Neural Correlates of Pain-Autonomic Coupling in Patients With Complex Regional Pain Syndrome Treated by Repetitive Transcranial Magnetic Stimulation of the Motor Cortex

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ABSTRACT

Objectives: Complex regional pain syndrome (CRPS) is a chronic pain condition involving autonomic dysregulation. In this study, we report the results of an ancillary study to a larger clinical trial investigating the treatment of CRPS by neuromodulation. This ancillary study, based on functional magnetic resonance imaging (fMRI), evaluated the neural correlates of pain in patients with CRPS in relation to the sympathetic nervous system and for its potential relief after repetitive transcranial magnetic stimulation of the motor cortex.

Materials and Methods: Eleven patients with CRPS at one limb (six women, five men, aged 52.0 ± 9.6 years) were assessed before and one month after the end of a five-month repetitive transcranial magnetic stimulation (rTMS) therapy targeting the motor cortex contralateral to the painful limb, by means of electrochemical skin conductance (ESC) measurement, daily pain intensity scores on a visual numerical scale (VNS), and fMRI with motor tasks (alternation of finger movements and rest). The fMRI scans were analyzed voxelwise using ESC and VNS pain score as regressors to derive their neural correlates. The criterion of response to rTMS therapy was defined as ≥30% reduction in VNS pain score one month after treatment compared with baseline.

Results: At baseline, ESC values were reduced in the affected limb vs the nonaffected limb. There was a covariance of VNS with brain activation in a small region of the primary somatosensory cortex (S1) contralateral to the painful side on fMRI investigation. After rTMS therapy on motor cortex related to the painful limb, the VNS pain scores significantly decreased by 22% on average. The criterion of response was met in six of 11 patients (55%). In these responders, at one month after treatment, ESC value increased and returned to normal in the CRPS-affected limb, and overall, the increase in ESC correlated with the decrease in VNS after motor cortex rTMS therapy. At one month after treatment, there also was a covariance of both variables (ESC and VNS) with fMRI activation of the S1 region previously mentioned. The fMRI activation of other brain regions (middle frontal gyrus and temporo-parietal junction) showed correlation with ESC values before and after treatment. Finally, we found a positive correlation at one month after treatment (not at baseline) between VNS pain score and fMRI activation in the temporo-parietal junction contralateral to painful side.

Conclusions: This study first shows a functional pain-autonomic coupling in patients with CRPS, which could involve a specific S1 region. However, the modulation of sympathetic sudomotor activities expressed by ESC changes was rather correlated with functional changes in other brain regions. Finally, the pain relief observed at one month after rTMS treatment was associated with a reduced activation of the temporo-parietal junction on the side in which rTMS was performed. These findings open perspectives to define new targets or biomarkers for using rTMS to treat CRPS-associated pain.

Clinical Trial Registration: The Clinicaltrials.gov registration number for the study is NCT02817880.

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INTRODUCTION

Complex regional pain syndrome (CRPS) is a chronic pain disorder that has the particularity of presenting prominent autonomic symptoms in the painful territory such as vasomotor disturbances (color, temperature, or trophic skin changes), edema (swelling), or sudomotor disturbances (abnormally increased or absent sweating).\(^1,2\) Sudomotor dysfunction can be assessed by various techniques, such as the quantitative sudomotor axon reflex test (QSART)\(^3\) or the measurement of electrochemical skin conductance (ESC) by Sudoscan\(^4\) (Impeto Medical, Paris, France).\(^4\) In the chronic stage, most patients with CRPS showed an increased sudomotor activity in the affected limb.\(^1\) 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 electrophysiological responses as a biomarker of sympathetic arousal during mental tasks. The amplitude or number of transient skin conductance responses was found to be associated with activity changes in a variety of brain regions, such as the dorsomedial prefrontal cortex and left hippocampus,\(^5\) the cerebellum, right inferior frontal cortex, and supplementary motor area (SMA),\(^6\) or the striate and extrastriate cortices, anterior cingulate, and insular cortices, thalamus, hypothalamus, ventromedial prefrontal cortex, and lateral regions of prefrontal cortex.\(^7\) To give a global overview of the brain correlates of the control of skin conductance, a no-task study (resting state) with spontaneous recording of skin conductance has been performed in the context of the Human Connectome Project in healthy adolescents.\(^8\) This study was not a functional connectivity study but a “classical” fMRI study, with skin conductance changes serving as a regressor in a standard fMRI analysis. The authors found neural correlates of skin conductance changes in many brain regions, namely, primary cortical areas (sensorimotor, auditory, and visual cortices), in addition to associative areas (parietal, cingulate, insular operculum, and temporoparieto-occipital junction areas), corresponding to a variety of brain functions. However, these data relate to normal subjects, and no studies have focused on CRPS, although autonomic nervous system dysfunction plays a prominent role in the pathophysiology of this syndrome.

