Migraine with and without aura: electrophysiological and functional neuroimaging evidence

Placido Bramanti a
Rosario Grugno a
Antongiulio Vitetta a
Paolo Di Bella a
Nunzio Muscarà a
Giuseppe Nappi b

a"Centro Studi Neurolesi", University of Messina, Italy
bDepartment of Neurology and Otolaryngology, University "La Sapienza", Rome, and IRCCS C. Mondino Institute of Neurology, Pavia, Italy

Reprint requests to: Dr Rosario Grugno
Centro Studi Neurolesi
Via Provinciale Palermo, C/da Casazza
98124 Messina, Italy
E-mail: rgrugno@virgilio.it

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Summary
The neuropathological processes believed to underlie migraine with and without aura are still widely debated in the literature.
In order to arrive at a more detailed and comprehensive picture of the altered processes present in migraineurs, electrophysiological data obtained through transcranial magnetic stimulation (TMS) and electroencephalography (EEG) were combined with haemodynamic data obtained through functional magnetic resonance imaging (fMRI).
Ten subjects affected by migraine (with or without aura) underwent TMS and EEG investigation prior to a visual stimulation task, studied in fMRI.
Our preliminary results showed a reduced cortical silent period especially in subjects affected by migraine with aura. The fMRI BOLD response was found to be weaker in occipital areas proportionally to the frequency and severity of migraine attacks.
The data obtained from our study seem to support the theory of cortical spreading depression recently observed in human subjects.
Moreover, the electrophysiological data were also correlated to migraine attack frequency, thus pointing to elevated cortical excitability between attacks.
Better understanding of the neuropathological processes that trigger migraine attacks will help in the selection of more adequate prophylactic therapies. The results of this preliminary study need to be confirmed in a large sample of subjects.

KEYWORDS: fMRI, migraine, pTMS.

Introduction
Migraine research in the past focused almost exclusively on changes in cerebral functions occurring during attacks. In recent years, however, there has been a shift towards the study of "abnormalities" occurring between attacks. Indeed, it is now felt that the interictal period probably holds the key to greater understanding of the pathogenetic mechanisms of migraine.
By combining electrophysiological data obtained through transcranial magnetic stimulation (TMS) and electroencephalography with haemodynamic data obtained through functional magnetic resonance imaging (fMRI), it may be possible to arrive at a more detailed and comprehensive picture of the altered processes present in migraineurs (1). To explore the hypothesis that hyperexcitability of the cerebral cortex may play a fundamental role in migraine pathogenesis, we studied cortical excitability in migraine with and without aura patients in the interictal period (2-4).

Materials and methods
Ten migraine patients (4 males and 6 females, mean age: 36.2 years) were enrolled in the study. Each patient received a diagnosis according to the revised criteria of the International Headache Society (ICHD-II) (5).
Five patients presented migraine without aura (ICHD-II code 1.1, mean disease duration: 23 years, mean attack frequency: 8/month); three patients presented typical aura with migraine headache (ICHD-II code 1.2.1, mean disease duration: 9.7 years, mean attack frequency: 1.9/month), and two patients presented both migraine with and migraine without aura (mean disease duration: 4 years, mean attack frequency: 2.6/month). All the patients were examined between attacks, at an interval of at least 72 hours from their last migraine attack; no patient was receiving prophylactic medication or using any drugs liable to affect the excitability of the central nervous system.
We also studied a group of 10 healthy volunteers (6 females and 4 males; mean age: 34.7 years) recruited among staff and students at our centre; the mean age of the control group did not differ significantly from that of the migraine subjects.
All the subjects gave their informed consent before participating in the study, which had received local ethics committee approval.
The MRI study was performed using a 1.5 Tesla Magnetom Vision scanner (Siemens Medical, http://www.siemensmedical.com) with echo-planar imaging sequences. A localizer pulse sequence was carried out for correct positioning of the patient along the anterior commissure/posterior commissure line; this was followed by acquisition of the T1-weighted images to be used for su-
perimposition on the statistical maps. The selected images extended from the rostral part of the external cortex to the culmen of the cerebellum caudally.

