Migraine-related permanent and transient changes in mood, cognition, and slow brain potentials

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The first question that the present thesis addresses is whether a migraine attack induces short term effects on mood, cognition, and neurophysiological functioning. This chapter first evaluates post-attack functioning that is similar to the real life situation, during the period shortly after an attack that was treated in the patients' customary way with habitual non-vasoactive medication. Next, the issue will be raised whether post-attack functioning can be influenced by treating a migraine attack with sumatriptan that is known to shorten attack duration. The second aim of this thesis is to examine permanent changes that accompany migraine irrespective of the direct effects of an attack. To this end, we examined mood, cognitive functioning, neurophysiological functioning, and personality characteristics in patients during a migraine free period and compared these characteristics to those of non-migrainous healthy control subjects.

The post-attack period after habitual medication

Briefly after a migraine attack, patients often report feelings of numbness, as if they were recovering from flue or being hung over. When asked "Do you feel you are still being influenced by your last migraine attack?", 58% of migraine patients responded affirmatively in our study. They also reported to invest more mental effort during task performance. In spite of this subjective post-attack impairment, its backgrounds in terms of affective, cognitive and neurophysiological functioning are unknown.

The first aim of the present thesis was to evaluate the direct and reversible effects of a migraine attack. Mood state and health state are interrelated concepts that both can have a negative influence on daily functioning. Internalising aspects of health state refer to mood state, whereas externalising aspects refer to the participation in daily and social activities. An attack that was untreated or treated with habitual medication did not affect externalising aspects of health state compared to the interictal period. Depression, anger, vigour, tension, or friendliness were not affected by an attack either, but emotional problems such as irritability, dejection, as well as fatigue were clearly elevated.

This raises the question of whether these elevated levels of fatigue and emotional problems are accompanied by impairments in cognitive functioning. Very little evidence was provided for this idea in the present thesis. After an attack was untreated or treated with habitual medication, cognitive

performance was normal in various cognitive domains. A migraine attack did not affect reasoning, reaction speed, selective attention, digit encoding, visual digit span, or pattern perception. The fact that overt behaviour such as response speed, and the amount of false responses during cognitive performance were not negatively affected by a preceding attack does not exclude the possibility of latent neuronal changes, especially since a migraine attack is believed to be associated with neuronal dysfunctions (Lauritzen,1987). We, therefore, assessed neurophysiological functioning by the contingent negative variation (CNV) which is an event-related slow brain potential that reflects preparation, attention, and arousal. Other studies have demonstrated that the amplitude of this CNV is significantly enhanced, and habituation over successive trials is slowed down in migraine patients without aura between attacks. These CNV alterations have been shown to resolve during a migraine attack (Kropp and Gerber, 1995), after which they gradually appear again during the days after an attack (Kropp and Gerber, 1998). The migraine patients in the present study showed normal CNV early and late wave amplitudes and normal habituation kinetics during the post-attack period after habitual medication. Taken together, we conclude that the subjective post-attack impairment that is reported by patients is reflected only in irritability, fatigue, and the investment of an extra amount of task-related mental effort. We neither found evidence for a depressive or anxious mood, nor for any significant cognitive or neurophysiological impairments.

The post-attack period after sumatriptan use

The above-mentioned conclusions apply to the patients' customary post-attack situation, after a migraine attack was untreated or treated with habitual medication. We also examined post-attack functioning after treating an attack with sumatriptan which is known to shorten attack duration considerably. The main goal of migraine medication is to apply substances that induce a quick headache relief, and it is generally assumed that headache relief yields normal functioning. Most clinical trials focus on meaningful relief as their main target, but it is reasonable to expect that effective medication in this regard could also reduce the extent of problems during the migraine recovery phase.