Therefore, we designed a study to explore brain-autonomic coupling with pain as a covariate in CRPS, which, to our knowledge, has not yet been performed. This is an ancillary study to a larger clinical trial, which aimed to assess the value of treating CRPS with a long-term (five months) protocol of repetitive transcranial magnetic stimulation (rTMS). The use of high-frequency rTMS (HF-rTMS) applied to the primary motor cortex (precentral gyrus) previously showed a good level of evidence of efficacy in treating different chronic pain syndromes,\(^9\) including CRPS.\(^10,11\) The first objective of this ancillary study was to determine whether sudomotor dysfunctions, assessed by ESC measures, could be associated with pain and activity changes in brain networks, as assessed by fMRI, in 11 patients with CRPS affecting an upper or a lower limb. In addition, there are very few data on changes in cerebral activity assessed by fMRI associated with the analgesic effects of motor cortex rTMS,\(^12\) and none in the context of CRPS, to our knowledge. The secondary objective of this study was therefore to determine the changes in the relationships between cerebral activation, pain, and sympathetic sudomotor function assessed before and one month after the completion of the five-month motor cortex HF-rTMS therapy. In particular, given targeting the motor cortex using neuromodulation can relieve pain, our hypothesis was based on the involvement of the sensorimotor brain network in the therapeutic modulation of pain associated with CRPS.

MATERIALS AND METHODS

Ethics

This study was part of a larger trial\(^13\) investigating the analgesic effect of various techniques of noninvasive brain or spinal stimulation in patients with CRPS, registered in clinicaltrials.gov (NCT02817880), and ethical acceptance was provided by the institutional review board of Sud-Est V, Grenoble, France (number 6705).

Only patients of the rTMS treatment group who underwent fMRI were enrolled in this ancillary study and gave written informed consent to participate.

Patients

Eleven patients were included in this study. All met the Budapest criteria for the diagnosis of CRPS, which was further supported by bone scintigraphy findings.\(^14\) In addition, the inclusion criteria met by the patients were age between 18 and 80 years; unilateral CRPS type I affecting either one upper limb or one lower limb; disease duration for more than one year; pain intensity >3/10 at screening; no change in drug treatments during the last month; and lack of response to conventional treatments. The exclusion criteria were pregnancy, presence of a neurologic lesion, intracranial ferromagnetic material or implanted device, history of drug addiction, epilepsy, severe traumatic brain injury, or neuropsychiatric comorbidities.

Study Design

The HF-rTMS therapy included an “induction phase” of one stimulation session per day for five consecutive days for two weeks, then two sessions in the next week for a total of 12 sessions, and a “maintenance phase” comprising one session in the fourth week, followed by bimonthly 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, pretreatment baseline) and one month after the end of the HF-rTMS protocol (day 180, after treatment). The schematic overview of the study design is presented in Figure 1.
Pain management was based on patients recording their daily pain intensity in a paper diary, completed at home every day for one 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). The VNS pain scores used in this study were the average of all daily VNS ratings for the week before each assessment. After completion of the protocol, these evaluations were copied to a digital spreadsheet for statistical analysis.

