Cortical excitability in migraine

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Abstract  Cortical hyperexcitability in migraine has been suggested to play a pivotal role in triggering migraine attacks, possibly via generation of spreading depression. Low levels of plasma, intracellular and brain magnesium as well as increased amplitudes of visual evoked potentials support this theory. More recent data on evoked and event related potentials, i.e. lack of habituation and low initial amplitudes during repetitive stimulation, however, may indicate reduced levels of cortical excitability. Transcranial magnetic stimulation of motor and visual cortices, a direct method to assess cortical excitability, yielded contradictory results. Lower or elevated motor thresholds, amplitudes and/or phosphene prevalence or even no significant differences at all were demonstrated suggesting also cortical hypo- rather than hyperexcitability in migraine. Methodological differences, selection of subjects, and timing of investigations might partly explain these marked differences. Clinical and genetic heterogeneity of migraine, for instance via opposite influence on neuronal excitability caused by recently described ion-channel mutations, might provide further explanation.

Key words Migraine • Excitability • Evoked potential • Transcranial magnetic stimulation • Biochemical data

Introduction

Migraine is a chronic, paroxysmal disorder, characterized by repetitive attacks of headache, nausea, vomiting, and photo- and phonophobia [1]. Any individual can suffer one or two migraine attacks in their lifetime [2] but more or less regular repetition of migraine attacks is regarded as a disease described as early as in the Egyptian times [3]. In recent years research on the pathomechanism of the migraine attack was stimulated by the introduction of selective serotonin receptor agonist drugs, the so-called triptans. Better understanding and, in parallel, more efficacious treatment of attacks have major importance for migraine sufferers. Another exciting issue of scientific research is the generation of repetitive attacks. A number of trigger factors for migraine attacks have been described previously but their mechanisms are still not clearly understood. Changes in cortical excitability might be a plausible explanation and, indeed, various studies of the visual system suggested cortical hyperexcitability of migraine patients between attacks [4–11]. Most recently, however, cortical hypo-, instead of hyperexcitability in the interictal period has also been demonstrated in some studies [12, 13]. Therefore, a review of current biochemical and electrophysiological data about cortical excitability in migraine seemed to be worthwhile.

Biochemical data

Serum, erythrocyte and saliva magnesium levels are reduced in patients with migraine with aura (MA) or without aura (MO) (Table 1) [14–17]. Lower magnesium levels
were also found in blood mononuclear cells which provide the most valid assessment of tissue magnesium stores [18]. Low levels of magnesium in cerebrospinal fluid (CSF) have been reported in migraineurs, but in the same study serum levels were normal [19]. On the other hand, Smeets et al. [20] failed to demonstrate any significant difference in whole blood cellular magnesium levels between groups of afflicted and non-afflicted members of 3 families with familial hemiplegic migraine (FHM), MO, MA and healthy controls. Using 31-phosphorus magnetic resonance spectroscopy (31P-MRS), a 20% decrease of brain magnesium was measured during a migraine attack and magnesium levels were lower, although not significantly so, in migraine patients studied between attacks [21, 22]. Welch et al. [23] were first to report a decrease of organic phosphates relative to inorganic phosphates (an index of phosphorylation potential in mitochondria) in the brain cortex using 31P-MRS. These findings were confirmed and further extended to show reduced mitochondrial phosphorylation potential and energy reserve in the occipital cortex of MO and MA patients compared to healthy controls [24, 25]. This appears to be a generalized mitochondrial dysfunction in migraine, as it was also demonstrated in platelets and muscles [26, 27]. More recently, low brain magnesium, low phosphocreatine and high inorganic phosphate concentrations were demonstrated in juvenile MA patients between attacks [28].

Magnesium is essential for the energy transport of the cell and has major influence on membrane stability and as a consequence, on cortical excitability. Low levels of brain magnesium might therefore predispose the brain to spontaneous initiation of spreading depression (SD) or its activation via trigger factors. Neuroexcitatory amino acids and NMDA receptors may also be involved in SD generation and mediation. Elevated plasma levels of glutamate (GLU) and aspartate (ASP) were found in migraine patients between attacks and were further elevated during the attack [29]. Martinez et al. [30] found lower plasma and elevated CSF levels of the same amino acids in migraineurs during the attack. Between attacks, Cananzi et al. [31] found higher levels of platelet GLU in MA and of serum GLU in MO patients compared to healthy controls in adults, whereas D’Eufemia et al. [32] found lower GLU and ASP plasma levels and high erythrocyte/plasma concentrations of GLU and ASP in juvenile migraineurs. NMDA antagonists blocked or

