaucheur, 2010). Neuronavigation systems integrate “individual” brain imaging data, usually provided by structural magnetic resonance imaging (MRI) of the subject who undergoes TMS. A neuronavigation system consists of a binocular camera detecting trackers mounted on the subject’s head and fixed to the TMS coil, allowing the co-registration of various cranial landmarks and the coil in the coordinate system of the brain MRI. Thus, a real-time frameless stereotaxic system can be used to position this coil over the cortical

target previously determined on MRI data. According to a 3D-reconstruction of the head and brain anatomy, the neuronavigation system allows the visualization of TMS coil location and orientation over the head in real time on a computer screen, and even the calculated electric field density produced in cortical layers by TMS.

However, the precise MRI localization of the three main motor cortical targets corresponding to the representation of the lower limb, upper limb, and face on the precentral gyrus for the practice of neuronavigated rTMS remains to be defined. We have previously reported standardized procedures to target the motor cortex representation of the hand, which is the “hand knob” (Ahdab et al., 2010, 2014; Mylius et al., 2013). In this article, we report a comparative study of the three respective targets of the lower limb, upper limb, and face representation in the motor cortex. This study was conducted by three experts (JPL, JPN, HH) in the use of neuronavigated rTMS for the treatment of chronic pain patients.

## **Methods**

### ***Subject images***

The study was performed on a data collection of 44 anonymized magnetic resonance images (MRI) of brains of healthy adults collected from several previously published studies. None of these subjects had any morphological brain MRI abnormalities after careful visual inspection. As there was some heterogeneity in MRI manufacturers (Phillips Acheiva, Siemens Verio, and GE Signa HDxt) and protocols (T1 3D N NAV, MPRAGE, and CRANE STANDARD/20), T1-weighted MR images (1 mm isotropic resolution) were normalized regarding intensities, using the 5 and 95 percentiles as the minimum and maximum intensity estimates, and were resampled to 256×256×256 voxels. All these images had a common orientation in the 3D space according to the so-called “MRI coordinate” system, based on a bounding box for the brain with an origin (0, 0, 0) located at the right inferior-anterior edge of the box. The x-axis was oriented from the right (0) to the left ear. The y-axis was oriented from nasion (0) to inion. The z-axis was oriented from the neck (0) to the top of the head.

In addition, two freely available and already published “standard” brain MRIs were used for the intra-rater reproducibility study: ‘Colin 27 Average Brain’ (Holmes et al., 1998, <https://www.mcgill.ca/bic/software/tools-data-analysis/anatomical-mri/atlasses/colin-27>) and ‘Jannin MRI BRAIN Template’ (Lalys et al., 2010, <http://www.jannin.org/mritemplate>).

### ***Procedure of target identification***

The objective of the study was to identify three targets on each hemisphere from all brain MRI data. The three targets corresponded to the representation of the lower limb, upper limb, and face in the motor cortex, which are the three main targets (T1, T2, T3) defined in the practical algorithm for using rTMS to treat patients with chronic pain we previously published (cf. Fig. 2 of this article) (Lefaucheur and Nguyen, 2019).

Briefly, the precentral gyrus (including the motor cortex) can be divided in three main regions on the lateromedial axis: a medial region facing the superior frontal gyrus (F1) with lower limb motor representation, a central region facing the middle frontal gyrus (F2) with upper limb motor representation, and a lateral region facing the inferior frontal gyrus (F3) with face motor representation. The three rTMS targets (T1, T2, T3) were more precisely defined in the middle of these regions, at their posterior edge (on the anterior wall of the central sulcus).

Three raters (JPL, JPN, HH) performed the procedure of target identification using a custom display and pointing software (Comet®, Syneika, Rennes, France), developed for this purpose. First, the raters were instructed about the procedure on a first series of four hemispheres. However, the aim of this training was to ensure that the raters performed the targeting task in the same way with the same rules and with a good command of the software, but without any quantified objective in terms of inter-rater reproducibility of x-y-z coordinate values.

In practice, each of these raters had to first identify the target corresponding to the left upper limb on the coronal, sagittal, and axial MRI slices, and then to validate the target on a 3D reconstruction of the head and brain anatomy. The determination of this first target was based on the identification of the central sulcus, superior and inferior frontal sulci, F1, F2, F3, and the three corresponding regions of the precentral gyrus. The determination of the location of the upper limb target was facilitated by the existence of the hand knob, which is a very conserved and easily identifiable region of the central sulcus, having a particular aspect of an inverted omega or a horizontal epsilon in the middle segment of the central sulcus (Ahdab et al., 2014; Yousry et al., 1997). After the validation of this first target corresponding to the left upper limb, the procedure was repeated to determine the location of the other targets, the left lower limb, the left face, the right upper limb, the right lower limb, and the right face, always in the same order.

### ***Intra-rater reliability***

Intra-rater reliability was assessed on four hemispheres corresponding to the two ‘standard’ brain MRIs that were randomly included four times within the series of brain MRIs. The raters were not aware that in this series, two MRIs had been repeated four times to test the repeatability of their targeting. This procedure was not revealed to them until the end of the study, and none of the three raters had identified that two identical brain MRIs had been repeated four times within the series of brain MRIs to analyze.

Intra-rater reliability was studied for the three coordinates (x, y, z) of the three targets (lower limb, upper limb, face), i.e. nine variables, using repeated measures ANOVA with two fixed factors, the variables "rater" (n=3) and "repetition" (n=4), and an interaction factor ("rater x repetition"). In addition, intraclass correlation coefficients (ICC) were calculated for the nine variables from a 2-way ANOVA model (Shrout and Fleiss, 1979).

### ***Inter-rater reliability***

Intra-rater reliability was studied for the three coordinates (x, y, z) of the three targets (lower limb, upper limb, face) of each hemisphere (right, left), i.e. 18 variables, from the assessments performed by the three raters on the series of 44 brain MRIs, excluding the two ‘standard’ brain MRIs used for intra-rater reliability study.

To assess inter-rater reliability, a 4-layered approach was performed. First, one-way ANOVA with repeated measures was used, and when the test produced a significant result, multiple post-hoc pairwise signed-ranks tests were applied to compare raters.

Second, the variance (estimated bias) between the measurements performed by the three raters and the 95% limits of agreement were calculated and Bland-Altman plots were constructed using linear mixed models (Bland and Altman, 1986; Carstensen et al., 2008). The plots were constructed by assigning the mean of each pair of measurement made by the different raters as the x-axis value and the difference between these two values as the y-axis value.

Third, ICC were calculated for the 18 variables from a 2-way ANOVA model (Shrout and Fleiss, 1979).

Fourth, inter-rater coefficients of variation (CoVs, defined as the ratio of standard deviation to the mean) were calculated for each variable in each subject. Then, the CoVs were compared between the variables for each coordinate (x, y, z) using one-way ANOVA with multiple post-hoc pairwise tests when the ANOVA produced a significant result (Boërio et al., 2008; Mylius et al., 2013).

Statistical analyses were performed with Prism® (GraphPad, San Diego, CA, USA) and XLSTAT® (Addinsoft, Paris, France) softwares. The absence of normal distribution of all target coordinates was assessed by the Kolmogorov-Smirnov test and therefore nonparametric tests were used. Numerical data were usually expressed as mean [lower; upper limits of the 95% confidence interval]. Statistical significance was set to  $\alpha=0.05$ .

### ***Barycenters***

The whole data set of targets determined by the three raters were re-analyzed by two additional raters (LB, SC) only on the 3D reconstruction view of the head and brain anatomy. According to the pre-established definition of the different targets (at the posterior edge of the middle of the three regions of the precentral gyrus), these two additional raters assigned a ‘score of accuracy’ between 0 (target outside the precentral gyrus) and 3 (target at the optimal location) for each target defined by each of the three initial raters. For the three targets (lower limb, upper limb, face), this score of accuracy was compared between raters using the Fisher test.

From all the targeting values excluding those with a score of accuracy of 0, a barycenter was calculated for each of the three targets (lower limb, upper limb, face) of each hemisphere (right, left). The mean distance between the different target locations determined by each initial rater and the corresponding barycenter was calculated. Finally, the coordinates of the barycenters were transformed from the “MRI coordinate system” into the normalized spaces defined by the Talairach and Tournoux atlas (Talairach and Tournoux, 1988) or the Montreal Neurological Institute (Collins et al., 1998). The curvilinear distance between the scalp projection points of the barycenters of the three targets of each hemisphere was also calculated.

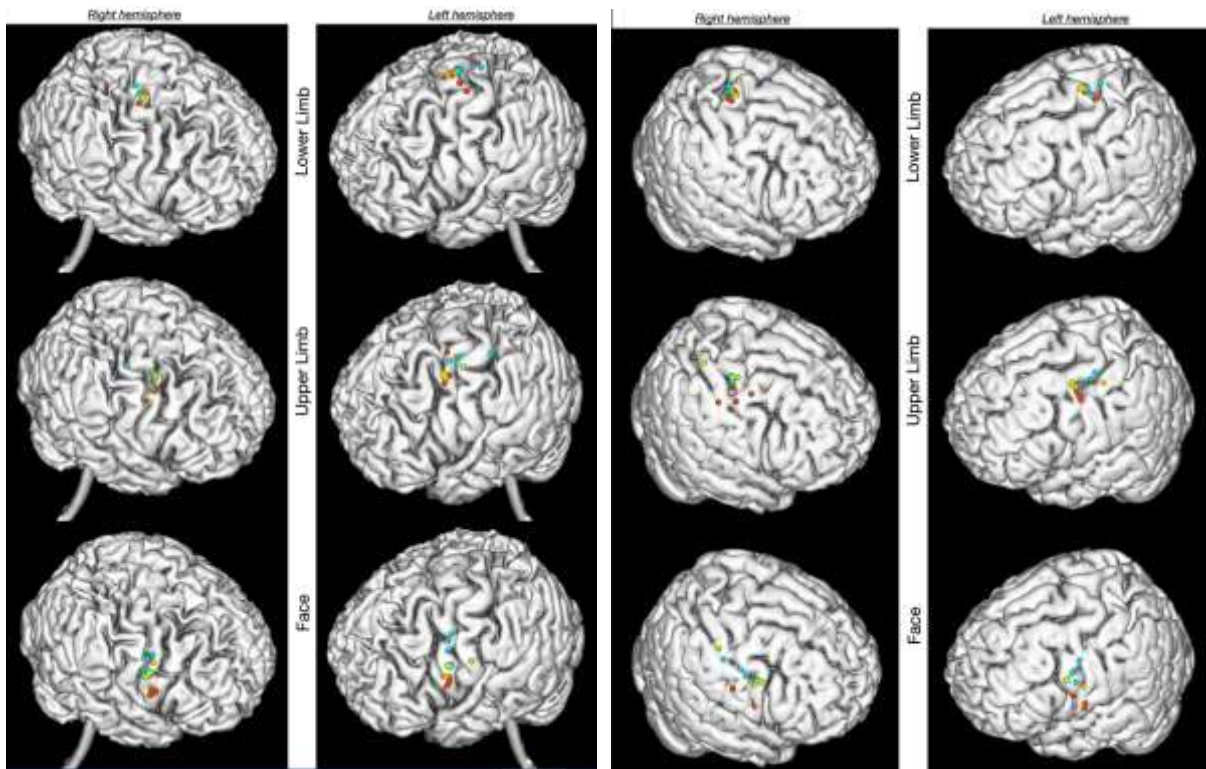
## **Results**

### ***Intra-rater reliability***

Intra-rater reliability assessed on the two ‘standard’ brain MRIs that were randomly included four times within the series of brain MRIs is illustrated in Figure 1 on the ‘Colin 27 Average Brain’.



**Figure 1. Intra-rater reliability**



*Intra-rater reliability assessed on the 'Colin 27 Average Brain' (left panel) and the 'Jannin MRI BRAIN Template' (right panel). The four target pointing for each of the three targets of the two hemispheres are indicated with red points for rater 1, blue points for rater 2, and yellow points for rater 3.*

First of all, no significant intra-rater individual effects (“repetition” factor) was observed for any the three coordinates (x, y, z) of the three targets (lower limb, upper limb, face) (p values ranging between 0.113 and 0.992) (Table 1). There was also no inter-rater effects (p values for the “rater” factor ranging between 0.523 and 0.999) and no "rater x repetition" interaction (p values ranging between 0.143 and 0.940) (Table 1).

The absence of a significant impact of measurement repetition was also obvious according to the very high ICC values ranging between 0.952 and 0.999 for the three coordinates (x, y, z) of the three targets (lower limb, upper limb, face) (Table 1).



**Table 1. Intra-rater reliability**

	x (Lower limb)	x (Upper limb)	x (Face)
<b><u>Repeated measures ANOVA</u></b>			
"Rater" factor (F(2,12), p)	F=0.001, p=0.999	F=0.001, p=0.999	F=0.001, p=0.999
"Repetition" factor (F(3,27), p)	F=0.174, p=0.913	F=1.146, p=0.344	F=0.994, p=0.407
"Rater x repetition" interaction (F(6,27), p)	F=0.459, p=0.834	F=1.726, p=0.143	F=0.285, p=0.940
<b><u>Intraclass correlation coefficient</u></b>			
Mean	0.989	0.998	0.999
95% confidence interval	[0.984;0.992]	[0.997;0.998]	[0.999;0.999]
	y (Lower limb)	y (Upper limb)	y (Face)
<b><u>Repeated measures ANOVA</u></b>			
"Rater" factor (F(2,12), p)	F=0.593, p=0.573	F=0.697, p=0.523	F=0.062, p=0.941
"Repetition" factor (F(3,27), p)	F=0.807, p=0.498	F=1.144, p=0.344	F=0.522, p=0.670
"Rater x repetition" interaction (F(6,27), p)	F=0.286, p=0.940	F=0.851, p=0.540	F=1.220, p=0.319
<b><u>Intraclass correlation coefficient</u></b>			
Mean	0.954	0.952	0.955
95% confidence interval	[0.935;0.969]	[0.932;0.967]	[0.936;0.969]
	z (Lower limb)	z (Upper limb)	z (Face)
<b><u>Repeated measures ANOVA</u></b>			
"Rater" factor (F(2,12), p)	F=0.028, p=0.972	F=0.077, p=0.927	F=0.409, p=0.676
"Repetition" factor (F(3,27), p)	F=0.032, p=0.992	F=1.359, p=0.271	F=2.130, p=0.113
"Rater x repetition" interaction (F(6,27), p)	F=1.430, p=0.230	F=0.619, p=0.714	F=1.300, p=0.282
<b><u>Intraclass correlation coefficient</u></b>			
Mean	0.994	0.986	0.973
95% confidence interval	[0.992;0.996]	[0.980;0.990]	[0.961;0.981]

***Inter-rater reliability***

The descriptive statistics (mean, standard deviation, median, lower and upper limits of the 95% confidence interval) of the x, y, and z coordinates of the three targets (lower limb, upper limb, face) on each hemisphere (right, left) obtained from the three raters are reported in Table 2.

**Table 2. Descriptive statistics of the x, y, and z coordinates of the three targets (lower limb, upper limb, face) on the right (r) and left (l) hemispheres for each rater**

	Rater 1	Rater 2	Rater 3	Rater 1	Rater 2	Rater 3	Rater 1	Rater 2	Rater 3
	<b>x (r. Lower limb)</b>			<b>x (r. Upper limb)</b>			<b>x (r. Face)</b>		
Mean	64.4	61.3	65.2	45.4	44.0	46.0	32.9	31.9	32.8
Std dev (SD)	11.5	12.0	12.6	10.9	12.0	12.7	11.3	10.7	11.3
Median (50th p.)	64.0	59.0	64.5	45.0	43.0	46.0	32.0	31.0	32.0
Lower 95% conf. lim.	60.9	57.7	61.4	42.0	40.3	42.2	29.4	28.7	29.3
Upper 95% conf. lim.	67.9	65.0	69.1	48.7	47.7	49.9	36.3	35.2	36.2
	<b>x (l. Lower limb)</b>			<b>x (l. Upper limb)</b>			<b>x (l. Face)</b>		
Mean	115.7	119.2	115.1	135.8	137.2	137.0	147.4	148.2	148.4
Std dev (SD)	11.5	10.4	14.0	11.7	11.5	12.5	12.2	10.9	11.3
Median (50th p.)	114.5	116.5	114.0	135.0	136.5	135.0	147.0	147.5	148.0
Lower 95% conf. lim.	112.2	116.0	110.8	132.3	133.7	133.2	143.7	144.9	145.0

<b>Upper 95% conf. lim.</b>	119.2	122.3	119.3	139.4	140.7	140.9	151.1	151.5	151.9
	<b>y (r. Lower limb)</b>			<b>y (r. Upper limb)</b>			<b>y (r. Face)</b>		
<b>Mean</b>	154.2	146.6	149.2	141.0	134.1	137.2	128.5	121.2	127.1
<b>Std dev (SD)</b>	16.4	15.4	18.2	16.2	15.4	16.8	14.7	14.8	17.5
<b>Median (50th p.)</b>	154.0	145.5	151.0	141.5	134.0	136.0	127.5	119.5	126.0
<b>Lower 95% conf. lim.</b>	149.2	142.0	143.7	136.1	129.5	132.1	124.1	116.7	121.8
<b>Upper 95% conf. lim.</b>	159.2	151.3	154.7	145.9	138.8	142.3	133.0	125.7	132.4
	<b>y (l. Lower limb)</b>			<b>y (l. Upper limb)</b>			<b>y (l. Face)</b>		
<b>Mean</b>	154.6	147.2	148.5	141.8	134.5	138.1	130.2	120.8	125.8
<b>Std dev (SD)</b>	16.7	16.6	16.6	16.9	14.6	18.4	14.8	12.3	15.0
<b>Median (50th p.)</b>	155.5	148.0	150.0	141.5	135.0	139.0	127.5	121.5	124.5
<b>Lower 95% conf. lim.</b>	149.5	142.1	143.4	136.6	130.1	132.5	125.7	117.1	121.2
<b>Upper 95% conf. lim.</b>	159.7	152.2	153.5	146.9	139.0	143.7	134.7	124.6	130.3
	<b>z (r. Lower limb)</b>			<b>z (r. Upper limb)</b>			<b>z (r. Face)</b>		
<b>Mean</b>	202.5	199.5	202.8	191.1	186.6	191.1	175.8	163.7	175.9
<b>Std dev (SD)</b>	19.2	18.1	18.2	19.3	17.8	17.7	20.1	18.3	19.2
<b>Median (50th p.)</b>	205.5	203.0	206.5	195.0	189.5	194.5	181.0	167.5	178.0
<b>Lower 95% conf. lim.</b>	196.7	194.0	197.3	185.3	181.2	185.7	169.7	158.1	170.1
<b>Upper 95% conf. lim.</b>	208.4	205.0	208.4	197.0	192.0	196.5	181.9	169.3	181.7
	<b>z (l. Lower limb)</b>			<b>z (l. Upper limb)</b>			<b>z (l. Face)</b>		
<b>Mean</b>	202.2	199.4	201.4	190.6	186.4	188.8	173.7	163.5	172.3
<b>Std dev (SD)</b>	18.8	18.1	18.9	18.4	18.2	19.3	20.0	19.7	18.7
<b>Median (50th p.)</b>	204.5	201.5	204.0	191.5	190.0	191.5	176.0	168.5	174.5
<b>Lower 95% conf. lim.</b>	196.5	193.9	195.6	185.0	180.9	182.9	167.6	157.5	166.6
<b>Upper 95% conf. lim.</b>	207.9	204.9	207.1	196.2	191.9	194.7	179.8	169.5	178.0

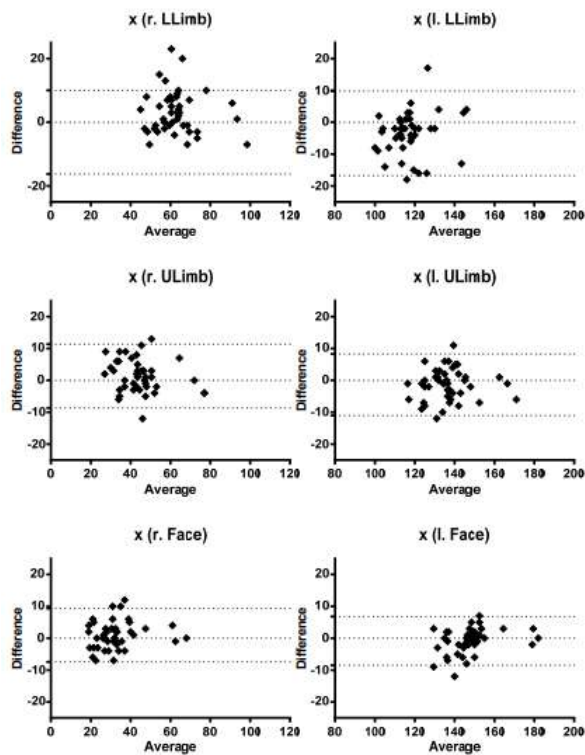
To assess inter-rater reliability, a first approach was based on one-way repeated measures ANOVA, which showed moderate inter-rater differences for the x coordinates (only significant for the right and left lower limb targets and the right upper limb target) but highly significant inter-rater differences for the y and z coordinates (Friedman test,  $p < 0.0001$  for all the targets) (Table 3). Multiple pairwise comparison post-hoc tests showed that inter-rater differences were mainly significant between raters 2 and rater 3 for the x coordinate, between rater 1 and raters 2 and 3 for the y coordinate, and between rater 2 and raters 1 and 3 for the z coordinate (Table 3).