In the present study, sumatriptan induced a significant shorter attack duration compared to an attack that was untreated or treated with habitual medi-

cation. Notwithstanding this successful treatment, 63% of the migraineurs still responded affirmatively to the question whether they still felt influenced during the post-attack period after sumatriptan use. Patients also reported more task-related mental effort compared to the interictal period. This subjective impairment was, again, not reflected in impairments in cognitive functioning. Although most migraine patients with aura (80%) reported subjective impairment, while this was the case in the minority of migraine patients without aura (45%), this striking difference between the migraine groups was not reflected in differences in post-attack performance.

Sumatriptan had beneficial effects on internalising aspects of health state (fatigue and emotional problems) compared to the post-attack period after habitual medication. Additionally, sumatriptan also had beneficial effects on externalising aspects of health state (pain, and engaging in social activities) compared to both the interictal measurement and habitual medication use. These positive effects on externalising aspects on health state are probably due to the shorter attack duration that sumatriptan induces. As a consequence, migraineurs are able to resume daily functioning sooner than in their usual treatment situation. These beneficial effects of sumatriptan on health state were paralleled by a higher reaction speed during selective attention. Finally, after an attack was treated with sumatriptan migraineurs showed a significant decrease in CNV early and late wave amplitudes over the frontal cortex. These cognitive and neurophysiological effects of sumatriptan are particularly striking considering the fact they are not present after an untreated attack or after habitual medication use. This suggests that sumatriptan has a central action and affects cognition, but raises the possibility that this effect is unrelated to a migraine attack as such. In retrospect, it is unfortunate that we were unable to verify this in our healthy control subjects, however, the administration of sumatriptan to healthy subjects posed ethical problems.

Differences between interictal migraineurs and healthy controls

Personality, mood, and health state

In early research, migraine patients have been stereotyped as obsessional, rigid, compulsive, perfectionistic, ambitious and competitive (Wolff, 1937). Recent studies based on clinic and convenience samples, indicated that

migraine patients show high levels of performance related debilitating anxiety (Leijdekkers et al., 1990; Passchier et al., 1984), achievement orientation (Passchier et al., 1984), depression, trait anxiety and neuroticism (Silberstein et al., 1995). Population-based studies have corroborated elevated levels of tension, anxiety, depression, hypochondriasis and neuroticism (Silberstein et al., 1995). Our migraine patients were more rigid and achievement oriented than healthy control subjects. These personality factors might predispose or increase the risk of the development of migraine. Alternatively, they could reflect a psychological reaction to living in constant anticipation of an upcoming migraine attack. We believe that the longer migraine attacks last, the more achievement oriented a patient is in a migraine free period to make up for this lost time. Rigidity was unrelated to migraine severity and the length of migraine history, and could therefore be a part of a predisposition to migraine.

Migraineurs with aura in this study reported more tension, anger and anxiety than their control subjects, which supports the higher levels of neuroticism that were previously observed in this migraine subtype (Merikangas et al., 1993). Migraineurs with aura and migraineurs without aura showed increased fatigue and decreased vigour, but normal levels of anger and depression. Migraine, depression, and anxiety disorders are comorbid conditions and high levels of depression have been found in other studies. We attribute the lack of depression in our sample to the homogenic nature (regarding age, medication use, and the absence of known comorbid conditions) of the non-clinical migraineurs in our study. The impact of a selection bias is illustrated by the finding that the prevalence of depressive disorder, panic disorder and social phobia is significantly higher in migraineurs with chronic substance abuse who are selected from a clinic compared to migraineurs outside the clinic (Radat et al., 1999). Moreover, we made a point of ensuring that our interictal session took place in a period that is unlikely to be influenced by pre or postictal changes. Such changes can easily be mistaken for migraine attributes unless interictal measurements take place in a truly migraine free period.