| Substance | Sample          | Patients                   | Reference         |
|-----------|-----------------|----------------------------|-------------------|
| Magnesium ↓ | Serum Erythrocytes Mononuclear cells Saliva CSF Brain | MO, MA interictal | [14–19, 21]       |
| Magnesium = | Serum Whole blood cellular | MO, MA interictal | [19] |
| Glutamate ↑ | Plasma CSF Platelet Plasma | MO, MA ictal and interictal | [29, 30] |
| Glutamate ↓ | Plasma Plasma | MO, MA ictal Juvenile MO, MA | [30, 32] |
| Aspartate ↑ | Plasma Plasma | MO, MA ictal and interictal | [29, 30] |
| Aspartate ↓ | Plasma CSF | Juvenile MO, MA | [32] |

MO, migraine without aura; MA, migraine with aura; FHM, familial hemiplegic migraine; CSF, cerebrospinal fluid
suppressed spreading depression, and capsaicin induced c-fos expression in the trigeminal nucleus caudalis in animal models [33–35]. Interestingly, other compounds used either in the acute or prophylactic migraine therapy failed to reduce the propagation of SD in animal models [36].

Magnesium has been applied as a prophylactic drug in migraine and has been found to be effective in 2 double-blind, placebo-controlled trials with a therapeutic gain of 18.4% over placebo [37, 38], whereas in one trial no significant difference was found compared to placebo [39]. There are some early reports on the use of magnesium sulfate as an acute migraine treatment. Mauskop et al. [40, 41] found magnesium sulfate injection to be highly effective in attacks of migraine and cluster headache and also in tension-type headache and transformed migraine.

**Psychophysical studies of the visual pathways**

Migraine patients are more sensitive to environmental light stimuli [9, 10] and they report more intense illusions and more discomfort after visual stimulation with grating patterns than normal subjects (Table 2) [6, 7]. The latter abnormality may be more pronounced in MA than in MO [42]. Wray et al. [9] demonstrated that MA patients react faster in tasks reflecting low-level visual processing which might be related to visual hypersensitivity. Palmer and Chronicle [43] were not able to replicate their results using the same study design. In another study assessing the speed of visual processing in tasks of different complexity, no difference was observed in the accuracy rate or in the speed of response between MO and MA patients and controls [44]. Metacontrast masking is a paradigm critically dependent on inhibitory interactions in the primary visual cortex. In MA patients the masking function was significantly shallower, indicating cortical hyperexcitability [45]. Background grating hinders most MA patients in detecting a target letter [46] and subtle deficits in chromatic processing can be found in these patients [47].

Most of the abnormalities reported in migraine were more pronounced in MA and reflect dysfunctions at the cortical level, i.e. a hyperexcitability of the visual cortex. They might favor the hypothesis [48] that visual dysfunctions in migraine with aura are secondary to a loss of inhibitory GABAergic interneurons in the visual cortex due to repeated parenchymal insults during the aura, although these abnormalities were not more pronounced in patients with more frequent attacks or longer disease duration.

**Table 2** Psychophysical studies in migraine patients

| Method                                | Results                                | Patients          | Reference |
|---------------------------------------|----------------------------------------|-------------------|-----------|
| Questionnaire                         | ↑ Sensitivity to environmental light stimuli | MO, MA           | [10]      |
| Visual stimulation with grating pattern | ↑ Illusions and ↑ discomfort            | MO, MA compared to HV | [7, 8]   |
|                                       | ↑ Illusions and ↑ discomfort            | MA compared to MO, HV | [42]      |
| Tasks of low-level visual processing   | Faster reaction                        | MA compared to HV | [9]       |
|                                       | No difference                          | MA, MO, HV       | [43]      |
| Tasks reflecting speed of visual processing | No difference                          | MO, MA compared to HV | [44]     |
| Metacontrast masking                  | Shallower masking                      | MA compared to MO, HV | [45]  |
| Target letter detection against background grating | Higher luminance needed for detection | MA compared to MO, HV | [46]  |
| Detection of target orientation       | ↓ Speed for red line detection         | MA compared to MO, HV | [47] |

*MO, migraine without aura; MA, migraine with aura; HV, healthy volunteers*
Evoked and event-related potentials

Amplitudes of visual evoked potentials (VEP) were higher in MA and MO compared to healthy volunteers in a number of studies using flash or pattern-reversal stimulation [4, 5, 49–52]. Other groups failed to demonstrate any difference between migraineurs and healthy volunteers (Table 3) [53–56]. High amplitudes of averaged evoked potentials might however be a consequence of a deficit in the physiological habituation of responses shown during repetitive stimulations for VEP [57, 58], auditory evoked cortical responses [59] as well as event-related potentials, such as auditory novelty P3 [60], visual evoked oddball P3 [61] and contingent negative variation (CNV) [62, 63]. High VEP and CNV amplitudes decreased after prophylactic treatment with a betablocker [6, 62].

