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Effects of levetiracetam vs topiramate and placebo on visually evoked phase synchronization changes of alpha rhythm in migraine

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Abstract

Objective: Recent theories about migraine pathogenesis have outlined an abnormal central processing of sensory signals, also suggested by an abnormal pattern of EEG hyper-synchronization under visual stimulation. The aim of the present study was to test the efficacy of topiramate and levetiracetam vs placebo in a double blind project observing the effects of the three treatments on the EEG synchronization in the alpha band under sustained flash stimulation.

Methods: Forty-five migraine without aura outpatients (MO) were selected and randomly assigned to 100 mg topiramate, 1000 mg levetiracetam or placebo treatment. In addition, 24 non-migraine healthy controls were submitted to EEG analysis. The EEG was recorded by 19 channels: flash stimuli with a luminosity of 0.2 J were delivered, in a frequency range from 3 to 30 Hz. We evaluated the phase synchronization index, that we previously applied in migraine, after EEG signals filtering in the alpha band. Our approach was based on the Hilbert transform.

Results: Both levetiracetam and topiramate significantly decreased migraine frequency, compared with placebo. MO patients displayed increased alpha-band phase synchronization as an effect of stimulus frequency; on the other hand the stimuli had an overall desynchronizing effect on control subjects. The phase synchronization index separates the two stages, before and after the treatment, only for levetiracetam, at stimulus frequencies of 9, 18, 24 and 27 Hz.

Conclusions: An abnormal alpha band synchronization under visual stimuli was confirmed in migraine; this phenomenon was reversed by levetiracetam preventive treatment.

Significance: These results confirmed in humans the inhibiting action of levetiracetam on neuronal hyper-synchronization.

Keywords: Migraine; Levetiracetam; Topiramate; EEG synchronization

1. Introduction

Migraine is a common and often disabling disorder that is increasingly being recognized as a fundamentally neurological problem. Studies of evoked and event-related potentials have provided further impetus for considering it as a neurological disorder (Goadsby, 2006). Migraine may thus be considered an aberrant physiological state

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with an interictal pattern of abnormal neuronal excitability (Welch, 2003).

In previous studies of visual evoked potentials in migraine the EEG during steady-state flash stimulation showed an amplitude increase in the alpha band (Simon et al., 1982) and in the frequency ranges corresponding to the flicker stimulation rates (F1 component) (Nyrke and Lang, 1982; Genco et al., 1994; de Tommaso et al., 2003), with more powerful spectra in the F1 and alpha band frequency ranges under fast Fourier analysis. These results concur with the pioneering finding of an increased photic driving of the EEG (Golla and Winter, 1959) in migraine patients, and suggest that sustained visual stimulation induces more synchronous net activity in the visual cortex of migraine patients between attacks. In a more recent study, we confirmed that migraine brain synchronizes to the rhythm of the visual areas under certain photic stimulations; in normal subjects however, brain regions involved in the processing of sensory information demonstrate desynchronized activity (Angelini et al., 2004). In light of these last results, it has been supposed that migraine is basically a sensory attentional problem with changes in cortical synchronization (Niebur et al., 2003) and all its clinical manifestations and electrophysiological changes might be accounted for by a disturbance of subcortical sensory modulation systems (Goadsby, 2005) which may be the trigger for the onset of the consequent cortical spreading depression and trigeminal activation. Understanding the basis for these abnormalities may improve the therapeutic approach (Goadsby, 2006).

Anti-Epileptic Drugs (AED) may increase the threshold for excitation and should be effective migraine preventive strategies: evidence of AED efficacy in migraine prophylaxis has grown progressively in the last years (Ramadan and Buchanan, 2006). To the best of our knowledge, few studies have been previously designed in order to test in humans the effects of AEDs on the main electrophysiological abnormalities subtending migraine, while most reports described the neurophysiologic effects of other preventive agents, such as beta-blockers, with contradictory results (for a review, see Schoenen et al., 2003).

Several modern, multicenter, multi-dose randomized controlled trials established the effectiveness of oral topiramate in episodic migraine prevention with the optimal dose of 100 mg/day (Brandes et al., 2004; Silberstein et al., 2004; Bussone et al., 2005). The biological substrate for the antimigraine effect of topiramate is likely a suppression of neuronal excitation. To this end, topiramate acts on cellular mechanisms of phosphorylation and blocks voltage-dependent Na-channels, potentiates GABA activity, inhibits AMPA/KA receptors, and blocks L- and N-calcium channels (Shank et al., 2004). Also, topiramate inhibits cortical spreading depression in cat and rat models that are relevant to migraine (Akerman and Goadsby, 2005).

Less evident is the efficacy of preventive therapy with levetiracetam in migraine (Cochran, 2004; Miller, 2004; Brighina et al., 2006). In animal models, levetiracetam contrasts to reference Anti-Epileptic Drugs by its ability to antagonize neuronal (hyper)synchronization, in the highly seizure-prone CA3 area of rat hippocampal slices (Margineanu and Klitgaard, 2000).