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

**Electrochemical Skin Conductance Measures**

Palmar and plantar ESC values were measured (in microSiemens, μS) with the Sudoscan® device before the first rTMS session and one month after the last rTMS session, on the same day as the fMRI examinations. 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 (<4V) 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). This reflects the production of chloride ions by sweat glands innervated by sympathetic C nerve fibers. The ESC values were obtained simultaneously from all four extremities during the same 2-minute examination, but we only used hand ESC values for patients with upper limb CRPS and foot ESC values for patients with lower limb CRPS, distinguishing between ESC values measured in the affected limb and the non-affected limb.

**rTMS Procedure**

Stimulation was performed using a MagPro stimulator (MagVenture (distr. Mag2Health), Farum, Denmark) and either a flat figure-of-eight B65 coil (MagVenture) in patients with upper limb pain or an angled figure-of-eight B70 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 10 Hz (HF-rTMS), with an intensity set at 80% of the resting motor threshold (measured only once on motor evoked potential recording at the beginning of the first rTMS session) and the coil held in postero-anterior orientation. Each rTMS session consisted of 40 trains of 5-second duration with intertrain interval of 25 seconds for a total of 2000 pulses in 20 minutes.

**fMRI Procedure and Preprocessing**

A 3T Philips Achieva-TX scanner was used at the IRMAGE platform of Grenoble with a 32-channel head coil. Each patient underwent two magnetic resonance imaging (MRI) examinations, one at day 1 and the other, one month after treatment. Each MRI session comprised a first morphologic three-dimensional T1-weighted sequence (which was used for neuronavigation-based rTMS targeting) and a set of two transverse relaxation in inhomogeneous magnetic field (T2*)-weighted blood oxygenation level dependent (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 and 2) a self-paced flexion-extension movement of the fifth finger of the left hand. Before fMRI examination, the task was presented to each patient, and the instruction was given not to try to inhibit the accompanying movement of the fourth finger. The resting condition was to allow the hand to relax completely. Given that pain was unilateral, each patient therefore performed a motor hand task from the side ipsilateral to the pain side and a motor hand task contralateral to the pain.

Each fMRI run was presented following a block design with three 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: repetition time 3000 ms, echo time 35 ms, flip angle 90°, 36 mm–thick slices within plane isotropic 3-mm spatial resolution, and 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 (http://www.fil.ion.ucl.ac.uk/spm/) software (The Wellcome Department of Cognitive Neurology, London, UK) in two steps. In the first step, individual analysis is performed in the individual’s referential, and in the second step, group analysis is performed in a common referential. In the first step, preprocessing is performed. This includes rigid-body motion parameters evaluation and inverse motion application to the fMRI images, mean fMRI image calculation, correction
for time delay between slices in each fMRI volume, registration of the mean fMRI image onto the anatomical image acquired at baseline, application of the registration to all fMRI images, and a spatial smoothing with a Gaussian isotropic filter of 3 mm (full width at half maximum). Eventually, because all the fMRI images are in the individual’s referential, individual statistical analysis was performed using a linear generalized model assessing the contrast images of cortical activation resulting from ipsilateral and contralateral motor tasks at baseline and one month after treatment. The second step was conducted for the purpose of group analysis. Each anatomical image of the pretreatment session was segmented to extract the gray-matter image and to compute the deformation field to be applied to each individual, using Diffeomorphic Anatomical Registration Using Exponentiated Lie Algebra (DARTEL) software, to match a symmetrical template, provided by the Computational Anatomy Toolbox12 software (neuro.uni-jena.de/cat12-html/cat_versions.html). The deformation fields computed for each patient were further applied to all individual contrast images.

To get rid of the pain laterality of the patients, those presenting a left-sided pain had their MRI scans left-right flipped across the midline. This flipping operation keeps the accuracy of the anatomical location owing to the symmetrical template that was used. In 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.

