# NORMAL SENSORIMOTOR PLASTICITY IN COMPLEX REGIONAL PAIN SYNDROME WITH FIXED POSTURE OF THE HAND

Francesca Morgante1, MD, PhD, Antonino Naro2, MD, PhD, Carmen Terranova1, MD, PhD, Margherita Russo2, MD, PhD, Vincenzo Rizzo1, MD, PhD, Giovanni Risitano3, MD, Paolo Girlanda1, MD, Angelo Quartarone4, MD, PhD

1 Dipartimento di Medicina Clinica e Sperimentale, Università di Messina

2 IRCCS Centro Neurolesi “Bonino-Pulejo”, Messina, Italy

3 Unità Funzionale di Ortopedia e Traumatologia, Casa di Cura “Cappellani-GIOMI”, Messina

4 Department of Biomedical, Dental Sciences, and Morphological and Functional Images, University of Messina, Italy,

**Running title:** Motor cortex plasticity in CRPS-I

**Keywords:** dystonia, psychogenic, functional movement disorders, CRPS type I, plasticity

**Word count:** 226 (abstract); 3696 (paper)

**Title count (included spaces)**: 95

**Number of references**: 53 ; **number of tables**: 3; **number of figures:** 2

**Supplementary materials online:** 2

**Financial disclosure related to research covered in this article**: the authors do not have any funding source or any conflict of interest related to the research covered in the article.

**Correspondence to:**

Dr. Francesca Morgante

Movement Disorders Unit, AOU G. Martino, University of Messina

Via Consolare Valeria 1, 98125 Messina, Italy

Telephone: +39 90 2212205, FAX: +39 90 2212789, E-mail: fmorgante@gmail.com

# ABSTRACT

**Objectives:** Movement disorders associated with complex regional pain syndrome type I have been a subject of controversy over the last ten years regarding their nature and pathophysiology, with an intense debate about the functional (psychogenic) nature of this disorder. Aim of this study was to test sensorimotor plasticity and cortical excitability in patients with complex regional pain syndrome type I who developed a fixed posture of the hand.

**Methods:** Ten patients with complex regional pain syndrome type I in the right upper limb and a fixed posture of the hand (disease duration less than 24 months) and 10 age-matched healthy subjects were enrolled. The following parameters of corticospinal excitability were recorded from the abductor pollicis brevis muscle of both hands by means of transcranial magnetic stimulation: resting and active motor thresholds, short-interval intracortical inhibition and facilitation, cortical silent period, short- and long-latency afferent inhibition. Sensorimotor plasticity was tested using the paired associative stimulation protocol.

**Results:** short-interval intracortical inhibition and long-latency afferent inhibition were reduced only in the affected right hand of patients compared to control subjects. Sensorimotor plasticity was comparable to normal subjects, with a preserved topographic specificity .

**Conclusions:** our data support the view that motor disorder in complex regional pain syndrome type I is not associated to abnormal sensorimotor plasticity and it shares pathophysiological abnormalities with functional (psychogenic) dystonia rather than with idiopathic dystonia.

# INTRODUCTION

Complex regional pain syndrome (CRPS) is a chronic progressive disease characterized by severe pain combined with sensory, autonomic and motor signs. CRPS type I (CRPS-I) occurs typically after a minor injury, it is characterized by absence of nerve lesions and its clinical features (i.e. pain, edema, changes in skin blood flow, limited range of motion) are disproportionate to the initial cause1.

Movement disorders, such as tremor, jerks, and fixed dystonic postures, occurs in about 15-20% of CRPS-I patients2,3 and their nature and pathophysiology are still controversial4. One line of research has speculated that the development of post-traumatic movement disorders might be triggered by an abnormal peripheral input that induces a reorganization of cortical and subcortical structures5,6. This is supported by functional neuroimaging studies showing a reorganization of the motor areas in CRPS-I along with alterations in the processing of sensory inputs7-9. On the other hand, there is growing evidence that abnormal movements in CRPS-I may have a functional (psychogenic) origin3,10. Indeed, functional (psychogenic) movement disorders and post-traumatic dystonia associated to CRPS-I share common clinical and historical features, such as minor trauma as precipitant, onset in leg, deliberate slowness of movements, tendency to spread to distant sites from the initial peripheral insult11. In addition, patients with the fixed dystonia syndrome, which often occurs after a minor peripheral trauma, usually overlap with CRPS-I and fulfill diagnostic criteria for functional (psychogenic) dystonia in 37% and somatizations disorder in 29%12.

The pathophysiology of CRPS-I is largely unknown and has been mostly focused on the peripheral and spinal mechanisms responsible for the origin and development of the syndrome. It has been also postulated that the peripheral (autonomic and somatosensory) changes in CRPS must be viewed as a manifestation of plastic changes of sensorimotor circuits within the brain13,14. Given these premises, we hypothesized that chronic pain and immobilization in CRPS-I may induce an alteration of sensorimotor integration and motor cortex excitability in the contralateral hemisphere to the dystonic fixed posture, without any abnormality of sensorimotor plasticity, which is a neurophysiological marker of idiopathic dystonia. Our hypothesis is that the clinical differences of the motor disorder between CPRS-I and idiopathic dystonia are sustained by a different pathophysiological mechanism. To this end, we employed Transcranial Magnetic Stimulation (TMS) to assess intra-cortical inhibition and facilitation, sensorimotor integration and sensorimotor plasticity in a group of patients affected by CRPS-I, who developed a fixed posture of the right hand.

