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Abnormal sensorimotor plasticity in migraine without aura patients

Francesco Pierelli [a,*], Elisa Iacovelli [b], Martina Bracaglia [c], Mariano Serrao [c], Gianluca Coppola [d]

[a] IRCCS Neuromed, Pozzilli (IS), Italy
[b] "Sapienza" University of Rome, Department of Medicosurgical Sciences and Biotechnologies, Neurology Section, Rome, Italy
[c] "Sapienza" University of Rome, Department of Medicosurgical Sciences and Biotechnologies, Latina, Italy
[d] G.B. Bietti Foundation-IRCCS, Department of Neurophysiology of Vision and Neurophthalmology, Rome, Italy

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ABSTRACT

The period between migraine attacks is characterized by paradoxical responses to repetitive sensory and transcranial magnetic stimulation (TMS). Abnormal long-term cortical functional plasticity may play a role and can be assessed experimentally by paired associative stimulation (PAS), in which somatosensory peripheral nerve stimuli are followed by TMS of the motor cortex. Changes in motor-evoked potential (MEP) amplitudes were recorded in 16 migraine without aura patients (MO) and 15 healthy volunteers (HV) before and after PAS, which consisted of 90 peripheral electrical right ulnar nerve stimulations and subsequent TMS pulses over the first dorsal interosseous (FDI) muscle activation site with a delay of 10 ms (excitability depressing) or 25 ms (excitability enhancing). As a control experiment of the 31 subjects studied, 8 (4 MO and 4 HV) also underwent PAS10 earlier, the recording of somatosensory high-frequency oscillations (HFOs) reflecting thalamocortical activation (early HFOs). Although PAS10 reduced MEP amplitudes in HV (−17.7%), it significantly increased amplitudes in MO (+35.9%). Although in HV MEP amplitudes were significantly potentiated (+55.1) after PAS25, only a slight, nonsignificant increase was observed in MO (+18.8%). In the control experiment, performed on 8 subjects pooled together, Pearson's correlation showed an inverse relationship between the percentage of MEP amplitude changes after PAS10 and early HFO amplitudes ($r = -0.81$; $P = .01$). Because we observed that the more deficient the long-term PAS-induced change, the more the thalamocortical activation decreased, we hypothesize that the abnormalities in long-term cortical plasticity observed in the interictal period between migraine episodes could be due to altered thalamic control.

1. Introduction

Abnormalities in cortical information processing in the periods between migraine attacks have been revealed through neurophysiological studies [11,36]. On the one hand, with evoked potentials, a deficient habituation mechanism has been repeatedly observed in migraine both with and without aura. On the other hand, studies with repetitive transcranial magnetic stimulation (rTMS) have reported abnormal cortical excitability manifesting as paradoxical effects in response to both depressing or enhancing rTMS methodologies, particularly in migraine with aura [6,7,9,10,16].

There is as yet no unifying hypothesis explaining these cortical abnormalities in migraine. Changes in cortical excitability and diminished cortical preactivation due to an insufficient thalamocortical drive have been considered to be possible culprits [2,8,11]. However, both the paradoxical rTMS response and habituation deficit point to altered synaptic plasticity mechanisms, which prevent the immediate and longer-lasting cortical changes that reflect adaptation to repeated stimulations, ie, learning and memory [12].

One of the experimental ways to induce durable changes in the excitability of cortical output circuits is to pair peripheral stimulation of somatosensory afferents with low-frequency TMS over the contralateral cortical hand motor area [39]. Paired associative stimulation (PAS), in fact, is a protocol that uses in humans a design principle very similar to those leading to long-term associative depression (LTD) or potentiation (LTP) in cortical slide preparations or in animal studies [3–5]. It has been shown in healthy subjects that delivering PAS at an interstimulus interval shorter than the time needed for the afferent inputs to reach the cerebral cortex (10 ms) the excitability decreases, and at an interstimulus interval

* Corresponding author. Address: Department of Medicosurgical Sciences and Biotechnologies, "Sapienza" University of Rome, Polo Pontino, Corso della Repubblica 79-04100, Latina, Italy. Tel.: +39 0773 6513313; fax: +39 0773 6513333.
E-mail address: francesco.pierelli@uniroma1.it (F. Pierelli).

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slightly longer than the time needed for the afferent inputs to reach the cerebral cortex (25 ms), the excitability of the sensorimotor cortex increases [19,39,41].

Here, with the aim of studying long-term cortical synaptic plasticity mechanisms in migraine, we designed this study to find out whether inhibiting and enhancing PAS protocols could induce sensorimotor cortical plasticity in patients affected by migraine without aura compared with healthy volunteers.

2. Materials and methods

2.1. Subjects

We enrolled 16 patients with migraine without aura (mean age ± SD, 28.8 ± 1.3 years, 14 women) from among those attending the Headache Clinic of the "Sapienza" University of Rome Polo Pontino. We included only data from patients who had an interval of at least 3 days between the recording and their last or their next migraine attack (checked by a telephone call). Subjects receiving any medication on a regular basis except the contraceptive pill were excluded. They were compared to 15 healthy volunteers (HV) with a comparable age and gender distribution (mean age ± SD, 33.1 ± 3.4 years, 12 women) without a personal or family history of migraine and without any detectable medical condition. All subjects were right-handed. Subjects were seated, fully relaxed, in a comfortable armchair. The physicians and the neurophysiologists were blinded to the electrophysiology and the clinical history, respectively.

