Pain-Motor Integration in the Primary Motor Cortex in Parkinson's Disease

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INTRODUCTION

Chronic pain is a common non-motor symptom in patients with Parkinson's disease (PD). Chronic pain is currently classified in nociceptive and neurophatic pain (Wasner et al., 2012). The pathophysiology of chronic pain in PD remains largely unknown. One way to investigate experimental pain in humans is to apply the **Laser-evoked potential (LEP)** technique that consists of laser pulses delivered over the skin able to activate the nociceptive system and evokes small lateralized negative component (N1) and a later negative-positive complex (N2-P2) (Cruccu et al., 2008). Previous studies suggest abnormal cortical processing of nociceptive inputs in PD (Cury et al., 2015). No studies however, have investigated whether and through which mechanisms chronic pain influences the cortical motor function in PD.

Laser-paired associative stimulation (Laser-PAS$_{50}$). protocol combines LEPs with transcranial magnetic stimulation (TMS) of M1 in a PAS design (Suppa et al., 2013). In healthy subjects (HS), Laser-PAS$_{50}$ elicits long-term increase of motor evoked potential (MEP) amplitudes through mechanisms long-term potentiation (LTP)-like plasticity in M1, that reflects the activation of pain-motor integration processes (Suppa et al., 2013). In this study we have investigated pain-motor integration by applying the Laser-PAS$_{50}$ technique, in patients with PD, with and without chronic pain.

SUBJECTS AND METHODS

Twenty patients and 20 age-matched HS participated. Motor signs were scored using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn & Yahr (H&Y) scale. The presence of chronic pain was evaluated and patients with chronic pain were asked to rate the intensity of pain on a 11-point numerical rating scale (NRS). Patients with chronic pain also underwent the questionnaire for the detection of neuropathic pain (Neuropathic Pain in 4 questions - DN4). Patients were then studied in on and off state of therapy. LEPs were recorded in all patients when on therapy, according to standardized techniques (Cruccu el al., 2008), following laser stimulation directed to the right ulnar region of the hand dorsum. TMS was delivered over the left hemisphere, to elicit MEPs of 1 mV in the abductor digiti minimi (ADM) muscle of the right hand. Twenty MEPs were recorded from the right ADM at baseline (T0) and at 10 (T2), 20 (T3), 30 (T4), 40 (T5), 50 (T6) and 60 (T7) after Laser-PAS$_{50}$. Laser-PAS$_{50}$ consisted of 60 rTMS pulses at 0.1 Hz, each TMS pulse following a single laser stimulus delivered at an ISI of LEP N1 latency+50 ms (total duration of intervention: 10 min) (Suppa et al., 2013).

RESULTS

ANOVA showed a significant interaction between factors "Group" and "Time" ($F_{7.266}$=6.16; p<0.001). In HS, Laser-PAS$_{50}$ increased MEPs for 60 minutes as demonstrated by the factor "Time" ($F_{7.133}$=8.34; p<0.001). Differently from HS, Laser-PAS$_{50}$ elicited reduced responses in PD patients, off therapy ($F_{7.133}$=1.02; p=0.42) and on therapy ($F_{7.133}$=1.50; p=0.17) **(Fig.1)**. When we compared responses to Laser-PAS$_{50}$ in patients with and without chronic pain, we found similar abnormalities in the two patients' subgroups as demonstrated by a non significant effect of the factor "Group" **(Fig.2)**.

When we compared however, patients with chronic pain in the right upper limb with those with pain in other body regions, we found prominent changes in patients with pain in the right upper limb as demonstrated by significant effect of the factor "Pain localization" in patients off ($F_{1.13}$=4.68; p=0.04) and on therapy ($F_{1.13}$=7.64; p=0.02) **(Fig. 3)**. We found a negative correlation between NRS score and MEPs at T5 (all p values < 0.05) **(Fig. 4 A-B)**.

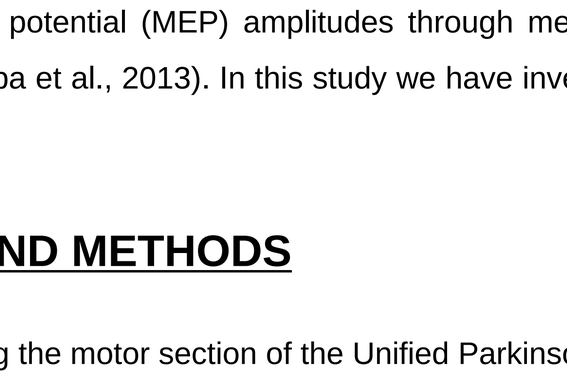

Fig. 1

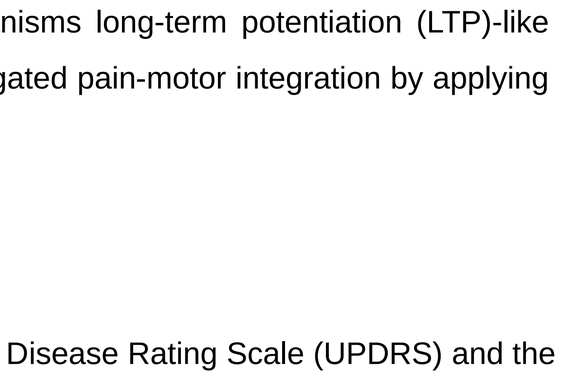

Fig. 2

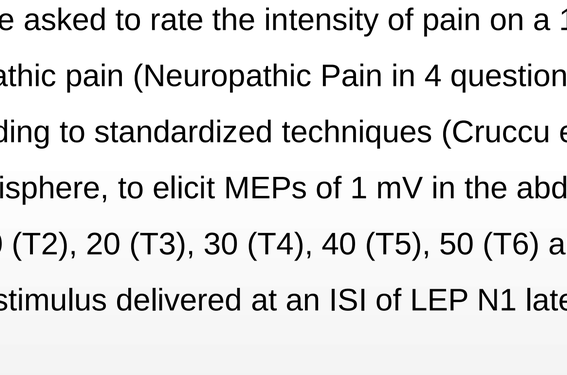

Fig. 3

CONCLUSIONS

We conclude that in PD, chronic pain further degrades the response to Laser-PAS$_{50}$ through mechanisms of abnormal pain-motor integration.

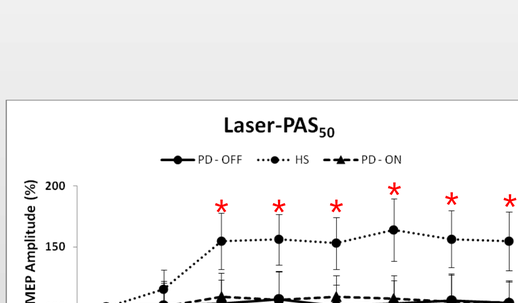

Fig. 4

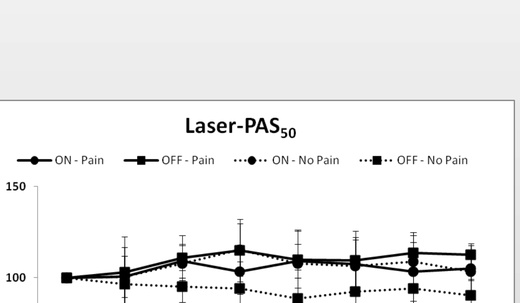

Fig. 4

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