# MATERIAL AND METHODS

***Subjects***

Ten subjects affected by CRPS-I (1 man, 9 women, mean age: 48.2±5.5 years, mean duration of disease 11.3±1.8 months) were enrolled for this study and matched with ten healthy subject (9 women, 1 man, mean age: 48.3±12.5 years). Patients satisfied the current IASP criteria for CRPS diagnosis1 and were right handed according to the Edinburgh Handedness Inventory. The inclusion criteria were: preceding noxious event without nerve lesion; presence of spontaneous pain or hyperalgesia not limited to a single nerve territory and disproportionate to the triggering event; and presence of a fixed posture limited the segment affected by CRPS-I. All the patients have developed CRPS-I in the right hand **(table 1)** and none of them had any sign or symptom in the contralateral limb at the time of the enrollment. Nerve conduction study and electromyography were carried out in all the patients to rule out even subclinical peripheral nerve lesions. None of the patients received drugs active on the central nervous system. All medication prescribed for pain were discontinued 24 hours before the experiment. The Local Ethics Committee approved the experimental procedure and written informed consent was obtained before the experiments.

***Study design and stimulation technique***

Patients underwent two distinct experimental sessions of TMS in different days, with a week of interval between each experimental session (supplementary materials 1). The order of the sessions was counterbalanced. The following parameters of corticospinal excitability were recorded from the abductor pollicis brevis (APB) muscle of both the hands: resting and active motor threshold (RMT and AMT), short-interval intracortical inhibition (SICI), intra-cortical facilitation (ICF), cortical silent period (CSP), and short- and long-latency afferent inhibition (SAI and LAI). In a separate experiment, we evaluated sensorimotor plasticity by means of the paired associative stimulation protocol (PAS)15, comparing the affected hand of CRPS-I patients (right side) and the right hand of the control subjects.

Focal TMS on the left primary motor hand area was performed with a High-Power Magstim200 stimulator wired to an eight-shaped coil with mean loop diameters of 9 cm (Magstim, Whitland, Dyfed, UK). Mixed electrical stimulation of the right median nerve was performed at the wrist using a Digitimer D160-stimulator. Further details on TMS and median nerve stimulation are given in supplementary materials 2.

***Measures of corticospinal excitability***

RMT was defined as the intensity of stimulation that elicits at least five MEPs of 50 µV in 10 consecutive trials, according to the recommendation of the International Federation of Clinical Neurophysiology (IFCN) Committee. AMT was defined as the lowest stimulus intensity at which at least five MEPs of 150 µV amplitude were elicited in 10 consecutive trials in the target muscle exerting a slight tonic activation16,17.

SICI and ICF were determined according to the method described by Kujirai18. The intensity of the conditioning stimulus was set at 80% of AMT. The intensity of the test stimulus was adjusted to elicit MEPs with a peak-to-peak amplitude of ~1 mV in the relaxed APB muscle. Stimulus intensities were kept constant across the blocks of measurement. SICI and ICF were assessed at ISIs (inter-stimulus intervals) of 2 and, respectively, 10 ms. The peak-to-peak amplitude of the unconditioned MEP was taken as a measure of corticospinal excitability. The relative change in MEP amplitude induced by the conditioning stimulus characterized the strength of SICI and ICF.

For CSP evaluation, ten trials were recorded during isometric contraction of the APB muscle (~15% of maximum voluntary contraction, kept constant with visual and auditory feedback through an oscilloscope and loudspeakers). TMS pulses had an intensity of 130% of RMT and a pre-stimulus EMG of 200 ms. CSP duration was measured by means of an automated method 19 from the MEP onsetto the initial return of EMG activity. CSP offset was determined from the processed waveform and was the first point to exceed 25% of the mean pre-stimulus EMG that consistently enclosed the EMG flat period after the end of the MEP.

SAI was tested using the conditioning-test protocol described by [Tokimura](http://www.ncbi.nlm.nih.gov/pubmed/10699092)[20](http://www.ncbi.nlm.nih.gov/pubmed/10699092) and the same procedure was used for LAI. Accordingly, an electrical conditioning stimulus was delivered to the median nerve at the wrist prior to TMS given to the contralateral M1. The intensity was set just above the threshold for evoking a visible twitch of the APB muscles. The intensity of the TMS was adjusted to evoke a muscle response in relaxed APB with a peak-to-peak amplitude of ~1 mV. SAI was probed at ISIs of 20 ms (SAI20ms) and 25 ms (SAI25ms) and LAI at an ISI of 200 ms. The mean amplitude of the conditioned MEP was expressed as percentage of the mean amplitude of the unconditioned MEP. The relative change in MEP amplitude induced by the peripheral stimulus was taken as a measure of SAI and LAI. For SICI, ICF, SAI and LAI, fifteen stimuli were delivered at each ISI and randomly intermingled with 15 trials in which MEP was elicited by the test stimulus alone (six conditions, 90 stimuli overall).

***Assessment of sensorimotor plasticity***

Motor cortex plasticity was assessed form the affected hand by means of the facilitatory paired associative protocol (PAS25ms)15,21, in which supra-threshold electrical  stimuli (3 times the perceptual threshold, pulse width = 500 µsec) on the right median nerve precede TMS pulses delivered to the left primary motor hand area at and ISI of 25 ms. Paired peripheral and cortical stimuli were delivered at 0.05 Hz for 30 minutes (90 stimuli overall). Peak-to-peak amplitude of MEP recorded from the right APB were assesses before (T0) and for 30 minutes after PAS25ms (after the end of PAS25ms: T1; 30 minutes after PAS25ms: T2). MEP were also recorded from FDI muscle to explore whether the conditioning effects of PAS were topographically specific15,22.

***Statistical analysis***

The peak-to-peak amplitude of conditioned and unconditioned MEP (mV) was measured off-line, and the mean MEP amplitude was calculated. For each dependent variable (SICI, ICF, SAI and LAI), a preliminary factorial ANOVA was employed to compare the right and the left hand in the control group using “side” (right, left) as independent variable. Conditional on demonstrating the absence of “side” differences, we calculated separate factorial ANOVA with the factor “group” (healthy controls right hand vs CRPS affected limb or healthy controls left hand vs CRPS unaffected limb) as independent variable.

