

STRESS AND DAILY FUNCTIONING IN MIGRAINE

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STRESS EN DAGELIJKS FUNCTIONEREN BIJ MIGRAINE

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Chapter 1

General introduction and outline of the thesis

1. Introduction

Migraine is an idiopathic, recurring headache disorder manifesting itself in attacks, lasting 4 to 72 hours. Typical characteristics of the headache are: unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, nausea, photo- and phonophobia (Headache Classification Committee of The International Headache Society, 1988). In about 15% of the patients, an aura may precede the migraine headache for about an hour (a distinguishing feature of 'migraine with aura', in contrast to the aura-less 'migraine without aura'). The term 'aura' has long been used to denote the sensory hallucinations immediately preceding certain epileptic seizures; it is also used to denote symptoms initiating certain migraine attacks. Usually the aura consists of visual symptoms such as scotoma and fortifications, but may also be sensory, motor- or speech-related.

Migraine has been recognized since the dawn of recorded history and described in the literature of antiquity: it was first mentioned by the Sumerians some 6,000 years ago. For two thousand years, its nature, forms, symptoms, and causes have been the subject of argument. It has affected numerous people, including many historical figures. Caesar, Saint Paul, Kant, Darwin, and Freud all had headaches, supposedly of a migrainous nature (Sacks, 1995).

In course of time, many etiological theories have been proposed and prevalence was hard to estimate, partly because no strict nosological definition of migraine existed. In 1988, however, the International Headache Society formulated strict and generally accepted diagnostic criteria for migraine with or without aura (see Appendix). Estimates of the prevalence now converged: in the western industrialized world about 6 % in men and 15-18 % in women (Rasmussen et al., 1991; Henry et al., 1992; Stewart et al., 1992; Lipton and Stewart 1994). The highest prevalence has been established between the ages of 25 and 55 (Russell and Olesen, 1996; Lipton and Stewart, 1997; Dowson and Jagger, 1999).

2. The pathophysiology of migraine

For centuries, experts believed that migraine pain was caused by swollen blood vessels in the head. A solid foundation of this classical 'vascular theory' was laid by Graham & Wolff (1938) and Schumacher & Wolff (1941). It states that migraine is a vascular disease initiated by cerebrovascular spasm causing local ischemia and the transient focal prodromata. A sterile inflammatory reaction follows around the cerebral vessel walls, resulting in an intra- and extracranial dilatation of blood vessels. This vasodilatation causes the throbbing and pulsating properties of migraine headaches (Graham and Wolff, 1938; Schumacher and Wolff, 1941). Since the publication of Graham and Wolff, views on migraine have changed much and progress is substantial. Several medical disciplines and special fields of research such as neurology, clinical and experimental neurophysiology, neuroradiology (especially technological advances in visualizing and studying blood flow in the brain, such as magnetic resonance imaging, positron emission tomography (PET), and transcranial doppler), psychiatry, medical psychology, psychosomatics, biochemistry, genetics, pharmacology, epidemiology contributed to the new cognitions. Current theories emphasize the interaction between vessels and nerves and propose that the primary dysfunction is located within the central nervous system (CNS). Hence, they are called neurovascular theories. Neural impulses are assumed to produce changes in the trigeminovascular system resulting in headache. Whether cortical, midbrain or brain stem centers generate the attack, is still a matter of debate (Diener and May, 1996; Welch, 1997 and 1999; Buzzi and Pellegrino, 1995). The putative changes in migraine may involve spreading cortical depression due to focal brain hypoxia and causing the prodrome of migraine (Amery, 1982 and 1985; Olesen and Jorgensen, 1986; Lance, 1993), an unstable trigeminovascular reflex causing headache, and associated activity in the brain producing the other nonspecific migraine symptoms such as nausea, vomiting, and dizziness (Edmeads, 1992). So, although blood vessels do ultimately become involved, they seem to play a secondary role (Welch, 1999; May and Goadsby, 1999).