All participants provided written informed consent to the study. The study was conducted in accordance with the Declaration of Helsinki. All procedures were approved by the ethical committee of the "Sapienza" University, Rome.

2.2. Experimental procedure

2.2.1. Paired associative stimulation (PAS)

PAS was delivered percutaneously by single electrical stimuli to the right ulnar nerve at the wrist by means of a Digitimer DS7A stimulator (Digitimer, UK) using a constant current square wave pulse (0.2 ms width) and a stimulus intensity set at 300% of the sensory threshold (ST) combined with single magnetic pulses with an intensity of 120% of the resting motor threshold (RMT). TMS was delivered through a high-frequency biphasic magnetic stimulator (MagstimRapid, Magstim Company Ltd, Whitland, South West Wales, UK) connected to a figure-8 coil with a maximal stimulator output of 1.2 T. The coil was positioned over the left motor area. We first identified the resting motor threshold (RMT) using single TMS pulses and the same procedure as previously described [34].

The interstimulus interval (ISI) between peripheral ulnar nerve stimulation and TMS of the primary motor hand area was set at 25 ms and 10 ms because these ISIs have been shown to be optimal for inducing a sustained increase and decrease, respectively, in motor cortex excitability [41]. The conditioning protocol consisted of 90 pairs of stimuli that were delivered at 0.05 Hz over 30 min. During PAS, patients were asked to remain fully relaxed and to ensure similar attention levels while keeping their eyes closed. Cortical excitability of the primary motor hand area was evaluated by delivering and averaging 10 single pulses of TMS before and immediately after associative stimulation using a stimulus intensity of 120% RMT at a rate of 0.1 Hz.

2.2.2. Recordings of somatosensory evoked potentials (SSEPs)

SSEPs were elicited after electrical stimulation of the right ulnar nerve at the wrist using a stimulus intensity set at twice the motor threshold. One series of 500 sweeps was collected and averaged at a repetition rate of 4.4 Hz. The active electrodes were placed over the contralateral parietal area (C30, 2 cm posterior to C3 in the international 10–20 system) referenced to Fz; the ground electrode was on the right arm. The evoked potential signals were amplified by Digitimer D360 preamplifiers and recorded by a CED power1401 device (Cambridge Electronic Design Ltd, Cambridge, UK). Subjects were seated relaxed on a comfortable chair in an illuminated room and asked to stay with their eyes open and to fix their attention on the wrist movement. Fifty milliseconds of the poststimulus period was sampled at 5000 Hz to collect higher-frequency oscillations. All recordings were averaged off-line using the Signal software package, version 4.08 (CED Ltd).

2.3. Data analysis

2.3.1. MEP

EMG activity was recorded through surface electrodes placed over the right FDI muscles, filtered (bandwidth 20 Hz to 1 kHz), and analyzed off-line. The size of MEPs evoked was measured peak to peak. Effects of PAS on MEP amplitude were expressed as the percentage difference compared with baseline MEP amplitudes.

2.3.2. High-frequency oscillations (HFOs)

According to the method described elsewhere [13,14], digital zero-phase shift band-pass filtering between 450 and 750 Hz (Barlett-Hanning window, 51 filter coefficients) was applied off-line in order to extract the HFOs embedded in the N20 SSEP component. In the majority of recorded traces, we were able to identify 2 separate bursts of HFOs. The first or early burst occurred in the latency interval of the ascending slope of the conventional N20 component, and the second or late burst occurred in the time interval of the descending slope of N20, sometimes extending into the ascending slope of the N33 peak. In general, the frequency of oscillations was higher in the first than in the second HFO burst, and in between the early and late bursts, there was a clear frequency and amplitude decrease, which allowed the 2 bursts to be separated. In recordings in which a clear distinction between the 2 components was not possible, we considered HFOs occurring before the N20 peak as early burst and those after the N20 peak as late burst.

After elimination of the stimulus artifact, we measured the maximum peak-to-peak amplitude separately on the 2 HFO bursts.

2.4. Study design

The 2 PAS sessions (PAS10 and PAS25) were performed in random order at $\geqslant$1-week intervals by the same investigators following the paradigm published by Stefan et al. [39].

As a control experiment, SSEPs were recorded in 4 patients with migraine and in 4 HV.

2.5. Statistical analysis

We used SPSS software for Windows, version 15.0, for all analyses. All results are expressed as means ± SD. The 1-way ANOVA test was used to compare the variables at baseline. Paired Student's *t* tests were used to compare the variables before and after PAS10 and PAS25, for each electrophysiological parameter, and for each group. Moreover, we performed a multivariate analysis of variance taking as between-subject factors Group (HV, MO), Time (before, after PAS), and Session (PAS10, PAS25) to verify the interaction between them. Pearson's correlation test was used to search for correlations between HFO amplitudes (early and late) and the percentage of MEP amplitude changes after PAS10 (after–before/before). *P* values of less than .05 were considered to indicate statistical significance.