In order to estimate the effects of protocol PAS25ms on MEP amplitude, we operated a repeated measure ANOVA with “group” (CRPS affected limb and controls) as *between-subject* factor and “time” (3 levels: T0, T1, T2) and muscle (APB and FDI) as *within-subject* factors. Conditional on a significant *F*-value, *post-hoc* paired-samples *t*-tests were performed to explore the strength of main effects and the patterns of interaction between experimental factors. Spearman's rank correlation was used to verify if any neurophysiological measure found to be significantly different between the two groups was correlated to disease duration or Numeric Pain Intensity Scale (NRS, 0-10). For post-hoc tests, in case of multiple comparisons, significance was set at *p*<0.025 by applying Bonferroni’s correction. For the other statistical tests, significance was set at *p*<0.05. Data are given as mean values ± standard error.

# RESULTS

The mean absolute values of the unconditioned RMT, AMT, MEP, SICI, ICF, CSP, SAI20ms, SAI25ms, and LAI in healthy controls (from both the hands) and CRPS-I patients (from affected and unaffected hand) are reported in table 2. Factorial ANOVA demonstrated comparable values of RMT (F1,18=0.35, p=0.56), AMT (F1,18=0.19, p=0.66) , SICI (F1,18= 2.39, p = 0.14), ICF (F1,18= 1.62, p = 0.22), CSP (F1,18= 0.45, p = 0.51), SAI20ms (F1,18= 0.35, p = 0.56), SAI25ms (F1,18= 1.03, p = 0.32), and LAI (F1,18= 3.22, p = 0.09) between the right and the left hand in healthy subjects.

SICI and LAI were significantly reduced and ICF was significantly increased in the affected hand of CRPS-I patients as compared to the right hand of control subjects (table 2, figure 2). No correlation was found respectively between disease duration or NRS and ratio of SICI (p=0.46; p=0.72), ICF (p=0.81; p=0.56), and LAI (p=0.95; p=0.52) in the affected hand. No differences were found concerning CSP duration (table 2), SAI20ms, and SAI25ms (table 2, figure 1)between the affected hand of CRPS-I patients and the right hand of healthy controls. Factorial ANOVA did not disclose significant differences in any parameter of cortical excitability and sensorimotor integration when comparing the left hand of healthy controls and the unaffected hand of CRPS-I patients (table 2, figure 1).

In the second experimental session, we tested the sensorimotor plasticity recording PAS after-effects from the affected hand of CRPS-I patients and from the right hand of healthy controls. PAS determined a long-lasting increase of MEP amplitude in both patients and controls, as confirmed by the main effect of the factor *time* (F2,36=12.10; p < 0.0001) and the absence of interaction between the factors *time* and *group* (F2,36=0.51; *p* = 0.60). Repeated measure ANOVA also showeda significant interaction between *time* and *muscle* (F2,36= 8.10; *p* = 0.0009) but not an interaction between the factors *time*, *muscle* and *group* (F2,36= 1.33; *p*=0.27)*,* since the facilitatory effects of PAS were topographically specific for the ABP muscle in both healthy subjects and CRPS-I patients. We computed separate repeated measures ANOVAs in each group (with *time* and *muscle* as within-subject factors) to further explore the topographic specificity of PAS after-effects. In healthy controls, PAS caused an increase in mean MEP amplitude at T1 and T2 in comparison with baseline values (T0), as disclosed by the main effect of *time* (F2,18= 11.29; *p* = 0.0003). The effects of PAS were somatotopically specific in healthy controls with an interaction between *time* and *muscle* (F2,18= 4.08; *p* = 0.02); that is, MEP amplitude increased at T1 and T2 as compared with baseline values only in the APB muscle (T0 vs T1: p = 0.03; T0 vs T2: p = 0.008). Likewise, PAS facilitation was specific for the APB muscle also in the affected hand of CRPS-I patients (main effect of *time*: F2,18= 4.13; *p* = 0.03; interaction between *time* and *muscle*: F2,18= 3.82; *p* = 0.03; T0 vs T1: p = 0.04; T0 vs T2: p = 0.03). Instead, MEP values in the FDI muscle did not differ at T1 and T2 from baseline in both healthy controls (T0 vs T1: p = 0.1; T0 vs T2: p = 0.1) and CRPS-I patients (T0 vs T1: p = 0.8; T0 vs T2: p = 0.5). Figure 2 shows the after-effects of PAS protocol in the APB (panel A) and the FDI muscle (panel B).

# DISCUSSION

Patients with CRPS-I with short disease duration and a fixed posture of the hand showed an impairment of the inhibitory intra-cortical circuits in the hemisphere contralateral to their affected hand, as demonstrated by a decreased SICI in the affected hand and a normal SICI in the unaffected hand. Sensorimotor integration, tested by means of LAI, was reduced in the affected side of CRPS-I patients. Finally, the effects of sensorimotor plasticity protocol were comparable between CRPS-I and healthy subjects, with a preserved topographic specificity of PAS after-effects.

**Electrophysiological abnormalities associated to CRPS-I: a comparison with functional and idiopathic dystonia**

Movement disorders associated with CRPS-I have been a subject of controversy over the last ten years regarding their nature and pathophysiology3,5,11,12,23, with an intense debate about the functional nature of this disorder. Ours and previous studies demonstrate a number of common electrophysiological findings in patients with CRPS-I and functional dystonia (table, supplementary material online 3). Specifically, sensorimotor plasticity is normal in both conditions, opposite to idiopathic dystonia; SAI and LAI, which measure sensorimotor integration, were variably reported normal or reduced in idiopathic dystonia and normal in functional dystonia, whereas in our study only LAI was reduced in CRPS-I. Finally CSP, a measure of corticospinal inhibition modulated by GABAB transmission, is normal in CPRS-I and reduced in idiopathic and functional dystonia.