In children suffering from migraine, high amplitudes of VEP to flash stimuli [64] and CNV amplitudes [65, 66] as well as lack of habituation measured by P3 amplitude and latency [67] have been demonstrated.

During repetitive stimulation, a low amplitude of evoked cortical potentials after a small number of averagings or low intensity auditory stimulations was found in migraine patients interictally in several studies [57–59, 68, 69]. This might be due to a low preactivation level of sensory cortices [70] which can be caused by hypofunctioning state setting subcortico-cortical pathways [71, 72]. Moreover, a negative correlation has been demonstrated between initial VEP amplitude and its change during repeated stimulation in migraine patients and healthy subjects. By contrast, intensity dependence of cortical auditory evoked potentials (IDAP) is influenced by initial AEP amplitudes at low intensities only in migraineurs [68]. Taken together, these observations suggest that cortical preactivation levels are pivotal for the pathophysiological abnormalities found in migraine and low levels are in favor of a cortical hypoexcitability.

In addition, VEP and IDAP as well as CNV were found to undergo marked changes in temporal relation to the attack. Amplitudes tended to normalize during the attack [62], but they increased 2 days before the attack and returned to interictal levels during the days following the attack [69, 73, 74]. In most previous studies of evoked- or event-related potentials, the delay between the recordings and the next attack was not determined, which may in part account for the variability of findings.

Red light activates the visual cortex more strongly than other wavelengths [75]. For instance, red light but not light of other colors was able to trigger a photoconvulsive response in epileptic patients [76]. In a study of repetitive pattern reversal stimulations with the use of tinted glasses, healthy subjects showed a marked increase of VEP amplitudes to red light stimulation which was not found in migraine patients [13]. This lack of amplitude increase in MA patients might also indicate cortical hypoexcitability.

Transcranial magnetic stimulation

Transcranial electromagnetic stimulation (TMS) is an atraumatic and well-studied tool which is able to directly assess excitability of both motor and visual cortices as well as intracortical inhibition in the motor cortex when paired stimuli are applied with short interstimulus intervals [77, 78].

Studies using percutaneous magnetic stimulation of the motor cortex were performed in migraine patients, yielding

| Method                        | Results                  | Patients                   | Reference |
|-------------------------------|--------------------------|----------------------------|-----------|
| Flash stimulus                | ↑ P1 amplitude           | MO, MA                     | [49]      |
|                               | ↑ N3 amplitude           | MO, MA                     | [4, 50]   |
| Pattern reversal              | No difference            | MO                         | [53–56]   |
|                               | ↑ P100 amplitude         | MA (duration < 10 years)   | [51]      |
|                               | ↑ P100 amplitude         | MO, MA                     | [52]      |
|                               | ↓ P100 amplitude         | MA (duration > 10 years)   | [51]      |
| Pattern reversal repetitive stimulation | Lack of habituation    | MO, MA                     | [57, 58]   |

MO, migraine without aura; MA, migraine with aura
partly contradictory results. Maertens de Noodhout et al. [79] previously observed increased motor thresholds and electromyography (EMG) responses of smaller amplitudes after stimulation of the usually affected hemisphere in patients suffering from migraine with aura. Abnormally high motor thresholds were found bilaterally during and between attacks of menstrual migraine [80] as well as over the affected hemisphere in FHM [81]. By contrast, the latter group [82] had significantly increased amplitudes of EMG responses after motor cortex TMS in MO and MA and a positive correlation with attack frequency, but no motor threshold differences (Table 4).

My colleagues and I found that motor thresholds during isometric contraction were significantly higher in MA patients than in healthy controls, whereas no differences were found between migraineurs and healthy volunteers for motor thresholds at rest, maximal response amplitudes, MEP_max/M_max ratios or motor evoked potential modulation by conditioning stimuli with short interstimulus intervals [12].

Besides methodological differences, one has to take into account the timing of the recording in relationship to the attack to interpret these partly contradictory observations. The possible occurrence of an attack shortly after the recording was not monitored in Van der Kamp et al.’s study [82]. Modifications of motor cortex excitability around a migraine attack might have been a confounding factor in the latter study, especially since the MEP_max/M_max ratio increase observed by these authors was highest in patients with the most frequent attacks.