Visual stimulation was carried out using MRI-compatible monitor (Vision 2000, MRIVISION Inc., Los Angeles) and Intel Pentium 4 PC. The latter was used to generate a chessboard with 3x3 cm red and green squares that flashed at a frequency of 2.5 Hz/sec. The task performed by the subjects comprised 8 rest/stimulus periods, each lasting 32 seconds (16 seconds rest vs. 16 seconds stimulus). During the rest periods, the subject was required to focus on a luminous signal located at the centre of a black screen; during the stimulus periods the black screen was replaced by the flashing chessboard. The images obtained were processed using SPM99 software (Wellcome Department of Cognitive Neurology, London). Following correction of the movement error, normalization of the images to the standard MNI template, and application of an 8-mm full-width half-maximum filter, we calculated the activation maps, with threshold for activation set at $p<0.05$.

The electroencephalogram (EEG) was acquired using a 32-channel system operating at a sampling frequency of 1024 Hz.

For the electrophysiological study of cortical excitability, surface electromyographic recordings were made from the abductor pollicis brevis of the dominant hand. TMS was carried out using a figure 8-shaped coil (external loop 70 mm; peak magnetic field 2.2 Tesla) connected to two Magstim 200 magnetic stimulators through a Bistim paired pulse stimulation module. The protocol required that the resting motor threshold ($rMTh$) be established prior to determining the optimal focal point. Intracortical excitability was then evaluated using the paired transcranial magnetic stimulation (pTMS) technique: two consecutive stimuli were delivered to the "hot spot" with a stimulus intensity 120-150% of the resting motor threshold (rMTh) (i.e., around 30 percentage points above the rMTh). Each trial comprised 10 stimuli. The duration of the silent period was measured for each stimulus.

The EEG was found to be normal in two of the migraine patients and altered in the other eight. The alterations observed were: i) increased frequency and reduced amplitude of background electrical brain activity in four patients; ii) paroxysmal spikes located in the occipital region in two patients; iii) paroxysmal spikes in the central region bilaterally + diffuse sharp waves in one patient; iv) slow paroxysmal activity in one patient.

Results

The migraine patients presented a significantly shorter CSP duration than the controls (mean 103.45 ms vs 143.6 ms) (Fig. 1). Assessment of SICI showed that the migraineurs had less intracortical inhibition than the controls. Indeed the amplitude of the MEP obtained with the second (test) stimulus (expressed as a percentage of the MEP amplitude recorded at baseline) was found to be 38.15% in the migraine patients and 16% in the healthy controls at ISIs of 3 ms, and 68.4% in the migraine patients vs 59% in the controls at ISIs of 5 ms. Furthermore, at ISIs of 15 ms, the migraine patients displayed more intracortical facilitation than the controls, recording a significantly higher MEP amplitude (mean 162.6% vs 122%) (Fig. 1).

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We looked for correlations of silent period durations, MEP amplitudes (acquired at ISIs of 3, 5 and 15 ms and expressed as percentages of MEP amplitudes acquired at baseline – conditioning stimulus), and EEG activity with the variables disease duration, and attack frequency, duration and intensity.

Figure 1 - Duration of the cortical silent period. A) a normal subject. B) a patient affected by migraine with aura attacks (sporadic) and by migraine without aura (frequency of attacks: 2/month; intensity: severe). C) patient affected by migraine without aura (frequency of attacks: several/month).
The silent period duration correlated weakly with disease duration ($c=-0.28 \quad R^2=0.0796$), and with duration ($c=0.47 \quad R^2=0.230$) and intensity ($c=0.23 \quad R^2=0.0561$) of attacks; on the other hand, it showed a statistically significant correlation with frequency of attacks ($c=0.81 \quad R^2=0.6567$). MEPs recorded at ISIs of 3, 5 and 15 ms (and expressed as percentages of baseline MEPs) did not show a significant correlation with disease or attack duration (respectively $c=+0.42 \quad R^2=0.177$ and $c=+0.10 \quad R^2=-0.02$ at ISIs of 15 ms), whereas they were found to correlate significantly with frequency and intensity of attacks (respectively $c=+0.73 \quad R^2=0.53$ and $c=+0.56 \quad R^2=0.32$ at ISIs of 15 ms).

Altered EEG activity did not correlate significantly with any of the parameters considered (disease duration: $c=+0.19 \quad R^2=0.037$; attack duration: $c=+0.038 \quad R^2=0.001$; intensity: $c=+0.14 \quad R^2=0.02$; and frequency: $c=+0.04 \quad R^2=0.02$).

On fMRI, the migraineurs' functional activation maps following visual stimulation showed significantly less activation at occipital level than those of the controls (Fig. 3). In the ten migraine patients, we tested correlations of the results of the activation maps (expressed as number of activated voxels) with disease duration, as well as with the frequency, duration and intensity of attacks in each single patient, and found a significant inverse correlation between the frequency of the attacks and the size of the area activated during the visual stimulation task ($c=-0.50 \quad R^2=0.257$), whereas no statistically significant correlations were found with disease duration, or with intensity or duration of attacks.