**Table 3. Inter-rater reliability**

	x (r. Lower limb)	x (r. Upper limb)	x (r. Face)	x (l. Lower limb)	x (l. Upper limb)	x (l. Face)
<b>Repeated measures ANOVA (Friedman test, p)</b>	<b>0.021</b>	<b>0.0259</b>	0.3799	<b>0.0018</b>	0.4682	0.2253
<b>Post-hoc pairwise tests:</b>						
Rater 1 vs. Rater 2	ns P>0.05	ns P>0.05	ns P>0.05	* <b>P&lt;0.05</b>	ns P>0.05	ns P>0.05
Rater 1 vs. Rater 3	ns P>0.05	ns P>0.05	ns P>0.05	ns P>0.05	ns P>0.05	ns P>0.05
Rater 2 vs. Rater 3	* <b>P&lt;0.05</b>	* <b>P&lt;0.05</b>	ns P>0.05	** <b>P&lt;0.01</b>	ns P>0.05	ns P>0.05
<b>Estimated bias (Bland-Altman)</b>	3.091 [-10.07;16.25]	1.364 [-8.649;11.38]	0.955 [-7.446;9.355]	-3.477 [-16.75;9.799]	-1.364 [-11.02;8.295]	-0.841 [-8.484;6.802]
<b>Intraclass correlation coefficient</b>	0.944 [0.908;0.968]	0.965 [0.942;0.980]	0.975 [0.959;0.986]	0.931 [0.887;0.960]	0.957 [0.928;0.975]	0.982 [0.970;0.990]
<b>Coefficient of variation</b>	0.072 [0.058;0.085]	0.077 [0.062;0.092]	0.085 [0.069;0.102]	0.041 [0.033;0.048]	0.027 [0.023;0.032]	0.015 [0.011;0.018]
<b>One-Way ANOVA (Kruskal-Wallis test, p)</b>	<b>&lt; 0.0001</b>					
<b>Post-hoc pairwise tests vs:</b>						
x (r. Lower limb)		ns P>0.05	ns P>0.05	* <b>P&lt;0.05</b>	*** <b>P&lt;0.001</b>	*** <b>P&lt;0.001</b>
x (r. Upper limb)			ns P>0.05	* <b>P&lt;0.05</b>	*** <b>P&lt;0.001</b>	*** <b>P&lt;0.001</b>
x (r. Face)				** <b>P&lt;0.01</b>	*** <b>P&lt;0.001</b>	*** <b>P&lt;0.001</b>
x (l. Lower limb)					ns P>0.05	*** <b>P&lt;0.001</b>
x (l. Upper limb)						ns P>0.05
x (l. Face)						
<b>Repeated measures ANOVA (Friedman test, p)</b>	<b>&lt; 0.0001</b>	<b>&lt; 0.0001</b>	<b>&lt; 0.0001</b>	<b>&lt; 0.0001</b>	<b>&lt; 0.0001</b>	<b>&lt; 0.0001</b>
<b>Post-hoc pairwise tests:</b>						
Rater 1 vs. Rater 2	*** <b>P&lt;0.001</b>	*** <b>P&lt;0.001</b>	*** <b>P&lt;0.001</b>	*** <b>P&lt;0.001</b>	*** <b>P&lt;0.001</b>	*** <b>P&lt;0.001</b>
Rater 1 vs. Rater 3	*** <b>P&lt;0.001</b>	* <b>P&lt;0.05</b>	ns P>0.05	*** <b>P&lt;0.001</b>	** <b>P&lt;0.01</b>	** <b>P&lt;0.01</b>
Rater 2 vs. Rater 3	ns P>0.05	* <b>P&lt;0.05</b>	*** <b>P&lt;0.001</b>	ns P>0.05	ns P>0.05	** <b>P&lt;0.01</b>
<b>Estimated bias (Bland-Altman)</b>	7.545 [-8.866;23.96]	6.864 [-8.381;22.11]	7.318 [-5.661;20.3]	7.386 [-7.92;22.69]	7.250 [-8.93;23.43]	9.341 [-4.132;22.81]
<b>Intraclass correlation coefficient</b>	0.948 [0.915;0.970]	0.951 [0.919;0.971]	0.959 [0.932;0.976]	0.960 [0.935;0.977]	0.954 [0.924;0.973]	0.952 [0.921;0.972]
<b>Coefficient of variation</b>	0.038 [0.029;0.047]	0.041 [0.033;0.049]	0.047 [0.041;0.053]	0.036 [0.028;0.045]	0.042 [0.034;0.049]	0.048 [0.040;0.055]
<b>One-Way ANOVA (Kruskal-Wallis test, p)</b>	<b>0.0153</b>					
<b>Post-hoc pairwise tests vs:</b>						
y (r. Lower limb)		ns P>0.05	ns P>0.05	ns P>0.05	ns P>0.05	ns P>0.05
y (r. Upper limb)			ns P>0.05	ns P>0.05	ns P>0.05	ns P>0.05
y (r. Face)				* <b>P&lt;0.05</b>	ns P>0.05	ns P>0.05
y (l. Lower limb)					ns P>0.05	ns P>0.05
y (l. Upper limb)						ns P>0.05
y (l. Face)						
<b>Repeated measures ANOVA (Friedman test, p)</b>	<b>&lt; 0.0001</b>	<b>&lt; 0.0001</b>	<b>&lt; 0.0001</b>	<b>&lt; 0.0001</b>	<b>&lt; 0.0001</b>	<b>&lt; 0.0001</b>
<b>Post-hoc pairwise tests:</b>						
Rater 1 vs. Rater 2	*** <b>P&lt;0.001</b>	*** <b>P&lt;0.001</b>	*** <b>P&lt;0.001</b>	*** <b>P&lt;0.001</b>	*** <b>P&lt;0.001</b>	*** <b>P&lt;0.001</b>
Rater 1 vs. Rater 3	ns P>0.05	ns P>0.05	ns P>0.05	ns P>0.05	ns P>0.05	ns P>0.05
Rater 2 vs. Rater 3	*** <b>P&lt;0.001</b>	*** <b>P&lt;0.001</b>	*** <b>P&lt;0.001</b>	** <b>P&lt;0.01</b>	* <b>P&lt;0.05</b>	*** <b>P&lt;0.001</b>
<b>Estimated bias (Bland-Altman)</b>	3.045 [-3.704;9.795]	4.568 [-4.561;13.7]	12.070 [-5.378;29.51]	2.773 [-4.337;9.882]	4.227 [-4.299;12.75]	10.200 [-4.678;25.09]
<b>Intraclass correlation coefficient</b>	0.995 [0.991;0.997]	0.988 [0.981;0.993]	0.970 [0.951;0.983]	0.994 [0.990;0.996]	0.984 [0.973;0.991]	0.976 [0.961;0.986]
<b>Coefficient of variation</b>	0.013 [0.012;0.015]	0.021 [0.018;0.024]	0.048 [0.041;0.054]	0.013 [0.011;0.015]	0.021 [0.017;0.024]	0.040 [0.034;0.047]
<b>One-Way ANOVA (Kruskal-Wallis test, p)</b>	<b>&lt; 0.0001</b>					
<b>Post-hoc pairwise tests vs:</b>						
z (r. Lower limb)		ns P>0.05	*** <b>P&lt;0.001</b>	ns P>0.05	ns P>0.05	*** <b>P&lt;0.001</b>
z (r. Upper limb)			*** <b>P&lt;0.001</b>	* <b>P&lt;0.05</b>	ns P>0.05	*** <b>P&lt;0.001</b>
z (r. Face)				*** <b>P&lt;0.001</b>	*** <b>P&lt;0.001</b>	ns P>0.05
z (l. Lower limb)					ns P>0.05	*** <b>P&lt;0.001</b>
z (l. Upper limb)						*** <b>P&lt;0.001</b>
z (l. Face)						*** <b>P&lt;0.001</b>

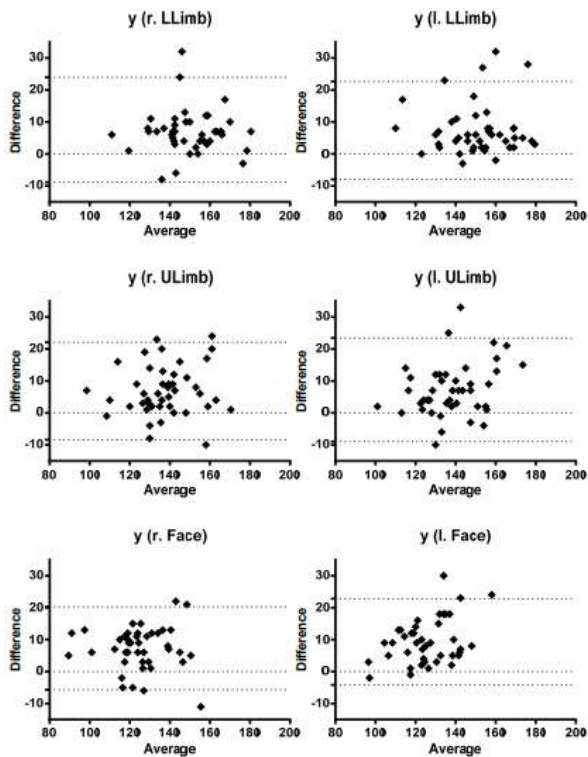
Second, the Bland-Altman plots showed a good agreement regarding target coordinate determination between the different raters (Figures 2, 3, 4). Among 132 calculated inter-rater coordinate differences, there were only 16 outliers (inter-rater coordinate differences outside the limits of agreement) for the x coordinate, 18 outliers for the y coordinate, and 13 outliers for the z coordinate. The estimated bias (in absolute value) between the measurements performed by the three raters ranged between 0.841 and 3.477 for the x coordinate, between 6.864 and 9.341 for the y coordinate, and between 2.773 and 12.070 for the z coordinate (Table 3). Thus, the bias (inter-rater variance) was lower for the x coordinate in general, and also the z coordinate of upper and lower limb targets, but higher for the y coordinate in general, and especially the z coordinate of the right and left face targets.

**Figure 2. Bland-Altman plot for inter-rater variance of the x coordinates**



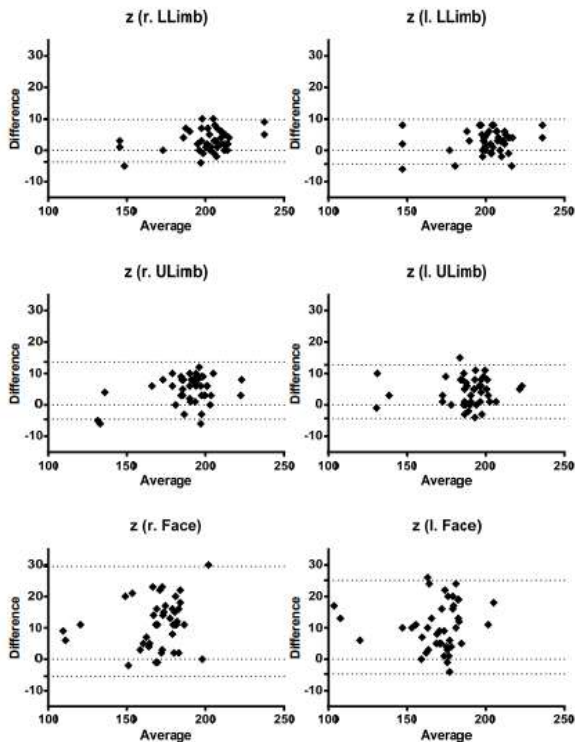
*LLimb: lower limb motor cortical target. ULimb: upper limb motor cortical target. Face: face motor cortical target. r.: right hemisphere. l.: left hemisphere. The 95% limits of agreement are indicated as dotted lines.*

**Figure 3. Bland-Altman plot for inter-rater variance of the y coordinates**



*LLimb: lower limb motor cortical target. ULimb: upper limb motor cortical target. Face: face motor cortical target. r.: right hemisphere. l.: left hemisphere. The 95% limits of agreement are indicated as dotted lines.*

**Figure 4. Bland-Altman plot for inter-rater variance of the z coordinates**



*LLimb: lower limb motor cortical target. ULimb: upper limb motor cortical target. Face: face motor cortical target. r.: right hemisphere. l.: left hemisphere. The 95% limits of agreement are indicated as dotted lines.*

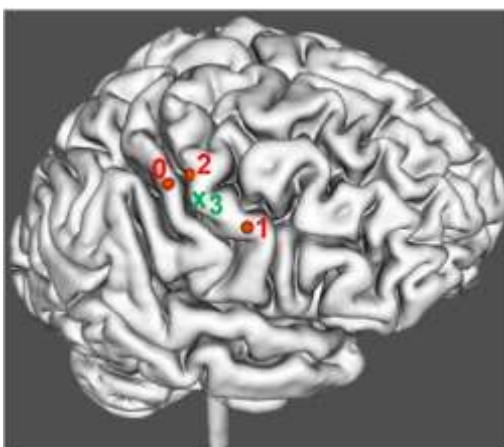
Finally, the ICCs were very high (mean values ranging between 0.931 and 0.995) and the CoVs were very low (mean values ranging between 0.013 and 0.085), confirming the low variability of the measurements between raters (Table 3). However, there were significant CoV differences between the targets, especially for the x and z coordinates (Kruskal-Wallis test,  $p < 0.0001$ ). Multiple pairwise comparison post-hoc tests mainly showed a lower CoV for the left face and upper limb targets regarding the x coordinate and a higher CoV for the right and left face targets regarding the y coordinate (Table 3).

### ***Barycenters***

First, the scores of accuracy, assigned by two additional raters for each targeting performed by the three initial raters, were compared between these raters. There was no inter-rater difference for the face target (Fisher test,  $p = 0.365$ ), but a tendency towards significance was found for the upper limb target ( $p = 0.062$ ) and the lower limb target ( $p = 0.072$ ). In particular, the percentage of outliers with a score of accuracy of 0 (target outside the precentral gyrus) was high for upper and lower limb target location for the rater 2 (22.7% vs. 5.7-11.4% for raters 1 and 3). Optimal target location (score of accuracy of 3) was obtained in 63.6 to 77.3% of the targeting procedures, except for the upper limb target for the rater 2 (54.5%) and for the face target for the three raters (46.6-54.5%).

This score of accuracy takes into account the functional anatomy of the gyri and is therefore probably of better relevance than the targeting analysis based solely on distance calculations (Figure 5).

**Figure 5. Example of the score of accuracy of upper limb targeting performed by the three initial raters on the right hemisphere**



*A score of accuracy of 0 was assigned for a targeting located outside the precentral gyrus (in this example a target is located on the postcentral gyrus). A score of accuracy of 1 or 2 was assigned for a targeting located within the correct region of the precentral gyrus (middle segment in this example), but not at the optimal location (green X with a score of 3 on the hand knob region in this example). One can notice that a score of 0 can be assigned even if the distance to the optimal target is very low, because the functional anatomy of the gyri is taken into account.*

From all the targeting measures excluding those with a score of accuracy of 0, a barycenter was calculated for each of the three targets (lower limb, upper limb, face) of each hemisphere (right, left). The x, y, and z coordinates of the barycenters for all the studied motor cortex targets are presented in Table 4. The mean distance between the different target locations determined by each initial rater and the corresponding barycenter was rather similar whatever the targeted motor region and the rater and ranged between 5.7 and 10.3 mm (Table 4).

**Table 4. Coordinates of the barycenters of all motor cortex targets**

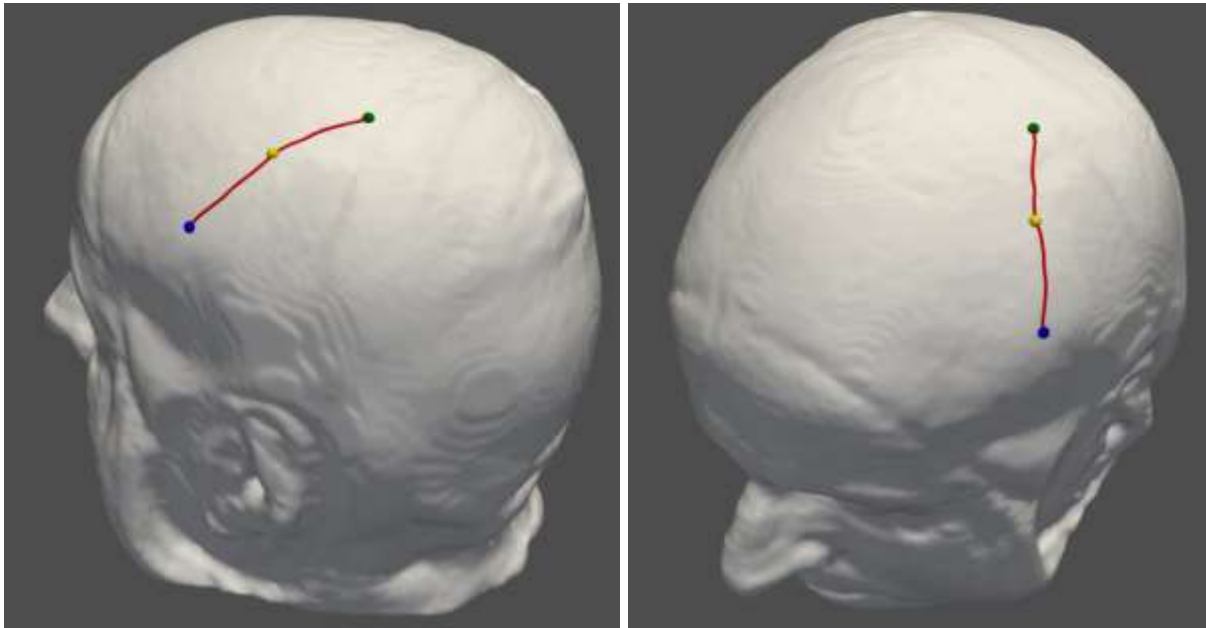
	<b>r. Lower limb</b>	<b>r. Upper limb</b>	<b>r. Face</b>	<b>l. Lower limb</b>	<b>l. Upper limb</b>	<b>l. Face</b>
<b>x coordinate</b>						
<b>MRI coordinate system</b>	63.7	45.1	32.5	116.7	136.7	148.0
<b>Talairach system</b>	24.5	41.9	54.1	-25.0	-43.2	-53.9
<b>MNI system</b>	23	41	55	-25	-43	-56
<b>y coordinate</b>						
<b>MRI coordinate system</b>	150.0	137.4	125.6	150.1	138.1	125.6
<b>Talairach system</b>	-30.1	-17.5	-6.0	-30.1	-17.0	-4.6
<b>MNI system</b>	-35	-22	-8	-34	-20	-6
<b>z coordinate</b>						
<b>MRI coordinate system</b>	201.6	189.6	171.8	201.0	188.6	169.9
<b>Talairach system</b>	62.2	51.3	34.8	61.2	49.1	31.6
<b>MNI system</b>	69	55	36	68	53	33
<b>Mean deviation (in MRI coordinates) with:</b>						
<b>rater 1</b>	6.9	6.4	10.3	6.5	6.7	8.8
<b>rater 2</b>	6.3	6.5	7.3	6.7	6.5	7.8
<b>rater 3</b>	6.0	5.7	7.1	6.0	6.4	5.9

Finally, the mean curvilinear (geodesic) distance between the scalp projection points of the barycenters (as illustrated in Figure 6) was of 32.4 and 34.7 mm between the lower and upper limb targets on the right and left hemispheres, respectively; and of 34.9 and 35.5 mm between the upper limb and face targets on the right and left hemispheres, respectively (Table 5). However, the inter-individual variability was very important, from 13-17 mm minimum to 55-70 mm maximum.

**Table 5. Geodesic distances between the different motor cortex targets**

	Geodesic distance at scalp level (mean $\pm$ sd; [min-max], in mm)	
	between lower and upper limb targets	between upper limb and face targets
<b>Right hemisphere</b>	32.4 $\pm$ 8.0 [15.3-54.9]	34.9 $\pm$ 11.1 [13.0-70.1]
<b>Left hemisphere</b>	34.7 $\pm$ 8.1 [17.0-63.4]	35.5 $\pm$ 9.5 [14.8-60.4]

**Figure 6. Examples of the geodesic distances between the different motor cortex targets**



*Geodesic distances at the level of the scalp (lower panel). The lower limb target is indicated by a green point, the upper limb target by a yellow point, and the face target by a blue point.*

## Discussion

The objective of the study was to identify on normal brain MRI the three motor cortical regions of the representation of the lower limb, the upper limb, and the face, respectively, in order to define the location of the three corresponding targets for rTMS practice.

First of all, we found a good intra-rater reliability for the three experts, as ‘blindly’ assessed on two ‘standard’ brain MRIs randomly interspersed with the other MRIs without the knowledge of the raters.

Regarding inter-rater reliability, we found a moderate variability between the raters for the x coordinate (especially for the lower limb targets) and a greater variability for the y and z coordinates. Inter-rater variance (bias) was lower for the x coordinate in general and higher for the y coordinate in general, and especially for the z coordinate of the face target. The highest CoV was observed for the y coordinate of the face target. However, overall the inter-rater



agreement remained good according to the Bland-Altman plots, while the ICCs were very high and the CoVs very low, confirming the low variability of the measurements between raters.

Thus, this study shows that experts can agree on the location of motor cortical targets corresponding to the representation of the three major body regions, namely the lower limb, the upper limb and the face, according to a mediolateral segmentation of the precentral gyrus depending on the identification of the superior and inferior frontal sulci. Overall, the location of the face target was the most variable between raters, both on the antero-posterior y-axis and the superior-inferior z-axis.