Confirming other research (Osterhaus et al., 1994; Dahlöf & Dimenäs, 1994; Essink-Bot, 1995), our patients reported a low health state even when being migraine free. This low health state was predominantly manifested in problems regarding externalising aspects of health state, such as the participation in daily and social activities, physical pain, and general health. It is

unclear what this low health state is caused by but it could be related to aspects of mood, personality, and the frequent incapacitation by migraine attacks. The elevated levels of rigidity and achievement motivation in our migraineurs were not accompanied by a more impaired health state, suggesting that these personality factors do not play a decisive role in the impaired health state. Since a worse health state and mood are not associated with a longer migraine history, attack duration or a higher migraine severity, I suspect that these merely pertain to a predisposition to migraine. In conclusion, we provided some evidence for a more negative mood in migraineurs, especially in those with aura, but migraineurs particularly show pronounced impairments in the field of health state and have a more rigid and achievement oriented personality.

Cognition

In addition to the lower health state, this study showed specific cognitive deficiencies in migraine patients in the interictal period. Migraineurs with aura and migraineurs without aura showed some motor slowing, which has been found before (Schoenen, 1986). The most consistent finding was that migraineurs with aura responded slower when sustained attention is required, and especially during selective attention where the suppression of responses is demanded. A wide range of cognitive deficiencies have been reported in migraine, but converging evidence from these studies has been hampered by the heterogeneity of migraine groups and the absence of appropriate control groups. Leijdekkers et al. (1990) suggested that cognitive impairment is found more frequently in patients with a long migraine history seeking medical help, who often have more neurologic complications. Within these individual studies, however, evidence for this idea is rather weak since test performance has not been found to be influenced by migraine severity or length of migraine history (Zeitlin & Oddy, 1984; Hooker & Raskin, 1986; Leijdekkers et al., 1990). Neuropsychological deficiencies have repeatedly been found within the visual processing domain in migraine patients and predominantly in migraine with aura. Visual changes in both types of migraine are believed to be due to dysfunctions in early visual processing (Coleston, Chronicle, Ruddock, & Kennard, 1994; Wray, Mijović-Prelec, & Kosslyn, 1995), whereas later processing stages from the visual cortex to the association cortices along the dorsal and ventral route are unaffected (Wray

et al., 1995). We did not find evidence for this but our tasks were probably not sensitive to detect these specific visual processing deficiencies.

Neurophysiology

We investigated the CNV early and late wave and its habituation course during a forewarned simple reaction time task to test the cortical hyperexcitability hypothesis in migraine. Previous studies indicated more negative CNV early and late wave amplitudes in migraine without aura (Böcker et al., 1990; Kropp & Gerber 1993, 1993b; Kropp & Gerber 1995; Kropp & Gerber, 1998). This is believed to emerge as a result of slow habituation kinetics (Schoenen et al., 1986; Maertens de Noordhout et al., 1986; Kropp & Gerber 1993a; Kropp & Gerber 1995), which is related to a hyperactivity of central catecholaminergic systems (Timsit-Berthier et al., 1986a; Timsit-Berthier et al., 1986b; Libet, 1979; Schoenen et al., 1986; Maertens de Noordhout et al., 1986; Nagel-Leiby et al., 1990). High catecholaminergic activity is assumed to induce a state of cortical hyperexcitability and arousal, which prevents normal habituation.

We aimed on replicating these CNV findings, and testing the cortical hyperexcitability hypothesis in migraine. Surprisingly, migraineurs without aura showed normal CNV early and late wave amplitudes as well as normal habituation kinetics. A bias in patient selection (Berkson, 1946) and the methodological rigour of our study may explain these diverging findings. We believe that a homogenous group of young migraineurs that have not been selected from a clinic or association show normal CNV characteristics, normal catecholaminergic activity, and normal cortical excitability during a forewarned simple reaction time task. This idea is strengthened by the recent observation that young migraineurs up to the age of 19 show a normal CNV early wave and habituation slope, whereas in older migraine groups diverging CNV characteristics gradually emerge (Kropp et al., 1999).

