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Pain-motor integration in the primary motor cortex in Parkinson's disease

A. Suppa [a, b], C. Leone [a], F. Di Stasio [b], L. Marsili [a], A. Di Santo [a, c], A. Biasiotta [a], S. La Cesa [a], A. Truini [a], G. Cruccu [a], A. Berardelli [a, b, *]

[a] Department of Neurology and Psychiatry, Sapienza University of Rome, Italy
[b] IRCCS Neuromed Institute, Pozzilli IS, Italy
[c] Neurology Unit, Campus Bio-Medico University, Rome, Italy

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ABSTRACT

Background: In Parkinson's disease (PD), the influence of chronic pain on motor features has never been investigated. We have recently designed a technique that combines nociceptive system activation by laser stimuli and primary motor cortex (M1) activation through transcranial magnetic stimulation (TMS), in a laser-paired associative stimulation design (Laser-PAS). In controls, Laser-PAS induces long-term changes in motor evoked potentials reflecting M1 long-term potentiation-like plasticity, arising from pain-motor integration.
Objective: We here examined the possible influence of chronic pain on motor responses to Laser-PAS in patients with PD, with and without chronic pain.
Methods: We compared motor responses to Laser-PAS in healthy subjects and in patients with PD, with and without chronic pain.
Results: Unlike controls, we found reduced responses to Laser-PAS in patients with PD, with and without pain. Patients off and on dopaminergic therapy had similar responses to Laser-PAS. When comparing responses to Laser-PAS in patients with and without pain, the two patients' subgroups had similar abnormalities. When we compared patients with pain in the body region investigated with Laser-PAS, with those with pain in other body regions, we found prominent changes in patients with homotopic pain. Finally, when comparing Laser-PAS with the original PAS protocol, which combines electric peripheral nerve stimuli and TMS, in patients without pain and those with homotopic pain, we found similar responses to both techniques in patients without pain, whereas Laser-PAS induced greater abnormalities than PAS in patients with pain.
Conclusions: In PD, chronic pain degrades response to Laser-PAS through abnormal pain-motor integration.

Chronic pain is a non-motor symptom observed in 40–85% of patients with Parkinson's disease (PD) [1–4]. In PD, chronic pain is currently classified in nociceptive (i.e. muscoloskeletal, visceral and cutaneus pain) and neurophatic pain (i.e. radicular and central pain) [1,5,6]. Similarly to other non-motor symptoms in PD, pain is currently considered to reflect extranigral pathology [7,8], but the pathophysiology of chronic pain in PD remains largely unknown [1,2,5,6,9].

Laser stimulation is widely considered a reliable tool for investigating pain pathways in humans [10]. Laser stimulation selectively activates Aδ and C nociceptors and evokes [11] scalp potentials (LEPs) comprising an early lateralized component (N1), generated by secondary sensory area (S2) area and a late negative-

Abbreviations: ACC, anterior cingulate cortex; ADM, abductor digiti minimi; ANOVA, analysis of variance; La DN4, douleur neuropatique en 4 questions; HAM-D, Hamilton Depression Rating Scale; Laser-PAS, laser-paired associative stimulation; LEDDs, L-Dopa equivalent daily doses; LEP, laser evoked potential; LTP, long-term potentiation; LTD, long-term depression; M1, primary motor cortex; MEP, motor evoked potential; MMSE, Mini Mental State Evaluation; NRS, numerical rating scale; PAS, paired associative stimulation; PD, Parkinson's disease; RMT, resting motor threshold; S2, secondary somatosensory area; STDP, spike timing-dependent plasticity; TMS, transcranial magnetic stimulation; MDS-UPDRS, Movement Disorders Society-Unified Parkinson's Disease Rating Scale.

* Corresponding author. Department of Neurology and Psychiatry, Neuromed Institute, Sapienza University of Rome, Viale dell'Università, 30, 00185 Rome, Italy.
E-mail address: alfredo.berardelli@uniroma1.it (A. Berardelli).

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positive complex (N2-P2) generated by anterior cingulate cortex (ACC) [11–13]. Previous studies in patients with PD demonstrated LEP abnormalities in patients with nociceptive and neuropathic pain [14,15], suggesting abnormal cortical processing of nociceptive inputs as a key pathophysiological mechanism underlying chronic pain in PD [2,4,9].

Recently we have designed a new technique, namely Laser-paired associative stimulation (Laser-PAS_{50}) [16]. This protocol combines laser pulses delivered to the hand with transcranial magnetic stimulation (TMS) of M1 in a PAS design. In healthy subjects, Laser-PAS_{50} elicits long-term increase of motor evoked potential (MEP) amplitude through mechanisms of long-term potentiation (LTP)-like plasticity in M1 possibly related to changes in *N*-Methyl-D-aspartate transmission [16].

No studies have previously investigated M1 plasticity as assessed with the Laser-PAS_{50} technique in PD with and without chronic pain. A better understanding of pain-related M1 plasticity might clarify the pathophysiological basis of chronic pain in PD and open new perspectives in the treatment of this non-motor symptom.