Excitability of the visual cortex can be estimated in individual subjects by determining the TMS threshold for phosphenes induction, and group differences can be sought by assessing the prevalence of phosphenes at maximal stimulator output [83]. Aurora et al. [84, 85] found that a significantly higher proportion of migraineurs experienced phosphenes and the probability of triggering an attack in migraineurs was higher than in controls (Table 5). They concluded that excitability of the visual cortex to TMS is increased in migraine with aura. Aguggia et al. [86] were not able to detect any difference in phosphen prevalence between MA, tension-type headache patients or healthy controls, whereas the threshold of phosphene generation was significantly lower in MA. As a striking difference to these findings [84–86], we demonstrated significantly lower prevalance of phosphenes in migraine with aura after occipital TMS without any significant threshold differences [12].

The reason for this may be multiple; first of all, methodological differences cannot be excluded. Patient selection might be an explanation, as patients were selected according to their propensity to having attacks triggered by visual stimuli in Aurora et al.’s study (personal communication) but not in ours. Another interesting factor is the low prevalence of phosphenes in the control group (25%) in Aurora et al.’s study which was not the case in the other studies cited (89% and 100%).

### Table 4 Transcranial magnetic stimulation of motor cortex in migraine patients compared to healthy controls

| Method                        | Results                        | Patients                        | Reference |
|-------------------------------|--------------------------------|---------------------------------|-----------|
| **Threshold**                 |跟你 usually affected hemisphere| MA interictal                   | [79]      |
|                               | ↑ Bilaterally                  | Menstrual migraine ictal and interictal | [80]     |
|                               | ↑ Over the affected hemisphere | FHM interictal                  | [81]      |
|                               | ↑ During isometric contraction | MA interictal                   | [12]      |
| **Amplitudes (MEP_max/M_max ratio)** | ↑ Bilaterally                  | MO, MA interictal in positive correlation with attack frequency | [82]     |
|                               | No difference                  | MO, MA interictal               | [12]      |
| **Paired stimulation with short interstimulus interval** | No difference                  | MO, MA interictal               | [12]      |

*MO*, migraine without aura; *MA*, migraine with aura; *FHM*, familial hemiplegic migraine
Conclusions

Biochemical and electrophysiological data reviewed in this article do not unanimously favor cortical hypo- or hyperexcitability in migraine. Low magnesium levels, reduced mitochondrial energy reserves and elevated levels of neuroexcitatory amino acids might suggest cortical hyperexcitability. However, therapeutic trials with magnesium show low efficacy rates, which does not indicate a major role of magnesium in attack generation. Electrophysiological data are even more contradictory. Some of these contradictions can be explained by recent findings, like lack of habituation of evoked and event-related potentials between attacks and their marked changes in the peri-attack period which were not taken into account in previous studies. Most striking differences are presented in studies using transcranial magnetic stimulation. Besides methodological differences, selection of migraine patients and controls and timing of investigations might provide some explanation. Migraine is undoubtedly heterogenous from both clinical and pathophysiological points of view. It is most probably a polygenic disorder and the weight of the various genes might also differ between patients [87]. The only gene that has hitherto identified codes for the alpha subunit of a P/Q calcium channel (CACNL1A4) and may contain various missense mutations or deletions [88]. Depending on the site of the mutation within the gene, the functional consequence on the ion channel is either a loss or a gain in function [89, 90]. Such mutations will exert opposite influences on cortical neurons.

References

1. Headache Classification Committee of the International Headache Society (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 8[Suppl 7]:1–96
2. Blau JN (1987) Adult migraine: the patient observed. In: Blau JN (ed) Migraine: Clinical, therapeutic, conceptual and research aspects. Chapman and Hall, London, p 30
3. Venzmer G (1972) Five thousand years of medicine. Taplinger. New York, p 19
4. Gawel M, Connolly JF, Clifford Rose F (1983) Migraine patients exhibit abnormalities in the visual evoked potential. Headache 23:49–52