Statistical Analysis
Statistical comparisons of VNS and ESC data between baseline and one month after the rTMS treatment were performed using Wilcoxon’s signed rank test for paired values. Correlation between VNS and ESC in the affected limb were performed using Spearman’s correlation test, both at baseline and after treatment. In all cases, the level of statistical p value significance was set at 0.05, and calculations were performed with R software.

The inference of neuroimaging data was conducted at the group level. First, the main sensorimotor network was investigated for the influence of chronic pain and rTMS therapy as follows: The contrasts corresponding to the ipsilateral task and flipped contralateral task at baseline 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 ipsilateral and flipped contralateral tasks using a paired t-test. The effect of rTMS treatment on the sensorimotor network was tested on contrast images corresponding to the ipsilateral task between baseline and one month after treatment using a paired t-test. Statistical significance was considered when $p < 0.001$ at voxel level and extent $>25$ voxels.

Second, to seek neural correlates of skin conductance and pain, a multiple regression model was applied to the contrast images corresponding to the ipsilateral task, using the ESC of the hand ipsilateral to the painful limb and the VNS at time of MRI as covariates. This was performed both specifically within the mask of the sensorimotor network and without mask to explore regions located out of the sensorimotor network. Because the covariates are orthogonalized before the multiple regression in the SPM software, the estimated neural correlates of each covariate are further independent. The patterns corresponding to each of these covariates, in addition to 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 the 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 posttreatment time, the multiple regression analysis was conducted separately between mean activation, ESC, and VNS.

RESULTS

Demographics and Clinical Characteristics
The sample of 11 patients (Table 1) comprised six women and five men, with a median age of 56 years (interquartile range (IQR): 48.5–59 years). The median (IQR) duration of pain history was 24 months (13–29 months). The origin of CRPS was related to limb trauma in six cases and surgical lesion in five cases. Pain was located at one upper limb in six cases and one lower limb in five cases, located on the right side in seven cases and on the left side in four cases. Ten patients received analgesic drugs at the time of the study, with two types of medication on average, including nonopioid analgesics (two patients), weak opioid analgesics (seven patients), antiepileptics (seven patients), and/or antidepressants (seven patients).

Baseline Assessment
At baseline (Table 1), the median (IQR) VNS pain score was 5.1 (4–6.5). The ESC value was significantly reduced in the CRPS-affected limb compared with the contralateral nonaffected limb (median (IQR) in μS (range): 77 (36–92) vs 80 (38–92), $p = 0.029$, Wilcoxon test).

A tendency toward a correlation between lower ESC values in the CRPS-affected limb and higher VNS pain scores was found at baseline ($r = -0.572$, $p = 0.066$, Spearman test) (Fig. 2, left). However, this finding may have been driven by the result of a patient who had both the lowest ESC values and the highest VNS pain score.

Regarding fMRI, the brain activation in response to the ipsilateral 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 SMA bilaterally, forming a large sensorimotor network. The comparison between the fMRI response to the ipsilateral task and the contralateral task (after symmetrization regarding the interhemispherial 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 (Fig. 3).

Post-rTMS assessment
All patients completed the five-month motor cortex rTMS protocol without any adverse event. Individual values of VNS pain scores and ESC values are reported in Table 1. At one month after the end of rTMS therapy, the median (IQR) VNS pain score was 3.4 (2.3–5.85), showing a significant reduction (median [IQR]: $-1.7$ [-2.25 to −0.05]) compared with baseline ($p = 0.012$, Wilcoxon 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 ≥4). According to a response criterion defined as a ≥30% reduction in VNS pain score at one month after treatment compared with baseline, we found that six patients were responders to rTMS therapy, and five patients were not responders. It is noted that the responder and nonresponder subgroups corresponded to those who had a CGI-I score of 1 or 2 for responders and a score ≥3 for nonresponders, respectively.