Many of these neurovascular theories emphasize the role of neurotransmitters, such as serotonin, (nor)epinephrine, and dopamine in the genesis of an attack. Changed circulating levels of serotonin and its metabolites during the phases of an attack, the ability of serotonin-releasing agents to induce migraine-like symptoms and that of serotonin receptor agonists to alleviate migraine pain, the high incidence of comorbidity of migraine with depression, anxiety and eating disorders (Haythornthwaite, 1993; Brewerton and George, 1993; Brewerton et al., 1993), and the recently proposed neural theory of migraine by Eggers in which abnormally-functioning serotonergic pacemaker cells in the raphe nuclei inappropriately activate and inhibit large areas of the brain (Eggers, 2001), now leave little doubt as to their relevance to the etiology of migraine. As regards plasma catecholamines, plasma norepinephrine levels have been found to rise before (Hsu et al., 1978) or during (Fog-Moller et al., 1978; Anthony, 1981) migraine attacks, probably signifying the physiological stress patients experience in consequence of headaches (Anthony, 1987). However, the few studies on plasma levels and urinary excretion patterns of catecholamines and their metabolites in relation to migraine, allow little room for reaching firm conclusions on their role in the migraine disorder (Anthony, 1981; Ferrari, 1993; Mascia and Schoenen, 1998).

Genetic abnormalities may play a role in the aetiology of migraine. They may be responsible for altering the threshold for migraine-specific trigger factors in the nervous system of the migraineur compared to a normal individual (Elkinton and Graham, 1985; Lance, 1993; Honkasalo et al., 1995; Welch, 1997; D'Amico et al., 1997; Freilich, 1998; Ziegler et al., 1998; Hargreaves and Shephard, 1999; Gervil et al., 1999;). Twin studies are most important in establishing the multifactorial nature of migraine with heritability approaching 50% (Gardner, 1999). A mutation in the brain-specific P/Q type calcium channel alpha 1A subunit gene (CACNA1A) on chromosome 19p13 was shown to be involved in familial hemiplegic migraine (FHM), an autosomal dominant, though rare form of migraine (Ophoff et al., 1996). In addition, evidence is accumulating that the same gene is also involved in the more common forms of migraine with and without aura (Terwindt et al., 1998).

Despite the many studies performed and the many hypotheses postulated, the exact pathomechanisms of migraine still have to be determined (Diamond, 1993; Buzzi and Pellegrino, 1995; Hargreaves and Shephard, 1999), although there has been important progress. Altogether, migraine may be defined as a specific dysfunction in neuronal information processing and neurovascular reactivity corresponding with imbalance of certain neurotransmitters (norepinephrine, 5-HT) and leading to ictal reactions of brain areas and intracranial vessels in phases of hyperreactivity and hyperreactivity. In the pathogenetical process both genetic and acquired mechanisms might be involved (Soyka, 1999).

3. Precipitants of a migraine attack

As migraine is a paroxysmal disorder, many studies have addressed the question: 'which internal or external triggers provoke the pathophysiological mechanism of migraine?' Ascertaining the precipitants is important, because a comprehensive migraine pathophysiological theory must incorporate how and where precipitants act (Martin, 2001). This knowledge has also heuristic value in proposing such a theory. Moreover, because the precipitants may induce the pathophysiological mechanism in migraine patients and not or to a lesser extent in nonmigraineurs, comparing the different somatic responses of both groups to those triggers, can help finding the pathological mechanism of migraine or testing current pathophysiological theories. It may also provide behavioral treatments for patients and a means of counseling them to avoid or reduce these factors, thereby diminishing the frequency and severity of attacks. Interpretation of migraine-triggering factors however, is difficult because two or more factors occurring in close time proximity, may or must act in union (Scopp, 1992a and 1992b). Furthermore, an external factor may provoke an attack only if the migraine "milieu interieur" is set appropriately, e.g. the hormonal state in a woman's menstrual cycle (Blau, 1992).

4. The association between stress and migraine

The precipitating factors of a migraine attack most frequently mentioned are mental and emotional stress, consumption of alcoholic beverages (particularly red wine), and the menstrual cycle. But also factors like smoking, glaring light, noise, smells, wheather changes, exercise, excitement, somatical pain, effects of drugs, special food, high levels of blood lipids and free fatty acid, and sexual activity are mentioned (Rasmussen, 1993; Robbins, 1994; Bic et al., 1998; Spierings et al., 2001).