Table 5 Tran cranial magnetic stimulation of occipital cortex in migraine patients and healthy volunteers

| Method                                | Results                  | Patients | Reference |
|---------------------------------------|--------------------------|----------|-----------|
| Phosphen prevalence                    | 27% in HV                | 11 MA    | [84]      |
|                                       | 100% in MA               | 11 HV    |           |
|                                       | 25% in HV                | 8 HV     | [85]      |
|                                       | 87% in MA+MO             | 1 MO     |           |
|                                       |                          | 14 MA    |           |
|                                       | 89% in HV                | 19 HV    | [12]      |
|                                       | 82% in MO                | 22 MO    |           |
|                                       | 56% in MA                | 18 MA    |           |
|                                       | 100% in HV               | 10 MA    | [86]      |
|                                       | 100% in MA 10 HV         |          |           |
| Threshold for phosphen generation     | ↓ in MA                  | 3 HV     | [84]      |
|                                       |                          | 11 MA    |           |
|                                       | ↓ in MA                  | 2 HV     | [85]      |
|                                       |                          | 13 MA    |           |
| No significant difference             | 17 HV                    | [12]     |
|                                       | 18 MO                    |          |
|                                       | 10 MA                    |          |
| Significantly ↓ in MA                 | 10 HV                    | [86]     |
|                                       | 10 MA                    |          |

MO, migraine without aura; MA, migraine with aura; HV, healthy volunteers
5. Diener HC, Ndosi NK, Koletzki E, Langohr HD (1984) Visual evoked potentials in migraine. In: Pfaffenrath V, Lundberg PJ, Sjaastad O (eds) Updating in headache. Springer, Berlin Heidelberg New York, pp 439–465

6. Diener HC, Scholz E, Dciągans J, Gerber WD (1989) Central effects of drugs used in migraine prophylaxis evaluated by visual evoked potentials. Ann Neurol 25:125–130

7. Wilkins AJ, Nimmo-Smith I, Tait A, McManus C, Della Sala S, Tilley A (1994) A neurological basis for visual discomfort. Brain 107:989–1017

8. Marcus DA, Soso MJ (1989) Migraine and cardiovascular disease. Arch Neurol 46:1129–1132

9. Wray SH, Mijovic-Prelec D, Kosslyn S, Williams and Wilkins, Baltimore

10. Hay KM, Mortimer MJ, Barker DC, Debye LM, Good PA (1994) 1044 Women with migraine: the effect of environmental stimuli. Headache 34:166–168

11. Miller NR (1985) Walsh and Hoyt’s clinical neuro-ophthalmology, 4th edn. Williams and Wilkins, Baltimore

12. Afra J, Mascia A, Gérard P, Maertens de Noordhout A, Schoenen J (1998) Intercortical excitability in migraine: a study using transcranial magnetic stimulation of motor and visual cortices. Ann Neurol 44:209–215

13. Afra J, Mascia A, Genicot R, Albert A, Schoenen J (2000) Influence of colours on habituation of visual evoked potentials in migraine with aura and healthy volunteers. Headache 40:36–40

14. Schoenen J, Sianard-Gainko J, Lenaerts M (1991) Blood magnesium levels in migraine. Cephalalgia 11:97–99

15. Sarchielli P, Costa G, Fiererize C, Morucci P, Abbrighi G, Gallai V (1992) Serum and salivary magnesium levels in migraine and tension-type headaches. Results in a group of adult patients. Cephalalgia 12:21–27

16. Thomas J, Thomas E, Tomb E (1992) Serum and erythrocyte magnesium concentrations and migraine. Magn Res 5:127–130

17. Mauskop A, Altura BT, Cracco RQ, Altura BM (1993) Deficiency in serum ionized magnesium but not total magnesium in patients with migraines. Possible role of Ica2+/Img2+ ratio. Headache 33:135–138

18. Gallai V, Sarchielli P, Paciarini M, Usai F (1993) Mononuclear magnesium content in migraine and tension-type headache patients. Cephalalgia 13:297

19. Jain AC, Sethi NC, Babbar PK (1985) A clinical electroencephalographic and trace element study with special reference to zinc, copper and magnesium in serum and cerebral fluid (CSF) in cases of migraine. J Neurol Suppl 232:161

20. Smeets MC, Vernooy CB, Souverijn JH, Ferrari MD (1994) Intracellular and plasma magnesium in familial hemiplegic migraine and migraine with and without aura. Cephalalgia 14:29–32

21. Ramadan NM, Halvorson H, van de Wiel A, Levine SR, Helpren JA, Welch KMA (1989) Low brain magnesium in migraine. Cephalalgia 29:590–593

22. Welch KMA, Ramadan NM (1995) Mitochondria, magnesium and migraine. J Neurol Sci 134:9–14

23. Welch KMA, Levine SR, D’Andrea G, Schulz L, Helpren JA (1989) Preliminary observations on brain energy metabolism in migraine studied by in vivo 31P magnetic resonance spectroscopy. Neurology 39:538–541