At one month after treatment, in the whole group, the ESC values in the CRPS-affected limb were not significantly changed compared with baseline (median [IQR] in μS: 78 [74–84] vs 77 [69–84], p = 0.312, Wilcoxon test), whereas there was a significant increase in the responder subgroup (median [IQR] in μS: 80 [75–83.5] vs 69 [68–78.25], p = 0.029). Thus, at one month after treatment, the ESC of painful limb was restored to a value not different from the nonpainful limb (median [IQR] in μS: 80 [75–83.5] vs 76 [72.5–82.5], p = 0.588) in responders (Fig. 4).

At one month after treatment, the VNS pain scores did not correlate with ESC values in the CRPS-affected limb (r = 0.069, p = 0.841, Spearman test) (Fig. 2, right). However, we calculated the change in VNS pain score and ESC value in the CRPS-affected limb between baseline and one month after treatment and found that the decrease in VNS correlated with the increase in ESC after motor cortex rTMS therapy (r = 0.698, p = 0.017, Spearman test) (Fig. 2, middle). The six dots on the left side of this plot correspond to responders who experienced both reduced VNS and increased ESC after rTMS treatment. The five dots on the right side correspond to nonresponders.

The cerebral activation observed in a sensorimotor network (S1, M1, SMA, cerebellum) in response to the ipsilateral task was not significantly changed after one month after rTMS treatment compared with baseline (data not shown). In addition, after treatment as at baseline, no significant difference was observed in brain activation patterns, whether the ipsilateral or contralateral task was applied. The influence of the location of CRPS at upper or lower limb was tested for significance at both time points, and no significant differences were found according to CRPS location.

Neural Covariates of ESC and VNS

At baseline, within the sensorimotor network activated by motor hand tasks in fMRI, a positive correlation was found with the VNS pain scores in an S1 region located in the posterior bank of the central sulcus at the level of the hand knob, contralateral to the painful side (peak at Montreal Neurological Institute (MNI) coordinates x = −38, y = −26, z = 58, t = 3.71, k = 83) (r = 0.62, p = 0.047, Spearman test). In the same S1 region (peak at MNI coordinates x = −39, y = −27, z = 56, t = 3.09, k = 27), fMRI activation tended to show a negative correlation with the ESC values in the CRPS-affected limb (r = −0.56, p = 0.080).

At one month after rTMS treatment, these opposed correlations of S1 activation were both significant, positively with VNS pain scores (r = 0.66, p = 0.029) and negatively with ESC values in the CRPS-affected limb (r = −0.64, p = 0.037). Thus, a small spot in S1 region (Fig. 5) showed an inverse coupling, with the levels of ongoing pain intensity and the sympathetic activity in the CRPS-affected limb significantly 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,
whereas these last two parameters significantly correlated with each other.

Outside the above described sensorimotor network, we found positive correlations, at baseline and/or after treatment, between ESC values in the CRPS-affected limb and fMRI activation by the ipsilateral task in the middle frontal gyrus (mFG) ipsilateral to pain side (peak at MNI coordinates x=28, y=30, z=38, t=5.14, k=15) (both at day 1 [D1]: r = 0.612, p = 0.045; and day 180 [D180]: r = 0.724, p = 0.012, Spearman test), and the temporo-parietal junction (TPJ) contralateral to pain side (peak at MNI coordinates x=−46, y=−69, z=22, t=3.86, k=10) (both at D1: r = 0.712, p = 0.014; and D180: r = 0.603, p = 0.049) (Figs. 6 and 7). An additional brain region, the precuneus (PCu) ipsilateral to pain side (peak at MNI coordinates x=6, y=−63, z=34, t=4.28, k=54), also may have shown correlation (not at D1: r = 0.469, p = 0.146, but at D180: r = 0.729, p = 0.011), although this finding may have been driven by the result of a single patient with low ESC value at baseline and with high ESC value after rTMS treatment. Finally, we found a positive correlation, at D180 but not at D1, between VNS pain score and fMRI activation by the ipsilateral task in the TPJ contralateral to pain side only (peak at MNI coordinates x=42, y=−62, z=21, t=4.95, k=33) (D1: r = 0.457, p = 0.158 (not significant); D180: r = 0.88, p < 10^-3, Spearman 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 (Fig. 8), in the same hemisphere in which rTMS was applied.