The reduction in SICI in CRPS-I conforms to what is reported in literature24, although we did not observe a decrease of SICI in the hemisphere contralateral to the non-affected limb25. Our findings suggest that at an early stage of the disease the impairment of cortical excitability in CRPS-I occurs only within the representation of the affected limb. It is likely that the mono- or bilateral involvement of intra-cortical inhibitory circuits might be secondary to a different disease duration or methodological differences (including the use of a circular coil for TMS, which induces a less focal stimulation of motor cortex)25. Even though SICI alterations were clear, it should be recognized that SICI reduction does not represent a specific finding but is instead common to several conditions associated with involuntary muscular contraction, such as idiopathic dystonia26, functional or fixed dystonia27,28, Tourette’s syndrome29, and Parkinson’s disease30. Moreover, patients with fibromyalgia display a reduced SICI that correlates with the level of fatigue and depression. Besides, several psychiatric disorders, such as anxiety31, depression32, and obsessive compulsive disorder33 show the same abnormalities of SICI.

SAI20ms and SAI25ms in CRPS-I patients were not different from healthy subjects, in analogy with a previous study assessing SAI in eight CRPS-I patients without contractures34. The novel finding of our study is that LAI was significantly decreased in the affected hand of CRPS-I patients in comparison with their unaffected hand and the right hand in healthy subjects. Even if SAI reflects the direct connection between the sensory pathway and the motor cortex20, LAI is thought to involve second and third order somatosensory cortical areas, the posterior parietal cortex, and their projections to the motor cortex35. LAI reduction is in agreement with a previous magnetoencephalography (MEG) study on six CRPS-I patients, which showed that the rebound of the 20 Hz rhythm in the affected motor cortex following tactile stimulation was shorter and smaller in amplitude9. The 20 Hz rhythm is expression of motor cortex inhibition and normally displays a typical pattern of suppression and subsequent rebound occurring usually about 400–900 ms after electric median nerve stimuli9,36. Altogether, such results suggest that the late sensorimotor inhibition of the motor cortex may be altered in patients with chronic pain. It is interesting to note that Avanzino and co-workers reported no differences in LAI between normal subjects, idiopathic dystonia, and patients with chronic fixed dystonia28. This discrepancy of results between our work and the study by Avanzino and co-workers28 might be due to the heterogeneity of the sample concerning the onset of fixed dystonia and the affected limb (lower limbs).

Sensorimotor cortex plasticity, as tested by PAS, was normal in our patients with CRPS-I, similarly to patients with functional dystonia37. Abnormal sensorimotor plasticity is neurophysiological marker of idiopathic dystonia38-40, which extends beyond anatomical motor circuits affected by dystonia itself39. However, the abnormalities of sensorimotor plasticity in writing dystonia were recently challenged to be related to the pathophysiology of dystonia, since an huge variability of PAS after-effects has been reported in healthy subjects and patients with dystonic writer’s cramp41. Yet, abnormalities of PAS-related plasticity were consistently demonstrated in other forms of focal39,42 and generalized43 dystonia; interestingly, abnormalities of sensorimotor plasticity were found only in idiopathic dystonia, but nor in dystonia secondary to basal ganglia lesions44 or in functional dystonia37. The assumption that this form of plasticity might be related to the development of dystonic symptoms is further supported by a study demonstrating that the retention of clinical benefit when turning off deep brain stimulation in dystonia is correlated to the level of plasticity when the stimulator is turned on43.

***CRPS-I and fixed dystonic postures: a pathophysiological hypothesis***

Despite many studies on CRPS-I have focused on the peripheral and spinal mechanisms, a line of research postulates that the peripheral changes in CRPS-I must be viewed as a trigger for inducing plastic changes within cortical sensorimotor circuits45; chronic pain associated with CRPS-I could affect the transmission of impulses at the spinal cord level by sensitizing spinal dorsal horn neurons to input from primary afferent fibers, which in turn may lead to an abnormal cortical sensorimotor reorganization. This hypothesis is supported by studies on hand-amputated subjects which revealed extensive cortical reorganization correlating with the intensity of experienced pain46.

We believe that the cortical reorganization demonstrated in CRPS-I patients might be rather caused by the sustained fixed posture determining immobilization of the hand; this might account for the lateralize reduction of short-interval intracortical inhibition we found at an early stage of CRPS-I. Our hypothesis is supported by the following experiments in normal subjects: 1) immobilization of a limb produces reduced intracortical inhibition and cortical hyper-excitability in the hemisphere contralateral to casting47; 2) a short ischemic peripheral nerve block inducing a forearm deafferentation48 is associated to reduced intracortical inhibition in the contralateral hemisphere. On the other hand, chronic immobilization of a limb induces in humans a shrinkage of the motor map in the contralateral hemisphere49,50 and it is been associated to decreased intracortical inhibition in both hemispheres after long-term forelimb immobilization in adult rats. This may account for the bi-hemispheric alterations of inhibitory intracortical circuits in chronic fixed dystonia28 and CRPS-I25. The alteration of inhibitory intracortical circuits in CRPS-I might be also responsible for the increased activation of motor cortices in these patients, as demonstrated in the primary motor cortex and supplementary motor area by functional magnetic resonance imaging (fMRI) during simple finger tapping7.