In addition to the assessment of targeting reliability between the three experts, a second step of the study was based on ‘scores of accuracy’, assigned by two additional raters, taking into account the appropriate location of the target on the precentral gyrus on a 3D reconstruction of brain MRI. Again, a lower accuracy was observed for the face target among the three experts, although inter-rater variability of this score was higher for the upper limb due to rater 2.

Finally, a barycenter was calculated for each target from all the measures weighted according to the score of accuracy. On the antero-posterior y-axis, the lower limb target was about 12 mm posterior to the upper limb target, which was also about 12 mm posterior to the face target. On the superior-inferior z-axis, the lower limb target was about 12 mm superior to the upper limb target, which was about 18 mm superior to the face target. Thus, the mean curvilinear (geodesic) distance between the scalp projection points of the different TMS targets (lower-limb-to-upper-limb targets or upper-limb-to-face targets) ranged between 32.4 and 35.5 mm. Overall, no difference was observed for any of the targeting measures between the right and left hemispheres.

Using a commercial figure-of-8 coil classically used for the practice of rTMS, the radius of the spread of the electric field (E-field) produced by the TMS pulse in the cortical layers at 1.2-1.5 cm from the scalp (optimal depth) was shown to range between 17 and 22 mm (Deng et al., 2013; Gomez et al., 2018). Another study showed that significant changes in the assessment of cortical excitability by navigated TMS pulses occur for variations in coil positioning ranging between 2 and 10 mm only (Schmidt et al., 2015). However, this value obviously depends on the intensity of stimulation (Thielscher and Kammer, 2004). According to the relatively low intensity of stimulation applied for the treatment of chronic pain by motor cortex stimulation (usually 80-90% of the resting motor threshold), the E-field could be much more focal in this application. Also, under these conditions, it is surely not trivial to move the coil by more than 3 cm on the scalp to switch from lower limb to upper limb targeting or from upper limb to face targeting. In some individuals, the distance between two different motor region targets even

reached 5.5 to 7 cm on scalp projections. Therefore, it is highly probable that the impacted neural structures will not be similar according to the stimulation of distinct motor cortical targets. This study confirms that it is necessary to consider that the motor cortex includes different targets and this justifies the algorithm that we have proposed (Lefaucheur and Nguyen, 2019). Actually, it is legitimate to evaluate other rTMS targets at the level of the motor cortex when a first target does not produce significant analgesic efficacy. This also justifies the differential results of motor cortex stimulation published in the literature obtained in a given painful patient, depending on whether the area of the face, the upper, or the lower limb was targeted (Andre-Obadia et al., 2018; Jetté et al., 2013; Lefaucheur et al., 2006). However, it remains to be defined whether the best target is the area of the hand regardless of the location of the pain or the homotopic area of the motor cortical representation of the painful region.

This study is also an important step to validate a predefined targeting algorithm for a navigation system in its use for rTMS application in clinical practice. Indeed, it is not always easy for a practitioner involved in the use of rTMS for therapeutic purposes to have a good knowledge of cortical anatomy. In this case, it will be helpful to be able to help him/her to automatically identify these three large targeting regions defined at the level of the precentral gyrus. In a first step of development, based on a previous study (Nauczyciel et al., 2011), only the identification of the motor cortex of the hand and the dorsolateral prefrontal cortex have been provided in the navigation system we used. We hope that the new targeting aid that results from this work will facilitate the procedure of high-frequency rTMS of the motor cortex in the treatment of chronic pain and thus optimize its effects in clinical practice.

## **Funding**

No specific financial or non-financial support was received.

## **Declaration of Competing Interest**

Jean-Pascal Lefaucheur, Jean-Paul Nguyen, Hasan Hodaj: no competing interest regarding this work. Antoine Delmas, Stéphane Croci, Luc Bredoux: employees and CEO of the Syneika company.

## **Credit authorship contribution statement**

Jean-Pascal Lefaucheur: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. Jean-Paul Nguyen: Investigation, Writing – review &

editing. Antoine Delmas: Conceptualization, Methodology, Writing – review & editing. Stéphane Croci: Conceptualization, Methodology, Writing – review & editing. Luc Bredoux: Conceptualization, Methodology, Writing – review & editing. Hasan Hodaj: Investigation, Writing – review & editing.

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## **5.7. Role of S1 in pain-autonomic coupling and the analgesic effect of motor cortex rTMS in complex regional pain syndrome (CRPS)**

*Article soumis, Décembre 2022*

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## 1. Abstract

Complex regional pain syndrome (CRPS) is a chronic pain condition involving autonomic dysregulation. In the present study, we sought for neural correlates of pain in CRPS patients in relation with sympathetic nervous system and for its potential alleviation following a noninvasive brain stimulation protocol using repetitive transcranial magnetic stimulation (rTMS) delivered at high-frequency over the motor cortex. Eleven patients with CRPS at one limb were assessed before (D1) and one month after the end of a 5-month motor cortex rTMS therapy (D180) by means of: electrochemical skin conductance (ESC) measurement, daily pain intensity scored on a visual numerical scale (VNS), and functional magnetic resonance imaging (fMRI) with motor tasks. At baseline (D1), reduction in ESC values in the CRPS-affected limb correlated with elevated VNS pain scores. In addition, there was a covariance of both variables (ESC and VNS) with brain activation in a limited region of the primary somatosensory cortex (S1) contralateral to the painful side on fMRI investigation. Following motor cortex rTMS therapy (D180), the VNS pain scores significantly decreased by 22% on average and 6/11 patients were considered responders ( $\geq 30\%$  reduction in VNS scores). In these responders, ESC values in the CRPS-affected limb increased and returned to normal. After rTMS, VNS pain scores and ESC measurements were no longer correlated, but still covaried with S1 activation on fMRI. The activation of other brain regions, i.e. precuneus, middle frontal gyrus, and temporo-parietal junction, correlated with sympathetic sudomotor activity and the potential impact of rTMS on this activity. Finally, we found a positive correlation at D180 (not at D1) between VNS pain score and fMRI activation in the temporo-parietal junction contralateral to painful side. This study first shows a functional pain-autonomic coupling in CRPS patients, which could involve a specific S1 region. However, the modulation of sympathetic sudomotor activities by rTMS may be rather associated with functional changes in other brain regions. This study also shows that rTMS efficacy may be revealed by a reduced activation of the temporo-parietal junction on the side where cortical stimulation is performed.

**Keywords:** complex regional pain syndrome, electrochemical skin conductance- sympathetic activity, fMRI, primary sensory cortex, rTMS, temporo-parietal junction.



## 2. Introduction

Chronic Regional Pain Syndrome (CRPS) is a chronic pain disorder, which has the particularity of presenting prominent autonomic symptoms in the painful territory, notably including a sudomotor dysfunction (Birklein et al., 1998; Sandroni et al., 1998). Sudomotor dysfunction can be assessed by various techniques, such as the quantitative sudomotor axon reflex test (QSART) (Buchmann et al., 2019) or the measurement of electrochemical skin conductance (ESC) by SudoScan® (Novak et al., 2019). To study brain-autonomic coupling, variations in skin conductance level can be correlated with changes in brain activity, as assessed by functional magnetic resonance imaging (fMRI). A few fMRI studies have been performed in healthy subjects, primarily assessing correlations with electrodermal responses as a biomarker of sympathetic arousal during mental tasks. The amplitude or number of transient skin conductance responses were found to be associated with activity changes in a variety of brain regions, such as the dorsomedial prefrontal cortex and left hippocampus (Weissman et al., 2018), the cerebellum, right inferior frontal cortex, and supplementary motor area (SMA) (Gamer et al., 2007), or the striate and extrastriate cortices, anterior cingulate and insular cortices, thalamus, hypothalamus and lateral regions of prefrontal cortex (Nagai et al., 2004). On the other hand, spontaneous changes in resting-state basal sympathetic tone were associated with the modulation of brain activities in the ventromedial prefrontal and orbitofrontal cortices in one study (Nagai et al., 2004) and mostly with the sensorimotor central region in a resting-state fMRI study (Gertler et al., 2020). Because autonomic nervous system dysfunction plays a prominent role in the pathophysiology of CRPS, this could be of interest to explore brain-autonomic coupling, which has not yet been performed to our knowledge.

Hence, we designed a study to determine whether sudomotor dysfunction, assessed by ESC measures, could be associated with pain and activity changes in brain networks, as assessed by fMRI, in patients with CRPS.

In addition, this study took place in a research trial of long-term (5 months) CRPS treatment with repetitive transcranial magnetic stimulation (rTMS). The use of high frequency rTMS applied to the primary motor cortex (precentral gyrus) showed a good level of evidence of efficacy in the treatment of different chronic pain syndromes (Lefaucheur et al., 2020), including CRPS (Nardone et al., 2018; Zangrandi et al., 2021). However, there are very few data on changes in cerebral activity assessed by fMRI associated with the analgesic effects of motor cortex rTMS (review in Aceves-Serrano et al., 2022), and in particular none in the context of CRPS to our knowledge. The secondary objective of this study will therefore be to determine

the impact of high-frequency motor cortex rTMS on the relationships between cerebral activation on fMRI, pain, and sympathetic sudomotor function assessed before and one month after the completion of the 5-month rTMS therapy.

### **3. Methods**

This study was part of a larger trial investigating the analgesic effect of various techniques of non-invasive brain or spinal stimulation in patients with CRPS, registered in clinicaltrials.gov (NCT02817880) and ethic acceptance was provided by Institutional Review Board of Sud-Est V, Grenoble, France (N ° 6705).

Only patients of the rTMS treatment group that underwent fMRI were enrolled in this ancillary study.

#### **3.1. Patients**

Eleven patients with CRPS type I were included and gave written informed consent to participate in this study. They met the following inclusion criteria: age between 18 and 80 years; disease duration for more than one year; diagnosis confirmed by bone scintigraphy (Sorel et al., 2018a); pain intensity > 3/10 at screening; no change in drug treatments during the last month; lack of response to conventional treatments. The exclusion criteria were as follows: pregnancy, presence of a neurological lesion, intracranial ferro-magnetic material or implanted device, history of drug addiction, epilepsy, severe traumatic brain injury or neuropsychiatric comorbidities.

#### **3.2. Study design**

The HF-rTMS therapy included an “induction phase” of one stimulation session per day for five consecutive days during two weeks, then 2 sessions in the next week for a total of 12 sessions, and a “maintenance phase” consisting of one session in the 4<sup>th</sup> week and then bi-monthly sessions for four months, for a total of 11 sessions.

For this study, the time-point assessments were the working day before rTMS (Day 1 (D1), pre-treatment baseline) and one month after the end of the HF-rTMS protocol (Day 180 (D180), post-treatment).

#### **3.3. Pain assessment**

Pain assessment was based on the report made by the patients of their daily pain intensity on a diary filled at home for a week before each time-point assessment. Daily pain intensity was

rated on a visual numeric scale (VNS) ranging from 0 (no pain) to 10 (the worst pain imaginable).

In addition, the overall effect of the rTMS therapy was estimated on the 7-point Clinical Global Impression – global Improvement (CGI-I) scale, from 1 (very much improved) to 7 (very much worsened) compared to the pre-treatment baseline period.

### **3.4. Electrochemical skin conductance (ESC) measures**

Palmar and plantar ESC values were measured (in microSiemens,  $\mu\text{S}$ ) with the Sudoscan® device (Impeto Medical, Paris, France). For this test, the patients stood for 2 minutes with their palms and soles placed on large stainless-steel electrode plates. A low direct current voltage ( $<4\text{V}$ ) is applied through these electrodes and the skin generates a current proportional to the chloride ion flow drawn from the sweat glands (reverse iontophoresis). The ESC value is calculated as the ratio between the current generated by the skin and the voltage of the direct current delivered by the electrodes (Ohm's law) and reflects the production of chloride ions by sweat glands innervated by sympathetic C nerve fibers.

### **3.5. rTMS procedure**

Stimulation was performed using a MagPro stimulator (MagVenture (distr. Mag2Health), Farum, Denmark) and either a flat B65 coil (MagVenture) in patients with upper limb pain or an angled B70 figure-of-eight coil (MagVenture) in patients with lower limb. The motor cortical representation of the painful region was targeted using a TMS Navigator system, integrating individual brain MRI data (Localite, Sankt Augustin, Germany). Stimulation was performed at 10Hz with an intensity set at 80% of the rest motor threshold (previously determined with motor evoked potential recording) and the coil held in postero-anterior orientation. Each rTMS session consisted of 40 trains of 5-sec duration with intertrain interval of 25 sec for a total of 2000 pulses in 20 minutes.

### **3.6. fMRI procedure and pre-processing**

A 3T Philips Achieva-TX scanner was used at the IRMAGE platform of Grenoble with a 32-channel head coil. Each patient undergone two MRI examinations, one at D1 and the other at D180. Each MRI session consisted of a first morphological 3D T1-weighted sequence (which was used for neuronavigation-based rTMS targeting) and a set of two T2\*-weighted BOLD fMRI runs. The two fMRI runs corresponded to two different motor tasks: (1) a self-paced flexion-extension movement of the fifth finger of the right hand; (2) a self-paced flexion-extension movement of the fifth finger of the left hand. Given the fact that pain was unilateral,

each patient therefore performed a motor hand task from the side ipsilateral to the pain side (IL task) and a motor hand task contralateral to the pain side (CL task).

Each fMRI run was presented following a block design with 3 task epochs of 30 seconds alternating with rest epochs of 30 seconds, for a total duration of 3 minutes and 30 seconds per run. The main parameters of the T2\*-weighted BOLD sensitive sequence were: TR 3000 ms, TE 35 ms, flip angle 90°, 36 3mm-thick slices with in plane isotropic 3mm spatial resolution, gap = 0.35 mm. Four dummy images were discarded to achieve steady-state, followed by the acquisition of 70 images, providing a duration of 7 minutes for the two functional runs.

The fMRI analysis was performed using SPM12 software (The Wellcome Department of Cognitive Neurology, London<sup>1</sup>) in two steps. In the first step, individual analysis is done in the individual's referential with image pre-processing (motion correction, slice timing and registration to the anatomical image of the pre-treatment session) followed by individual statistical analysis using a linear generalized model assessing the contrast images of cortical activation resulting from IL and CL motor tasks at D1 and D180. The second step was conducted for group analysis purpose. Each anatomical image of the pre-treatment session was segmented to extract the grey matter image and to compute the deformation field to be applied to each individual, using DARTEL software (Ashburner, 2007), to match a symmetrical template, provided by the CAT12 software<sup>2</sup>. The deformation fields computed for each patient were further applied to all individual contrast images.

In order to get rid of the pain laterality of the patients, those presenting a left-sided pain had their MR images left-right flipped across the midline. This flipping operation keeps the accuracy of the anatomical location thanks to the symmetrical template that was used (Pizzagalli et al., 2013). Doing so, the left side on the brain images corresponds to the hemisphere contralateral to the painful side and the right side corresponds to the hemisphere ipsilateral to the painful side.

### **3.7. Statistical analysis**

Statistical comparisons of VNS and ESC data were performed longitudinally using paired t-test. Comparisons between ESC in the CRPS-affected and in the non-affected limb were tested using paired t-test. Correlation between VNS and ESC were performed using the Pearson's test

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1. <http://www.fil.ion.ucl.ac.uk/spm/>

2. [neuro.uni-jena.de/cat12-html/cat\\_versions.html](http://neuro.uni-jena.de/cat12-html/cat_versions.html)

both at baseline and after treatment. In all cases, the level of statistical p value significance was set at 0.05.

The inference of neuroimaging data were conducted at the group level in the following way. First, main sensorimotor network was investigated for the influence of chronic pain and rTMS therapy in the following manner. The contrasts corresponding to the IL task and flipped CL task at D1 were tested against null hypothesis and their common pattern elicited by these two tasks was computed using conjunction analysis. For conjunction analysis, statistical significance was considered when  $p < 0.001$  at voxel level and extent  $> 200$  voxels. This pattern was further used to derive a mask of the sensorimotor network. The central effect of chronic pain on the sensorimotor activity was tested at baseline between the contrast images corresponding to the IL and flipped CL tasks using paired t-test. The effect of rTMS treatment on the sensorimotor network was tested on contrast images corresponding to the IL task between D1 and D180 using paired t-test. Statistical significance was considered when  $p < 0.001$  at voxel level and extent  $> 25$  voxels.

Second, in order to seek for neural correlates of skin conductance and pain, a multiple regression model was applied to the contrast images corresponding to the IL task using the ESC of the hand ipsilateral to the painful limb and the VNS at time of MRI as covariates. This was done both specifically within the mask of the sensorimotor network and without mask to explore regions located out of the sensorimotor network. Since the covariates are orthogonalized previous to the multiple regression in the SPM software, the estimated neural correlates of each covariate are further independent. The patterns corresponding to each of those covariates as well as the common pattern were further derived. For the regression analysis in the sensorimotor network, the statistical significance was considered when  $p < 0.001$  at voxel level and extent  $> 25$  voxels. Outside this network, for sake of exploration, we reported regions where  $p < 0.001$  at voxel level and extent  $> 10$  voxels. Within the areas correlated to the covariates, the mean activation was extracted for each subject and time-point. To distinguish between baseline and post-treatment time, the multiple regression analysis was conducted separately between mean activation, ESC and VNS.

## 4. Results

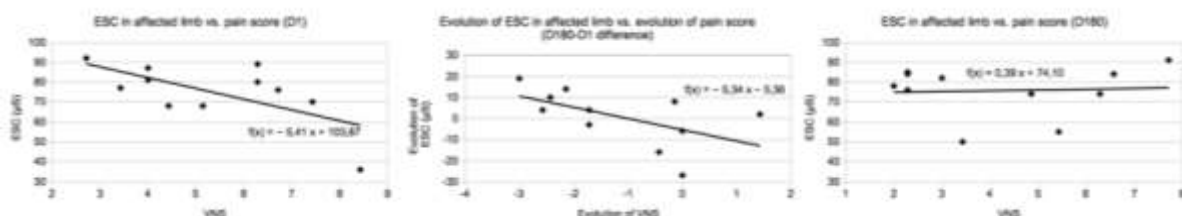
### 4.1. Demographics and clinical characteristics

The sample of 11 patients consisted of 6 women and 5 men, with a mean age of  $52.0 \pm 9.6$  years (range 29-61 years). The median duration of pain history was 24 months with interquartile interval 13-29 months. The origin of CRPS was related to limb trauma in 6 cases and surgical lesion in 5 cases. Pain was located at one upper limb in 6 cases and one lower limb in 5 cases, located on the right side in 7 cases and on the left side in 4 cases. Ten patients received analgesic drugs at the time of the study, with two types of medication on average, including non-opioid analgesics (2 patients), weak opioid analgesics (7 patients), antiepileptics (7 patients), and/or antidepressants (7 patients).

### 4.2. Baseline assessment

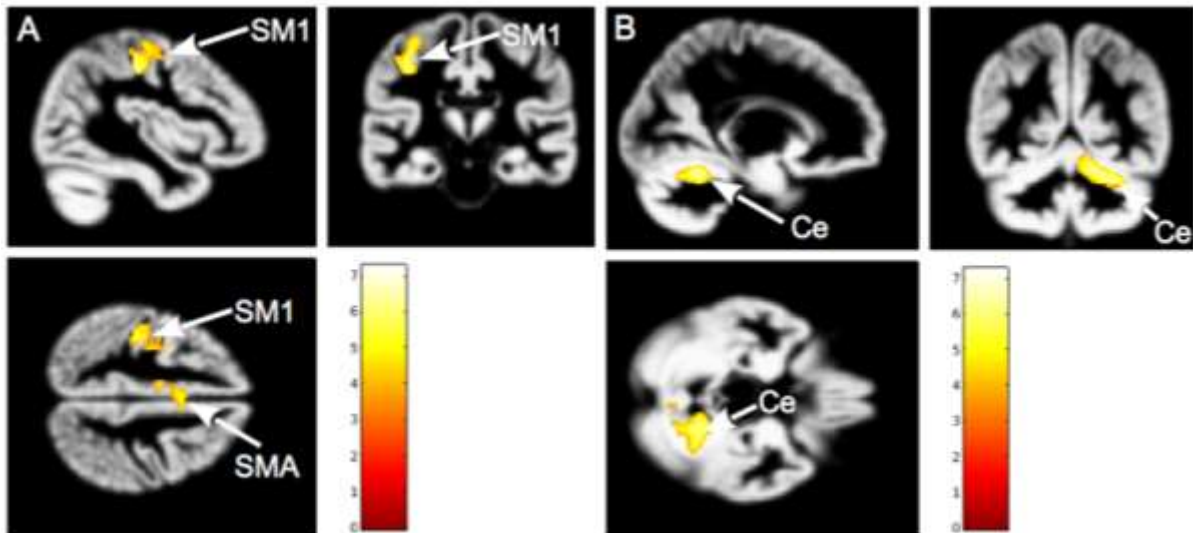
At baseline (D1), the mean ( $\pm$  SD) VNS pain score was  $5.4 \pm 1.8$  (range 2.7-8.4). The ESC value was significantly reduced in the CRPS-affected limb compared to the contralateral non-affected limb (mean ( $\mu$ S)  $\pm$  SD:  $74.9 \pm 15.3$  vs.  $77.4 \pm 14.5$ ,  $p = 0.048$ , paired t test).

A significant negative correlation was found between VNS scores ([0-10] range) and ESC values (in  $\mu$ S) in the CRPS-affected limb ( $r = -0.63$ ,  $p = 0.037$ , Pearson test) (Figure 1, left). In other words, the higher was the pain intensity the lower was the ESC.