In addition, levetiracetam has shown efficacy in reducing photosensitivity in idiopathic generalized epilepsies (Covanis, 2005). These evidences suggest a possible action of levetiracetam on the phenomenon of alpha band synchronization induced by photostimulation in migraine patients.

The aim of the present study was to test the efficacy of topiramate and levetiracetam vs placebo in a double blind project, observing the effects of the three treatments on the alpha band synchronization pattern induced by photic stimulation.

2. Methods

2.1. Subjects

Forty-five migraine without aura outpatients (MO) (Headache Classification Committee, 2004), ages 18–49 (37.86 ± 12.35), 10 males and 35 females, eligible for migraine prophylaxis (Lipton et al., 2006), were selected and randomly assigned to a daily assumption of 100 mg topiramate BD, 1000 mg levetiracetam BD or placebo treatment. For one patient assuming placebo, two patients were randomly assigned to topiramate or levetiracetam. This was a double-blind, controlled study. The study design provided recordings in a pain-free state before (T0) and after 2 months treatment (T1). We also selected 24 non-migraine healthy subjects (17 F), aged 18–48 (mean age 35.2 ± 5.56), for EEG evaluation. All selected subjects were free from any psychoactive drugs, except for the assigned treatment, and none of them suffered from general, neurological and psychiatric diseases, according to DSM IV (1994). The study was approved by the Ethic Committee of the Bari Policlinico General Hospital, and the subjects gave their informed consent before selection. The frequency of headache (average number of days with headache/month, in the previous 2 months) was checked in all cases at T0 and T1 times. The univariate ANOVA with the type of treatment × the condition (before and after the treatment) as factors and the frequency of headache as dependent variable was employed. The percentage rate between the frequency of headache before and after treatment was further computed and the effects of the three treatments were tested by ANOVA and post-hoc Bonferroni test. We then used the Spearman test to correlate the percentage variations of headache frequency and phase synchronization induced by the drugs.

2.2. Recordings

The EEG was recorded by 19 channels, according to the 10–20 International System. The reference electrode was positioned at the linked earlobes (A1–A2), with the ground electrode placed over the nasion. Eye movements were

monitored by a pair of electrodes placed at the outer canthi of both eyes. EEG was digitized at 256 Hz sampling rate. For a preliminary visual inspection, EEG was filtered off line by means of a digital filter with a bandpass of 0.3–70 Hz and 70 μV sensibility.

At T0 and T1 times, all MA patients were free from pain in the prior 72 h and in the 48 h following the recording session (ascertained by telephonic interview).

2.3. Stimuli

Flash stimuli with a luminosity of 0.2 J were used. Subjects were tested in a dimly lit room while seated in a comfortable chair. The distance to the stroboscope was 20 cm. For each stimulus frequency, a 40 s stimulus interval was followed by a 20 s rest period. The subjects were instructed to relax during the experiment and keep their eyes closed; to avoid drowsiness they were requested to open their eyes for almost 10 s during the rest periods and talk to the experimenter; EEG tracks recorded with eyes open were not used for the analysis. Stimulus frequencies were presented in a random order. In this experiment, we used frequencies of 3, 6, 9, 12, 15, 18, 21, 24 and 27 Hz.

2.4. Phase synchronization

For all stimulus frequencies, we evaluated the phase synchronization index proposed by Tass et al. (2003), that we have successfully applied in a previous study (Angelini et al., 2004). Our approach was based on the Hilbert transform. Instantaneous phases for a bandpass filtered signal $s(t)$ were estimated via an analytic signal $\xi(t)$, which is defined as a complex function of time:

$$\xi(t) = s(t) + \mathrm{j}w(t) = A(t)\mathrm{e}^{\mathrm{j}\phi(t)}, \tag{1}$$

where $w(t)$ is the Hilbert transformation of $s(t)$:

$$w(t) = \frac{1}{\pi}\mathrm{P.V.}\int_{-\infty}^{\infty}\frac{s(\tau)}{t-\tau}\,\mathrm{d}\tau. \tag{2}$$

The notation P.V. denotes that the integral is evaluated according to the Cauchy principal value. In practice the transformation can be realized by a filter whose amplitude response is uniform, with a phase response that is a constant $\pi/2$ lag (Rosenblum et al., 1996). We used the specific MATLAB function that calculates the Fourier transformation of the signal and sets to zero those coefficients that correspond to negative frequencies, and applies the inverse transformation. To quantify the phase synchronization, the index proposed by Tass et al. (2003) was used. For all pairs of electrodes, the corresponding EEG signals were filtered in the alpha band and the instantaneous phases of the two selected channels $\phi_1(t)$ and $\phi_2(t)$ were evaluated as described above. The phase difference $\Delta\Phi(t) = [\phi_1(t) - \phi_2(t)]_{\mathrm{mod}\ 2\pi}$ was then evaluated for all times, t. The interval $[0, 2\pi]$, where the phase difference is defined, was divided into K bins. Phase synchronization is characterized by the appearance of peaks in the distribution, {n_k – relative frequency of phase differences in kth bin}, and of $\Delta\Phi$ onto the K bins. Given the entropy of the actual distribution of phase differences:

$$S = -\sum_{k=1}^{K} n_k \mathrm{Log}(n_k), \tag{3}$$

and naming $S_{\max} = \mathrm{Log}(K)$ the entropy of the uniform distribution, the synchronization index ρ is defined as follows:

$$\rho = \frac{S_{\max} - S}{S_{\max}}. \tag{4}$$

The index ρ ranges from 0 to 1, where 1 represents complete phase coupling.

EEG signals were filtered in the alpha band (8–12.5 Hz) with a second order, double-sided Butterworth filter. The phase synchronization index described above was evaluated for all pairs of electrodes, for all subjects and for all frequencies of the flash stimuli. These indexes were subsequently averaged over all the possible pairs of sensors, for each subject, both in the presence of stimuli and in spontaneous conditions.

For each stimulation frequency, we then calculated the difference

$$\Gamma = \rho^{\mathrm{flash}} - \rho^{\mathrm{spont}}, \tag{5}$$

where ρ^{flash} is the mean phase synchronization in presence of flash stimuli, and ρ^{spont} is the mean spontaneous phase synchronization. This difference measures how phase synchronization varies, in the presence of the stimuli, with respect to basal conditions (i.e., the net effect of the stimulus). Our supervised analysis (hypothesis testing) tested how much the index Γ separates the patients and the controls. For each of the nine frequencies, we applied the Wilcoxon rank sum test to Γ values and evaluated the probability p_ω that all the indexes were drawn from the same distribution (the null hypothesis). However, this approach to our data results in multiple comparisons. To control the number of false positives, we applied the Bonferroni correction to the threshold value.

A topographic analysis has also been performed, in order to check whether the phenomenon was localized in some cortical region. For each sensor s we evaluated the average synchronization with all the remaining electrodes, and computed an index Γ_s defined by

$$\Gamma_s = \rho_s^{\mathrm{flash}} - \rho_s^{\mathrm{spont}}. \tag{6}$$

For each stimulus frequency we applied our test, again with Bonferroni correction, to select among the 19 electrodes those whose synchronization separated the behaviour before and after the treatment, according to their Γ_s.

3. Results

3.1. Clinical data

At T0, the frequency of headache was similar across the three randomized groups (ANOVA with treatment as factor : $F(0.98) = 35$, ns; DF: 2).

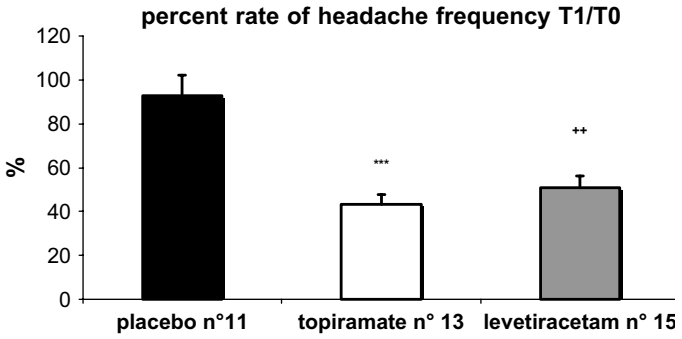

Fig. 1. Mean values and standard deviations of the percent rate (T1/T0) between the headache frequency before (T0) and after 2 months treatment (T1). Results of Bonferroni multiple comparison are showed: *** topiramate vs placebo: $p < 0.001$; levetiracetam vs placebo: $^{++}p < 0.01$.

Four patients in the placebo group and two patients in the topiramate groups dropped out for non compliance; one patient in the topiramate group withdrew due to adverse events (drowsiness and sedation). Three patients in the topiramate group reported drowsiness, eight a slight weight loss, and seven distal paresthesias, while five patients assuming levetiracetam referred sedation and dizziness in the first days of therapy. However, these side effects were tolerated and did not request drug cessation.

In the topiramate group at T1 8 patients exhibited a migraine frequency less than 50% of the basal frequency, 3 patients reported a migraine frequency between 55% and 65% of the basal one, in 2 patients it was left quite unmodified (between 95% and 98%). Eight patients assuming levetiracetam treatment reported a migraine frequency less than 50% of the basal frequency; in five patients levetiracetam reduced the attack's frequency to a rate between 55% and 65% of the basal one, in two patients it was the 85% and 95% of the frequency at T0. In the placebo group, the migraine frequency at T1 was between the 70% and 110% of the original frequency. The univariate ANOVA with the frequency of headache as dependent variable showed a significant difference between T0 and T1 (condition as factor: $F(14.22) = 74$, $p = 0.0001$; DF: 1) and a different outcome for the three treatments (condition × treatment $F(3.16) = 70$, $p = 0.049$; DF: 2). The rate between the frequency at T1 and T0 was significantly different in the placebo in respect with both topiramate and levetiracetam groups (Fig. 1).