**DISCUSSION**

In this study, including 11 patients with chronic unilateral limb pain associated with CRPS type I, 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 HF-rTMS sessions delivered over M1 for a period of five months.

**Autonomic-Brain Coupling**

At baseline, sudomotor function in the CRPS-affected limb extremity was significantly altered, as revealed by a reduction in ESC values compared with the contralateral nonaffected limb. This result agrees with the well-known sudomotor dysfunction and asymmetry present in patients with CRPS. However, it should be noted that no significant alteration in ESC was observed in a group of 19 patients with CRPS previously reported in the only
study, to our knowledge, that evaluated ESC in this clinical setting.\(^\text{17}\) Similarly, QSART, another method used to evaluate sudomotor dysfunction, showed a low rate of abnormalities in CRPS.\(^\text{18}\)

Also at baseline, regarding the neural correlates of ESC values in the CRPS-affected limb, there was a trend toward a correlation with an S1 region located at the level of the hand knob, contralateral to the painful side. In contrast, the main correlations were found outside the sensorimotor network, namely, with the mFG ipsilateral to painful side and the TPJ contralateral to painful side. One month after rTMS, the correlation of ESC values in the CRPS-affected limb with the S1 region was significant, as were again the correlations with fMRI activation of mFG and TPJ.

As reported in the introduction, several studies assessed the correlates of brain activation with changes in skin conductance in healthy subjects.\(^\text{5–8}\) Overall, the core of the central autonomic

![Figure 4](image_url). ESC in the CRPS-affected limb (left) and nonaffected limb (right) before (D1) and one month after rTMS therapy (D180) in the Resp and No Resp subgroups (median, first and third quartiles displayed). Statistical analyses showed an increase in ESC (*p = 0.029, Wilcoxon test) only in the CRPS-affected limb of the Resp subgroup. D1, day 1; D180, day 180; Resp, responder; No Resp, nonresponder.

![Figure 5](image_url). Location in the S1 of a small region (in yellow) both correlated with ESC values (negatively, at least one month after rTMS treatment) and VNS pain scores (positively, both before and one month after rTMS treatment). Activation pattern presented on the average gray-matter image from our group of patients. Color bars represent statistical t-values. [Color figure can be viewed at www.neuromodulationjournal.org]
network included the amygdala, anterior and posterior insula, and midcingulate cortex in a meta-analysis\textsuperscript{19}. Although the correlations we found were very exploratory, given the small sample size and the various methodologic limitations mentioned at the end of the discussion, they suggest that sympathetic sudomotor activities may be associated with the functioning of other brain structures, such as the sensorimotor network presenting a positive correlation with ESC measures at baseline and/or one month after rTMS treatment: in the PCu ipsilateral to pain side in red, in the mFG ipsilateral to pain side in yellow, and in the TPJ contralateral to pain side in cyan. MNI coordinates are presented in the text. [Color figure can be viewed at www.neuromodulationjournal.org]

**Figure 6.** Regions outside the sensorimotor network presenting a positive correlation with ESC measures at baseline and/or one month after rTMS treatment: in the PCu ipsilateral to pain side in red, in the mFG ipsilateral to pain side in yellow, and in the TPJ contralateral to pain side in cyan. MNI coordinates are presented in the text. [Color figure can be viewed at www.neuromodulationjournal.org]

**Figure 7.** Neural activity in the PCu ipsilateral to pain side (left column), the mFG ipsilateral to pain side (middle column), and the TPJ contralateral to pain side (right column) as a function of ESC in the hand of affected side. Upper row: before rTMS treatment (D1). Lower row: one month after rTMS treatment (D180). All correlations except for PCu at baseline are significant. D1, day 1; D180, day 180; n.s., non significant.
as mFG or TPJ, included in large-scale brain networks that may be part of the default mode network.