24. Barbiroli B, Montagna P, Cortelli P, Funicello R, Iotti S, Monari L (1992) Abnormal brain and muscle energy metabolism shown by 31P magnetic resonance spectroscopy in patients affected by migraine with aura. Neurology 42:1209–1214

25. Montagna P, Cortelli P, Monari L, Piazzelli G, Parchi P, Lodi R (1994) 31P-Magnetic resonance spectroscopy in migraine without aura. Neurology 44:666–668

26. Bresolin N, Martinelli P, Barbiroli B, Zaniol P, Ausenda C, Montagna P (1991) Muscle mitochondrial DNA deletion and 31P NMR spectroscopy alterations in migraine patients. J Neurol Sci 104:182–189

27. Sangiorgi S, Mochi M, Riva R, Cortelli P, Monari L, Pierangel G (1994) Abnormal platelet mitochondrial function in patients affected by migraine with and without aura. Cephalalgia 14:21–23

28. Lodi R, Montagna P, Soriani S, Iotti S, Arnaldi C, Cortelli P, Pierangel G, Patuelli A, Zaniol P, Barbironi B (1997) Deficit of brain and skeletal muscle bioenergetics and low brain magnesium in juvenile migraine: an in vivo 31P magnetic resonance spectroscopy interictal study. Pediatr Res 42:866–871

29. Ferrari MD, Odink J, Bos KD, Malesy MJA, Bruyn GW (1990) Neuroexcitatory plasma aminoacids are elevated in migraine. Neurology 40:1582–1586

30. Martinez F, Castillo J, Rodriguez JR, Leira R, Noya M (1993) Neuroexcitatory amino acid levels in plasma and cerebrospinal fluid during migraine attacks. Cephalalgia 13:89–93

31. Cananzi AR, D’Andrea G, Perini F, Zamberlan F, Welch KM (1995) Platelet and plasma levels of glutamate and glutamine in migraine with and without aura. Cephalalgia 15:132–135

32. D’Eufemia F, Pinocchiario R, Lendvai D, Cilli M, Viozzi L, Troiani P, Turri E, Giarini O (1997) Erythrocyte and plasma levels of glutamate and aspartate in children affected by migraine, Cephalalgia 17:652–657

33. McLachlan RS (1992) Suppression of spreading depression of Leao in neocortex by N-methyl-D-aspartate receptor antagonist. Can J Neurol Sci 19:487–491

34. Obrenovich TP, Zilkha E (1996) Inhibition of cortical spreading depression by L-701,324, a novel antagonist at the glycine site of the N-methyl-D-aspartate receptor complex. Br J Pharmacol 117:931–937

35. Mitsikostas DD, Sanchez del Rio M, Waeger C, Moskowitz MA, Cutrer FM (1998) The NMDA receptor antagonist MK-801 reduces capsaicin-induced c-fos expression within rat trigeminal nucleus caudalis. Pain 76:239–248

36. Kaube H, Goadsby PJ (1994) Anti-migraine compounds fail to modulate the propagation of cortical spreading depression in the cat. Eur Neurol 34:30–35

37. Facchetti F, Sances G, Borella P, Genazzani AR, Nappi G (1991) Magnesium prophylaxis of menstrual migraine: effects on intracellular magnesium. Headache 31:298–301
38. Peikert A, Wilimzig C, Kohnle-Volland R (1996) Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study. Cephalalgia 16:257–263

39. Pfaffenrath V, Wessely P, Meyer C, Isler HR, Evers S, Grottemeyer KH, Taneri Z, Soyka D, Gobel H, Fischer M (1996) Magnesium in the prophylaxis of migraine – a double-blind placebo-controlled study. Cephalalgia 16:436–440

40. Maukopf A, Altura BT, Cracco RQ, Altura BM (1995) Intravenous magnesium sulphate relieves migraine attacks in patients with low serum ionized magnesium levels: a pilot study. Clin Sci Colch 89:633–636

41. Mauskop A, Altura BT, Cracco RQ, Mauskop A, Altura BM, Cracco RQ (1996) Intravenous magnesium sulfate rapidly alleviates headaches of various types. Headache 36:154–160

42. Coleston DM (1994) Visual changes in migraine. In: Hogenhuis LAH, Steiner TJ (eds) Headache and migraine, 3. Bunge, Utrecht, pp 55–62

43. Palmer JE, Chronicle EP (1998) Cognitive processing in migraine: a failure to find facilitation in patients with aura. Cephalalgia 18:125–132