A second new finding of our study is that sensorimotor plasticity tested with PAS is normal in CRPS-I patients, as in functional (psychogenic) dystonia, a condition that also shares with CRPS-I phenomenological feature and modality of disease progression12,51. How could we reconcile the finding of normal plasticity in CRPS-I with the evidence of increased metabolic activation within the motor cortices?7 The distinct patterns of PAS-induced sensorimotor plasticity in idiopathic dystonia and CRPS-I suggest that the abnormal sensorimotor substrate is different with an involvement of large fibers in idiopathic dystonia and of small fibers in CRPS-I. Indeed, PAS-induced plasticity is mediated by large afferent fibers15, which are involved in idiopathic dystonia pathophysiology52. Here, we speculate that the hyperactivity of brain areas in CRPS-I is probably related to an abnormal somatosensory integration within the small fibers system and the motor cortex. Despite this has not been specifically addressed in the present study, we could hypothesize an abnormal interaction between noxious stimuli and motor cortex that leads to alterations within sensorimotor maps13. This hypothesis is supported by two evidences in CRPS-I: 1) thermo-nociceptive pathways tested by laser evoked potentials are dysfunctional53; 2) chronic noxious stimulation of the upper limb results in overlapping or smeared cortical finger representations9. Future studies are needed to better explore the interplay between small fibers and the motor cortex and its possible role in the development of the motor disturbance in CRPS-I.

We recognizes that inter-subject variability of neurophysiological data, which is a common bias of experimental studies, and the small sample size represent important limitation of our study which might have produced false negative results in the sensorimotor plasticity protocol. Among the limitations of our study, we also acknowledge the lack of follow-up assessment which might have provided further clues on the reorganization of primary motor cortex with longer disease duration; moreover, concomitant functional neuroimaging would have greatly help understand the neural basis of the electrophysiological abnormalities here described. Nevertheless, the short duration of the disease and the clinical homogeneity of the patients enrolled, all having a fixed posture of the right hand, represent a strength of this study compared to previous ones.

In conclusion, our study demonstrates a reduction of SICI and LAI in the affected hand of patients with CRPS-I with a short disease duration and a fixed posture of the hand; moreover, we did not find any alteration of sensorimotor plasticity. This data support the view that motor disorder in CRPS-I is different from idiopathic dystonia at clinical and pathophysiological level; in addition, our work points out the need of prospective neurophysiological studies combing electrophysiology and functional neuroimaging in CPRS-I to better understand its neural basis.

# DOCUMENTATION OF AUTHOR ROLES

1.       Research project: A. Conception, B. Organization, C. Execution;

2.       Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

3.       Manuscript: A. Writing of the first draft, B. Review and Critique;

FM: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

AN: 1C, 2C, 3A, 3B

CT: 1C, 2C, 3B

MR: 1C, 2C, 3B

VR: 1, 2C, 3B

GR: 1B, 2C, 3B

PG: 1B, 2C, 3B

AQ: 1A, 2C, 2B, 3B

# FULL FINANCIAL DISCLOSURE FOR THE PREVIOUS 12 MONTHS

**FM**

|  |  |
| --- | --- |
| Stock ownership in medically related fields | none |
| Intellectual property rights | none |
| Consultancies | Medtronic and Chiesi |
| Expert testimony | none |
| Advisory boards | none |
| Employment | none |
| Partnerships | none |
| Contracts | none |
| Honoraria | UCB Pharma, Medtronic, Lundbeck, Chiesi, Abbvie, Allergan, Merz |
| Royalties | FM receives royalties from Springer for her book “Disorders of movement” |
| Grants: | none |
| Other | none |

**AN, CT, MR, VR, GR, PG, AQ**

|  |  |
| --- | --- |
| Stock ownership in medically related fields | none |
| Intellectual property rights | none |
| Consultancies | none |
| Expert testimony | none |
| Advisory boards | none |
| Employment | none |
| Partnerships | none |
| Contracts | none |
| Honoraria | none |
| Royalties | none |
| Grants: | none |
| Other | none |

# REFERENCES

1. Stanton-Hicks M, Janig W, Hassenbusch S, Haddox JD, Boas R, Wilson P. Reflex sympathetic dystrophy: changing concepts and taxonomy. Pain 1995; 63(1):127-133.

2. Schwartzman RJ, Kerrigan J. The movement disorder of reflex sympathetic dystrophy. Neurology 1990; 40(1):57-61.

3. Verdugo RJ, Ochoa JL. Abnormal movements in complex regional pain syndrome: assessment of their nature. Muscle Nerve 2000; 23(2):198-205.

4. Gupta A, Lang AE. Psychogenic movement disorders. Curr Opin Neurol 2009; 22(4):430-436.

5. Jankovic J. Can peripheral trauma induce dystonia and other movement disorders? Yes! Mov Disord 2001; 16(1):7-12.

6. van Rooijen DE, Geraedts EJ, Marinus J, Jankovic J, van Hilten JJ. Peripheral trauma and movement disorders: a systematic review of reported cases. J Neurol Neurosurg Psychiatry 2011; 82(8):892-898.

7. Maihofner C, Baron R, DeCol R, Binder A, Birklein F, Deuschl G et al. The motor system shows adaptive changes in complex regional pain syndrome. Brain 2007; 130(Pt 10):2671-2687.

8. Fukumoto M, Ushida T, Zinchuk VS, Yamamoto H, Yoshida S. Contralateral thalamic perfusion in patients with reflex sympathetic dystrophy syndrome. Lancet 1999; 354(9192):1790-1791.

9. Juottonen K, Gockel M, Silen T, Hurri H, Hari R, Forss N. Altered central sensorimotor processing in patients with complex regional pain syndrome. Pain 2002; 98(3):315-323.

10. Lang AE, Angel M, Bhatia K, Chen R, Fahn S, Hallett M et al. Myoclonus in complex regional pain syndrome. Mov Disord 2009; 24(2):314-316.

11. Lang AE, Chen R. Dystonia in complex regional pain syndrome type I. Ann Neurol 2010; 67(3):412-414.

12. Schrag A, Trimble M, Quinn N, Bhatia K. The syndrome of fixed dystonia: an evaluation of 103 patients. Brain 2004; 127(Pt 10):2360-2372.

13. Maihofner C, Handwerker HO, Neundorfer B, Birklein F. Cortical reorganization during recovery from complex regional pain syndrome. Neurology 2004; 63(4):693-701.