The impairments in sustained and selective attention that we found in migraineurs are unlikely to be explained by cortical hyperexcitability. For this reason, we investigated the alternative idea that migraineurs show inadequate anticipation towards relevant stimuli, in a forewarned choice reaction time task during which the CNV was recorded. This particular study enabled the manipulation of anticipatory state and the examination of Stimulus Preceding Negativity (SPN). Migraineurs indeed showed alterations in appropriately anticipating task relevant stimuli during a forewarned choice reaction time

task. This was expressed in a reduced CNV late wave amplitude, and a deviant topograhic distribution of the SPN prior to the motor response in migraineurs without aura. We believe that this reflects a low anticipation that is possibly related to a reduced effortful control of task performance. In contrast to the lower CNV late waves during the forewarned choice reaction time task, the same migraineurs showed normal CNV late waves during the forewarned simple reaction time task. Attentional and anticipatory problems in migraineurs probably become especially evident during effortfull cognitive tasks rather than tasks requiring less mental effort or automatic attention. These deficiencies could also contribute to the impairments that we observed in migraineurs during cognitive tasks that specifically require selective attention.

Migraine with aura and migraine without aura

There is an ongoing debate whether migraine without aura and migraine with aura are either distinct pathogenic entities or different grades of severity of the same continuum. About 5% of migraine patients (Russell et al., 1996) experience both types of migraine equally often, while others experience aura symptoms more often or have occasional aura symptoms without headache. These cases are all diagnosed as "migraine with aura" (IHS, 1988) and this arbitrary distinction hampers the research of the underlying mechanisms in these migraine subtypes. Migraine with aura and migraine without aura show strong clinical similarities in pain characteristics, accompanying symptoms and efficacy of drugs, whereas the dissimilarities are manifested in age of onset, sensitivity to female hormones, and blood flow alterations. From these observations it was concluded that migraine with aura and without aura are distinct but closely related entities (Russell et al., 1996). Unfortunately, systematic comparisons have rarely been performed on the affective, cognitive an neurophysiological differences between these migraine types. If aura and non aura patients are on a single continuum, they are expected to differ from healthy controls only in degree, whereas a dichotomy assumes qualitative rather than quantitative differences.

In the present study migraine patients with aura and migraine patients without aura did not differ qualitatively in cognitive functioning and health state. In 74% of all administered neuropsychological tests, however, migraine patients without aura performed somewhat slower than control subjects,

whereas migraineurs with aura were the slowest. Migraineurs with aura showed significant slower speed during selective attention and had a worse mood state than control subjects. Other studies also reported more cognitive impairments in migraine with aura (Hooker & Raskin, 1986), but predominantly in visual processing (e.g. Chronicle et al., 1995; Chronicle & Mulleners, 1994). Such visual deficiencies have been attributed to the selective neuronal damage in the visual cortex, since this is the locus where the strongest decrease in blood flow takes place. Chronicle et al. (1995) contend that GABA-ergic neurons are the most sensitive to hypoperfusion and are therefore selectively damaged in migraine with aura, which is believed to give rise to a over sensitivity to visual stimuli in the visual cortex. We were not equipped to measure such visual disturbances but we did demonstrate that impairments in migraineurs with aura that are not precluded to visual processing.

On the whole, the relatively small group of migraineurs with aura (n=10) showed a slightly worse performance than migraineurs without aura, but showed the most pronounced differences compared to healthy controls. These results are less compatible with a dichotomous viewpoint on the migraine subtypes but more applicable to a single continuum viewpoint where migraine with aura is of greater severity than migraine without aura.

Proposed mechanisms in migraine

The most consistent finding during interictal neuropsychological testing was that migraineurs show deficiencies during tasks that require selective attention and response suppression. Since the frontal cortex is involved in these aspects of attention (Fuster, 1997) a functional disturbance could be present in these cerebral areas of migraineurs. More specifically, we speculate that a deficiency in the anterior cingulate cortex (ACC) could be present in migraine. Various imaging studies showed that the ACC (Brodmann areas 24/32) is activated during attention demanding tasks (see Hsieh et al., 1995; Picard & Strick, 1996). Based on PET imaging and lesion studies, Posner & Raichle (1994) refer to this brain area as the executive area for attention. Functional MRI studies further suggest that ACC activation during attention demanding tasks merely depends on anticipatory state rather than the task itself (Murtha et al., 1996; Davis et al. (1997).