**Figure 1:** Electrochemical skin conductance (ESC) in the CRPS-affected limb as a function of the intensity of average daily pain (VNS). Left: before rTMS treatment (D1). Middle: evolution in ESC and VNS from D1 to D180. Right: after rTMS treatment (D180).

Regarding fMRI, the brain activation in response to the IL task was found encompassing the primary somatosensory cortex (S1) and the primary motor cortex (M1) contralateral to the painful side, the cerebellum ipsilateral to the painful side, and the supplementary motor area (SMA) bilaterally, forming a large sensorimotor network. The comparison between the fMRI response to the IL task vs. the CL task (after symmetrization with respect to the inter-hemispherical plane) showed no significant difference, thus reflecting the absence of impact of the painful side on cortical activation. The common pattern between both tasks was then computed and, after thresholding, served as a mask for correlation analysis (Figure 2).



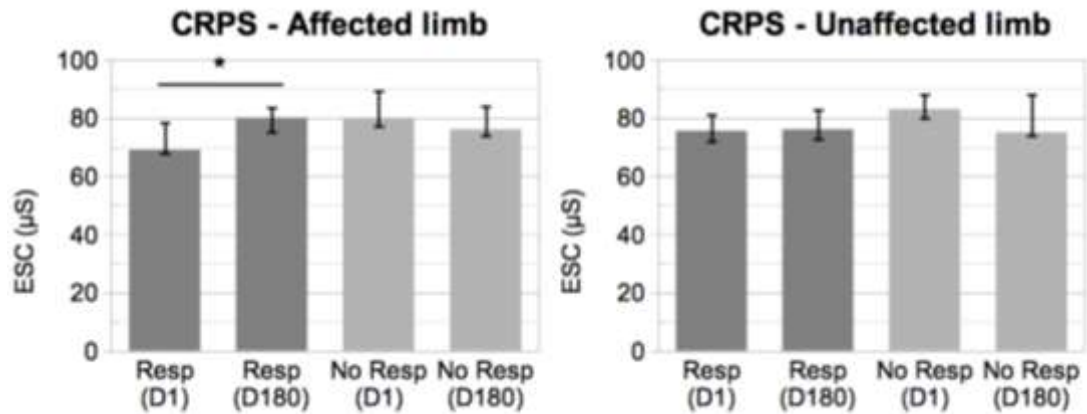
**Figure 2:** Common brain regions activated in response to motor task performed with hand ipsilateral and with hand contralateral to the painful side after symmetrization with respect to the inter-hemispherical plane, including (A): primary somatosensory and motor areas (SM1) and supplementary motor area (SMA); (B): cerebellum (Ce). Activation patterns presented on the average grey-matter image from our group of patients.

### 4.3. Post-rTMS assessment

All patients completed the 5-month motor cortex rTMS protocol without any adverse event. At one month after the end of rTMS therapy (D180), the mean ( $\pm$  SD) VNS pain score was  $4.2 \pm 2.1$  (range 2.0-7.7), showing a significant reduction ( $-1.2$  on average) compared to baseline ( $p = 0.02$ , paired t test).

On the CGI-I scale, six patients were much or very much improved (scores 1-2), three patients were minimally improved (score 3), and two patients were not improved or worsened (scores  $\geq 4$ ). According to a response criterion defined as a  $\geq 30\%$  reduction in VNS pain score at D180 compared to D1, we found that six patients were responders to rTMS therapy and five patients were not responders. Note that the responders and non-responders subgroups corresponded to those who had a CGI-I score of 1 or 2 for responders and a score  $\geq 3$  for non-responders, respectively.

At one-month post treatment (D180), the ESC values in the CRPS-affected limb were similar compared to baseline (mean ( $\mu$ S)  $\pm$  SD:  $75.7 \pm 12.6$  vs.  $74.9 \pm 15.3$ ,  $p > 0.05$ , paired t-test), while there was a tendency towards a significant increase in the responder subgroup (mean ( $\mu$ S)  $\pm$  SD:  $76.3 \pm 11.2$  vs.  $68.3 \pm 17.6$ ,  $p = 0.056$ ). Therefore, at D180, the ESC of painful limb was restored to a value not different from the non-painful limb (mean ( $\mu$ S)  $\pm$  SD:  $76.3 \pm 11.2$  vs.  $75.8 \pm 8.0$ ,  $p = 0.96$ ) in responders (Figure 3).



**Figure 3:** Electrochemical skin conductance (ESC) in the CRPS-affected limb (left) and non-affected limb (right) at D1 and D180 (before and after rTMS therapy) in the responder (Resp) and non-responder (No Resp) subgroups (median, 1st and 3rd quartiles displayed). Statistical analyses showed an increase in ESC tended towards significance (\*,  $p = 0.056$ ) only in the CRPS-affected limb of the responder subgroup.

We calculated the change in VNS pain score and ESC value in the CRPS-affected limb between D1 and D180 (D180-D1 difference) and found that the decrease in VNS correlated with the increase of ESC after motor cortex rTMS therapy ( $r = 0.561$ ,  $p = 0.073$ , Pearson test) (Figure 1, middle). The six dots on the left side of this plot correspond to responders who both experienced reduced VNS and increased ESC after rTMS treatment. The five dots on the right side correspond to non-responders.

However, at D180, VNS pain scores were no longer correlated with ESC values in the CRPS-affected limb ( $r = 0.069$ ,  $p = 0.841$ , Pearson test) (Figure 3, right), contrary to the situation at D1.

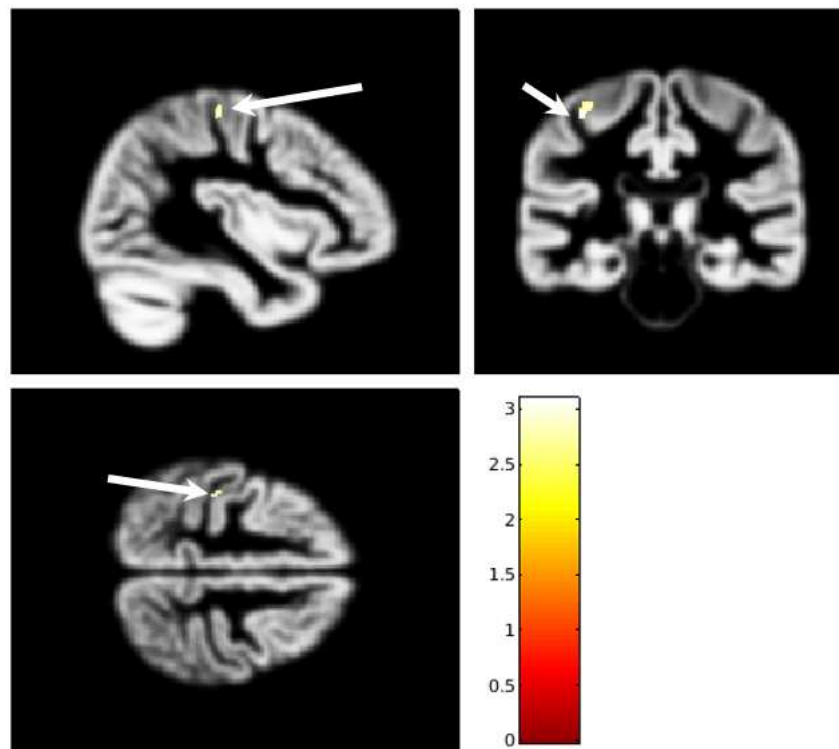
The cerebral activation observed in a sensorimotor network (S1, M1, SMA, cerebellum) in response to the IL task was similar after rTMS (D180) compared to baseline (D1) (data not shown). Also, at D180 as at D1, no significant difference was observed in brain activation patterns whether the IL or CL task was applied.

#### 4.4. Neural covariates of ESC and VNS

Within the sensorimotor network activated by motor hand tasks in fMRI, a negative correlation with the ESC values was found in the posterior bank of the central sulcus, i.e. S1, at the level of the hand knob, contralateral to the painful side (peak at MNI coordinates -39,-27,56,  $t=3.09$ ,  $k=27$ ). A positive correlation was also found with the VNS pain scores in a close S1 region (peak at MNI coordinates -38,-26,58,  $t=3.71$ ,  $k=83$ ). In fact, the two S1 regions presenting a negative correlation with ESC and a positive correlation with VNS were overlapping. The



common conjunction of these two conditions provided a small spot in S1 (Figure 4) whose activity was extracted for detailed analysis.

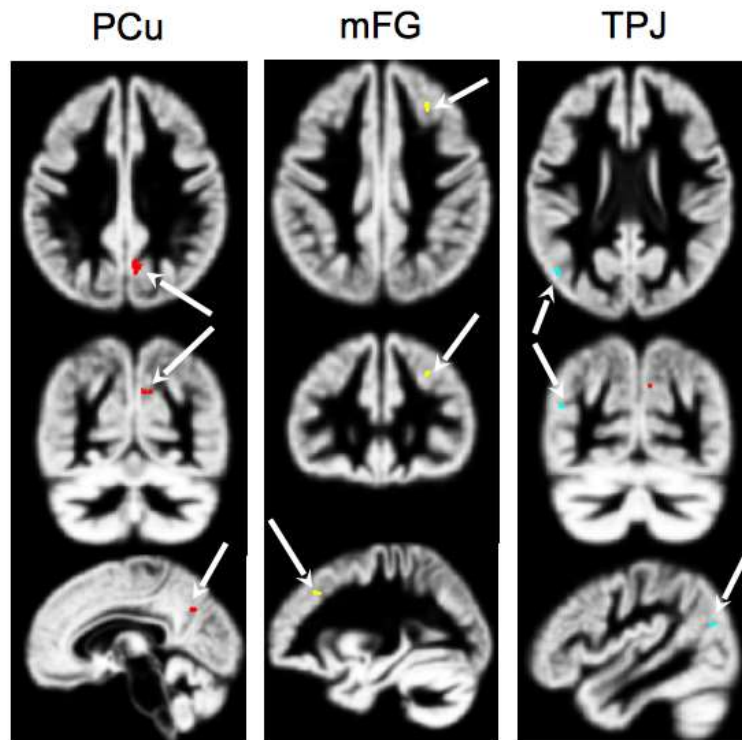


**Figure 4:** Location in the primary somatosensory cortex (S1) of a small region (in yellow) both correlated with ESC values (negatively) and VNS pain scores (positively). Activation pattern presented on the average grey-matter image from our group of patients.

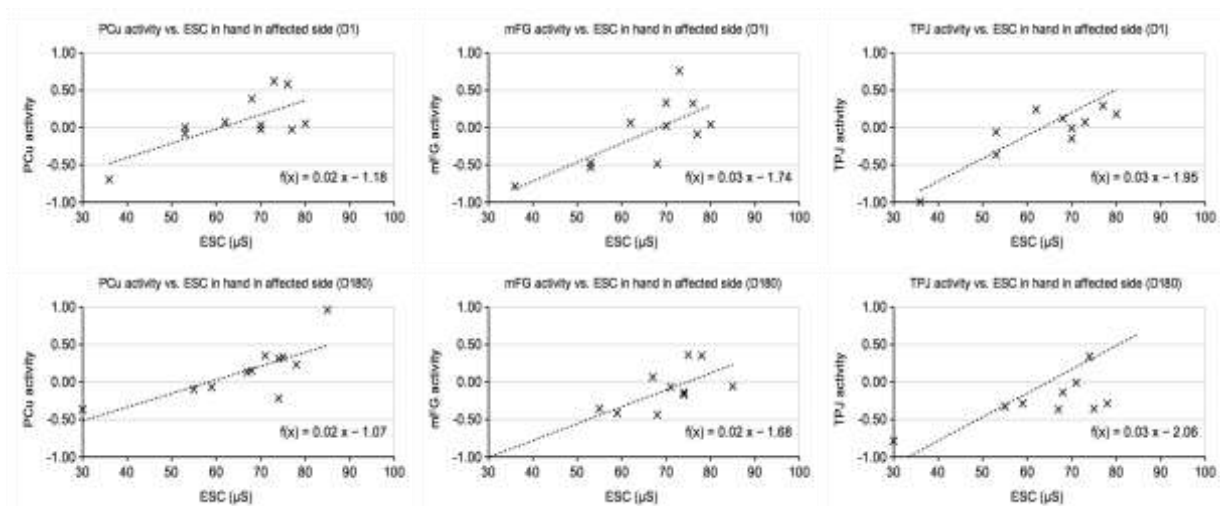
At baseline (D1), the fMRI activation of this S1 spot positively correlated with VNS pain scores ( $r = 0.62$ ,  $p=0.047$ , Pearson test) and tended to negatively correlated with ESC values in the CRPS-affected limb ( $r = -0.56$ ,  $p = 0.080$ ). At D180, these opposed correlations of S1 activation were still observed, positively with VNS pain scores ( $r = 0.66$ ,  $p=0.029$ ) and negatively correlated with ESC values in the CRPS-affected limb ( $r = -0.64$ ,  $p = 0.037$ ). This showed that S1 brain coupling with both the level of ongoing pain and the sympathetic activity in the CRPS-affected limb was persisting after rTMS therapy. Moreover, pre-post rTMS changes in S1 activation did not correlate with pre-post rTMS changes in VNS pain scores or ESC measures, while these last two parameters significantly correlated with each other.

Outside the above described sensorimotor network, we found positive correlations, both at D1 and D180, between ESC values in the CRPS-affected limb and fMRI activation by the IL task in the precuneus (PCu) ipsilateral to pain side (peak at MNI coordinates 6,-63,34,  $t=4.28$ ,  $k=54$ ) (D1:  $r = 0.71$ ,  $p = 0.015$ ; D180:  $r = 0.76$ ,  $p = 0.007$ , Pearson test), the middle frontal gyrus (mFG) ipsilateral to pain side (peak at MNI coordinates 28,30,38,  $t=5.14$ ,  $k=15$ ) (D1:  $r = 0.73$ ,  $p = 0.010$ ; D180:  $r = 0.84$ ,  $p = 0.001$ ), and the temporo-parietal junction (TPJ) contralateral to

pain side (peak at MNI coordinates -46,-69,22,  $t=3.86$ ,  $k=10$ ) (D1:  $r = 0.74$ ,  $p = 0.009$ ; D180:  $r = 0.62$ ,  $p = 0.041$ ) (Figure 5). No significant change in these correlations was observed before and after rTMS treatment (Figure 6), while pre-post rTMS changes in the fMRI activation of these three regions correlated with changes in ESC measures after rTMS ( $p = 0.024$  for PCu,  $p = 0.027$  for mFG, and a tendency ( $p=0.063$ ) for TPJ).

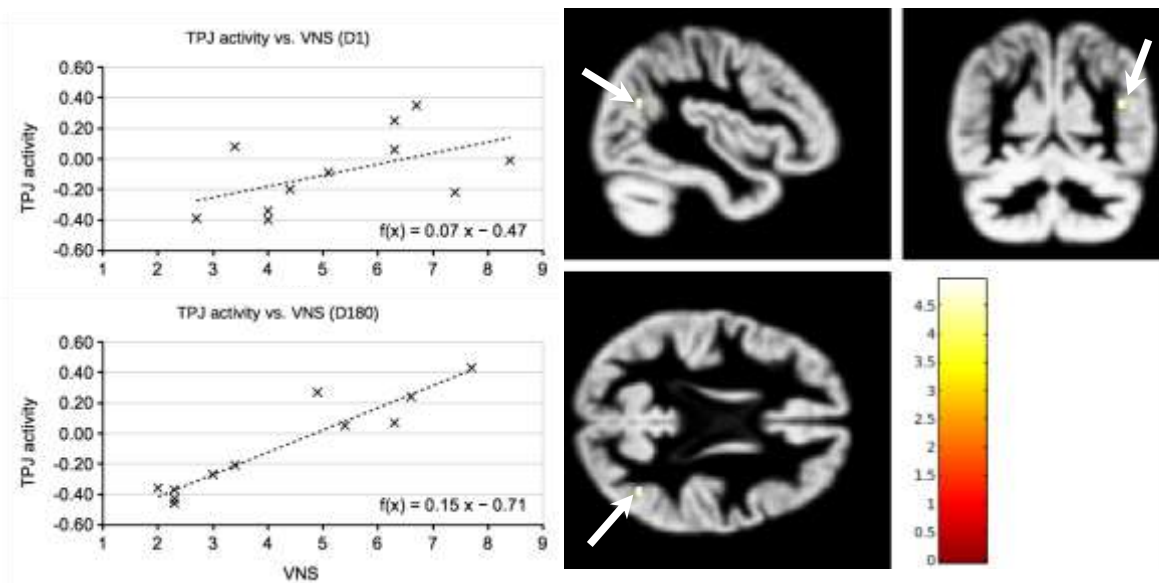


**Figure 5:** Regions outside the sensorimotor network presenting a positive correlation with ESC measures at D1 and D180: in the precuneus (Pcu) in red, in the middle frontal gyrus (mFG) in yellow and in the temporoparietal junction (TPJ) in cyan. For MNI coordinates, see text.



**Figure 6:** Neural activity in the precuneus (PCu) (left column), the middle frontal gyrus (mFG) (middle column) and the temporoparietal junction (TPJ) (right column) as a function of electrochemical skin conductance (ESC) in the hand of affected side. Upper row: before rTMS treatment (D1). Lower row: after rTMS treatment (D180). Equation of the regression line is displayed in each plot. All correlations are significant.

Finally, we found a positive correlation, at D180 but not at D1, between VNS pain score and fMRI activation by the IL task in the TPJ contralateral to painful side only (peak at MNI coordinates 42,-62,21,  $t=4.95$ ,  $k=33$ ) (D1:  $r = 0.52$ ,  $p = 0.10$  (not significant); D180:  $r = 0.95$ ,  $p = 10^{-5}$ , Pearson test). Pre-post rTMS changes in the fMRI activation of this region did not correlate with changes in VNS pain scores after rTMS. However, higher pain intensity remaining after rTMS was clearly associated with more activation in the TPJ. In other words, the six responders were characterized by a lower activation in the TPJ after rTMS therapy (Figure 7), in the same hemisphere where rTMS was applied.



**Figure 7:** Neural activity in the temporoparietal junction (TPJ) IL to the painful side as a function of pain intensity scored on visual numerical scale (VNS) (left panel). Upper row: before rTMS treatment (D1). Lower row: after rTMS treatment (D180). Equation of the regression line is displayed in each plot. Correlation is significant at D180 but not at D1. It should be noted that at D180, the 6 patients with a VNS pain score of less than 3.5 (rTMS responders) had reduced TPJ activity (negative values), while the 5 patients with a pain score greater than 4 (non-responders) had increased TPJ activity (positive values). Right panel: location of fMRI activation in the TPJ (white arrow).

## 5. Discussion

In this study, including eleven CRPS type I patients with unilateral pain, the relationships between sudomotor function (ESC) in the CRPS-affected limb, mean daily pain intensity (VNS), and brain fMRI activation in response to a hand motor task were assessed before and one month after 23 rTMS sessions delivered at high-frequency over M1 in a period of five months.

### 5.1. Autonomic-pain coupling and covariance with S1 activation in CRPS

At baseline, sudomotor function in the CRPS-affected limb extremity was significantly altered, as revealed by a reduction in ESC values compared to the contralateral non-affected limb. This

result is original, since ESC has only been evaluated in a series of 19 CRPS patients to our knowledge (Sorel et al., 2018b), with no clear alteration associated with the disease. Similarly, QSART, another method used to evaluate sudomotor dysfunction, showed a low rate of abnormalities in CRPS (Lee et al., 2019). In the present study, beyond their alteration, ESC values in the CRPS-affected limb were found negatively correlated with VNS pain scores, reflecting a possible functional coupling between sudomotor dysfunction and ongoing pain in CRPS.

Within a sensorimotor cortical network, these intercorrelated variables (ESC and VNS) were also found to be correlated with a small region of cerebral activation located at S1 contralateral to the painful side, as revealed by fMRI. The correlates of brain activation with changes in skin conductance have been studied in healthy subjects using fMRI in several studies, as reported in the introduction (Gamer et al., 2007; Gertler et al., 2020; Nagai et al., 2004; Weissman et al., 2018). The activation of various brain regions was found to be associated with sympathetic sudomotor function and overall the core of the central autonomic network included the amygdala, anterior and posterior insula, and midcingulate cortex in a meta-analysis (Beissner et al., 2013).

However, in our study, the goal was to link autonomic (sympathetic) function and brain activation, but with pain as a covariate. This type of study has rarely been performed, in the context of experimentally induced muscle or skin pain. Regarding provoked cutaneous pain experiments in healthy subjects, first, Mobascher et al. (2009) showed that elevated electrodermal activity associated with laser-induced pain primarily activated somatosensory cortical areas (the insula and somatosensory cortical areas: postcentral gyrus -S1 and parietal operculum -S2). In a second study, Dubé et al. (2009) also found that skin conductance reactivity was associated with brain activation in the somato-motor cortical regions (S1/M1, S2, and insula), but more specifically with the anterior cingulate cortex, amygdala, thalamus, and hypothalamus when pain (provoked by noxious thermal stimuli) was entered as a covariate. The same team then reported a low covariance between acute pain caused by noxious electrical stimuli, autonomic activities (changes in skin conductance) and brain activation, involving the cingulate and orbitofrontal cortices instead (Piché et al., 2010). Following mechanical pain produced by a projectile and using laser Doppler flowmetry to measure vasomotor sympathetic reaction, Maihöfner et al. (2011) showed a covariance with brain activation in the anterior insula, ventrolateral prefrontal cortex, anterior cingulate cortex, and S2. The same team then reported a similar correlation between sympathetic outflow and activation in the insula,

prefrontal cortex, anterior cingulate cortex, thalamus, posterior parietal cortex, and S2, whether pain (noxious thermal stimuli) was produced or anticipated (Seifert et al., 2013). The relationship between pain-related brain activation (by noxious heat) and the sympathetic components of heart-rate variability was found to involve negatively the medial prefrontal cortex (Perlaki et al., 2015). Another study rather found that the dorsal anterior cingulate cortex and periaqueductal gray matter were involved in pain-induced changes in the sympathetic components of heart-rate variability (Hohenschurz-Schmidt et al., 2020). Finally, a repeated noxious heat stimulation was found to specifically activate the BA3a part of S1 (Panchuelo et al., 2020), which is a ‘transitional zone’ located between M1 and S1 located in the depth of the central sulcus and likely engaged in the sympathetic response to noxious stimulation (Favorov et al., 2019).

