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PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 16, No 1 (January), 2015: pp 87-94
Available online at www.jpain.org and www.sciencedirect.com

Motor Cortical Activity During Motor Tasks Is Normal in Patients With Complex Regional Pain Syndrome

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Abstract: Motor dysfunction in complex regional pain syndrome (CRPS) is often considered a functional movement disorder. Earlier studies in patients with functional movement disorders found evidence of cortical inhibition during explicit but not implicit motor tasks, suggesting active inhibition from other brain areas. In this study, we explored whether active inhibition occurs in CRPS patients. We compared patients with CRPS with 2 control groups: healthy controls matched for age and sex, and patients whose hand was immobilized to treat a scaphoid fracture. We used transcranial magnetic stimulation to measure corticospinal excitability at rest and during motor imagery (explicit motor task) and motor observation (implicit motor task). Motor corticospinal excitation measured at rest and during implicit and explicit motor tasks was similar for CRPS patients and healthy controls. Patients with an immobilized hand showed an absence of motor cortical excitation of the corresponding hemisphere during motor imagery of tasks involving the immobilized hand, but not during motor observation. The normal motor cortical processing during motor imagery and motor observation found in the corresponding hemisphere of CPRS patients suggests that the nature of motor dysfunction in this condition differs from that described in literature for patients with functional paresis or under circumstances of limb immobilization.

***Perspective:** This study shows that the nature of motor dysfunction in CRPS patients differs from that encountered in patients with functional paresis or under circumstances of limb immobilization. This information is important for patients and pain clinicians and could help prevent implementation of therapeutic strategies based on incorrect assumptions.*

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***Key words:** Complex regional pain syndrome, transcranial magnetic stimulation, cortical excitability, psychogenic.*

Complex regional pain syndrome (CRPS) is a debilitating pain syndrome that usually develops after a minor trauma to a limb. The condition is clinically characterized by neuropathic pain, autonomic disturbances, and motor dysfunction.[21] Examples of the latter are a loss of voluntary motor control, slowness of movement, weakness, and postural abnormalities ("fixed dystonia") of the affected limb.[33] The nature of motor dysfunction in CRPS, particularly "fixed dystonia," has been a continuous source of debate.[7,15,38] On the one hand, fixed dystonia in CRPS has been viewed as a consequence of maladaptive neuronal plasticity or so-called central sensitization,[11] whereas some, on the other hand, emphasized a resemblance with functional movement disorders (ie, movement disorders without a demonstrable organic substrate), such as a prior peripheral trauma, the prominent presence of pain, and the occurrence of fixed postures.[7,15,37,38]

Given the lack of a gold standard for the diagnosis of functional movement disorders,[7,41] Schwingenschuh et al[34] attempted to develop laboratory tests to help establish the presence of a functional movement disorder. One such promising technique could be transcranial magnetic stimulation (TMS) during motor imagery (MI) and motor observation (MO). During MI, subjects rehearse a movement mentally without actually

Received April 11, 2014; Revised October 11, 2014; Accepted October 21, 2014.
This study was performed within TREND and supported by a grant from the Netherlands' Ministry of Economic Affairs [grant number BSIK03016].
The authors report no conflicts of interest that pertain to the subject of this study.
Supplementary data accompanying this article are available online at www.jpain.org and www.sciencedirect.com.
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1526-5900/$36.00
© 2015 by the American Pain Society
http://dx.doi.org/10.1016/j.jpain.2014.10.010

executing the movement, whereas in MO, subjects observe someone else moving. In healthy controls [HCs], both conditions activate similar brain areas involved in motor planning comparable to the actual execution of these movements, without being influenced by nerve or muscle disorders.[8,13,26] In patients with functional paresis, MI results in reduced primary motor cortex activation, whereas normal activation is seen during MO.[17,18] This dissociation of motor cortex activation between the explicit, voluntary MI and the implicit, automatic MO is attributed to the inhibitory activity of frontal or limbic brain areas during voluntary motor tasks.[16,18]

In view of the clinical resemblance between the movement disorders seen in patients with CRPS and patients with functional movement disorders, this study sought to investigate if CRPS patients also exhibit the different pattern of corticospinal excitability during explicit and implicit motor tasks found in patients with functional movement disorders. In order to accomplish this, we first measured baseline cortical excitability at rest using different intensities of TMS. Next, TMS measurements during MO and MI of weightlifting were performed using 2 distinct weights, to check the assumption that observed and imagined weightlifting results in a corresponding increase of cortical spinal excitability for heavier weights.[1] In addition, an extra control group was recruited consisting of patients who had 1 hand immobilized for a period of at least 4 weeks because of cast treatment for a scaphoid bone fracture (SBF) to control for the effects of underutilization of a limb, such as often seen in CRPS patients.