According to the modern, interactional stress paradigm factors such as how subjects appraise and cope with potentially stressful events are important, and stress arises only and insofar there exists an imbalance between a perceived external or internal demand and a person's perception of his ability to cope with this demand (Cox and Mackay 1977; Lazarus and Launier 1978; Lazarus and Folkman, 1984). From this point of view, the somato-psychological impact of a stressor depends on the individual's appraisal of the stressor, his coping abilities, and on his social network as a source of social support.

In many studies migraine patients report stress as one of the most common headache triggers. Migraine patients also report that the perception of headache onset is stressful; and this stress, in turn, may amplify pain intensity (van den Bergh et al., 1987; Amery, 1987; Scopp, 1992b; Dowson and Jagger, 1999). Assuming that stress may be a major precipitant or cause of a migraine attack, studying the temporal relation between stress and migraine activity, the somatical and behavioral responses of migraineurs to stress, as well as their social situation and cognitive appraisal of a stressor, is therefore important to conceptualizing the stress-migraine association. Moreover, it can provide the rationale for psychological interventions aimed at teaching migraine sufferers more efficient coping strategies and/or to mobilize social support (Martin and Theunissen, 1993; Martin and Soon, 1993).

The variability within and across studies of the relation between stress and the occurrence of migraine headaches has been large. In retrospective self-report studies migraineurs were asked to recall the number, types, and sometimes their

perceptions of stressful events in their lives over a given period of time. These studies have generally found migraine to be associated with more life stressors which are often appraised as threatening and coped with in a more passive or avoiding manner (Sorbi and Tellegen, 1984; de Benedittis et al., 1990; de Benedittis and Lorenzetti, 1992; Ehde and Holm, 1992). These retrospective studies, however, suffer from a methodological shortcoming. The data of these studies might be confounded by factors shown to influence memory of personal relevant experiences (Loftus, 1995). To avoid this threat to internal validity, two other study designs have been used. In prospective self-report studies, migraine patients keep a (n) (electronic) headache diary by which the time relation between stressful events and migraine attacks is analyzed (Levor et al., 1986; Koehler and Haimerl, 1990; Spierings et al., 1997). These studies showed significant elevations of daily hassles (microstressors or minor life events, as opposed to major life events) preceding a migraine attack. Studying headache patients, Fernandez and Sheffield (1996) found that both headache frequency and intensity were significantly predicted by daily hassles; they also found a negligible relation between any headache parameter and major life event measures, but a significant relation between these events and daily hassles. Major life events nevertheless constitute a risk: recent findings indicate that life events may trigger a succession of hassles which culminate in headaches. In many of these studies, however, the patients merely monitored the occurrence of stressful events. Therefore, in the absence of an experimental design, no causal inferences can be made as to a link between daily stress and migraine. From this perspective, and because most investigators ignored factors pertinent to a time-series analytical approach (resulting in artificially inflated relations between the two variables collected over time (West et al., 1991), the assessment of stress and its association with migraine in these studies has been limited.

Other investigators of the 'stress-migraine' association have manipulated characteristics of stressful situations in the laboratory and assessed migraineurs' psychological and physiological reactivity. Many of these tested whether patients suffering from migraine headache complaints demonstrate 'symptom specificity',

i.e., whether they show a dysregulation in the sympatho-adrenomedullary system, which becomes most prominent in response to stress (Flor and Turk, 1989; Passchier and Andrasik, 1993). They predominantly focused on the intra- and extracranial vascular responses (mainly the temporal artery blood flow) (Drummond, 1982; McCaffrey et al., 1986; Leijdekkers and Passchier, 1990; Passchier and Andrasik, 1993; Passchier et al., 1993) and the frontalis muscle tension levels (Lichstein et al., 1991), while parameters such as electrodermal activity (Leijdekkers and Passchier, 1990; Passchier et al., 1993), heart rate and blood pressure were measured as responses reflecting general sympathetic nervous system activity (Leijdekkers and Passchier, 1990; Appel et al., 1992; Passchier and Andrasik, 1993; Passchier et al., 1993). Several of these manipulation studies yielded positive findings (McCaffrey et al., 1986; Passchier et al., 1993) while some resulted in the development of headaches (Gannon et al., 1987; Haynes et al., 1990). However, most of them showed no differences between migraine patients and control subjects, neither in autonomic baseline levels nor in autonomic reactivity to stress as shown by their autonomic baseline levels (Flor and Turk, 1989; Leijdekkers and Passchier, 1990), their autonomic reactivity to stress (Passchier and Andrasik, 1993; Passchier, 1994), their intra- or extracranial vascular activity or frontalis muscle activity (Leijdekkers and Passchier, 1990; Passchier and Andrasik, 1993; Sacks, 1995).