Our results are consistent with this latter study, showing covariance of sympathetically-mediated ESC values and VNS pain score selectively with the activation of the anterior part of the postcentral S1 area in CRPS patients. Importantly, this provides further evidence for a critical role of S1 in the coding of pain intensity, as highlighted by some authors (reviewed in Vierck et al., 2013), while others favor the role of the operculo-insular region, i.e. the posterior insula and S2 (Garcia-Larrea and Peyron, 2013). The involvement of S1 in coding pain and in particular that of BA3a located deeper in the central sulcus could be especially relevant in functions associating interoceptive sensory system and the autonomic nervous system, like the autonomic aspects of nociception, as suggested by Favorov et al. (2019) and supported by experimental animal data (Ito and Craig, 2003). It is also important to point out that this S1 region (the transition zone represented by BA3a) could be one of the main cortical projection structures of the medial spinothalamic tract system and probably has privileged connections with M1 via corticocortical connections contributing to the control of fine motor skills (Favorov et al., 2019).

In the context of CRPS, the particular involvement of functional cortical reorganization located in the S1 area has been highlighted by numerous studies. For example, S1 activation is significantly increased and sensory cortex representation maps are frankly modified in response to tactile stimulation of the CRPS-affected limb compared to the non-affected limb (Di Pietro et al., 2015; Juottonen et al., 2002; Maihöfner et al., 2003; Pleger et al., 2004; Vartiainen et al., 2008). Abnormal sensory integration of innocuous stimuli (Lenz et al., 2011) or interaction between innocuous and noxious stimuli (Larbig et al., 2006) in S1 were also shown in the context of CRPS. On the other hand, an effective neuromodulation therapy (using invasive

spinal cord stimulation) was able to restore normal somatosensory representation maps within S1 in a CRPS patient (Pahapill and Zhang, 2014). Overall, S1 activation changes in CRPS patients were associated with pain intensity (Pleger et al., 2004), a reduced tactile acuity (Di Pietro et al., 2020), increased oscillations in the delta-theta band (Walton et al., 2010), and an alteration of a related 20-Hz motor cortex rhythm (Juottonen et al., 2002), while the S1-M1 connections were preserved and functionally normal (Turton et al., 2007).

### **5.2. Analgesic effect of motor cortex rTMS in CRPS**

One month after the end of a 5-month therapy of high-frequency rTMS of the motor cortex, the VNS score of daily pain was significantly reduced by 22% on average, and 6/11 patients were clinically responders with  $\geq 30\%$  reduction in VNS pain score. Motor cortex rTMS also improved the ESC values in the CRPS-affected limb compared to baseline, but only significantly in the group of responders (10% increase on average) and not in the whole series of patients. The reduction in VNS pain scores correlated with the increase of ESC values after motor cortex rTMS, but these two parameters no longer correlated with each other, although they remained correlated with S1 activation. Therefore, it can be hypothesized that motor cortex rTMS is able to concomitantly produce pain relief and sympathetic sudomotor activity improvement in the CRPS-affected limb, but this does not imply causality between these two changes, as revealed by the loss of correlation between these two variables after rTMS therapy. On the other hand, as brain coupling with S1 activation has not been modified, this S1 region cannot be considered as the functional core of the therapeutic changes induced, but as the “hub” in the coupling of pain and autonomic functions.

Thus, after rTMS treatment, VNS scores no longer correlated with ESC values in the CRPS-affected limb. This finding suggests that the analgesic effect of motor cortex rTMS does not only depend on coupling with autonomic modulation and involvement of the S1 region. The amount (22% on average) and extent of pain relief after rTMS was more striking than the improvement in sudomotor activities revealed by ESC measurement (10% increase only in the best responders). Therefore, this "uncoupling" of pain-autonomy function likely reveals that rTMS of the motor cortex produces pain relief through modulation of various other brain circuits involved in the sensory, cognitive, or affective components of pain (Lefaucheur, 2016; Nguyen et al., 2011).

### **5.3. Involvement of other cortical regions in skin conductance and pain**

The functional activity in other brain regions, such as the PCu and the mFG ipsilateral to painful side and the TPJ contralateral to painful side in response to IL task, showed positive correlation

with the ESC values in the CRPS-affected side. Although these correlations were not modified after rTMS, the pre-post rTMS changes of these two factors (brain activation and ESC measures) were correlated with each other. This suggests that the effect of rTMS on sympathetic sudomotor activities was at least associated with, or even caused by, a modulation of this network of brain structures, which is a part of the default mode network (DMN).

Regarding pain intensity (VNS score), a correlation was found outside the sensorimotor network only with the activation of the TPJ contralateral to painful side after rTMS therapy, but not at baseline. The level of TPJ activation after rTMS clearly distinguished between rTMS responders and non-responders: responders had negative TPJ activation values, while non-responders had positive TPJ activation values at D180. Therefore, one may wonder whether a lower residual activation of this region could be a biomarker of the efficacy of motor cortex stimulation, and why. The TPJ is a large cortical region involved in a wide variety of brain functions, such as self–other distinction, theory of mind, social belief... This result is therefore in favor of a change in social cognition abilities associated with pain relief secondary to motor cortex stimulation. This is an original and potentially major discovery in the search for objective biomarkers of the efficacy of pain therapies.

#### **5.4. Limits of the study**

The main limit of the study relates to the small number of patients included in this ancillary study. They all present a lateralized pain, some patients have pain in the upper limb while other in the lower limb. Accordingly, the rTMS stimulation of the motor cortex was not in the same location for all patients. In addition, this study included only patients treated by active rTMS condition and therefore our results could be related to placebo-related pain relief. Thus, our results need being replicated in a larger sham-controlled study.

#### **5.5. Conclusion**

This study showed an alteration of sudomotor function (as assessed by ESC measurement) in CRPS-affected limbs, which was correlated with daily pain intensity in a series of CRPS patients. These two parameters improved after motor cortex rTMS therapy in a statistically correlated manner, although this does not necessarily imply causality between the two changes. If dysautonomia is known to be associated with CRPS (Knudsen et al., 2019; Lee et al., 2021), it is the first study showing direct correlation of sudomotor measures with pain intensity and improving in parallel according to the analgesic efficacy of a treatment. These results underline the importance of studying the sudomotor dysfunction in the context of CRPS and suggests that interventions to restore this dysfunction might be a therapeutic option to alleviate pain. In

addition, in the current search for neuroimaging-based biomarkers for pain (van der Miesen et al., 2019), this work supports the view that the central autonomic network should be taken into account.

Our study also opens important perspectives to better understand the mechanisms of analgesic action of motor cortex rTMS, especially in pain syndromes with strong autonomic (sympathetic) nervous system involvement, such as CRPS. Our results suggest a potentially major role of the S1 region as a functional hub in the interaction between the nociceptive sensory system and the autonomic nervous system in this clinical condition. In particular, the ‘transitional zone’ located between M1 and S1 in the depth of the central sulcus (BA3a part of S1) could be a new rTMS target to be evaluated for the treatment of CRPS. This would require the use of a dedicated rTMS coil able to stimulate deep in the central sulcus (Hodaj et al., 2018, 2020). Such a target could also apply in other pain conditions, such as fibromyalgia, in which a critical correlation of functional and connectivity impairment of S1 with sensory and behavioral aspects of pain and associated autonomic responses has also been observed (Kim et al., 2015).

On the other hand, this study highlights the involvement of other brain regions, included in the DMN, such as PCu, mFG and TPJ, in the correlation with sympathetic sudomotor activity and the potential impact of rTMS on this activity. Finally, we were able to distinguish between responders and non-responders to rTMS according to the activation of the TPJ contralateral to pain, which could be a biomarker of the efficacy of motor cortex stimulation to be further studied.

## **Declaration of Interest**

The authors report no conflict of interest.

## **Credit authorship contribution statement**

Chantal Delon-Martin: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. Jean-Pascal Lefaucheur: Writing – original draft, Writing – review & editing. Enkeledja Hodaj: Investigation, Writing – review & editing. Marc Sorel: Investigation, Writing – review & editing. Anne Dumolard: Investigation, Writing – review & editing. Jean-François Payen: Supervision, Writing – review & editing. Hasan Hodaj: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing.



## Acknowledgments

This work was performed on the IRMaGe facility, member of France Life Imaging network (grant ANR-11-INBS-0006). Johan Pietras, Irene Tropres and Laurent Lamalle are acknowledged for their support with MRI acquisitions. We also thank Zaza Putkaradze for his help with the management of this study.

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## 6. Projet de recherche en cours

### 6.1. Protocole Neurostim

#### PROTOCOLE DE RECHERCHE IMPLIQUANT LA PERSONNE HUMAINE

#### RECHERCHE DE TYPE 2 A RISQUES ET CONTRAINTES MINIMES

Etude randomisée en double aveugle de l'effet antalgique de la rTMS dans le traitement des douleurs neuropathiques chroniques, comparant trois groupes : stimulation du cortex moteur par la bobine classique B65, stimulation plus profonde par la bobine B70 et stimulation placebo. Analyse des modifications cérébrales induites par la rTMS à long terme, au moyen de l'IRMf.

### Etude NEUROSTIM

#### Etude Monocentrique

N° ID/RCB : 2020-A01562-37

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## JUSTIFICATION SCIENTIFIQUE ET DESCRIPTION GENERALE DE LA RECHERCHE

### Connaissances actuelles sur la pathologie

La prévalence de la douleur neuropathique s'élève à 6,9 % dans la population générale



(Bouhassira et al. 2008). Cette condition pathologique demeure donc un problème de santé majeur d'autant que l'efficacité des traitements disponibles à ce jour reste limitée. Seulement 30 à 40% des patients sont soulagés de plus de 50% de leurs douleurs par une approche pharmacologique (Attal et al. 2006).

En cas d'échec des traitements médicamenteux ou en complément de ceux-ci, les techniques de stimulation cérébrale non-invasives du cortex moteur, principalement la stimulation magnétique transcrânienne répétitive (rTMS), constituent des alternatives nouvelles dans le traitement des douleurs chroniques réfractaires. L'application de la rTMS sur le cortex moteur pour soulager les douleurs chroniques est basée sur les résultats obtenus par la stimulation invasive épidurale du cortex moteur réalisée depuis le début des années 90. Compte tenu des effets bénéfiques qui peuvent être obtenus dans le traitement des douleurs chroniques réfractaires par les techniques de stimulation corticale utilisant des électrodes implantées chirurgicalement, il apparaît licite d'étudier les effets antalgiques que pourraient produire la stimulation non-invasive du cortex moteur par la rTMS. Cette technique montre une bonne tolérance, pas d'effet secondaire notable et un bon niveau de preuve quant à l'efficacité de la stimulation active dans des études contrôlées contre placebo, mais la plupart des études sont limitées par un suivi à court terme (1). La limitation principale de ces études contrôlées, réside sur le fait qu'elles sont basées sur un petit nombre de sessions (5 à 10) et une courte durée de suivi (moins de 3 semaines) (2). Cependant, des effectifs hétérogènes de patients et des protocoles variés quant aux paramètres de stimulation et à la durée du traitement, ne permettent pas de transposer l'utilisation courante de la rTMS en pratique clinique.

### **Connaissances actuelles sur les explorations prévues par le protocole**

La rTMS constitue une alternative nouvelle et intéressante dans le traitement des douleurs chroniques réfractaires. Dans les recommandations françaises et internationales pour l'utilisation de la rTMS, les experts ont retenu un niveau de preuve A concernant l'effet antalgique de la rTMS (Fréquence  $\geq$  5Hz) dans les douleurs neuropathiques chroniques-et un effet antalgique de plus de 30% a été observé chez 46 à 62% des patients (1,2,3). Mais d'autres méta-analyses ont rapporté un faible niveau de preuve des études contrôlées versus placebo (4) ou ont émis des faibles recommandations concernant l'utilisation de la rTMS dans le traitement des douleurs neuroathiques chroniques réfractaires (5).

A noter qu'en général les protocoles sont de courte durée (4, 5, 6, 7, 8). Seulement quelques études (principalement ouvertes) ont rapporté l'efficacité de la rTMS à long terme, (9, 10, 11, 12, 13, 14)

Dans ce cadre, les experts évoquent la nécessité des études futures contrôlées versus placebo avec ciblage précis et reproductible, l'utilisation de la neuronavigation, le développement de nouvelles formes de bobines et d'explorations de neuro-imagerie (2). La conception de ce projet de recherche est basée dans les recommandations citées des experts.

A noter que dans la plupart des études, les auteurs stimulent l'aire corticale de la main controlatérale à la douleur (17) et utilisent la bobine classique B65 (18).

Depuis les travaux de Penfield, on sait que le cortex moteur présente une organisation somatotopique avec une large région dédiée à la commande motrice de la main. Or la région représentative de la main n'est pas localisée seulement dans la surface du cortex, mais aussi dans la profondeur du sillon central.

Récemment, notre équipe utilise la bobine MCF-B70, plus adaptée pour stimuler le cortex moteur correspondant aux territoires pelvi-périnéaux et des membres inférieurs au niveau du vertex, grâce à son angle 150° (14). La bobine B70 génère un champ électromagnétique plus focal et plus puissant que la bobine plate B65 (Fig. 1 et 2) conduisant à baisser le seuil moteur de 10 à 33% et *stimulant plus en profondeur* (15, 16, 17).

Une étude très récente ex-vivo, montre que la sonde circonflexe B80 (angle 120°), se révèle plus efficace que la sonde plane B65 pour délivrer un champ-magnétique pour des distances de cibles supérieures ou égales à 3cm. (18). Selon cette étude, l'amplitude du champ-magnétique produit par la sonde B65 décroît plus rapidement (-75% à 3cm de la sonde) que celui de la sonde circonflexe (-75% à 4,5cm). Par ailleurs, le champ-magnétique ne semble pas être modifié par le milieu tissulaire qu'il traverse, seule la distance à la sonde de stimulation semble intervenir dans l'intensité délivrée.

Nous souhaitons évaluer l'effet antalgique induit grâce à une sonde permettant de stimuler plus en profondeur l'aire corticale (bobine B70), par rapport à une bobine superficielle (bobine classique B65) versus la stimulation placebo. Nous ciblerons la représentation corticale de la main, sachant que l'effet antalgique somatotopique strict de la rTMS n'a pas été démontré (19, 20, 21). A cet égard, la zone motrice de la main pourrait être privilégiée, puisqu'elle est plus facile à cibler (22).



## **Originalité et Caractère Innovant**

A notre connaissance aucune étude n'a évalué l'efficacité antalgique de la stimulation corticale superficielle (bobine classique B65) comparée à la stimulation plus profonde (B70), et versus placebo, dans le traitement des douleurs neuropathiques chroniques, ainsi que les modifications éventuelles de la **cartographie cérébrale** et de la perfusion cérébrale induites par ces techniques à long terme.

Comme nous l'avons déjà évoqué la région représentative de la main n'est pas localisée à la surface du cortex, mais dans la profondeur du sillon central. De plus, la somatotopie dépend de chacun des patients, notamment il peut avoir été réorganisé suite à une pathologie (AVC...). Il apparaît donc pertinent de mieux cibler la région de la main grâce à une sonde permettant de stimuler dans la profondeur du sillon (bobine B70, en bleu sur le schéma, Fig. 2) par rapport à une bobine plus superficielle (bobine classique B65, en noir sur le schéma, Fig. 2) d'une part, et de mieux définir la région cible grâce à l'IRM fonctionnelle individuelle, d'autre part. L'hypothèse de cette étude est que ces 2 innovations combinées conduiront à un meilleur taux de réponse clinique.

Nous proposons dans ce projet de réaliser en pré-cure, non seulement une IRM structurelle classique mais également une IRM fonctionnelle. De plus, de récents travaux montrent une altération de la perfusion cérébrale dans diverses pathologies douloureuses, telles les fibromyalgies (23), les douleurs post chirurgicales (24) ou les douleurs dorsales (25). Il apparaît donc pertinent d'explorer **les modifications centrales de la perfusion cérébrale à l'état basal**, qui pourraient être en lien avec les douleurs neuropathiques chroniques. Depuis peu, cette séquence se pratique en clinique de manière non invasive grâce à la séquence pCASL (arterial-spin-labelling pseudo continu) qui fait aujourd'hui consensus dans la communauté scientifique grâce aux travaux du groupe de travail sur la perfusion de l'ISMRM (International Society for Magnetic Resonance in Medicine) (26) et qui bénéficie d'une implémentation sur la toute nouvelle version de la machine IRM recherche du CHU (plateforme IRMaGe, IRM Achieva 3.0T dStream, Philips).

Par ailleurs, il sera pertinent de chercher d'autres **différences structurelles ou fonctionnelles à l'état basal entre les 2 hémisphères**, donc coté douloureux versus non douloureux.

L'IRMf pour l'évaluation de la cure rTMS :

Pour évaluer le bénéfice de la cure de rTMS à long terme, le même protocole IRM sera répété à la fin de la cure, afin d'évaluer les modifications éventuelles de la *cartographie cérébrale apportées par la cure*, et ce de manière différentielle selon le groupe répondeur versus non-répondeur comparée à l'état basal. En particulier, une *hypoperfusion post cure de rTMS* a été observée entre les répondeurs et les non-répondeurs dans le traitement de la dépression (27). Nous pourrions ainsi évaluer si des résultats analogues seraient obtenus sur les patients souffrant de douleurs neuropathiques chroniques.

## **Rapport bénéfice / risques**

### **Bénéfices**

#### **Bénéfice(s) individuel(s) :**

Il est attendu pour les patients participant à l'étude une amélioration de leurs douleurs et de leur qualité de vie.

Par ailleurs, les patients du groupe placebo bénéficieront en fin de l'étude d'un traitement par des séances de la rTMS, conforme à notre protocole thérapeutique utilisant la bobine B65 (à titre compassionnel).

#### **Bénéfice(s) collectif(s) :**

La rTMS est une technique de la stimulation cérébrale non invasive qui constitue une alternative nouvelle et intéressante dans le traitement à long terme des douleurs chroniques réfractaires.

L'intérêt de cette technique réside dans son innocuité et la bonne tolérance. Chez les patients répondeurs, son utilisation évite la polymédication et ses effets secondaires ou la pratique de techniques invasives.

Cette étude innovante pourra contribuer à mieux comprendre les mécanismes d'action de la rTMS et améliorer les paramètres de la stimulation, afin d'obtenir une meilleure réponse thérapeutique.

### **Risques**

#### **Risque(s) individuel(s) (cf § 11.3)**

Les risques principaux décrits de la rTMS sont les suivants :

- Céphalées de tension (10 à 30% : Rossi et al, 2009) ;

- Légers vertiges ;
- Somnolence ;
- Le risque de crise comitiale est quasiment nul compte tenu des paramètres de stimulation retenus et des critères d'inclusion et d'exclusion appliqués.

### **Balance bénéfique/risque**

Nous estimons compte tenu des faibles risques liés à la rTMS que la balance bénéfique risque est très en faveur de la réalisation de l'étude.

## **OBJECTIFS DE LA RECHERCHE ET CRITERES DE JUGEMENTS**

### **OBJECTIF PRINCIPAL**

Comparaison de l'effet antalgique de la stimulation corticale profonde (bobine B70) ou superficielle (bobine classique B65) par la rTMS, dans les douleurs neuropathiques chroniques pharmacorésistantes, de façon contrôlée en double aveugle versus une stimulation placebo.

### **Critère de jugement principal**

Comparaison, entre les trois groupes (stimulation placebo, stimulation profonde par la bobine B70 et stimulation superficielle par la bobine classique B65) de la valeur journalière de l'échelle de douleur visuelle numérique (EVN), moyennée sur 7 jours par ANOVA par mesures répétées avec étude de l'interaction TEMPS (S-1 (baseline) : semaine avant le traitement ; S1 à 7 : semaines pendant le traitement) x TRAITEMENT (rTMS placebo, rTMS B70, rTMS B65). Evaluer l'efficacité de la stimulation profonde (bobine B70) par rapport à la stimulation superficielle (bobine classique B65) si la comparaison entre les trois groupes est significative.

### **Objectifs secondaires**

1. Analyse, au moyen de l'IRMf, des modifications éventuelles des cartes corticales sensori-motrices induites par la rTMS (stimulation superficielle, profonde ou placebo) et corrélation entre ces modifications et l'effet antalgique de la stimulation corticale.
2. Etude du taux de patients répondeurs (réduction de l'intensité de la douleur  $\geq 30\%$ ) entre les groupes de traitement (stimulation superficielle, profonde ou placebo).
3. Analyser le maintien de l'effet antalgique de chaque technique à long-long terme (S7 : fin du traitement ; S8 à S9 : suivi post traitement) entre les groupes de traitement (stimulation superficielle, profonde ou placebo).