If the discrepancy in corticospinal excitability during explicit and implicit motor tasks is observed in patients with CRPS-related motor dysfunction, this condition shares an important characteristic with functional movement disorders, which would require modification of therapeutic strategies.

Methods

Subjects

Patients with documented CRPS of an upper limb followed up at the neurology outpatient clinic of the Leiden University Medical Center in Leiden, The Netherlands, were contacted by the principal investigator (G.A.J.V.) and informed about the purpose and procedures of the study, after which they were asked if they would consider participating in this study. If a patient was interested, a patient information sheet was sent to his or her home 2 weeks before the potential entry in the study. On the study day, a neurologic examination was performed by the principal investigator, and Budapest Criteria[10] were checked to include or exclude a patient. Additional inclusion criteria were loss of voluntary motor control of the affected limb for more than 6 months; weakness; and slowness of movement, whether or not in combination with decreased active range of motion or fixed dystonia. These characteristics were evaluated without the use of extra instrumentation. Exclusion criteria were any relevant neurologic illness or any other condition with pain or functional impairment of an arm.

Between July 2012 and July 2013, we specifically included patients with a unilateral SBF because in this patient group, as opposed to patients with other forearm and wrist fractures, the pincher grip (first dorsal interosseus muscle; see below) was immobilized for at least 4 weeks. These patients were approached during their immobilization period and included only if pain was minimal or absent (eg, $\leq$1 on a numeric rating scale ranging from 0 to 10). These patients were evaluated within an hour after cast removal. Lastly, HCs were age and sex matched to the CRPS patients. These control subjects were volunteers from the hospital staff or relatives of the CRPS patients. Exclusion criteria were pain, neurologic disease, or any other condition that might affect proper hand function.

The study was approved by the Medical Ethics Committee of the Leiden University Medical Center, and written informed consent was obtained from all patients and control subjects.

Transcranial Magnetic Stimulation

Subjects sat in an adjustable chair with supports for the head, arms, and legs. They rested their hands on a pillow, with the palms downward. A computer screen was then placed before the subjects at eye level (Supplementary Appendix A).

We used a Magstim Rapid 2 (Whitland, Dyfed, United Kingdom) with a figure-of-8 shaped coil supported by a standard. We positioned the coil over the motor cortex and locked the coil on the position where the lowest stimulus intensity was needed to evoke a 100-μV motor evoked potential (MEP). This position was considered as the "motor hotspot." An optical measurement and positioning system (Polis Spectra, software: ANT ASA 4.7.3; NDI, Enschede, The Netherlands) ensured that the position of the coil was held constant.

We recorded and stored MEPs (Medelec Synergy 10; Oxford Instruments, Abingdon, Oxfordshire, United Kingdom) from the first dorsal interosseus muscle of both hands using 23-mm-diameter Ag/AgCl surface electrodes. MEP amplitudes were measured peak to peak with a 30- to 3000-Hz bandpass filter. All consecutive TMS stimuli were given with an interstimulus interval of 4 to 6 seconds. The sequence of testing was always motor threshold (MT), input-output (IO) curve, MO, and MI with a 5-minute break between the tests. The sequence in which hands were measured during the different tests was determined at random.

MT

Patients were asked to relax and look in front of them. We defined the MT as the lowest stimulus intensity needed to evoke MEPs with amplitudes of 50 to 100 μV in at least 5 of 10 trials during muscle relaxation.[32]

IO Curve

We first established the stimulus intensity (SI) needed to evoke a 1-mV MEP at rest (SI 1mV) using the median

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