3.2. Phase synchronization

Coming to the analysis of phase synchronization, migraine patients displayed an increased alpha-band phase synchronization as an effect of the stimulus frequency, mainly localized in the occipital electrodes. On the other hand, the stimuli have an overall desynchronizing effect on control subjects. As displayed in Fig. 2a, at T0 there

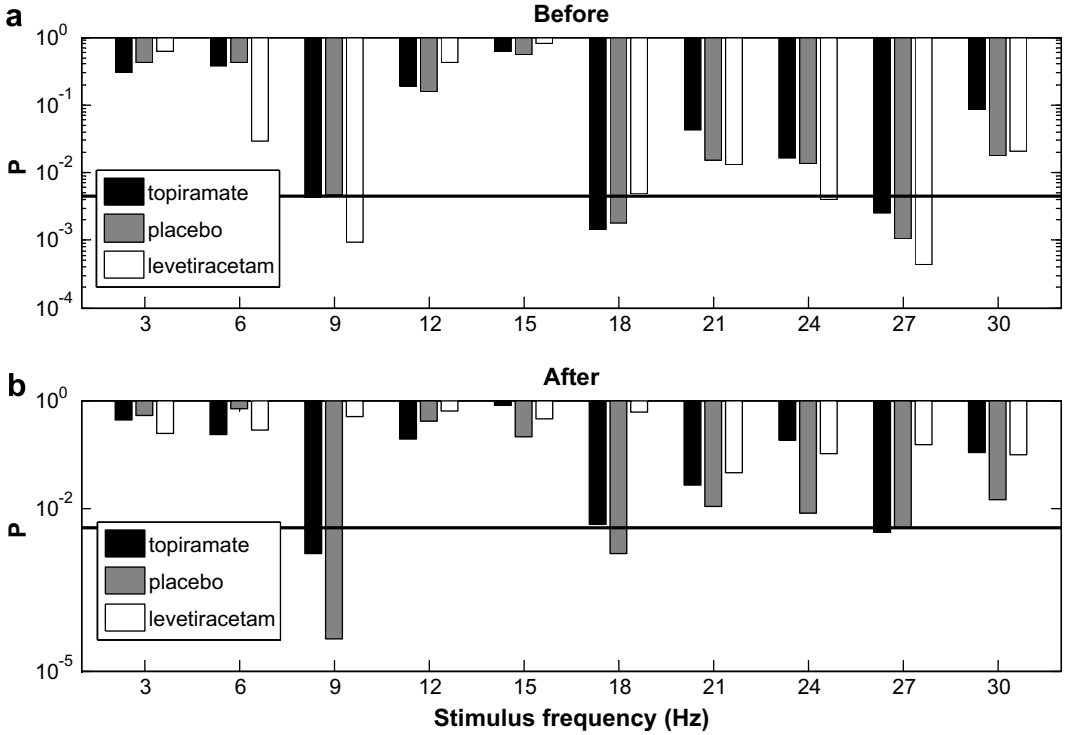

Fig. 2. (a) The probability p that values of Γ ($\Gamma = \rho^{\text{flash}} - \rho^{\text{spont}}$) at the stimulus flicker frequency, for control subjects and the three groups of patients before treatment, are drawn from the same distribution, evaluated according to the Wilcoxon Rank Sum test, displayed for all stimulation frequencies. (b) The probability p that values of Γ ($\Gamma = \rho^{\text{flash}} - \rho^{\text{spont}}$) at the stimulus flicker frequency, for control subjects and the three groups of patients after treatment, are drawn from the same distribution, evaluated according to the Wilcoxon Rank Sum test, displayed for all stimulation frequencies. The horizontal line is the threshold after Bonferroni correction. Values below this line discriminate between patients and healthy subjects.