4. Evaluer par l'échelle CGI l'amélioration globale du patient ~~vis-à-vis du traitement~~ entre les groupes de traitement (stimulation superficielle, profonde ou placebo).
5. Evaluer par l'échelle SF-12 l'amélioration de la qualité de vie entre les groupes de traitement (stimulation superficielle, profonde ou placebo).
6. Evaluer par l'échelle HAD l'évolution des traits anxieux et dépressifs entre les groupes de traitement (stimulation superficielle, profonde ou placebo).
7. Evaluer par l'échelle NPSI, les modifications des profils symptomatologiques des douleurs neuropathiques entre les groupes de traitement (stimulation superficielle, profonde ou placebo).
8. Evaluer entre les groupes de traitement (stimulation superficielle, profonde ou placebo) l'atteinte du système autonome sympathique et la neuropathie des petites fibres par la technique de Sudoscan<sup>®</sup>.
9. Etude du système autonome par la mesure de l'activité électrodermale, lors de l'examen IRMf entre les groupes de traitement (stimulation superficielle, profonde ou placebo).
10. Analyse de la réponse antalgique de la rTMS au long cours en fonction du profil clinique des patients douloureux chroniques.
11. Evaluer entre les groupes de traitement (stimulation superficielle, profonde ou placebo) la réduction du recours aux traitements antalgiques des crises ou des pics douloureux.
12. Evaluer entre les groupes de traitement (stimulation superficielle, profonde ou placebo) l'amélioration de l'allodynie chez les patients présentant un déficit sensitivo- moteur.

### **Critères de jugement secondaires**

1. Comparaison de la localisation tridimensionnelle des pics d'activation sur les cartes statistiques d'activation corticale par analyse cartographique paramétrique (SPM) des données obtenues sur l'IRMf effectuée avant et après la stimulation par rTMS, puis corrélation entre ces modifications et un éventuel effet antalgique de la stimulation corticale selon le groupe de traitement (stimulation superficielle, profonde ou placebo). Les données de cartographie corticale tirées de l'IRMf motrice seront analysées grâce aux logiciels SPM8 et Matlab, en se focalisant sur les modifications de la distance euclidienne dans les plans x, y, z entre les barycentres des zones d'activation corticale avant et après rTMS.
2. Comparaison, entre les groupes des patients répondeurs : les patients seront classés en 5 groupes selon leur réponse antalgique : très bonne réponse (réduction de l'EVN  $\geq 70\%$ ); bonne réponse (réduction de l'EVN de 50% à 69 %) ; réponse modérée (réduction de l'EVN

de 30% à 49%) ; faible réponse (réduction de l'EVN de 15% à 30%) et absence de réponse (réduction de l'EVN < 15%) (3,7,28, 29).

Les patients seront définis « répondeurs » si réduction de l'EVN égale ou supérieure à 30%  $((\text{post-rTMS} - \text{pré-rTMS EVN scores}) * 100 / (\text{pré-rTMS EVN score}) \geq 30\%$ .

3. Comparaison, entre les groupes de la valeur journalière de l'échelle de douleur visuelle numérique (EVN), moyennée sur 7 jours entre S-7 : fin du traitement et S8 à S9 : suivi post traitement.
4. Comparaison, entre les groupes de l'échelle CGI à J30 et J60.
5. Comparaison, entre les groupes de l'échelle SF-12 à J0, J30 et J60.
6. Comparaison, entre les groupes de l'échelle HAD à J0, J30 et J60.
7. Comparaison, entre les groupes de l'échelle NPSI à J0, J30 et J60.
8. Comparaison, entre les groupes de la mesure de la conductance électro chimique de la sueur (CES) avant et après le traitement.
9. Comparaison, entre les groupes des variations de tension et des variations de conductance de la peau lors de l'examen IRMf avant et après le traitement.
10. Comparaison, entre les groupes de la consommation des traitements antalgiques.
11. Comparaison, en fonction du profil clinique des patients de la valeur journalière de l'échelle de douleur visuelle numérique (EVN), moyennée sur 7 jours de S-1 à S9.
12. Comparaison, entre les groupes du pourcentage d'amélioration de l'allodynie ressentie par le patient à J30 et J60.

## **CONCEPTION/METHODOLOGIE DE LA RECHERCHE**

- Etude thérapeutique randomisée en double aveugle, comparative de trois groupes parallèles :
  - o *Groupe expérimental 1*: stimulation plus profonde (bobine B70)
  - o *Groupe expérimental 2*: stimulation superficielle (bobine classique B65)
  - o *Groupe contrôle* : stimulation placebo
- Prospective
- Monocentrique

## **CRITERES D'eligibilite/caractéristiques des sujets**

## **CRITERES D'INCLUSION**



- Personne affiliée à la sécurité sociale ou bénéficiaire d'un régime assimilé.
- Patient ayant donné son consentement écrit.
- Patient âgé de 18 à 80 ans, homme ou femme, souffrant depuis plus d'une année de douleurs neuropathiques réfractaires unilatérales : héli-corporelles, membre supérieur, membre inferieure et algies faciales.
- Patient dont le traitement médicamenteux en cours, antalgique ou non, est stable depuis au moins 1 mois.
- Patient dont l'absence de réponse aux traitements conventionnels, conduit son algologue ou médecin référent à étudier la possibilité de proposer des solutions thérapeutiques non pharmacologiques.
- Patient ayant une intensité de la douleur évaluée selon EVN >3, lors de la présélection.

### **Critères de non inclusion**

- Antécédent d'addiction à une drogue, d'épilepsie, ou de traumatisme crânien sévère.
- Antécédent de pathologie psychiatrique susceptible d'interférer avec la bonne marche de l'étude.
- Patients ayant déjà bénéficié d'un traitement par la rTMS ou ayant participé dans un protocole de recherche impliquant la rTMS.
- Présence de matériel ferromagnétique intracrânien ou d'un stimulateur implanté (implant cochléaire, pacemaker, stimulateur médullaire ou intracrânien ou du nerf vague).
- Introduction d'un nouveau traitement depuis moins d'un mois.
- Femme enceinte, parturiente, ou qui allaite, ou étant en absence de contraception efficace durant la durée de l'étude pour les patientes en âge de procréer.
- Personne ne comprenant pas le protocole de l'étude.
- Personnes visées aux articles L1121-5 à L1121-8 du CSP (correspond à l'ensemble des personnes protégées : femme enceinte, parturiente, mère qui allaite, personne privée de liberté par décision judiciaire ou administrative, personne ne faisant l'objet d'une mesure de protection légale).

### **Traitement(s)/ procédure(s) autorise(s)**

Il n'y a pas de traitements interdits pendant la participation à l'étude.

Les patients poursuivront leur traitement de fond tel qu'il leur a été prescrit par leur neurologue traitant. Dans la mesure du possible le traitement devra rester stable durant toute la durée du protocole. Bien sûr les médecins en charge du patient garderont toute latitude pour modifier le traitement médicamenteux en fonction des besoins du patient.

La consommation des médicaments (type de traitement et dose reçue) sera recueillie sur le CRF durant toute l'étude.

### **Modalités de recrutement**

La participation au protocole sera proposée aux patients par les praticiens du Centre de la Douleur du CHU Grenoble Alpes lors d'une consultation habituelle et en cas d'échec des traitements pharmacologiques. Il leur sera alors proposé de rencontrer en consultation un médecin participant à l'étude afin qu'il lui présente le protocole en détail, lui remette la notice d'explication et le consentement de participation.

### **PROCEDURE(S) UTILISE(S) POUR LA RECHERCHE**

#### **DISPOSITIF MEDICAL UTILISE DANS LE CADRE DE LA RECHERCHE**

Aucun produit expérimental n'est administré aux participants, et aucun dispositif médical non marqué CE n'est utilisé dans le cadre de cette recherche.

#### **Stimulateur Magnétique (dispositif rTMS)**

Stimulateur Magnétique (dispositif rTMS), MagVenture, MagPro 30®

Stimulateur Magnétique (dispositif rTMS), Classe IIa

Certificat pour dispositifs médicaux : EC Certificate DGM-512. Marquage CE (CE 0543).

Certification en conformité avec les exigences de l'Annexe II, section 3.2- Système complet d'assurance de qualité de la Directive du Conseil Européen 93/42/EEC concernant les dispositifs médicaux.

#### **Station de Neuronavigation et fusion d'images IRM**

Station de Neuronavigation et fusion d'images IRM, Classe I.

Certificat pour dispositifs médicaux. Marquage CE (CE 0124)

Le produit est conforme aux règles énoncées dans la directive 93/42/CEE du Conseil du 14 Juin 1993 relative aux dispositifs médicaux.

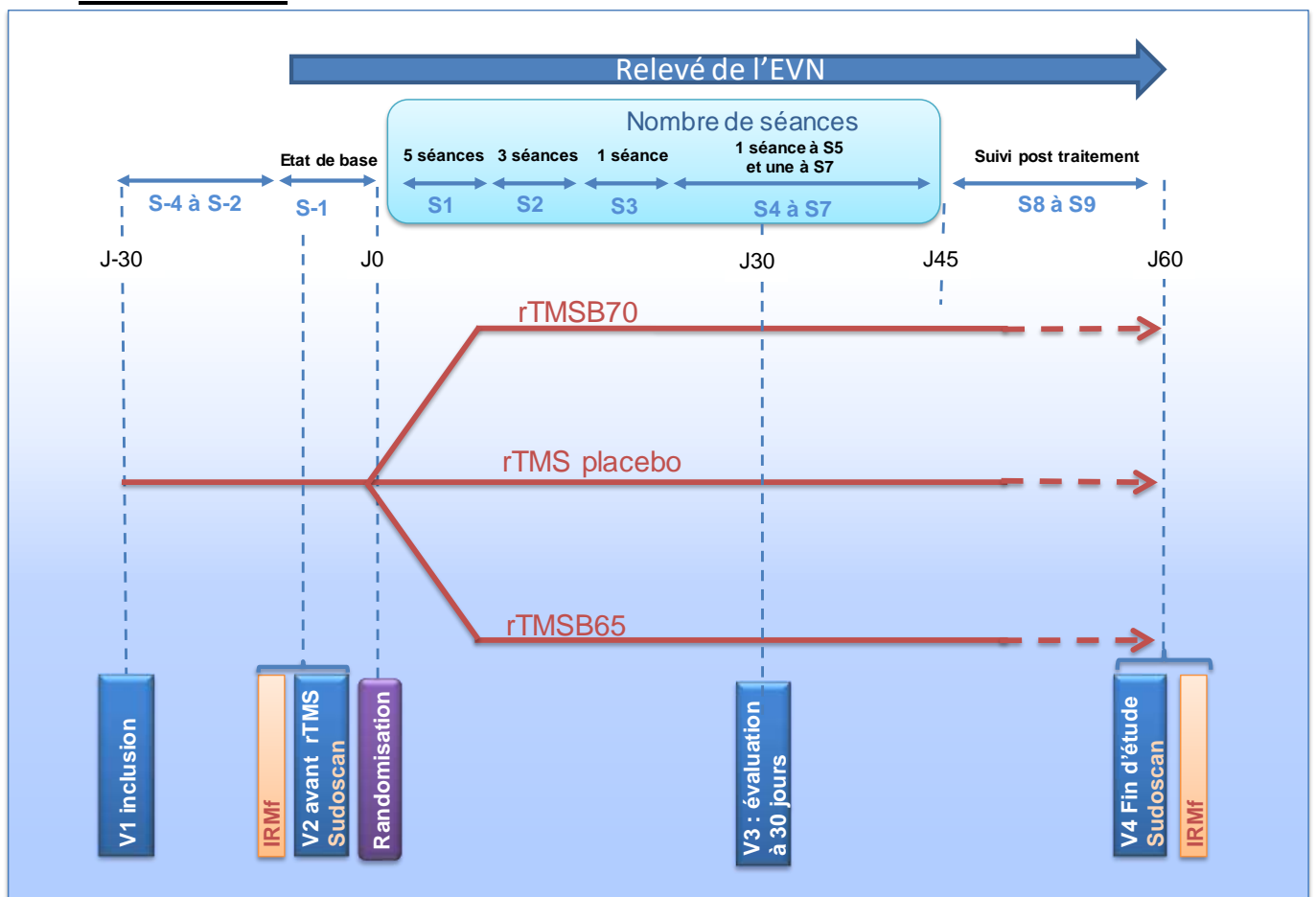
Références du matériel utilisé : LC020224 TMS Navigation Systeme- Value Edition

## DEROULEMENT DE LA RECHERCHE

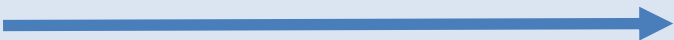
### CALENDRIER PREVISIONNEL DE LA RECHERCHE

- Début des inclusions : Septembre 2020
- Durée de la période d'inclusion : 3 ans
- Durée du traitement ou de la procédure/stratégie: 45 jours
- Durée de participation de chaque sujet : 3 mois
- Durée totale de la recherche : 3 ans et demi
- Fin des inclusions : septembre 2023
- Fin de la recherche (si différente de la fin des inclusions) : Février 2024

### Schéma d'étude



## Tableau récapitulatif du suivi sujet

PHASE D'ETUDE	SELECTION	INCLUSION	PERIODE D'EVALUATION		
Visites cliniques	Sélection	Visite V1 d'inclusion	Visite V2 avant le ttt	Visite V3 à J30	Visite V4 fin d'étude J60
<b>Repère temporaire</b>		Jusqu'à 30 jours avant V2	Dans la semaine avant le début du ttt J-7 ± 3	Entre J30 ± 3 jours après le début du ttt	Entre J60 et J70 après le début du ttt
Critères de sélection	X	X			
Information	X	X			
Signature consentement		X			
Randomisation			à J0		
Anamnèse		X			
Examen clinique		X	X	X	X
Traitements associés		X	X	X	X
Evènements médicaux			X	X	X
Echelles : SF-12, HAD, NPSI			X	X + CGI	X + CGI
IRM fonctionnelle + Activité électrodermale			X		X
Sudoscan®			X		X
Allodynie			X	X	X
Relevé quotidien d'EVN et des traitements antalgiques		Remise du carnet d'EVN 			

### Visite de sélection

Au cours d'une consultation auprès d'un praticien du Centre de la Douleur, les patients répondant aux critères de sélection seront sollicités pour participer à l'étude.

Les investigateurs vérifieront les critères d'inclusion et de non inclusion dans l'étude. Chaque sujet sera informé par ce médecin du déroulement et des contraintes et risques liés à l'étude. Un formulaire d'information et de consentement pour son éventuelle participation à l'étude lui sera remis.

Après un délai de réflexion de 1 à 3 semaines, le patient sera recontacté et s'il le souhaite un rendez-vous sera programmé pour la visite d'inclusion.

### **Visite d'inclusion V1**

Après avoir répondu aux éventuelles questions du patient, les critères d'inclusion et de non inclusion, seront une nouvelle fois vérifiés puis validés par l'investigateur.

Le patient sera alors invité à signer le consentement de participation à l'étude, un exemplaire de ce consentement lui sera remis.

Le patient aura ensuite un entretien médical avec relevé des antécédents et traitement en cours. Puis un examen clinique avec une mesure de la taille du poids, de la tension artérielle, de la fréquence cardiaque. Un test urinaire de grossesse pour les femmes en âge de procréer (*conformément à la définition du CTFG, une femme est considérée en capacité de procréer, c'est-à-dire fertile, à la suite des premières règles et jusqu'à devenir ménopausée, sauf stérilité permanente (les méthodes de stérilisation permanentes incluent l'hystérectomie, la salpingectomie bilatérale, l'ovariectomie bilatérale). Une femme sera considérée comme ménopausée en l'absence de règles durant 12 mois sans autre cause médicale identifiée*) sera réalisé.

Un cahier d'évaluation quotidienne de l'intensité de la douleur (EVN) et des traitements associés, sera remis au patient. Il lui sera expliqué comment compléter ce carnet durant la durée de l'investigation.

A l'issue de la visite, une planification des séances de neurostimulation et un rendez-vous pour la prochaine visite d'évaluation seront proposés au patient. De plus des rendez-vous pour les deux IRM fonctionnelle seront programmés. La première IRMf aura lieu avant le début des séances de rTMS. Cette première IRMf sera couplée à l'IRM anatomique nécessaire pour le positionnement des électrodes de rTMS et au monitoring physiologique permettant de mesurer la variabilité de l'activité électrodermale. La deuxième IRMf aura lieu en fin d'étude.

### **Visites d'évaluation V2 avant traitement**

Cette visite aura lieu dans la semaine précédant le début du traitement, elle sera réalisée par un investigateur autre que celui qui réalise les séances de stimulation. Cette visite comportera un

examen clinique comprenant une mesure de la tension artérielle, de la fréquence cardiaque et un relevé des éventuels évènements médicaux et modifications de traitements. Une copie du carnet de relevé des EVN sera faite et conservée dans le cahier d'observation.

Le patient aura ensuite, une série de questionnaires et d'échelles à compléter (Echelles : SF-12, HAD, NPSI).

L'investigateur évaluateur fera ensuite passer un Sudoscan au patient puis évaluera l'allodynie du patient.

A l'issue de la visite l'investigateur évaluateur adressera un mail à l'investigateur chargé de réaliser les séances de rTMS afin que celui-ci procède à la randomisation via une application internet dédiée (IWRS).

### **Visites d'évaluation V3, 30 jours après le début du traitement**

Cette visite aura lieu 30 jours après le début des séances de rTMS, elle sera réalisée par un investigateur autre que celui qui réalise les séances de stimulation. Cette visite comportera un examen clinique avec une mesure du poids, de la tension artérielle, de la fréquence cardiaque et un relevé des éventuels évènements médicaux et modifications de traitements. L'investigateur évaluera l'Allodynie du patient. Le patient aura ensuite, une série de questionnaires et d'échelles à compléter (Echelles : SF-12, HAD, NPSI, CGI).

Une copie du carnet de relevé des EVN sera faite et conservé dans le cahier d'observation.

### **Visites V4, fin d'étude à 60 jours du début du traitement**

Cette dernière visite d'évaluation aura lieu dans l'intervalle de 60 à 70 jours après le début des séances de rTMS.

Elle comporte un relevé des évènements médicaux survenus depuis la dernière visite, un recueil des éventuels changements de traitement. Le carnet de suivi des EVN sera collecté par l'investigateur et inséré dans le cahier d'observation papier.

Le patient aura ensuite un examen médical avec une mesure de la tension artérielle, de la fréquence cardiaque et une série de questionnaires à compléter (Echelles : SF-12, HAD, NPSI, CGI- Patient).

De la même manière que la visite 2, L'investigateur évaluateur fera passer un Sudoscan au patient puis évaluera l'Allodynie.

Le patient aura également si possible le même jour la deuxième IRMf couplée au monitoring physiologique.

### **Déroulement des Séances de rTMS**

Le site de stimulation corticale sera déterminé à l'aide d'un système de neuronavigation et de l'IRMf. La cible à stimuler est située au niveau de l'aire motrice de la main, controlatérale au site douloureux. Les séances seront guidées par le système de neuronavigation.

**Paramètres de stimulation :** Intensité de la stimulation : 80% du seuil moteur ; Fréquence: 10 Hz ; Trains : 5 sec. ; Inter trains: 25 sec. ; soit 2000 stimulations pendant 20 minutes.

**Nombre des séances :** une séance par jour pendant 5 jours consécutifs, puis 3 séances/ semaine (S2), puis 1 séance S3, puis 1 séance bimensuelle S5 et S7.

**IRMf pré-cure :** J-7 à J0

**IRMf postcure :** J60 ± 5 jours

Durée de la participation de chaque patient : 3 mois

Durée prévisionnelle de recrutement : 3 ans

Nombre de patients / observations prévu(e)s à recruter : 45

### **Examens prévus**

#### **Protocole IRM**

Le protocole IRM sera effectué sur plateforme IRMaGe, IRM Achieva 3.0T dStream, Philips du CHU de Grenoble. Il sera réalisé avec l'antenne 32 canaux.

Le protocole IRM comporte :

*Une séquence anatomique transverse 3D T1* qui sera utilisée pour la neuronavigation (volume d'acquisition englobant le nez et sortant du crâne en haut).

**Cartographie cérébrale par IRMf des régions sensori-motrices de la main:** paramètres de la séquence de contraste BOLD: 36 coupes, volume couvrant le cortex moteur, le thalamus, la partie supérieure du cervelet (TR=3000 ms, TE=35 ms, flip angle = 90°, coupes de 3 mm, voxels cubiques 3x3x3, 70 scans fonctionnels, durée =3 min 30 s).

Les séries fonctionnelles alternent 30 sec de repos, 30 sec d'activation, 30 sec de repos, avec démarrage aux scans n°11-31-51.

Ces 2 séries correspondent chacune à des mouvements différents présentés via le logiciel Presentation et synchronisés avec l'acquisition IRM:

- de mouvements à 1Hz de l'opposition du pouce avec les autres doigts de la main droite (1 série) ;

- de mouvements à 1Hz de l'opposition du pouce avec les autres doigts de la main gauche (1 série) ;

Ces séries produisent les cartographies cérébrales de base, utilisées pour la neuronavigation rTMS, ainsi que celles à J60 pour évaluer le bénéfice de la cure (comparaison avant/après) en lien avec les répondeurs/non-répondeurs.