14. Maihofner C, Seifert F, Markovic K. Complex regional pain syndromes: new pathophysiological concepts and therapies. Eur J Neurol 2010; 17(5):649-660.

15. Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J. Induction of plasticity in the human motor cortex by paired associative stimulation. Brain 2000; 123 Pt 3:572-584.

16. Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 1994; 91(2):79-92.

17. Rothwell JC, Hallett M, Berardelli A, Eisen A, Rossini P, Paulus W. Magnetic stimulation: motor evoked potentials. The International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol Suppl 1999; 52:97-103.

18. Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A et al. Corticocortical inhibition in human motor cortex. J Physiol 1993; 471:501-519.

19. Daskalakis ZJ, Molnar GF, Christensen BK, Sailer A, Fitzgerald PB, Chen R. An automated method to determine the transcranial magnetic stimulation-induced contralateral silent period. Clin Neurophysiol 2003; 114(5):938-944.

20. Tokimura H, Di L, V, Tokimura Y, Oliviero A, Profice P, Insola A et al. Short latency inhibition of human hand motor cortex by somatosensory input from the hand. J Physiol 2000; 523 Pt 2:503-513.

21. Wolters A, Sandbrink F, Schlottmann A, Kunesch E, Stefan K, Cohen LG et al. A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex. J Neurophysiol 2003; 89(5):2339-2345.

22. Quartarone A, Rizzo V, Morgante F. Clinical features of dystonia: a pathophysiological revisitation. Curr Opin Neurol 2008; 21(4):484-490.

23. van Rijn MA, Marinus J, Putter H, van Hilten JJ. Onset and progression of dystonia in complex regional pain syndrome. Pain 2007; 130(3):287-293.

24. Eisenberg E, Chistyakov AV, Yudashkin M, Kaplan B, Hafner H, Feinsod M. Evidence for cortical hyperexcitability of the affected limb representation area in CRPS: a psychophysical and transcranial magnetic stimulation study. Pain 2005; 113(1-2):99-105.

25. Schwenkreis P, Janssen F, Rommel O, Pleger B, Volker B, Hosbach I et al. Bilateral motor cortex disinhibition in complex regional pain syndrome (CRPS) type I of the hand. Neurology 2003; 61(4):515-519.

26. Ridding MC, Sheean G, Rothwell JC, Inzelberg R, Kujirai T. Changes in the balance between motor cortical excitation and inhibition in focal, task specific dystonia. J Neurol Neurosurg Psychiatry 1995; 59(5):493-498.

27. Espay AJ, Morgante F, Purzner J, Gunraj CA, Lang AE, Chen R. Cortical and spinal abnormalities in psychogenic dystonia. Ann Neurol 2006; 59(5):825-834.

28. Avanzino L, Martino D, van de Warrenburg BP, Schneider SA, Abbruzzese G, Defazio G et al. Cortical excitability is abnormal in patients with the "fixed dystonia" syndrome. Mov Disord 2008; 23(5):646-652.

29. Orth M, Amann B, Robertson MM, Rothwell JC. Excitability of motor cortex inhibitory circuits in Tourette syndrome before and after single dose nicotine. Brain 2005; 128(Pt 6):1292-1300.

30. Ridding MC, Inzelberg R, Rothwell JC. Changes in excitability of motor cortical circuitry in patients with Parkinson's disease. Ann Neurol 1995; 37(2):181-188.

31. Wassermann EM, Greenberg BD, Nguyen MB, Murphy DL. Motor cortex excitability correlates with an anxiety-related personality trait. Biol Psychiatry 2001; 50(5):377-382.

32. Maeda F, Keenan JP, Pascual-Leone A. Interhemispheric asymmetry of motor cortical excitability in major depression as measured by transcranial magnetic stimulation. Br J Psychiatry 2000; 177:169-173.

33. Greenberg BD, Ziemann U, Cora-Locatelli G, Harmon A, Murphy DL, Keel JC et al. Altered cortical excitability in obsessive-compulsive disorder. Neurology 2000; 54(1):142-147.

34. Turton AJ, McCabe CS, Harris N, Filipovic SR. Sensorimotor integration in Complex Regional Pain Syndrome: a transcranial magnetic stimulation study. Pain 2007; 127(3):270-275.

35. Sailer A, Molnar GF, Cunic DI, Chen R. Effects of peripheral sensory input on cortical inhibition in humans. J Physiol 2002; 544(Pt 2):617-629.

36. Salmelin R, Hari R. Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. Neuroscience 1994; 60(2):537-550.

37. Quartarone A, Rizzo V, Terranova C, Morgante F, Schneider S, Ibrahim N et al. Abnormal sensorimotor plasticity in organic but not in psychogenic dystonia. Brain 2009; 132(Pt 10):2871-2877.

38. Quartarone A, Bagnato S, Rizzo V, Siebner HR, Dattola V, Scalfari A et al. Abnormal associative plasticity of the human motor cortex in writer's cramp. Brain 2003; 126(Pt 12):2586-2596.

39. Quartarone A, Morgante F, Sant'angelo A, Rizzo V, Bagnato S, Terranova C et al. Abnormal plasticity of sensorimotor circuits extends beyond the affected body part in focal dystonia. J Neurol Neurosurg Psychiatry 2008; 79(9):985-990.

40. Weise D, Schramm A, Stefan K, Wolters A, Reiners K, Naumann M et al. The two sides of associative plasticity in writer's cramp. Brain 2006; 129(Pt 10):2709-2721.

41. Sadnicka A, Hamada M, Bhatia KP, Rothwell JC, Edwards MJ. A reflection on plasticity research in writing dystonia. Mov Disord 2014; 29(8):980-987.

42. Kojovic M, Caronni A, Bologna M, Rothwell JC, Bhatia KP, Edwards MJ. Botulinum toxin injections reduce associative plasticity in patients with primary dystonia. Mov Disord 2011; 26(7):1282-1289.