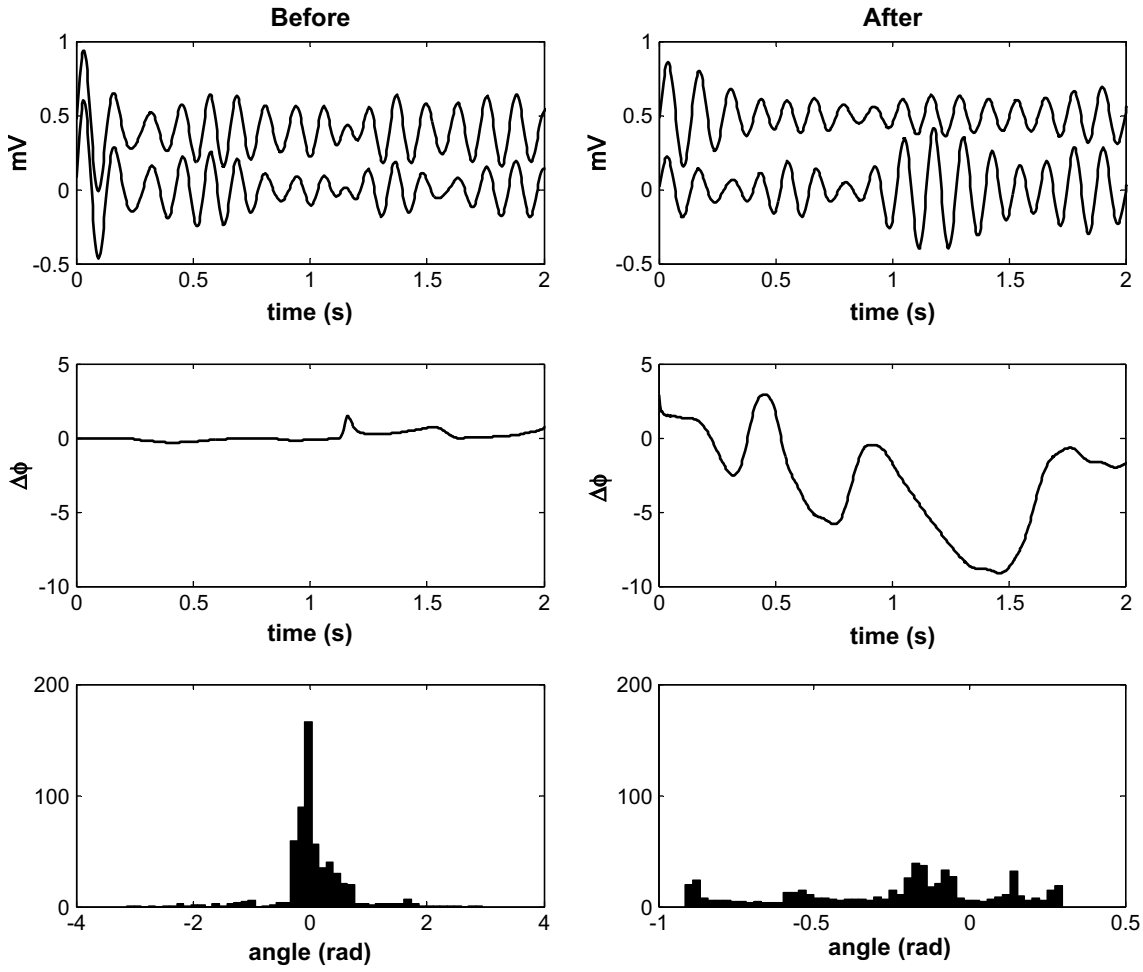

Fig. 3. Presence and absence of phase synchronization. Left: one patient before treatment with levetiracetam; Right: the same patient after the treatment. Top: EEG signals from O1 (lower trace) and O2 (upper trace, with an offset) electrodes, normalized and filtered in the alpha band. Middle: The phase synchronization $\Delta\phi$; as a function of time. Bottom: The histogram of the values of $\Delta\Phi = [\Delta\phi] \bmod 2\pi$.

was a significant difference between the index Γ ($\Gamma = \rho^{\text{flash}} - \rho^{\text{spont}}$) computed in normal subjects and the same index in the three groups of migraine subjects, for the stimulus frequencies 9, 18, 24 and 27 Hz.

At T1, patients treated with placebo and topiramate showed a persisting hyper-synchronization pattern of alpha rhythm with respect to controls at 9, 18 and 27 Hz flicker frequency (Fig. 2b). On the other hand, the synchronization pattern recovered within normal limits in patients treated with levetiracetam at all the stimulus frequencies detailed above (Figs. 2b and 3). As it concerns the spatial analysis of the synchronization pattern we observed that, for the above-mentioned separating stimulus frequencies, the stimulus-induced synchronization decreases after the treatment with levetiracetam, mainly in correspondence of the occipital electrodes. This behaviour was common to all the separating frequencies, and is depicted in Fig. 4 for the case of 9 Hz flicker (Fig. 4). The explanation for this spatial characterization is more evident when one considers the difference in synchronization for all the couples of electrodes. The desynchronizing effect of levetiracetam acts mainly on the interactions between occipital electrodes, as shown in Fig. 5.

The percentage variation of the Γ index ($\Gamma = \rho^{\text{flash}} - \rho^{\text{spont}}$) and the headache frequency were significantly correlated in the levetiracetam group for the 9 and 18 Hz flickering frequency (Spearman correlation: 9 Hz 0.625; 18 Hz 0. 619: $p < 0.05$) (Fig. 6) and approached statistical significance for the 24 (Spearman correlation: 0.518: $p = 0.055$) and 27 Hz (0.520: $p = 0.051$) stimulation frequencies.