Besides the role of the ACC in anticipatory state, this structure is of significant importance in pain perception (Vogt et al., 1993; Davis et al., 1997), which furthermore emphasises its possible involvement in migraine. This idea is even more strengthened by the changes that occur in this structure after a migraine attack has been initiated. Weiller et al. (1995) demonstrated with PET that during a spontaneous migraine attack without aura activation takes place in the auditory and visual association cortices, the brain stem, and the cingulate cortex (BA 24/25/32). After an injection of sumatriptan had induced complete relief from headache and photo and phonophobia, the ACC activation disappeared. These studies show that the ACC is activated during a migraine attack and might be involved in migraine pain. We tentatively suggest that a functional ACC deficiency could also explain the attentional (Chapter 5) and anticipatory (Chapter 7) deficits found in our migraine subjects.

In addition, the frontal cortex and the ACC might play a pivotal role in the effects of sumatriptan on attention and slow brain potentials. During the post-attack period after sumatriptan use, migraineurs show an improved reaction speed during sustained and selective attention tasks as well as decreased CNV amplitudes over the frontal cortex, and elevated levels of subjective mental effort during task performance. It is possible that sumatriptan influences attentional processes through the catecholaminergic system. The first possible route is that the serotonergic agent sumatriptan interacts with attentional processes through its action on the dopaminergic system in the frontal cortex. The serotonergic system inhibits dopaminergic function at the level of the midbrain as well as at the level of terminal dopaminergic fields in the forebrain (Kapur and Remington, 1996). Interactions between serotonergic and dopaminergic systems within the frontal cortex have been shown to play an important role in the modulation of sustained attention and response control (Puumala and Sirviö, 1998). The second possible route is that sumatriptan influences attentional processes by modulating noradrenergic activity that in turn influences the anterior cingulate cortex. Cole and Robbins (1992) demonstrated that through the dorsal noradrenergic bundle which projects from the locus coeruleus in the brainstem to the frontal cortex, noradrenaline could have a role in effortful processing while leaving automatic processing largely unchanged. These noradrenergic fibres are shown to be especially dense in the frontal cortex and the cingulate gyrus (Descarries & Lapierre, 1973). Interesting in the context of cognitive func-

tioning is the finding that noradrenergic frontal activity normally functions to preserve attentional selectivity under arousing circumstances (Everitt, Robbins, & Selden, 1990). Although this thesis provides indirect evidence bearing on this issue, we speculate that sumatriptan modulates the frontal attentional system by reducing frontal catecholaminergic activity. This would also explain the decrease in CNV early and late wave amplitudes that we observed after sumatriptan.

Causality issue of migraine-related changes

We hypothesise a functional deficiency in the frontal cortex manifested in alterations in attentional processes. The question remains whether this results from the cumulative effects of repeated and prolonged exposure to migraine attacks or whether it is part of the migraine predisposition. Although this thesis cannot be conclusive on this matter, both possibilities will be briefly discussed.

If the migraine attributes (such as a low health state and attentional problems) are a consequence of cumulative effects of migraine, one expects these to positively correlate with length of migraine history or migraine severity. Conclusive evidence is lacking as we, for instance, showed that general attack severity is significantly lower in migraineurs with aura (Table 1; Chapter 4) yet this group shows the most pronounced cognitive changes. Alternatively, permanent differences could reflect a genetic predisposition that could lead, under certain environmental conditions, to elevated levels of anxiety or depression, and ultimately to the manifestation of migraine. There are two ways to gain clarity in the causality of migraine and its attributes. First, a longitudinal study starting at an early age in subjects that are at risk for migraine or already suffering from migraine could investigate the sequence of the development of changes in cognitive functioning, personality and mood, and the onset of migraine. A longer migraine history could be associated with more impairment than a short migraine history. In favour of this, Kropp et al. (1999) showed that young migraineurs (age 8-19) show normal CNV characteristics, whereas older migraineurs (age 20-59) show higher early wave amplitudes and slower habituation than healthy control subjects. Based on these CNV studies, Kropp et al. (1999) suggested that migraineurs show a disturbed maturation of the brain. They suggested that maturation in non migrainous subjects takes place in two developmental stages. The first