44. Geraud G, Aubertin A, Fabre-Thorpe M, Fabre N (1999) Processing speed of migraineurs in fast visual categorization. Cephalalgia 19:348–351

45. Palmer JE, Chronicle EP (1999) Confirmation of visual cortical hyperexcitability in migraine with aura using a novel and targeted psychophysical probe. Cephalalgia 19:462

46. Chronicle EP, Wilkins AJ, Coleston DM (1995) Thresholds for detection of a target against a background gratings suggest visual dysfunction in migraine with aura but not migraine without aura. Cephalalgia 15:177

47. Coleston DM, Kennard C (1994) Visual deficits in migraine with aura: problems in processing coloured stimuli. In: Clifford Rose F (ed) New advances in headache research. Smith-Gordon, London, p 103

48. Chronicle EP, Mulleners W (1994) Might migraine damage the brain? Cephalalgia 14:415–418

49. Lehtonen JB (1974) Visual evoked potentials for single flashes and flickering light in migraine. Headache 14:1–12

50. Connolly JF, Gawel M, Rose FC (1982) Migraine patients exhibit abnormalities in the visual evoked potential. J Neurol Neurosurg Psychiatry 45:464–467

51. Khalil NM (1991) Investigations of visual function in migraine using visual evoked potentials and visual psychophysical tests. Thesis, University of London, London

52. Shibata K, Osawa M, Iwata M (1997) Pattern reversal visual evoked potentials in classic and common migraine. J Neurol Sci 145:177–181

53. Benna P, Bianco C, Costa P, Piazza D, Bergamasco B (1985) Visual evoked potentials and branstem auditory evoked potential in migraine and transient ischemic attacks. Cephalalgia Suppl 2:53–58

54. Mariani E, Moschini V, Pastorino G, Rizzi F, Serevigni A, Tiengo M (1988) Pattern-reversal visual evoked potentials and EEG correlations in common migraine patients. Headache 28:269–271

55. Drake ME, Pakalnis A, Hietter SA, Padamadan H (1990) Visual and auditory evoked potentials in migraine. Electromyogr Clin Neurophysiol 30:77–81

56. Tagliati M, Sabbadini M, Bernardi G, Silvestrini M (1995) Multichannel visual evoked potentials in migraine. Electroencephalogr Clin Neurophysiol 96:1–5

57. Schoenen J, Wang W, Albert A, Delwaide PJ (1995) Potentiation instead of habituation characterizes visual evoked potentials in migraine patients between attacks. Eur J Neurol 2:115–122

58. Áfra J, Proietti Cecchini A, De Pasqua V, Albert A, Schoenen J (1998) Visual evoked potentials during long periods of pattern-reversal stimulation in migraine. Brain 121:233–241

59. Wang W, Timsit-Bertier M, Schoenen J (1996) Intensity dependence of auditory evoked potentials in migraine: an indication of cortical potentiation and low serotonergic neurotransmission? Neurology 46:1404–1409

60. Wang W, Schoenen J, Timsit-Bertier M (1995) Cognitive functions in migraine without aura between attacks: a psychophysiological approach using the “oddball” paradigm. Neurophysiologie Clinique 25:3–11

61. Evers S, Bauer B, Suhr B, Husstedt IW, Grottemeyer KH (1997) Cognitive processing in primary headache: A study on event-related potentials. Neurology 48:108–113

62. Schoeno J, Maertens de Noordhout A, Timsit-Bertier M, Timsit M (1985) Contingent negative variation (CNV) as a diagnostic and physiopathologic tool in headache patients. In: Clifford Rose F (ed) Migraine, Proc 5th Int Migraine Symp, London, 1984. Karger, Basel, pp 17–25

63. Kropp P, Gerber WD (1993) Is increased amplitude of contingent negative variation in migraine due to cortical hyperexcitability or to reduced habituation? Cephalalgia 13:37–41

64. Brincioti M, Guidetti V, Matricardi M, Cortesi F (1986) Responsiveness of the visual system in childhood migraine studied by means of VEPs. Cephalalgia 6:183–185

65. Sartory G, Busken E, Pothmann R (1997) Contingent negative variation in childhood migraine. J Psychophysiol 11:138–146

66. Besken E, Pothmann R, Sartory G (1993) Contingent negative variation in childhood migraine. Cephalalgia 13:42–43

67. Evers S, Bauer B, Grottemeyer KH, Kurlemann G, Husstedt IW (1998) Event-related potentials (P300) in primary headache in childhood and adolescence. J Child Neurol 13:322–326