***Une série pour évaluer la perfusion cérébrale :***

Une séquence pcASL et M0 (durée de marquage 1800 ms, délai 1400 ms, voxels de 3.5 x 3.5 x4 mm) qui donnera l'information de la perfusion de base et à J60. Seront comparés : au niveau basal la perfusion côté douloureux vs. côté non douloureux et l'évolution de la perfusion suite à la cure (avant/après) en fonction du groupe répondeurs/non-répondeurs.

***Une séquence d'IRMf de repos, pour étudier les réseaux de la connectivité fonctionnelle.***

Ces séries permettront l'étude de l'évolution suite à la cure (avant/après) de deux réseaux d'intérêt : le réseau sensori-moteur qui est directement impacté par la stimulation magnétique et d'autre part, le réseau de la douleur qui peut être modulé par la cure.

***Le monitoring physiologique*** (enregistrement de la PPU, permettant de mesurer la variabilité du rythme cardiaque et de l'activité électrodermale, indicatif du système autonome lors de l'examen IRMf)

En cas de découverte fortuite d'anomalie : le médecin investigateur informera le patient et cordonnera sa prise en charge médicale si nécessaire.

**Sudoscan**

Cette évaluation sera réalisée lors des visites V2 et V4.

L'exploration de la fonction sudorale a été proposée pour évaluer l'atteinte du système autonome sympathique et la neuropathie des petites fibres par la technique de Sudoscan. Les glandes sudorales sont innervées par des fibres sympathiques amyéliniques de petit diamètre.

La méthode repose sur la mesure d'un signal électrique produit par une réaction électrochimique entre les ions chlorures présents dans la sueur et des électrodes, au niveau



desquelles est appliquée une faible tension continue inférieure à 4 volts. Le phénomène de l'iontophorèse inverse entraîne l'attraction des ions chlorures au niveau de l'électrode utilisée comme anode et permet la mesure de la conductance électro chimique de la sueur (CES). Cette technique s'applique donc à l'évaluation précise du degré d'atteinte végétative sudorale et permet un suivi de l'évolution et de la réponse à un traitement.

Quatre larges électrodes sont placées au contact des paumes et des plantes des pieds, qui sont des zones présentant une forte densité en glandes sudorales. La mesure est complètement indolore et dure au total moins de 3 minutes. Il est simplement demandé au sujet de se tenir debout avec les paumes et les plantes au contact des électrodes Les résultats sont affichés sous forme d'une représentation graphique la conductance électro chimique de la sueur (CES).

## **VARIABLES MESUREES ET METHODES DE MESURE**

### **PARAMETRES CLINIQUES**

Age, Sexe, Poids, Taille, Pression artérielle, Fréquence cardiaque

Allodynie

### **Questionnaires/échelles**

- Auto-questionnaire de qualité de vie SF-12
- Auto-questionnaire d'évaluation de l'état d'anxiété de la dépression : HAD (Hospital Anxiety And Depression)
- Echelle multi-dimensionnelle d'évaluation de la douleur neuropathique : NPSI (Neuropathic Pain Symptom Inventory)
- Echelle de l'impression clinique globale du changement : CGI (Clinical Global Impression of Change)

### **Paramètres para-cliniques**

- Paramètres de l'IRMf
- Paramètres du Sudoscan
- Paramètres de l'Activité électrodermale

### **Paramètres biologiques et pathologie**

Aucun paramètre de biologie ne sera relevé.

## **ASPECTS DATA MANAGEMENT STATISTIQUES**

### **RECUEIL ET PROTECTION DES DONNEES**

Un cahier d'observation papier (CRF) sera créé pour l'étude.

Le(s) personne(s) responsables du remplissage du CRF devra/devront être clairement identifié(s) dans le document de délégation de tâches.

La collecte des données clinique reposera sur une base clinique de données conforme aux données présentes dans le CRF papier.

La saisie des données se fera sur une base de données hébergées sur un serveur sécurisé du CHUGA et accessible uniquement aux personnes impliquées dans le traitement des données de l'étude.

### **Calcul du nombre de sujets nécessaire**

#### **Nombre de personnes à inclure : 45**

La stratégie d'analyse consiste en une comparaison de la valeur journalière de l'échelle de douleur visuelle numérique (EVN), moyennée sur 7 jours par ANOVA par mesures répétées avec étude de l'interaction TEMPS (S-1 (baseline) : semaine avant le traitement ; S1 à 7 : semaines pendant le traitement) x TRAITEMENT (rTMS placebo, rTMS B70, rTMS B65).

Nous commencerons par une analyse globale de la différence des trois groupes au risque alpha de 5% ; et en cas de significativité nous réaliserons les comparaisons 2 à 2 au risque alpha de 1,7% (après correction de Bonferroni pour 3 comparaisons). Donc, le nombre de sujets est calculé par rapport aux comparaisons 2 à 2.

Le nombre de sujets nécessaire pour notre étude est estimé avec les hypothèses suivantes :

- un niveau basal de la valeur moyenne journalière de l'EVN, moyenné sur 7 jours de 6,35/10 +/-1,47/10 (Pommier et al, 2016) (9) ;
- une différence de réduction entre 2 groupes d'au moins 1,3/10 de l'EVN ;
- une estimation du coefficient de corrélation entre les mesures avant et après de 0,7 au moins ;
- un risque alpha de 1ère espèce consenti sera égal à 1,7% ;

- un risque beta de 2<sup>ème</sup> espèce consenti sera égal à 20% (puissance statistique de 80%).

Selon logiciel NQuery Advisor<sup>®</sup> 7.0, le nombre de patients à inclure serait égal à 15 par groupe, soit 45 patients au total. Une analyse intermédiaire est prévue pour tester l'hypothèse nulle après l'inclusion du 30<sup>e</sup> patient. Les règles de décisions seront déterminées par les frontières de Haybittle–Peto au moment de l'analyse. La nécessité d'une réestimation du nombre de sujet sera discutée.

### **Randomisation**

Une randomisation centralisée sera réalisée, par le biais d'un IWRS (interactive web réponse system). Celle-ci mettra en œuvre la technique de minimisation (30) pour assurer l'équilibre des principaux facteurs de risque entre groupes (31). Le nombre important de paramètres rend, en effet, difficile la mise en œuvre d'une stratification.

Cette randomisation par minimisation sera réalisée sur les paramètres suivants : l'âge, le sexe, le site douloureux. La méthode de minimisation inclura une part d'aléa (définie par un facteur de randomisation précisant un pourcentage de patients recevant une des deux interventions).

La liste de randomisation est conservée par le promoteur

### **Méthodes statistiques employées**

#### **Populations d'analyse et méthode de remplacement des données**

L'analyse descriptive sera réalisée sur tous les patients randomisés.

Une première analyse comparative sera réalisée sur tous les patients randomisés (population en intention de traiter modifiée) ayant eu au moins une séance d'activation, et pour lesquels la moyenne journalière de l'EVN est disponible à l'état basal et au moins une des 9 semaines de traitement. Une méthode de remplacement des données manquantes par la méthode itérative des chaînes de Markov (MCMC) sera appliquée si nécessaire. Dans ce cas, deux analyses seront faites, l'une sur les données effectivement disponibles (analyse en per protocole avec des données manquantes), l'autre en utilisant la procédure de remplacement des données manquantes (analyse en intention de traiter avec remplacement des données). La robustesse des conclusions sera vérifiée, et une éventuelle discordance sera analysée en fonction des biais de recueil qui auront pu être identifiés. Une analyse en per protocole de l'efficacité du traitement sera réalisé sur tous les patients ayant eu toutes les séances du traitement et ne présentent pas de déviations majeures du protocole.

D'une manière générale, l'analyse des différents questionnaires et la stratégie de remplacement ou non des données manquantes se fera conformément au manuel d'utilisation des questionnaires (CGI, SF-12, HAD, NPSI).

### **Approche générale**

L'analyse statistique sera réalisée après les procédures habituelles de management des données et gel de base selon les procédures internes du CIC de CHUGA.

L'analyse descriptive portera sur l'ensemble des variables recueillies. Elle comprendra pour chaque paramètre quantitatif à chaque temps d'évaluation et dans chaque groupe : moyenne, déviation standard, intervalles de confiance bilatéraux à 95% associés, médiane et quartiles, nombre de valeurs manquantes. Les paramètres qualitatifs seront exprimés à chaque temps et dans chaque groupe d'évaluation par l'effectif et la fréquence de distribution et les intervalles de confiance bilatéraux à 95% associés.

Le seuil statistique ( $\alpha$ ) retenu pour considérer une différence comme statistiquement significative sera  $p$  inférieur ou égal à 0,05; tous les tests seront bilatéraux.

Le test de Shapiro-Wilks sera utilisé pour démontrer la normalité des paramètres, et le test de Levene pour démontrer l'homogénéité des variances. Lorsque les conditions d'application des tests paramétriques ne seront pas satisfaites, des tests non paramétriques seront utilisés.

Concernant les paramètres présents dans le cahier d'observation et dont l'analyse n'est pas décrite, ils seront utilisés à des fins descriptives, pour le suivi du patient ou en analyse exploratoire à posteriori.

### **Analyse comparative**

L'analyse comparative est la même pour toutes les échelles. L'analyse d'ANOVA par mesures répétées sera utilisée pour analyser l'évolution de différentes échelles avec le temps pour les trois groupes de traitement (rTMS placebo, rTMS B65, rTMS B70). La sphéricité sera analysée par le test de Mauchly. L'absence de sphéricité sera compensée par l'ajustement de Greenhouse-Geisser. Pour les comparaisons post hoc 2 à 2, le test de Bonferroni sera utilisé.

En cas de violation de leurs conditions d'application, les tests non-paramétriques seront utilisés.

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## 6.2. Etude Neurostim : resultats preliminaires

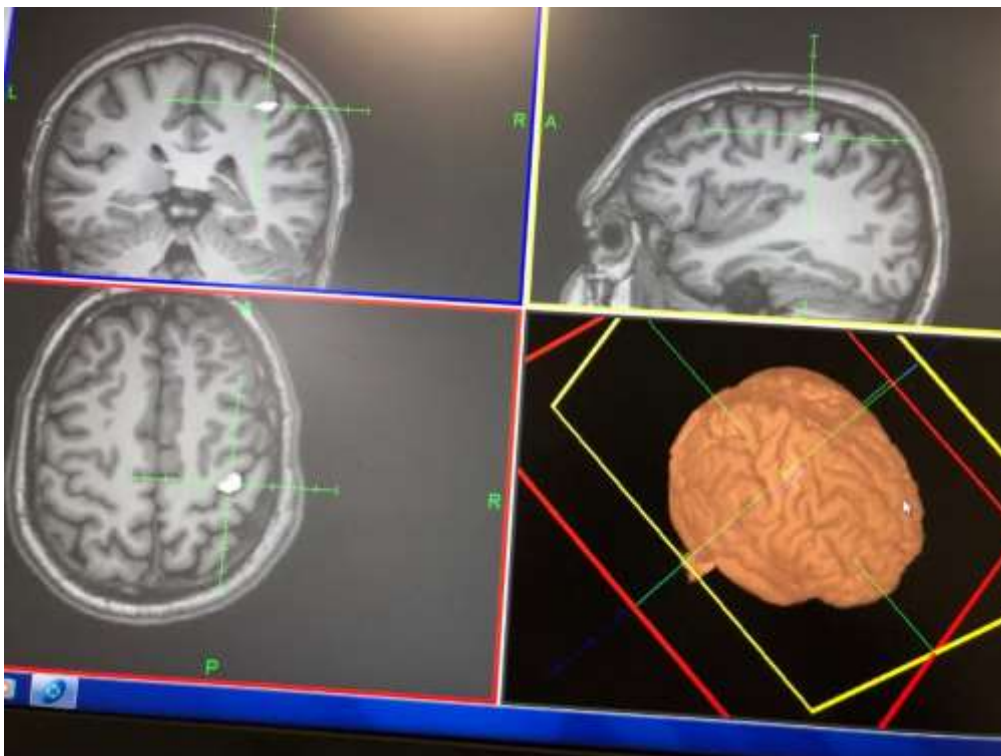
Cette étude préliminaire concerne seulement le volet neuroimagerie et uniquement en pré-cure (J0). Etant donné que le protocole Neurostim est une étude contrôlée en double aveugle, nous n'avons pas accès aux données cliniques des patients et leurs groupes de randomisation.

12 patients ont terminé le protocole en mai 2022 : 9 hommes, 3 femmes, âge moyenne 49 ans.

Chez tous les patients a été réalisée l'IRMf en pré-cure et postcure.

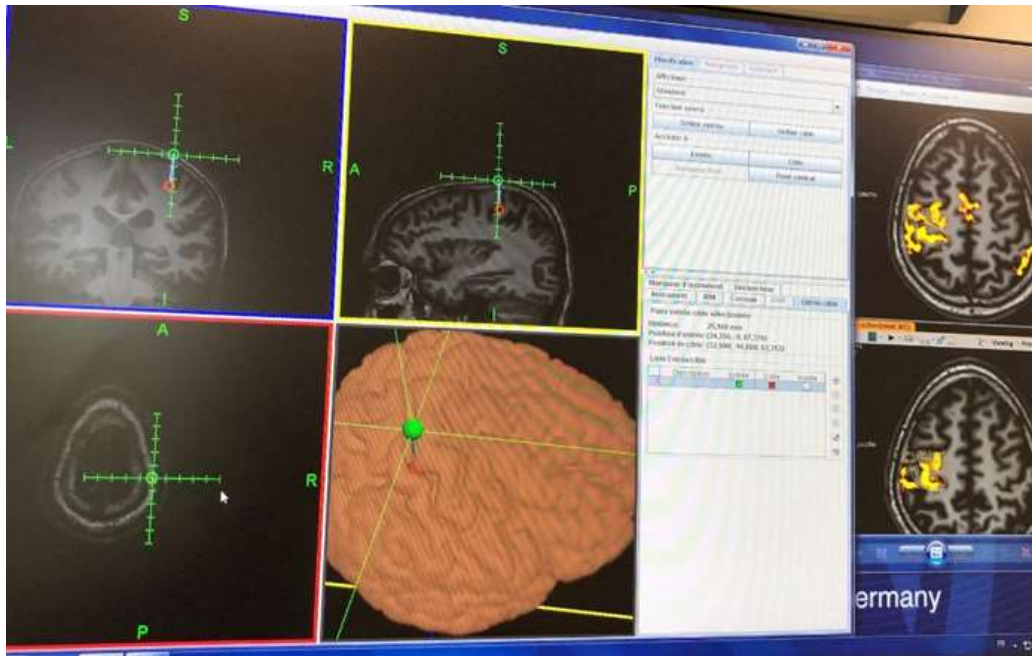
1. La cible de la zone à stimuler a été déterminée lors de l'IRMf en pré-cure (fig.1A). Chez tous les patients la cible déterminée se situait au niveau de la zone d'activation de l'aire corticale de la main lors de l'IRMf (utilisée par le système de neuronavigation) et se trouvait dans le sillon central (fig.1B). Ce ciblage s'avère plus précis par rapport que celui obtenu au moyen de l'IRM anatomique 3D, qui est praticien-dépendant et ne tient pas compte des modifications de la plasticité cérébrale et des variations anatomiques (comme déjà observé dans l'article 6 de cette thèse).

**Fig. 1 A : Ciblage obtenu par l'activation de l'aire corticale de la main pendant l'IRMf**





**Fig. 1B : Ciblage IRMf utilisé pendant les séances de la rTMS guidée par le système de neuronavigation.**



2. Nous n'avons pas trouvé de différence significative entre la perfusion cérébrale de l'hémisphère controlatéral à la douleur comparé à l'hémisphère ipsilatéral à J0 (pré-cure).

3. Nous n'avons pas trouvé de différence significative sur les cartes d'activation cérébrale en réponse à une tâche motrice de la main du côté douloureux comparé au côté non-douloureux.

4. Nous avons analysé par IRMf la connectivité fonctionnelle de repos, en étudiant les 4 réseaux les plus impliqués dans la douleur : le réseau sensori-moteur ; le réseau de la saillance ; le réseau du mode par défaut (Default Mode Network) ; le réseau attentionnel fronto-pariétal.

Nous n'avons pas mis en évidence de différence statistiquement significative de la connectivité fonctionnelle, pour les réseaux étudiés aussi bien dans l'hémisphère controlatéral à la douleur que dans l'hémisphère ipsilatéral.

## 7. DISCUSSION GENERALE

### *Etude de l'effet antalgique de la rTMS à long terme en pratique clinique : Articles 1 et 2*

Nous avons étudié l'efficacité antalgique de la rTMS à long terme en pratique clinique. Il s'agit d'une étude observationnelle rétrospective de 57 patients souffrant de douleurs neuropathiques chroniques réfractaires et traités par des séances de rTMS entre mars 2014 et avril 2018. Cette étude concerne l'utilisation d'un protocole de stimulation comportant les mêmes paramètres pendant toute la période citée dans les indications suivantes : algies oro-faciales, douleurs neuropathiques centrales cérébrales ou médullaires et névralgies pudendales.

Comme déjà évoqué dans l'introduction, seulement quelques études ont rapporté l'efficacité de la rTMS à long terme. Dans l'ensemble de notre série, à la fin de la phase d'induction, un effet antalgique supérieur ou égal à 30% est observé chez 68,4 % des patients et cette efficacité a pu être maintenue chez 47,4 % à J180. Par ailleurs, les patients répondeurs à J180 présentent aussi une amélioration significative de la qualité de vie, de l'anxiété et de la perception douloureuse.

Une originalité de cette étude concerne l'analyse de l'évolution de l'EVN lors de la phase d'induction, afin de déterminer le nombre des séances indispensables pour obtenir un effet antalgique significatif, permettant de sélectionner les patients « répondeurs ». Dans notre étude, nous constatons une diminution significative du niveau moyen des 3 paramètres de la douleur (l'intensité de la douleur permanente, le nombre des pics douloureux et leur intensité) le lendemain de la 7ème séance. A noter qu'après la 7ème séance, la réduction de l'EVN chez les patients « répondeurs » est très significative tandis que chez les « non répondeurs » il n'y a aucun changement. Ces résultats s'avèrent très intéressants pour définir le nombre optimal des séances de la phase d'induction pour obtenir une réponse antalgique suffisante chez les patients « répondeurs » et programmer les séances de maintien. En pratique clinique, cette observation est pertinente, puisqu'elle permet d'éviter la pratique des séances inutiles, particulièrement chez les patients « non répondeurs ».

Notre étude retrouve par ailleurs que le meilleur effet antalgique est obtenu par les séances quotidiennes lors de la phase d'induction et qu'il est moindre suite à l'espacement des séances de maintien. Par ailleurs, lors de la phase de maintien, les séances bimensuelles s'avèrent plus efficaces que les séances mensuelles. Dans une étude précédente sur l'efficacité à long terme de la rTMS dans le traitement des algies faciales chez 55 patients [34], nous avons observé que parmi les 73% de répondeurs à la phase d'induction, les récurrences étaient fréquentes par l'espacement mensuel des séances de maintien, et seulement 40% des patients étaient encore

répondeurs à J180 (-33%). Depuis 2014, nous pratiquons des séances de maintien bimensuelles et le taux de répondeurs dans notre série actuelle de 57 patients est passé entre la fin de la phase d'induction et J180 de 68% à 47% (-21%) et dans le sous-groupe des algies faciales de 80% à 65% (-15%).

L'intérêt particulier de notre étude réside dans l'exploration des facteurs prédictifs pouvant influencer la réponse thérapeutique à la rTMS et son maintien à long terme. Nous constatons que les patients récidivants en cours de phase de maintien, avaient plus de traits anxiodépressifs avant la cure rTMS (J0), que les patients encore répondeurs à J180. Cette constatation pourra s'avérer très utile en pratique clinique : l'accompagnement psychologique et la prise en charge thérapeutique adaptée des patients anxiodépressifs, avant et pendant la phase de maintien, pourrait diminuer le nombre des patients récidivants. Par ailleurs, on remarque que les patients « non répondeurs » à la rTMS, sont en moyenne significativement plus douloureux que les patients répondeurs. Une prise en charge multimodale, concomitante à la rTMS des patients très algiques, pourrait éventuellement augmenter le taux des répondeurs.

Chez les patients répondeurs, la rTMS permet de diminuer les traitements médicamenteux évitant ainsi la polymédication et ses effets secondaires, comme nous l'avons déjà observé dans notre cohorte précédente [34].

Un autre intérêt particulier de notre étude consiste dans l'utilisation de la rTMS et de la bobine B70 dans les névralgies pudendales chroniques réfractaires. La bobine B70 (angulée) est plus puissante et stimule plus profondément le cortex que la sonde classique B65 (plate) [41]. Nous n'avons connaissance d'aucune étude publiée stimulant la représentation corticale bi-hémisphérique du périnée ou évaluant l'utilisation à long terme de la rTMS dans cette indication. Dans les névralgies pudendales, la stimulation bi-hémisphérique par la bobine B70 paraît plus pertinente et adaptée que la stimulation unilatérale par la bobine B65 afin d'atteindre le cortex moteur correspondant à la représentation des territoires pelvi-périnéaux [42]. En pratique clinique, la stimulation bilatérale des aires motrices médianes par la bobine B70 pourrait aussi s'appliquer aux douleurs neuropathiques des membres inférieurs et est facile à réaliser puisqu'un positionnement au niveau du vertex (Cz) est suffisant, sans nécessiter de recourir à l'utilisation d'un système de neuronavigation pour optimiser le ciblage.