In this study, we applied Laser-PAS_{50} in a cohort of patients with PD. Then to clarify whether in PD chronic pain influences the responses to Laser-PAS_{50}, we compared Laser-PAS_{50} in patients with and without pain. To understand whether pain has a segmental or generalized effect, we compared responses to Laser-PAS_{50} in patients with pain in the right upper limb, the same body region examined by Laser-PAS_{50}, and patients with pain in other body regions. Finally, to verify whether abnormal responses to Laser-PAS_{50} in patients with chronic pain depends on intrinsic M1 plasticity abnormalities regardless of the specific PAS protocol used, we compared responses to Laser-PAS_{50} and to the original PAS protocol, which combines electric peripheral nerve stimuli and transcranial magnetic stimulation (TMS) at interstimulus interval of 25ms (PAS_{25}) [17], in the same cohort of patients, with and without pain.

Material and methods

Subjects

Twenty patients with PD (14 men and 6 women, mean age±SD: 62.5 ± 9.5) and 20 age-matched healthy subjects (10 men and 10 women, mean age±SD: 59.7 ± 15.8) participated in the study. All participants were right-handed. The diagnosis of idiopathic PD was made according to the Queen Square Brain Bank criteria and the EFNS/MDS-ES recommendations [18,19]. Patients were recruited from the Movement Disorder Clinic at the Department of Neurology and Psychiatry, Sapienza University of Rome. Patients had a predominantly akinetic-rigid syndrome without dementia. Patients were studied while they were under their usual dopaminergic treatment (on) and after drugs had been withdrawn for at least 12 h (off). None of the patients received other neuropsychiatric medications. Patients were clinically evaluated before starting each experimental session. Motor signs were scored using the motor section of the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [20,21] and the Hoehn & Yahr (H&Y) scale. Cognitive function was evaluated using the Mini Mental State Evaluation (MMSE) [22] and the Frontal Assessment Battery (FAB) [23]. Depression was assessed with the Hamilton Depression Rating Scale (HAM-D) [24]. According to the criteria suggested by Wasner et al. [5], we first evaluated the presence of chronic pain. None of the healthy controls reported any type of pain. Patients were asked to rate the intensity of pain on an 11-point numerical rating scale (NRS) from 0 (no pain) to 10 (strongest imaginable pain) [10] before the first experimental session and relative to the previous 6 months. Those rating pain ≥4 and reporting it from at least 6 months were considered "chronic-pain" patients. Patients with chronic pain also underwent the screening tool for the detection of neuropathic pain (La douleur neuropatique en 4 questions - DN4) [25]. No patients were being administered with any treatment for pain at the time of the study. Demographic and clinical features of parkinsonian patients, with and without pain are summarized in Table 1. Subjects gave their written informed consent. The study was approved by the institutional review Board of Sapienza, University of Rome, Italy and conformed to the Declaration of Helsinki.

Laser stimulation technique and LEP recordings

Laser stimuli were delivered with a neodymium:yttrium-aluminium-perovskite laser stimulator (Nd:YAP, wave length 1.34 μm, pulse duration 2–20 ms, maximum energy 7 J El.En - Florence, Italy) under fiber-optic guidance. The laser perceptive threshold was determined by increasing and decreasing the stimulus energy in steps of 0.25 J in series of three stimuli, and defined as the lowest intensity at which the subjects perceived at least the 50% of the stimuli [26]. To evoke clear and stable LEPs, laser stimuli were set to induce a clear painful pinprick sensation (intensity 119.4–150 mJ/mm2; duration 5 ms; spot diameter 5 mm) and directed to the ulnar region of the right hand dorsum. The target of the laser beam was shifted by at least 1 cm in a random direction, to allow for passive skin cooling and avoid nociceptor fatigue or sensitization and the interstimulus interval was varied pseudo-randomly (10–15 s) [26]. Subjects, wearing protective goggles, rested comfortably on a medical examination table. LEPs were recorded through surface electrodes from the scalp: T3 referenced to Fz for recording the early lateralized N1 component, and Cz referenced to the nose, for recording the late vertex N2-P2 complex. Electro-oculographic recordings monitored possible eye movements or blinks. We averaged 15 artefact-free trials off line using dedicated equipment (Synergy 10.1; EL.EN, Florence, Italy). The recording bandpass was between 0.3 and 30 Hz and the sampling frequency 50 kHz. We measured the peak latency and amplitude of the lateralized N1 and the vertex N2-P2 complex. These methods adhered to the recommendations given by the International Federation of Clinical Neurophysiology [11]. LEP recordings were taken at least 30 min before TMS, while the patients were on therapy (1 h after taking their usually antiparkinsonian therapy).

TMS and MEP recordings

TMS was delivered through a repetitive magnetic stimulator (Magstim Super Rapid-The Magstim Company Ltd, Whitland, United Kingdom) connected to a figure-of-eight coil (external wing 9 cm in diameter) placed tangentially to the scalp on the left hemisphere, with the handle pointing back and away from the midline at 45° inducing postero-anterior and antero-posterior biphasic currents in the brain. The coil was placed over the optimum scalp position (hot spot) to elicit MEPs in the abductor digiti minimi (ADM) muscle of the right hand. To ensure that the stimulating coil remained in a constant position throughout the experiments, the hot spot was marked on the scalp with a soft-tipped pen. Motor threshold was determined at rest (RMT) as the lowest intensity able to evoke a MEP of more than 50 μV in at least 5 of 10 consecutive trials in the ADM muscle. RMT was determined in steps of 1% maximum stimulator output intensity. Electromyographic activity was recorded through a pair of surface electrodes placed over the right ADM muscle, using a belly-tendon montage. Electromyographic raw signals were recorded, sampled at 5 kHz with a CED 1401 A/D laboratory interface (Cambridge Electronic Design,