Finally we tested for correlations between the fMRI activation maps of the migraineurs and CSP duration ($c=+0.57 \quad R^2=0.32$), amplitude of MEP as a % of baseline MEP ($c=-0.41 \quad R^2=-0.174$), and EEG ($c=-0.31 \quad R^2=-0.096$).

Discussion

The increased interictal reactivity of the visual cortex, revealed by fMRI, and of the primary motor area, recorded in response to TMS, would appear to support the hypothesis that abnormal cortical excitability is an important physiopathological mechanism in migraine with and without aura.

The shortened CSP, and the increased MEP amplitudes observed in our patients vs our control group may support the hypothesis of reduced cortical inhibition in migraine (6,7). Furthermore, the correlations observed in our CSP study are probably the result of a "disturbance" of the cortical inhibitory mechanisms (8): GABAergic inhibitory neurons in fact influence the duration of the CSP, as others have observed (9).

As regards the MEP amplitudes, our search for possible correlations produced results that make for a complex and variable picture requiring a dynamic interpretation that takes into account the continuous facilitatory and inhibitory phenomena to which the cerebral cortex is subject: indeed, at ISIs of between 1 and 5 ms, the conditioning stimulus activates intracortical GABAergic inhibitory circuits that induce a reduction of the amplitude of the MEP evoked by the test stimulus; at ISIs of between 6 and 15 ms the conditioning stimulus activates slower circuits, producing a facilitatory effect. Our study adds to the evidence of increased cortical excitability in migraineurs, which appears to condition significantly, and above all, the frequency and the intensity of migraine attacks. The absence of a significant correlation between MEP amplitude and attack intensity may be due in part to the fact that attack intensity, being conditioned by the use of analgesic drugs, by the patient’s psychological state, and by environmental factors, etc., cannot be considered a clear-cut parameter.

Numerous studies have reported EEG abnormalities in migraine patients in the headache-free periods and the literature data seem to suggest that there is no specific...
EEG picture that is characteristic of migraine (4). The correlations we considered in our study were not significant.

Finally, correlating electrophysiological findings with fMRI data, we found that increased cortical excitability documented through electrophysiological variables (reduced CSP; less inhibition of the MEP amplitude in response to the test vs the conditioning stimulus in the context of pTMS, and altered EEG activity) corresponded to reduced activation of the fMRI maps following photic stimulation, which would seem to indicate that less extensive activation of the fMRI maps correlates with increased cortical excitability. The results of our fMRI study showed less extensive and less marked activation in the occipital regions in the migraine subjects compared with the controls. Unlike fMRI studies of sensory and motor stimulation in which the extent and intensity of cortical activation is proportional to blood flow and thus to cortical excitability at the moment of stimulation, the activation we found in our study showed an inverse correlation with cortical excitability in migraineurs, who, according to electrophysiological studies in the literature, display a high basal level of cortical excitability (10, 11). Since the BOLD signal depends mainly on cortical perfusion of oxyhaemoglobin, it can be hypothesized that the reduced activation found on fMRI is due to a reduction of perfusion attributable not to vascular problems but to problems with neurotransmitter signalling. Abnormal signalling, as reported by the above cited electrophysiological studies, is due fundamentally to the heightened basal cortical excitability present in migraineurs. Furthermore, since the visual stimulus we used in our study can (as seen in other study protocols) easily trigger the onset of a migraine attack, it is possible that the cortical spreading depression (CSD) phenomenon—in which an initial phase of cortical excitability is followed by a long period of depression—was involved in our patients. Indeed, event-related fMRI studies have shown that with persistence of the visual stimulation, CSD “deactivates” the occipital areas previously activated. Our block-designed protocol, while failing to show the temporal advance of CSD, provides activation maps with greater statistical power, given that these were obtained from the means of eight rest vs activation periods (12).

This is, to our knowledge, the first neurophysiological and fMRI study of migraineurs in the interictal phase. Its results add weight to the suggestion that it may be possible, in migraineurs, to demonstrate an interictal cerebral dysfunction that significantly influences, above all, the frequency of the attacks. Our results are preliminary findings relating to a small number of subjects. Were they to be confirmed in larger series they would open up new avenues likely to further our understanding of migraine pathogenesis and treatment.

References