4. Discussion

In the present study we confirmed previous findings about a hyper-synchronization pattern of alpha rhythm under repetitive flash stimulation in migraine patients and an opposite pattern of de-synchronization in controls. Indeed in basal conditions the three migraine groups exhibited an increased value of phase synchronization of alpha band under flash stimulation at different frequencies, particularly 9, 18, 24 and 27 Hz, with respect to controls (Angelini et al., 2004). Whilst it is comprehensible that

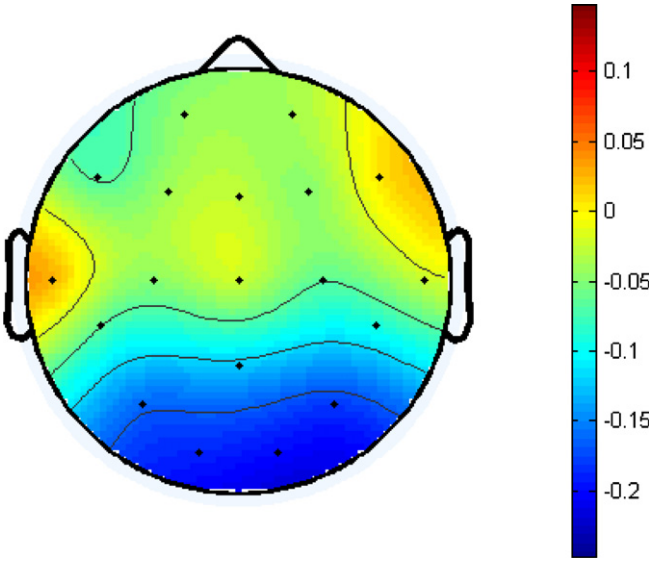

Fig. 4. Map of the difference between synchronization indexes $\Gamma_s(\Gamma_s = \rho_s^{\text{flash}} - \rho_s^{\text{spont}})$ averaged over all patients, before and after the treatment with levetiracetam; the frequency of the flicker is 9 Hz. Note that the decrease in synchronization after the treatment is mostly localized in the occipital electrodes.

9 Hz stimuli might cause hyper-synchronization in the alpha band (8–12.5 Hz), the 18–24 and 27 Hz frequencies of stimulation may have caused alpha band synchronization through their sub-harmonics (Angelini et al., 2004). Unlike classical methods such as coherence, phase extraction by means of the Hilbert transform separates the effects of amplitude and phase in the interrelations between two signals. So we observed phase locking across neighbouring scalp electrodes even if the amplitudes remained uncorrelated, under the hypothesis that amplitudes of the signals are sufficiently large so that the estimated phases reflect the signals more than the background uncorrelated noise (Le Van Quyen et al., 2001).

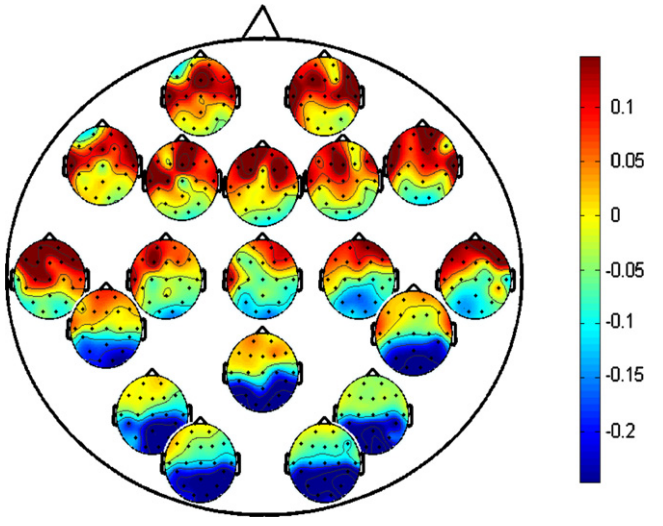

Fig. 5. We display the variation of the synchronization index $\rho^{\text{flash}} - \rho^{\text{spont}}$, averaged over all patients, for stimulus frequency of 9 Hz, before and after the treatment with levetiracetam. At every channel location, the map of the synchronization index with all the other channels is shown.