stage covers the period up to 14 years of age and is characterised by high CNV early waves in both healthy control subjects and migraine patients. The second maturation stage begins with a jump in the increase of habituation in the CNV early wave between the age of 15 and 19 that slowly progresses, but this second stage is not observed in migraineurs. Incomplete brain maturation, as mirrored in event-related brain potentials, can be the basis of deficiencies regarding selective attention and selective information processing (Oades et al., 1997). This ERP perspective on brain maturation bears similarities with the increasing EEG complexity that shows maximum gain during puberty as an indication of the development of the frontal cortex and its cortico-cortical connections (Anokhin et al., 1996). Such maturation deficiencies of the frontal cortex, or possibly the ACC, might be associated with the attentional problems in migraineurs that we reported in the present study. It would be interesting to confirm such deficiencies in frontal brain maturation, and to further examine these using functional brain imaging techniques.

A second approach to elucidate the causality issue of migraine and its attributes is that of genetic epidemiology. The examination of subjects with varying degrees of genotypic resemblance (monozygotic, dizygotic twins, and their siblings) of which at least one family member is affected, can clearify the relative contribution of genetic and environmental factors in permanent differences in migraine. A multivariate extension of this twin design can be used to test the presence of common genetic effects underlying a set of phenotypic characteristics. This method would be suitable to test whether attentional impairments are caused by migraine, or whether migraine and attentional impairments share an underlying genetic factor.

Conclusions

Migraine is a multifactorial and complex neurological disease and calls for a multidisciplinary approach to gain understanding its pathophysiology. The present thesis combined neurophysiological, cognitive, affective measures, and clinical observations to examine the changes that are induced by a migraine attack, as well as permanent changes that are not directly related to an attack The main results of this study are summarised in the following:

The post-attack period following an attack that was untreated or treated with habitual medication is characterised by an increase of fatigue and emo-

tional problems. These complaints are, however, not present after an attack that is treated with sumatriptan. Migraine patients report physical pain and social hindrance when they are migraine-free and to the same extend during the post-attack period after habitual medication use, whereas sumatriptan improves these complaints. Cognitive and neurophysiological functioning during the post-attack period after habitual medication use is similar to functioning during the migraine free period. After sumatriptan use cognitive functioning improved and neurophysiological functioning changed, which suggests a central action of the serotonergic agent. Moreover, migraineurs invest more mental effort during the performance of simple reaction time tasks during the post-attack period, irrespective of medication use and attack duration.

In the migraine free period between attacks, migraineurs report a low health state and low levels of vigour. Furthermore, migraine patients have a more rigid and achievement oriented personality compared to healthy control subjects. Migraineurs, and especially those with aura, show cognitive impairments during tasks that specifically require selective attention, demanding profound levels of mental effort and anticipation. These migraine-related changes in the migraine free periode might revert to a predisposition rather than to a consequence of migraine. Finally, migraine with aura and migraine without aura probably share a common underlying pathophysiology but migraine with aura is of greater severity and has a greater impact on mood and cognition.

To gain further insight in the pathophysiology of migraine, it would be interesting for future research to elucidate the causality of the association between migraine, deficiencies in selective attention, and changes in personality and mood. A promising approach to identify factors contributing to migraine-related changes would be to examine migraine-related changes in healthy nonmigrainous control subjects, and homogenic migraine and other headache groups that vary in headache or migraine subtype, comorbidity of depression, medication use, length of migraine history, and age.