68. Áfra J, Sándor PS, Proietti Cecchini A, Schoenen J (2000) Comparison of visual and auditory evoked cortical potentials in migraine patients between attacks. EEG J (submitted)

69. Áfra J, Sándor PS, Schoenen J (2000) Habituation of visual and intensity dependence of auditory evoked cortical potentials tend to normalize just before and during the migraine attack. Cephalalgia (submitted)

70. Grossberg S, Gutowsky WE (1987) Neural dynamics of decision making under risk: affective balance and cognitive-emotional interactions. Psychol Rev 94:300–318

71. Mesulam MM (1990) Large-scale neurocognitive networks and distributed processing for attention language and memory. Ann Neurol 28:597–613

72. Hegert U, Juckel G (1993) Intensity dependence of auditory evoked potentials as an indicator of central serotonergic neurotransmission: a new hypothesis. Biol Psychiatr 33:173–187
73. Kropp P, Gerber WD (1995) Contingent negative variation during migraine attack and interval: evidence for normalization of slow cortical potentials during the attack. Cephalalgia 15:123–128
74. Kropp P, Gerber WD (1998) Prediction of migraine attacks using a slow cortical potential, the contingent negative variation. Neurosci Lett 257:73–76
75. Regan D (1989) The visual pathway – Color. In: Human brain electrophysiology. Evoked potentials and evoked magnetic fields in science and medicine. Elsevier, New York, pp 436–451
76. Takahashi T, Tsukahara Y (1976) Influence of color on the photoconvulsive response. Electroencephalogr Clin Neurophysiol 41:124–136
77. Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD (1993) Corticocortical inhibition in human motor cortex. J Physiol 471:501–519
78. Hallett M (1996) Transcranial magnetic stimulation: a useful tool for clinical neurophysiology. Ann Neurol 40:344–345
79. Maertens de Noordhout A, Pepin JL, Schoenen J, Delwaide PJ (1992) Percutaneous magnetic stimulation of the motor cortex in migraine. Electroencephalogr Clin Neurophysiol 85:110–115
80. Bettucci D, Cantello M, Gianelli M, Naldi P, Mutani R (1992) Menstrual migraine without aura: cortical excitability to magnetic stimulation. Headache 32:345–347
81. Van der Kamp W, Maassen VanDenBrink A, Ferrari MD, van Dijk JG (1997) Interictal cortical excitability to magnetic stimulation in familial hemiplegic migraine. Neurology 48:1462–1464
82. Van der Kamp W, Maassen VanDenBrink A, Ferrari MD, van Dijk JG (1996) Interictal cortical hyperexcitability in migraine patients demonstrated with transcranial magnetic stimulation. J Neurol Sci 139:106–110
83. MacCabe PJ, Amassian VE, Cracco JB, Radell EP, Eberle LP, Zemon V (1991) Magnetic coil stimulation of human visual cortex: studies of perception. Electroencephalogr Clin Neurophysiol 43:111–120
84. Aurora SK, Ahmad BK, Welch KMA, Bhardhwaj P, Ramadan NM (1998) Transcranial magnetic stimulation confirms hyperexcitability of occipital cortex in migraine. Neurology 50:1111–1114
85. Aurora SK, Cao Y, Bowyer SM, Welch KMA (1999) The occipital cortex is hyperexcitable in migraine: experimental evidence. Headache 39:469–476
86. Aguggia M, Zibetti M, Febbraro A, Mutani R (1999) Transcranial magnetic stimulation in migraine with aura: further evidence of occipital cortex hyperexcitability. Cephalalgia 19:465
87. Ferrari MD (1998) Migraine. Lancet 351:1043–1051
88. Ophoff RA, Terwindt GM, Vergouwe MN, van Eijk R, Oefner PJ, Hoffman MG, Lamerdin JE, Mohrenweiser HW, Bulman DE, Ferrari M, Haan J, Lindhout D, van Ommeren GJB, Hofker MH, Ferrari MD, Frants RR (1996) Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. Cell 87:543–552
89. Kraus RL, Sinneger MJ, Glossmann H, Hering S, Stryinsg J (1998) Familial hemiplegic migraine mutations change alpha1A Ca2+ channel kinetics. J Biol Chem 273:5586–5590
90. Hans M, Lavissette S, Williams ME, Spagnolo M, Urrutia A, Totene A, Brust PF, Johnson EC, Harpold MM, Staudehman KA, Pietrobon D (1999) Functional consequences of mutations in the human alpha (1A) calcium channel subunit linked to familial hemiplegic migraine. J Neurosci 19:1610–1619