43. Ruge D, Cif L, Limousin P, Gonzalez V, Vasques X, Hariz MI et al. Shaping reversibility? Long-term deep brain stimulation in dystonia: the relationship between effects on electrophysiology and clinical symptoms. Brain 2011; 134(Pt 7):2106-2115.

44. Kojovic M, Parees I, Kassavetis P, Palomar FJ, Mir P, Teo JT et al. Secondary and primary dystonia: pathophysiological differences. Brain 2013; 136(Pt 7):2038-2049.

45. Janig W, Baron R. Complex regional pain syndrome: mystery explained? Lancet Neurol 2003; 2(11):687-697.

46. Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N et al. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature 1995; 375(6531):482-484.

47. Zanette G, Manganotti P, Fiaschi A, Tamburin S. Modulation of motor cortex excitability after upper limb immobilization. Clin Neurophysiol 2004; 115(6):1264-1275.

48. Ziemann U, Corwell B, Cohen LG. Modulation of plasticity in human motor cortex after forearm ischemic nerve block. J Neurosci 1998; 18(3):1115-1123.

49. Viaro R, Budri M, Parmiani P, Franchi G. Adaptive changes in the motor cortex during and after longterm forelimb immobilization in adult rats. J Physiol 2014; 592(10):2137-2152.

50. Liepert J, Tegenthoff M, Malin JP. Changes of cortical motor area size during immobilization. Electroencephalogr Clin Neurophysiol 1995; 97(6):382-386.

51. Ganos C, Edwards MJ, Bhatia KP. The Phenomenology of Functional (Psychogenic) Dystonia. Movement Disorders Clinical Practice 2014; 1(1):36-44.

52. Quartarone A, Rizzo V, Terranova C, Milardi D, Bruschetta D, Ghilardi MF et al. Sensory abnormalities in focal hand dystonia and non-invasive brain stimulation. Front Hum Neurosci 2014;(8):956.

53. Caty G, Hu L, Legrain V, Plaghki L, Mouraux A. Psychophysical and electrophysiological evidence for nociceptive dysfunction in complex regional pain syndrome. Pain 2013; 154(11):2521-2528.

# FIGURE LEGEND

**Figure 1: cortical excitability in CRPS-I.** Short intracortical inhibition (SICI) and facilitation (ICF), short afferent inhibition at 20 and 25 inter-stimulus intervals (SAI20 and SAI25) and long afferent inhibition (LAI) in control subjects and in patients with CRPS-I. Box plots display 10th, 25th, 50th, 75th and 90th percentile of each variable; dots refer to outlier values.

**Figure 2: Sensorimotor plasticity in CRPS-I**. Motor evoked potential (MEP) amplitude increases after the PAS protocol only in the APB muscle in both the groups (panel A; FDI muscle in panel B).

**Supplementary material 1, figure. Design of the study**. Session A: short-interval intracortical inhibition (SICI) and facilitation (ICF), short afferent inhibition (SAI), long afferent inhibition (LAI). Session B: sensorimotor plasticity by the paired associative stimulation protocol (PAS). MEP: motor evoked potentials.

**Supplementary materials online 2**

All subjects were seated in a comfortable reclining chair. During the experiments, EMG activity was continuously monitored with visual (oscilloscope) and auditory (speakers) feedback to ensure either complete relaxation at rest or a constant level of EMG activity during tonic contraction. Focal TMS on the left primary motor hand area was performed with a High-Power Magstim200 stimulator wired to an eight-shaped coil with mean loop diameters of 9 cm (Magstim, Whitland, Dyfed, UK). The magnetic stimulus had a monophasic pulse configuration, with a rise time of about 100 µs decaying back to zero over about 0.8 ms. The coil was held tangentially to the skull with the handle pointing backward and laterally at an angle of 45° to the sagittal plane. Thus, the electrical current induced in the brain was approximately perpendicular to the central sulcus. This orientation of the induced electrical field is thought to produce predominantly a trans-synaptic activation of the corticospinal neurons (Rothwell et al., 1999). The site at which stimuli at slightly supra-threshold intensity consistently produced the largest MEP in the relaxed target muscle was marked with a pen as the “motor hot spot” and used for TMS on the motor cortex.

The median nerve was stimulated through bipolar electrodes at the wrist (cathode proximal) using square wave pulse with a pulse-width of 200 μs for SAI and LAI and 500 µs for the PAS protocol. EMG activity was recorded from the right APB and FDI muscles with Ag-AgCl surface electrodes using a belly-tendon montage. EMG signals were amplified and filtered using a time constant of 3 ms and a high-pass filter set a 3 kHz (Neurolog System; Digitimer Ltd, Welwyn Garden City, UK). Signals were acquired at a rate of 5 kHz (CED-1401 laboratory interface, Cambridge Electronic Design, Cambridge, UK) and stored on a personal computer for off-line analysis.