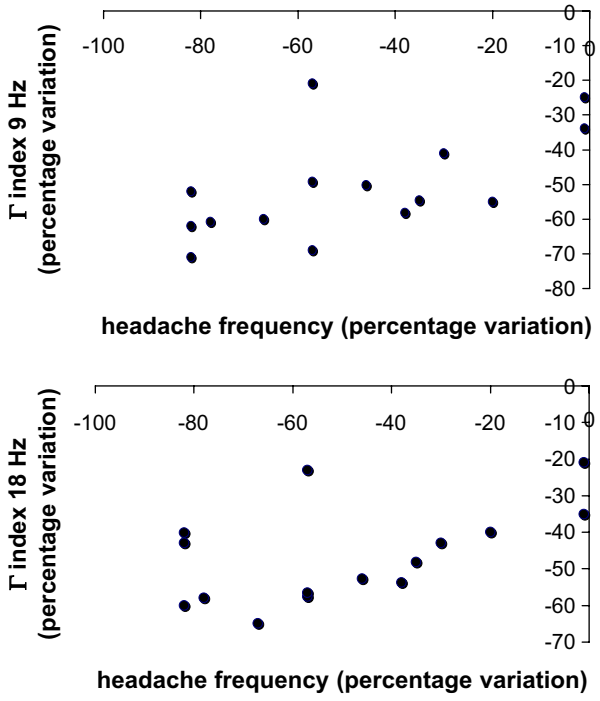

Fig. 6. Scatter-plots of the relationships between percentage variation of headache frequency and Γ index ($\Gamma = \rho^{\text{flash}} - \rho^{\text{spont}}$) induced by levetiracetam treatment.

In light of the present results we can confirm the hypothesis suggested by Goadsby (2006) that migraine is subtended by an abnormal central processing of sensory signals, probably due to a disturbance of sub-cortical sensory modulation systems. Both topiramate and levetiracetam exerted a positive effect on migraine frequency, reducing by 50% the days of headache, which was significant in respect to placebo. This is a confirmatory result about the efficacy and tolerability of both drugs in migraine, well defined for topiramate (Brandes et al., 2004; Silberstein et al., 2004; Bussone et al., 2005) and reported only in few studies for levetiracetam (Cochran, 2004; Miller, 2004; Brighina et al., 2006).

Despite this similar effect on clinical outcome of migraine the two drugs acted in a different way on the EEG synchronization pattern, which was left absolutely unmodified by topiramate as well as by placebo, and completely reversed by levetiracetam.

The biological substrate for the anti-migraine effect of topiramate is likely a suppression of neuronal excitation (Ramadan and Buchanan, 2006). To this end, topiramate blocks voltage-dependent Na-channels and L- and N-calcium channels, potentiates GABA activity and inhibits AMPA/KA receptors (Shank et al., 2004).

The above-mentioned action mechanisms of topiramate are probably linked with the inhibition of cortical spread-

ing depression (Akerman and Goadsby, 2005) and of the trigeminal neurons activated by nociceptive intracranial afferents (Storer and Goadsby, 2004), which explained its efficacy in reducing migraine onset.

These actions on neuronal excitation did not exert any effect on alpha hyper-synchronization patients found in migraine, which was on the other hand reversed by levetiracetam.

In animal models the antagonizing action on the neuronal (hyper)synchronization seemed peculiar for levetiracetam in respect to valproate, clonazepam and carbamazepine (Margineanu and Klitgaard, 2000). The present result constitutes the first acknowledgment of this action in a human model of EEG hyper-synchronization. The correlation between the reducing effect on alpha rhythm hyper-synchronization and headache frequency in the levetiracetam group confirmed that the EEG changes induced by the drug were linked to its therapeutic action. According to the most recent pathophysiological hypothesis of migraine (Goadsby, 2006), levetiracetam may reverse the effects of the abnormal sub-cortical modulation on the rhythmic cortical activities through its desynchronizing action, thus avoiding the triggering of the consequent phenomena of cortical spreading depression and trigeminal activation, whose development is probably inhibited by topiramate (Storer and Goadsby, 2004; Akerman and Goadsby, 2005).

We confirm here the efficacy of EEG nonlinear analysis in providing insights into the biological mechanisms of migraine (de Tommaso et al., 1999; Angelini et al., 2004) and further outline their utility in the monitoring of central effects of drugs (Fingelkurts et al., 2005).

In a previous study we failed to observe a significant correlation between the severity of migraine and the expression of EEG hyper-synchronization pattern (de Tommaso et al., 2005), and thus the markers of this predisposing neuronal condition may not support the indication for migraine prophylaxis, which is based on clinical criteria of headache frequency and impairment (Lipton et al., 2006). In the present study, however, we observed two and three non-responding patients, respectively, in topiramate and levetiracetam group: in the latter group the non-responding patients did not exhibit a strong desynchronizing effect on their EEG, according to the correlation between the clinical and electrophysiological effects of levetiracetam.

In light of these results we can suppose that the identification of subgroups of migraine patients with pronounced expression of some neuro-physiological index of migraine predisposition – e.g., hyper-synchronization – may optimize the choice of the preventive agent: this should be tested in further studies.

References

Akerman S, Goadsby PJ. Topiramate inhibits cortical spreading depression in rat and cat: impact in migraine aura. NeuroReport 2005;16:1383–7.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-IV). 4th ed. Washington, DC: American Psychiatric Association; 1994.

Angelini L, de Tommaso M, Guido M, Hu K, Ivanov PCh, Marinazzo D, et al. Steady-state visual evoked potentials and phase synchronization in migraine. Phys Rev Lett 2004;93:038103-1–3-4.

Brandes JL, Saper JR, Diamond M, Couch JR, Lewis DW, Schmit J, et al. Topiramate for migraine prevention: a randomized controlled trial. JAMA 2004;291:965–73.