**Brain Imaging Correlates of Autonomic-Pain Coupling in CRPS Potentially Involving S1**

However, in our study, the goal was to link autonomic (sympathetic) function and brain activation but with pain as a covariate. Activation in the previously described S1 region covaried positively with the VNS pain scores and negatively with the ESC values in the CRPS-affected limb, especially after rTMS treatment.

Functional neuroimaging of autonomic-pain coupling has been rarely investigated, and only in the context of experimentally induced muscle or skin pain in healthy subjects. First, Mobascher et al. 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–secondary sensory cortex (S2)). In a second study, Dubé et al. 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 pain intensity scored on VNS and sympathetic response to noxious stimulation. It also is important to point out that this S1 region (the transition zone between M1 and S1) was involved in pain-induced changes in the sympathetic components of heart-rate variability. Finally, a repeated noxious heat stimulation was found to specifically activate the Brodmann Area (BA) 3a part of S1, which is a "transitional zone" located between M1 and S1 in the depth of the central sulcus and likely engaged in the sympathetic response to noxious stimulation.

The involvement of S1 is consistent with studies on the BA3a subpart, 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 patients with CRPS.

Importantly, this provides further evidence for a critical role of S1 in the coding of pain intensity, as highlighted by some authors, whereas others favor the role of the operculo-insular region, that is, the posterior insula and S2. The involvement of S1 in coding pain and particularly that of BA3a located deeper in the central sulcus could be especially relevant in functions associating interoceptive sensory system and the autonomic nervous system, such as the autonomic aspects of nociception, as suggested by Favorov et al. and supported by experimental animal data. It also is 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 through cortico-cortical connections contributing to the control of fine motor skills.

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 was significantly
increased, and sensory cortex representation maps were frankly modified in response to tactile stimulation of the CRPS-affected limb compared with the nonaffected limb in cross-sectional studies conducted with magnetoencephalography, electroencephalography, or fMRI. Overall, S1 activation changes in patients with CRPS were associated with pain intensity, a reduced tactile acuity, increased oscillations in the delta-theta band, and an alteration of a related 20-Hz motor cortex rhythm, whereas the S1–M1 connections were preserved and functionally normal. Abnormal sensory integration of innocuous stimuli or interaction between innocuous and noxious stimuli in S1 also was shown in the context of CRPS. In addition, an effective neuro-modulation therapy (using invasive spinal cord stimulation) was able to restore normal somatosensory representation maps within S1 in a patient with CRPS. However, two studies showed no change in the fMRI maps or the y-amino butyric acid or glutamate concentrations in magnetic resonance spectroscopy concerning the S1 representation of the hand affected by CRPS, compared with both the unaffected hand and healthy controls.

**Analgesic effect and autonomic changes after motor cortex rTMS in CRPS**

One month after the end of a five-month therapy of HF-rTMS of the motor cortex, the VNS score of daily pain was significantly reduced by 22% on average, and six of 11 patients were clinically responders with ≥30% reduction in VNS pain score. These results are consistent with the current rTMS literature.

In addition, after motor cortex rTMS, an improvement in the ESC values in the CRPS-affected limb compared with baseline was observed but only significant in the group of responders (10% increase on average) and not in the whole group of patients. Actually, this result may be related to a ceiling effect in nonresponders due to their baseline ESC values being normal or near-normal. The fact remains that low values of ESC were observed in responders, that these values overall increased significantly after treatment, and that there was a correlation between the increase in ESC values and the reduction in VNS pain scores (Fig. 2, middle panel). Even if we must remain cautious given the small number of patients, the possibility of a ceiling effect, and the influence of a few individual values, this result justifies serving as a working foundation for future studies based on larger samples. Indeed, to our knowledge, it is the first time that an analgesic effect associated with rTMS treatment is correlated with autonomic changes. However, because there was no control treatment condition, we cannot be sure that rTMS caused the pain relief observed.