Cependant, cette étude observationnelle comporte comme limitations l'absence d'un groupe témoin et d'évaluation de l'effet placebo. A noter que sur le plan éthique et clinique, il s'avère difficile de proposer aux patients, déjà très souffrants et réfractaires aux traitements conventionnels, une thérapie placebo pendant 6 mois. En pratique clinique, l'objectif principal

du praticien est l'obtention de l'effet antalgique de la rTMS et l'amélioration global du patient. Dans cette optique, les études cliniques explorant l'efficacité des techniques de neuromodulation non-invasive à long terme dans la vie réelle ont leur place et permettent d'évaluer nombreux aspects pratiques et paramètres cliniques.

### ***Effet antalgique de la tDCS : Article 3***

Nous avons exploré l'effet prophylactique de la stimulation anodique (versus placebo) du cortex moteur dans la migraine chronique et son maintien à long terme : 36 patients ont été inclus et randomisés en deux groupes : 18 patients ont reçu la stimulation active et 18 patients ont reçu une stimulation placebo. Les points forts de cette étude sont sa conception (essai randomisé et contrôlé en double aveugle, stimulation active vraie versus placebo) et l'homogénéité de la population (résistante à au moins 3 traitements médicamenteux prophylactiques et ayant une ancienneté moyenne des symptômes de  $25.9 \pm 14.6$  années).

A notre connaissance, il s'agit de la 1ère étude contrôlée évaluant la réduction de la fréquence des crises dans la migraine chronique résistante à long terme. Dans la conception de cette étude, nous sommes inspirées par les protocoles utilisant la rTMS à long terme dans le traitement des douleurs chroniques, comprenant une phase d'induction et une phase de maintien.

Nous observons une diminution significative du pourcentage de la fréquence mensuelle des crises entre le groupe actif et placebo dès la fin du 1er mois de stimulation. Cependant, la différence de la réduction des crises est en faveur du groupe actif et persiste tout au long du suivi. Cette réduction est encore plus prononcée à la fin de suivi (3 mois après le traitement) ( $-31.9\% \pm 33.1$  vs.  $-5.6\% \pm 39.4$ ). D'autre part, le taux de répondeurs ( $\geq 30\%$  de réduction de la fréquence des crises de migraine) à 5 mois de suivi (3 mois après le traitement) est significativement plus élevé dans le groupe actif par rapport au groupe placebo ( $50.0\%$  vs.  $14.3\%$ ). Enfin, le taux des répondeurs  $\geq 30\%$  tend à être plus élevé dans le groupe actif versus placebo, en regard des deux critères secondaires : les scores HIT-6 et MIDAS.

Ainsi, un effet prophylactique de la tDCS est observé, incluant des effets bénéfiques à long terme. Ce résultat est important, puisque l'utilisation de la tDCS pourrait être une alternative thérapeutique intéressante dans le traitement prophylactique des migraines chroniques résistantes, empêchant ainsi leur évolution vers une forme réfractaire (condition correspondant à l'échec d'au moins 5 traitements prophylactiques).

Par ailleurs, notre étude démontre que l'efficacité de la tDCS est comparable aux résultats des séries publiées évaluant l'efficacité du Topiramate [43,44], qui est suggéré comme un

traitement prophylactique de 1er choix dans les migraines chroniques selon les recommandations françaises récentes [45]. En termes de « taux de répondeurs », nos résultats sont comparables également à ceux des études récentes rapportant l'efficacité prophylactique de la toxine botulinique et des anticorps monoclonaux anti-CGRP [46,47]. Dans ce cadre, il paraît intéressant de déterminer la place de la tDCS dans l'arsenal thérapeutique de la migraine chronique et notamment son utilisation comme alternative ou en association avec les traitements médicamenteux prophylactiques et non seulement comme une approche de dernier recours dans les formes sévères ayant déjà fréquemment des retentissements majeurs de l'humeur, de la qualité de vie et des activités socio-professionnelles.

Malheureusement nous n'avons pas trouvé de facteurs prédictifs pouvant influencer la réponse clinique de la tDCS et son maintien à long terme, probablement à cause de la petite taille de notre échantillon.

L'intérêt de la tDCS réside dans son innocuité et sa bonne tolérance. Chez les patients répondeurs, la tDCS pourrait permettre de diminuer les traitements médicamenteux évitant ainsi la polymédication et ses effets secondaires, particulièrement les céphalées par abus médicamenteux. Par contre, il faut citer les contraintes de ce traitement : la nécessité de séances fréquentes et un temps médical incompressible. Le développement de l'utilisation de la tDCS à domicile constitue une alternative très intéressante dans ce contexte et moins onéreuse [48].

Malgré les résultats encourageants sur l'utilisation de la tDCS, comme une approche thérapeutique non médicamenteuse en termes d'efficacité et de tolérance, sa place dans le traitement des syndromes douloureux, y compris la migraine chronique, reste à définir, à cause d'un niveau de preuve insuffisant.

#### ***Comparaison de l'effet antalgique de la rTMS et de la tDCS : Article 4***

L'objectif principal de cette étude est la comparaison de l'effet antalgique de l'effet de deux méthodes de stimulation non-invasive du cortex moteur, la tDCS et la rTMS dans les douleurs neuropathiques chroniques pharmacorésistantes. Il s'agit d'un essai thérapeutique, en groupes croisés, et randomisée en mode « cross-over » : 56 patients ont reçu une 1 séance quotidienne de rTMS ou de tDCS pendant 5 jours et un mois plus tard, l'autre type de neuromodulation selon les mêmes modalités.

Afin de permettre des comparaisons inter-sujets, les scores quotidiens de la douleur (EVN) ont été normalisés à l'aide de Z-scores [55,56]. Les patients étaient considérés comme « répondeurs » si la réduction de leurs scores de douleur était supérieure à deux écarts-types

pendant au moins une semaine par rapport aux scores enregistrés la semaine pré-stimulation. Cette étude montre un pourcentage de répondeurs similaire dans les groupes rTMS et tDCS (42,0% versus 42,3%). Par contre, on observe un niveau de soulagement de la douleur légèrement supérieur en faveur de la rTMS au niveau individuel. D'autre part, presque la moitié des patients n'ont répondu qu'à une seule technique. Cette découverte est importante pour la pratique clinique : les deux techniques méritent d'être testées avant de déclarer un patient « non répondeur » à la neuromodulation corticale. Notre étude présente comme limitation principale la courte durée de stimulation, ne permettant pas d'explorer le maintien d'effet antalgique et le taux des répondeurs à long terme, mais au moins il démontre clairement que les mécanismes d'action de la tDCS et de la rTMS sont différents. Dans ce cadre, malgré un niveau de preuve d'efficacité insuffisant dans l'indication « douleur », la tDCS peut trouver déjà son indication en cas d'échec de la rTMS, afin d'augmenter le taux des patients répondeurs.

A noter que l'examen IRMf a été réalisé en pré-cure (J0) et post-cure (J5) chez 33 patients lors de la 1ère phase de l'étude. Leur analyse n'a pas trouvé de modifications des cartes corticales sensori-motrices induites par la rTMS ou la tDCS.

### ***Comparaison de l'effet antalgique de la tsDCS avec la rTMS et la tDCS : Article 5***

L'objectif principal de cette étude est la comparaison de l'effet antalgique de la stimulation médullaire trans-spinal (tsDCS) avec la stimulation non-invasive du cortex moteur (tDCS et rTMS) dans le syndrome douloureux régional complexe (SDRC, algoneurodystrophie) des membres : 36 patients ont été inclus et randomisés dans trois groupes (rTMS, n = 11 ; tDCS, n = 12 ; tsDCS, n = 13). Afin d'obtenir une population homogène, nous avons réservé cette étude aux patients souffrant d'une algoneurodystrophie depuis plus d'un an et ayant eu la confirmation du diagnostic par la scintigraphie osseuse.

Une amélioration significative de la douleur est observée dans le groupe tsDCS versus rTMS ( $P = 0.008$ ) et tDCS ( $P = 0.003$ ) à la fin de la phase d'induction. L'ANOVA à mesures répétées montre une réduction significative de l'EVN moyenne hebdomadaire à cette fin de phase d'induction comparée avec la semaine pré-cure dans le groupe tsDCS (S3 :  $P = 0.001$ ; S5 :  $P = 0.002$ ; S13 :  $P < 10^{-3}$  ; S21 :  $P < 10^{-3}$  ; S25 :  $P < 10^{-3}$ ), ainsi que pour les deux derniers temps d'évaluation dans le groupe rTMS (S21 :  $P = 0.010$ ; S25 :  $P = 0.029$ ), mais pas dans le groupe tDCS. Par ailleurs, à la fin du suivi (6 mois), l'évaluation par l'échelle CGI retrouve que le pourcentage des patients ayant ressenti une amélioration au moins modérée, est similaire dans les groupes rTMS et tsDCS, soit 82%, mais supérieur au groupe tDCS, soit 60%.

Cette étude montre une meilleure efficacité antalgique initiale de la stimulation médullaire au moyen de la tsDCS, par rapport aux techniques plus classiques de stimulation du cortex moteur (rTMS, tDCS), chez les patients atteints de SDRC réfractaire chronique. À plus long terme, la rTMS a également montré une efficacité significative.

Il s'agit de la première étude démontrant l'efficacité du tsDCS dans le SDRC, qui est par ailleurs une indication reconnue pour la stimulation médullaire implantée [49,50]. Une des pistes d'utilisation éventuelle de la tsDCS pourrait être de fournir un facteur prédictif de la réponse à une stimulation médullaire implantée, tel que c'est le cas pour la rTMS et la stimulation corticale implantée [51]. Peut-être l'effet antalgique de la tsDCS s'est produit au niveau de l'activation du ganglion spinal, compte tenu de la taille des électrodes (diamètre = 6,2 cm) et du fait que la stimulation implantée des ganglions spinaux serait plus efficace que la stimulation médullaire cordonale postérieure [52,53]. Dans tous les cas, la tsDCS pourrait être une solution alternative à la stimulation médullaire invasive pour le traitement de la douleur chronique. C'est déjà le cas de la rTMS qui a remplacé la stimulation épidurale du cortex moteur en pratique clinique pour le traitement des douleurs neuropathiques [54].

Dans cette étude, nous avons évalué également l'atteinte du système autonome sympathique et la neuropathie des petites fibres par la technique de Sudoscan<sup>®</sup> ainsi que ses éventuelles modifications en réponse aux techniques de neuromodulation centrale non-invasive. Dans notre étude nous observons que la diminution de la conductance cutanée (electrochemical skin conductance, ESC) au niveau du membre atteint par le SDRC avant le traitement (J0) semble être prédictive d'un bon soulagement de la douleur par les techniques de la neuromodulation non-invasive. De plus, l'amélioration de la douleur par la neuromodulation est associée à une augmentation significative (normalisation) de l'ESC initialement réduite. Ce résultat illustre l'implication du système nerveux sympathique dans le SDRC et son couplage fonctionnel avec l'intensité de douleur permanente perçue par les patients. Chez les patients présentant une altération des fonctions sympathiques (réduction de l'ESC) dans le membre affecté, la neuromodulation corticale ou spinale non-invasive pourrait corriger ce dysfonctionnement sympathique de façon concomitante et associée avec le soulagement de la douleur.

Des futures études contrôlées sont indispensables pour confirmer l'effet antalgique de la tsDCS observé dans cette étude.

## **Apport de la neuroimagerie.**

### ***Ciblage du cortex moteur et recherche d'un algorithme de localisation des 3 cibles anatomiques (IRM 3 D) : Article 6***

Cette étude a été réalisée sur une série de 44 examens anonymisés d'IRM cérébrale d'adultes en bonne santé provenant de plusieurs études publiées précédemment. L'objectif de l'étude était d'identifier sur les IRM cérébrales les trois régions corticales motrices de chaque hémisphère correspondant à la représentation du membre inférieur, du membre supérieur et du visage, afin de définir la localisation de ces trois cibles pour la pratique de la rTMS. A noter que la plupart des auteurs utilisent comme cible de stimulation la représentation corticale de la main, sachant que l'effet antalgique somatotopique strict de la rTMS n'a pas été démontré [57,58]. La zone motrice de la main est plus facile à cibler, grâce au repérage du « hot spot » moteur sur la base de l'enregistrement des potentiels évoqués moteurs. Mais d'autres cibles sont utiles en pratique clinique et leur ciblage est rendu possible grâce à l'utilisation d'un système de neuronavigation utilisant l'IRM individuelle du patient. Dans ce cadre, un algorithme d'utilisation des différentes cibles selon le contexte clinique a récemment été proposé [59].

Trois évaluateurs (JPL, JPN, HH) ont réalisé la procédure d'identification des cibles à l'aide d'un logiciel d'affichage et de pointage (Comet®, Syneika, Rennes, France), développé à cet effet. Ensuite, l'analyse de la fiabilité intra-évaluateur et inter-évaluateur a été effectuée. Cette fiabilité est bonne ou satisfaisante, surtout en ce qui concerne le ciblage des membres.

D'autre part, un barycentre a été calculé pour chaque cible, ainsi que la distance géodésique entre la projection du cuir chevelu de ces différentes cibles, qui variait entre 32,4 et 35,5 mm pour la distance cible membre inférieur-membre supérieur ou la distance cible membre supérieur-visage.

Ces résultats montrent clairement que les trois cibles du cortex moteur sont suffisamment espacées pour considérer que leur stimulation par le champ électrique focal d'une bobine de type B65 (que l'on peut estimer à 10-15 cm<sup>2</sup>, soit un rayon de 1,7-2,2 cm) [41,60,61] peut agir sur des réseaux de neurones distincts.

Ce travail ouvre la voie à la définition de ces trois cibles dans le cadre de la pratique de la rTMS guidée par neuronavigation, au moyen de l'IRM anatomique du patient. Cette étude est également une étape importante afin de valider un algorithme de ciblage prédéfini au moyen de l'identification automatique de ces trois régions dans un système de navigation.



***Analyse, au moyen de l'IRMf, des modifications cérébrales éventuelles induites par la rTMS à long terme : Article 7***

Dans cette étude, nous avons recherché des corrélats neuronaux entre la douleur chronique et l'activité du système nerveux sympathique chez des patients SDRC et leur évolution à six mois, suite à un protocole de stimulation cérébrale non invasive utilisant la rTMS délivrée à haute fréquence sur le cortex moteur. Onze patients atteints de SDRC unilatéral ont été évalués avant (J1) et un mois après la fin d'un protocole de rTMS de 5 mois (J180). L'évaluation comprenait la mesure de l'ESC dans le membre affecté par le SDRC et le membre controlatéral non affecté, l'intensité de la douleur quotidienne notée sur une échelle numérique visuelle (VNS) et l'IRMf basée sur des tâches motrices. Au départ (J1), la réduction des valeurs ESC dans le membre affecté par le SDRC était corrélée avec des scores de douleur VNS élevés. De plus, il y avait une covariance des deux variables (ESC et VNS) avec l'activation cérébrale dans une région limitée du cortex somatosensoriel primaire (S1) contralatéral au côté douloureux sur l'IRMf. Suite au traitement par rTMS (J180), les scores de douleur VNS ont significativement diminué (de 22 % en moyenne) avec 6/11 patients considérés comme cliniquement répondeurs (diminution  $\geq 30$  % de l'intensité quotidienne de la douleur). Au moins chez ces répondeurs, les valeurs ESC dans le membre affecté par le SDRC ont augmenté et sont revenues à la normale. L'amélioration globale des scores de douleur et des valeurs ESC s'est avérée corrélée et l'activation S1 sur l'IRMf a montré à nouveau une covariance significative avec les valeurs d'ESC et les scores VNS post-rTMS : l'activation S1 était négativement corrélée avec la normalisation des valeurs d'ESC et le soulagement de la douleur. Cette étude montre un couplage fonctionnel douleur-système nerveux autonome chez les patients SDRC, également associé à l'implication d'une région corticale spécifique dans la région S1. Nos résultats suggèrent que la rTMS du cortex moteur pourrait agir, au moins en partie, en modulant simultanément la douleur et les activités sympathiques grâce à une réduction significative de l'activation de S1, qui pourrait jouer un rôle de « plaque tournante » dans le couplage de la douleur et des fonctions autonomes.

***Données préliminaires de neuroimagerie (IRMf) : protocole Neurostim***

Cette étude préliminaire concerne uniquement le volet IRMf pré-cure du protocole Neurostim. Nous observons que le ciblage par l'IRMf est pertinent, homogène et reproductible, puisque la

zone à stimuler chez tous les patients se retrouve dans le sillon central correspondant à l'aire corticale de la main (repérée lors de sa tâche motrice en IRMf).

Nos résultats préliminaires ne montrent pas de différence de connectivité fonctionnelle ou de perfusion cérébrale qu'elles soient homolatérales ou controlatérales à la douleur. Aussi, nous n'avons pas trouvé d'effet de la douleur neuropathique sur les cartes d'activation cérébrale en réponse à une tâche motrice de la main du côté douloureux comparé au côté non-douloureux. L'étude est limitée par le faible nombre de patients inclus (12 patients) par rapport au projet Neurostim global (45 patients). A noter que l'inclusion des patients a été très significativement ralentie et perturbée par la crise sanitaire du Covid 19.

Malgré cela, les résultats préliminaires de cette étude pionnière témoignent de l'apport potentiel de la neuro-imagerie et des données fournies par l'IRMf dans la pratique de la rTMS. A la fin de l'étude, les données cliniques seront confrontées aux données complètes de neuroimagerie en pré-cure et post-cure, ce qui permettra de rechercher des biomarqueurs cliniques et de neuroimagerie corrélée à la réponse antalgique ou la non réponse à la rTMS à visée antalgique.

## 8. CONCLUSION

Ce travail de recherche nous a permis de démontrer que les techniques de neuromodulation non-invasive agissent sur la douleur par différents mécanismes et de ce fait, la rTMS, la tDCS et la tsDCS, peuvent avoir des indications sélectives dans le traitement de différents syndromes douloureux chroniques.

Nous avons démontré également la possibilité de maintenir l'efficacité antalgique à long terme des techniques de neuromodulation non-invasive, que ce soit par les études rétrospectives observationnelles ou comparatives randomisées et contrôlées versus placebo.

Concernant la rTMS, en se référant à nos cohortes précédentes, nous avons pu déterminer le nombre nécessaire des séances lors de la « phase d'induction » afin de pouvoir sélectionner les patients « répondeurs » et aussi la fréquence des séances lors de « la phase de maintien ».

Dans notre étude comparant l'effet antalgique de la tDCS et de la rTMS, nous avons observé que presque la moitié des patients n'ont répondu qu'à une seule technique. Cette découverte est importante dans la pratique clinique : elle ouvre la perspective de l'utilisation de la tDCS en cas d'échec de la rTMS, afin d'améliorer le taux de patients répondeurs.

La lourdeur et le coût non négligeable de l'équipement rTMS et particulièrement de la neuronavigation, limite l'utilisation courante de la rTMS en pratique clinique. Dans ce cadre, nos études comparant l'effet antalgique des techniques de neuromodulation non-invasive, contribuent au développement futur de la tDCS et de la tsDCS, tenant compte de leur faible coût et leur simplicité d'utilisation, ainsi que de la perspective de leur utilisation à domicile.

Nos travaux sur la définition avec précision des cibles à stimuler dans le cadre de la rTMS guidées par un système de neuronavigation, au moyen de l'IRM anatomique ou de l'IRM fonctionnelle du patient, pourraient conduire à un meilleur taux de réponse clinique.

Nos travaux sur la stimulation des aires corticales motrices bilatérales et l'utilisation d'une bobine de stimulation plus profonde (B70) démontrent leur apport clinique dans les névralgies pudendales et les douleurs neuropathiques des membres inférieurs.

Notre recherche a démontré également l'implication du système nerveux sympathique dans le SDRC : la réduction de la conductance cutanée du membre atteint avant le traitement par des techniques de neuromodulation non-invasive semble être prédictive d'un bon soulagement de la douleur. De plus son amélioration était associée à une réduction de l'intensité de la douleur après traitement.

La neuroimagerie fonctionnelle (IRMf) a montré que le couplage fonctionnel douleur-système nerveux autonome chez les patients SDRC est également associé à l'implication d'une région corticale spécifique dans la région S1.

Enfin, notre recherche a démontré l'efficacité prophylactique de la tDCS dans le traitement des migraines chroniques résistantes. Son utilisation pourrait être une alternative thérapeutique intéressante dans la prise en charge des migraines chroniques empêchant leur évolution vers une forme réfractaire.

D'autre part, nous poursuivons notre travail avec l'étude de recherche en cours « Neurostim » qui a pour but d'explorer l'effet antalgique de la rTMS en stimulant le cortex moteur au moyen de 3 bobines différentes (superficielle B65, plus profonde B70 et placebo) et les modifications cérébrales induites par la rTMS à long terme, au moyen de l'IRMf. Cette étude fournira probablement d'autres éléments utiles concernant la compréhension des mécanismes d'action de la rTMS et les facteurs prédictifs de la réponse antalgique.

Comme déjà évoqué, les protocoles de neuromodulation sont souvent hétérogènes en termes de paramètres de stimulation et d'étiologie des douleurs, de petite taille des échantillons et de courte durée d'application, rendant ainsi difficile leur diffusion sur une grande échelle en pratique clinique. Des essais multicentriques contrôlés utilisant les mêmes paramètres de stimulation seront nécessaires pour obtenir des résultats fiables et solides et augmenter le niveau de preuve d'efficacité. D'autre part, la recherche des facteurs prédictifs pouvant influencer la réponse clinique et son maintien à long terme, s'avère indispensable pour mettre en place des stratégies thérapeutiques multimodales et personnalisées selon le profil des patients.

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