Brighina F, Palermo A, Aloisio A, Francolini M, Giglia G, Fierro B. Levetiracetam in the prophylaxis of migraine with aura: a 6-month open-label study. Clin Neuropharmacol 2006;29(6):338–42.

Bussone G, Diener HC, Pfeil J, Schwalen S. Topiramate 100 mg/day in migraine prevention: a pooled analysis of double-blind randomised controlled trials. Int J Clin Pract 2005;59:961–8.

Cochran JW. Levetiracetam as migraine prophylaxis. Clin J Pain 2004;20:198–9.

Covanis A. Photosensitivity in idiopathic generalized epilepsies. Epilepsia 2005;46:67–72.

de Tommaso M, Marinazzo D, Guido M, Libro G, tramaglia S, Nitti L, et al. Visually evoked phase synchronization changes of alpha rhythm in migraine: correlations with clinical features. Int J Psychophysiol 2005;57:203–10.

de Tommaso M, Sciruicchio V, Bellotti R, Guido M, Sasanelli G, Specchio LM, et al. Photic driving response in primary headache: diagnostic value tested by discriminant analysis and artificial neural network classifiers. Ital J Neurol Sci 1999;20:23–8.

de Tommaso M, Stramaglia S, Schoffelen JM, Guido M, Libro G, Losito L, et al. Steady-state visual evoked potentials in the low frequency range in migraine: a study of habituation and variability phenomena. Int J Psychophysiol 2003;49:165–74.

Fingelkurts AA, Fingelkurts AA, Kahkonen S. New perspectives in pharmaco-electroencephalography. Prog Neuropsychopharmacol Biol Psychiatry 2005;29:193–9.

Genco S, de Tommaso M, Prudenzano AM, Savarese M, Puca FM. EEG features in juvenile migraine: topographic analysis of spontaneous and visual evoked brain electrical activity: a comparison with adult migraine. Cephalalgia 1994;14:41–6.

Goadsby P. Can we develop neurally acting drugs for the treatment of migraine? Nat Rev 2005;4:741–50.

Goadsby P. Recent advances in understanding migraine mechanisms, molecules and therapeutics. Trends Mol Med 2006;13:39–44.

Golla FL, Winter AL. Analysis of cerebral responses to flicker in patients complaining of episodic headache. Electroencephalogr Clin 1959;11:539–49.

Headache Classification Committee. The international classification of headache disorders II. Cephalalgia 2004;24:24–136.

Le Van Quyen M, Lachaux JP, Rodriguez E, Lutz A, Martinerie J, Varela FJ. Comparison of Hilbert transform and wavelet methods for the analysis of neuronal synchrony. J Neurosci Meth 2001;111:83–98.

Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2006;30(68):343–9.

Margineanu DG, Klitgaard H. Inhibition of neuronal hypersynchrony in vitro differentiates levetiracetam from classical antiepileptic drugs. Pharmacol Res 2000;42:281–5.

Miller GS. Efficacy and safety of levetiracetam in pediatric migraine. Headache 2004;44(3):238–43.

Niebur E, Hsiao SS, Johnson KO. Synchrony: a neural mechanism for attentional selection? Curr Opin Neurobiol 2003;12:190–4.

Nyrke T, Lang AH. Spectral analysis of visual evoked potentials by sine wave modulated light in migraine. Electroencephalogr Clin Neurophysiol 1982;53:436–42.

Ramadan NM, Buchanan TM. New and future migraine therapy. Pharmacol Ther 2006;112:199–212.

Rosenblum MG, Pikovsky AS, Kurths J. Phase synchronization of chaotic oscillators. Phys Rev Lett 1996;76:1804.

Schoenen J, Ambrosini A, Sandor PS, Maertens de Noordhout A. Evoked potentials and transcranial magnetic stimulation in migraine: published data and viewpoint on their pathophysiologic significance. Clin Neurophysiol 2003;114(6):955–72.

Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. Epilepsia 2004;41:S3–9.

Silberstein SD, Neto W, Schmitt J, Jacobs DMIGR-001 Study Group. Topiramate in migraine prevention: results of a large controlled trial. Arch Neurol 2004;61:490–5.

Simon RH, Zimmerman AW, Tasman A, Hale MS. Spectral analysis of photic stimulation in migraine. Electroencephalogr Clin Neurophysiol 1982;53:270–6.

Storer RJ, Goadsby PJ. Topiramate inhibits trigeminovascular neurons in the cat. Cephalalgia 2004;24:1049–56.

Tass PA, Fieseler T, Dammers J, Dolan K, Morosan P, Majtanik M, et al. Synchronization tomography: a method for three-dimensional localization of phase synchronized neuronal populations in the human brain using Magnetoencephalog. Phys Rev Lett 2003;90:1–4.

Welch KMA. Contemporary concepts of migraine pathogenesis. Neurology 2003;61:S2–8.