**Brain imaging correlates of pain relief**

It has been shown that motor cortex rTMS may produce pain relief through the modulation of various brain circuits involved in the sensory, cognitive, or affective components of pain. An alternative hypothesis could be the neuromodulation of the S1 region found in this fMRI study that lies in the vicinity of targeted M1. However, given pain coupling with S1 activation as measured with fMRI, this S1 region cannot be considered the functional core of the therapeutic changes induced but rather as a “hub” both for pain and autonomic functions.

In fact, regarding pain intensity (VNS score), a correlation was found outside the sensorimotor network with the fMRI 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 nonresponders: At one month after rTMS therapy, the responders reduced their brain activation in the TPJ during a motor task whereas nonresponders increased their brain activation in the TPJ during this same motor task. It is difficult to draw conclusions regarding the precise neuronal activities that correspond to these changes in fMRI activation, but this result suggests at least an involvement of this brain region in the association with rTMS analgesic efficacy. A previous study showed that decreased activation of the TPJ region by pressure pain (not by a motor task) also was associated with analgesic efficacy of treating patients who had chronic low back pain with self-compression psychologic training. These two results seem to indicate that a decrease in activation of the TPJ region could be an overall marker of the efficacy of certain analgesic treatments. In any case, this hypothesis deserves to be advanced and to be the subject of future studies. The TPJ is a large cortical region involved in a wide variety of brain functions related to attention, self–other distinction, theory of mind, or social belief, such as to orient attention to new stimuli from the external environment, to process spatial recognition of the world or social cues, to distinguish and predict between different possible perspectives on the same situation, to identify someone else’s belief, intention, or desire, to distinguish between the mental states of self and others, to create a comprehensive understanding of those mental states, or to make associations between memories, names of individuals or objects, and processing of both written and spoken language. 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.

**Limits of the study**

The main limitation of the study relates to the small number of patients included in this ancillary study. In fact, we took advantage of a larger clinical trial focusing on neuromodulation therapy in CRPS to conduct an ancillary study in patients with CRPS receiving rTMS, which could serve as a preliminary study for future work. All these patients present with unilateral pain, some patients having pain in the upper limb and others in the lower limb. Although motor cortex rTMS was targeted according to pain location, fMRI examination was based on a finger motor task regardless of CPRS location at the upper or limb, which may be another major limitation of this study. A last major limitation is the fact that this study included only patients treated by active rTMS (no control subjects), and therefore, our results could be due to a placebo-related pain relief, not reflecting a direct consequence of cortical stimulation. Thus, these findings need replication in a larger sham-controlled study.

**Conclusions**

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 group of patients with CRPS. 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, we believe ours is the first study showing direct correlation of sudomotor measures with pain intensity and improvement 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 suggest 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,54 this work supports the view that the central autonomic network should be considered.

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 using a dedicated rTMS coil able to stimulate deep in the central sulcus.55,56 Such a target also could 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 also has been observed.57

In contrast, this study highlights the involvement of other brain regions, such as the mFG and TPJ, in the correlation with sympathetic sudomotor activity. Finally, we were able to distinguish between responders and nonresponders 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.

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Authorship Statements

Chantal Delon-Martin was responsible for the conceptualization, methods, investigation, writing the original draft, review, and editing. Jean-Pascal Lefaucheur was responsible for writing the original draft, review, and editing. Enkeledja Hodaj, Anne Dumolard, and Mark Sorel were responsible for the investigation, writing, review, and editing. Jean-François Payen was responsible for the supervision, writing, review, and editing. Hasan Hodaj was responsible for the conceptualization, methods, investigation, writing the original draft, review, and editing. All authors have approved the final version of the manuscript.

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Delon-Martin et al show that pain ratings were significantly related to sudomotor dysfunction in 11 patients with CRPS type 1 of the upper or lower limb. After a five-month course of transcranial magnetic stimulation of the motor cortex contralateral to the affected limb, sudomotor dysfunction significantly improved in those patients who were classified as responders to this treatment (based on a >30% reduction in pain ratings). Using fMRI, they relate pain, sudomotor dysfunction, and their recovery to movement-evoked activity in several areas in the sensorimotor network, in addition to some areas outside this network.

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