**Table 1: Clinical features of CRPS-I patients**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Pt** | **Age** | **Disease**  **Duration**  **(months)** | **Precipitant** | **Pain**  **(NRS)** | **Phenomenology of Fixed posture of right upper limb** | **Autonomic**  **Disturbances** | **Psychiatric Comorbidity** |
| **1** | 50 | 22 | Contusive trauma of the right wrist, casting for 10 days | 8 | Wrist flexion; fingers flexion at metacarpal joint | Oedema, reddish skin | Anxiety |
| **2** | 21 | 11 | Wrist fracture | 7 | Fingers flexion at metacarpal joint | Oedema | None |
| **3** | 71 | 12 | Contusive trauma of the right elbow | 9 | Elbow flexion; inability to fingers flexion | Oedema, reddish skin | Anxiety |
| **4** | 54 | 9 | Wrist fracture | 8 | Fingers flexion at metacarpal joints, proximal and distal interphalangeal joints | Oedema, reddish skin | Anxiety |
| **5** | 49 | 20 | Carpal tunnel surgery\* | 8 | Clenched Fist | Oedema, reddish skin, ↑ skin temperature | Depression and anxiety |
| **6** | 61 | 6 | Hand crush while closing car door | 9 | Fingers flexion and thumb adduction | Oedema, cyanotic skin, ↓ skin temperature | Anxiety |
| **7** | 15 | 10 | Wrist fracture | 7 | Fingers flexion at metacarpal joint | Oedema | Anxiety |
| **8** | 56 | 11 | Contusive trauma of the fingers | 9 | Thumb adduction and index flexion | ↓ skin temperature | None |
| **9** | 47 | 7 | Elbow fracture in a car accident | 8 | Elbow flexion; fingers flexion at metacarpal joint | Oedema, cyanotic skin, ↓ skin temperature | Depression and anxiety |
| **10** | 58 | 5 | Contusive trauma of the hand | 8 | Fingers flexion at metacarpal and proximal interphalangeal joints | edema, reddish skin | Anxiety |

NRS: Numeric Pain Intensity Scale [0 = no pain:1- 3: mild pain; 4–7: moderate pain; 8-10: severe pain]. \* minimal carpal tunnel syndrome before surgery and normal nerve conduction studies after surgery.

**Table 2: Corticospinal excitability and sensorimotor integration in CRPS-I and controls**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Controls RH** | **CRPS-I**  **Affected hand** | **F-value**  ***p*-value** | **Controls LH** | **CRPS-I**  **Unaffected hand** | **F-value**  ***p*-value** |
| **RMT** | 47.1±2.9 | 51.5±3.8 | F = 1.12  *p* = 0.30 | 44.6±1.8 | 52.0±3.5 | F = 2.60  *p* = 0.13 |
| **AMT** | 39.1±2.5 | 43.2±3.4 | F = 0.32  *p* = 0.57 | 37.5±1.7 | 41.7±3.7 | F = 2.22  *p* = 0.16 |
| **Test MEP (mV)** | 1.07 ± 0.06 | 0.92 ± 0.08 | F = 2.19  *p* = 0.15 | 1.001 ± 0.15 | 0.87 ± 0.11 | F = 0.49  *p* = 0.49 |
| **SICI (mV)** | 0.37 ± 0.06 | 0.71 ± 0.17 | **F = 6.38**  ***p = 0.02\**** | 0.45 ± 0.06 | 0.34 ± 0.09 | F = 0.63  *p* = 0.44 |
| **ICF (mV)** | 1.37 ± 0.15 | 1.91 ± 0.19 | **F = 6.01**  ***p = 0.02\**** | 1.67 ± 0.37 | 1.53 ± 0.34 | F = 0.02  *p* = 0.87 |
| **SAI20ms (mV)** | 0.54 ± 0.06 | 0.64 ± 0.09 | F = 2.21  *p* = 0.15 | 0.53 ±0.09 | 0.46 ± 0.09 | F = 0.03  *p* = 0.87 |
| **SAI25ms (mV)** | 0.84 ± 0.16 | 1.07 ± 0.13 | F = 2.15  *p* = 0.15 | 0.59 ± 0.12 | 0.77 ± 0.19 | F = 3.89  *p* = 0.08 |
| **LAI (mV)** | 0.38 ± 0.06 | 0.7 ± 0.16 | **F = 5.86**  ***p = 0.02\**** | 0.44 ± 0.04 | 0.29 ± 0.05 | F = 0.76  *p* = 0.40 |
| **CSP (ms)** | 161.9 ± 2.3 | 146.1 ± 4.3 | F = 1.49  *p* = 0.24 | 155.3 ± 7.4 | 145.8 ± 6.8 | F = 0.03  *p* = 0.8 |

Absolute values of baseline MEP, short-interval intracortical inhibition (SICI), intracortical facilitation (ICF), cortical silent period (CSP), short afferent inhibition at interstimulus interval of 20 ms (SAI20ms) and 25 ms (SAI25ms), long afferent inhibition (LAI) in control subjects (RH = right hand, LH = left hand) and in patients with complex regional pain syndrome type I (CRPS I) (affected and unaffected hand). P-value refers to factorial ANOVA with “group” as independent variable comparing Controls RH vs CPRS-I affected hand and Controls LH vs CRPS-I unaffected hand. Degrees of freedom for all comparisons = 1,18. Bolded values are significant. Data are given as mean ± SE.

**Table, 3.** **Neurophysiological parameters of motor cortex excitability in CRPS-I, Idiopathic Dystonia and Functional Dystonia.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Test** | **Idiopathic dystonia** | **CRPS-I** | **Functional dystonia** |
| **SICI** | ↓26,38 | ↓24,25 | ↓27,28,37 |
| **LICI** | ↓27 | NA | ↔27 |
| **CSP** | ↓27 | ↔§ | ↓27 |
| **SAI** | ↔28,37 ↓42 | ↔§ | ↔ 28,37 |
| **LAI** | **↓**a **↔** a,28 | **↓**§ | ↔ 28,37 |
| **SMC plasticity** | ↑38 | ↔§ | ↔37 |

SICI: short intracortical inhibition; LICI: long intracortical inhibition; SAI: Short afferent inhibition; LAI: Long Afferent inhibition; SMC: sensorimotor cortex.

↓: decreased; ↑:increased; ↔: normal.

Numbers refer to references included in the text. Letters refer to references not included in the text: a (Abbruzzese et al, Brain. 2001 Mar;124(Pt 3):537-45). NA: not assessed.

\* Reduced in writer’s cramp, normal in other focal dystonias

**A picture containing clock

Description automatically generatedFigure 1**

**A close up of a piano

Description automatically generatedFigure 2**

**A picture containing clock

Description automatically generatedSupplementary figure**