The inconsistency in findings may be due to methodological factors: the subject population may vary in type of used classification and method of diagnosis; the lack of adequate control groups, adequate time for adaptation before psychophysiological data collection begins, and of prospective longitudinal studies. The experimental stressor may differ in nature, in ecological validity, duration and (individual) psychological impact.

Several experiments provided evidence that migraineurs differ from controls in their way of coping with a stressor or in the social support they (perceive to) have or seek (Martin and Soon, 1993; Martin and Theunissen, 1993; Hassinger et al., 1999; Siniatchkin et al., 1999; Materazzo et al., 2000). Migraine patients are reported to apply more wishful thinking and self-criticism in managing a stressor.

They reported the use of more social withdrawal and catastrophizing (Hassinger et al., 1999) and showed a trend towards more repression and significantly more self-aggression (Passchier et al., 1988).

Several investigators compared (post-hoc) chronic headache patients (diagnosed with migraine, tension-type and combined migraine and tension-type headaches) with controls. The results of these studies indicate that a number of similarities exist between these headache patients in their behavioral responses to stress (Ehde and Holm, 1992; Scharff and Turk, 1995). Headache patients are often found to use less effective coping strategies (Sorbi and Tellegen, 1984; De Benedittis et al., 1990; De Benedittis and Lorenzetti, 1992; Ehde and Holm, 1992) and report to have or seek less social support (Martin and Theunissen, 1993). However, other studies produced results contradictory of those mentioned above (Kroner-Herwig et al., 1993; Blomkvist et al., 1997).

In summary, retro- and prospective studies have yielded evidence of a temporal relation between stress and migraine activity. A definite conclusion, however, as to such a relation or about a specific autonomic or behavioral response pattern of migraine patients to psychological stress cannot be drawn at this moment, neither as to its presumed abnormalities nor to its etiological significance (Holm et al., 1997).

5. The association between migraine, personality characteristics and psychopathology

Research on psychological factors in head pain have generally focused upon personality traits and psychopathology. Investigators have frequently described migraine patients as sharing particular personality traits. From 1930 to 1970 the opinion was propagated that disturbances of personality were causally related to the pathogenesis of migraine. A classic among such studies was Wolff's research into the 'migraine personality'. He portrayed migraineurs as ambitious, successful, perfectionistic, rigid, orderly, cautious, and emotionally constipated (Wolff, 1963).

Subsequent research into this typical personality structure of migraineurs tended to disconfirm it (Schnarch and Hunter, 1979; Kohler and Kosanic, 1992). The former investigators found migraine sufferers only to have significantly more fears of expressing anger and suspicion of other people than nonmigraine subjects. In a study by Leijdekkers and Passchier, migraine patients reported higher levels of trait anxiety, greater fear of failure, lower stress tolerance, and higher levels of state anxiety than control subjects (Leijdekkers and Passchier, 1990). Schafer found higher levels of typus-melancholicus traits in migraineurs compared with normal subjects, neurotic, psychosomatic and pain patients (Schafer, 1994).

Recent clinical and epidemiological studies show strong evidence that migraine co-occurs with neuroticism, depression, somatization, alexithymia, and anxiety (mainly panic) and eating disorders (Merikangas et al., 1990; Brewerton et al., 1993; Brewerton and George, 1993; Merikangas, 1994; Stewart et al., 1994; Breslau and Andreski, 1995; Spierings and van Hoof, 1996; Guidetti et al., 1998; Dowson and Jagger, 1999; Calandre et al., 2002). The association appears to be strongest for migraine with aura (Keck et al., 1994; Merikangas, 1994; Marazziti et al., 1995). It is important to note that these measures are different from those observed in psychiatric patients: in the above mentioned studies scores still fell within the range of the normal population.

Just like the nature of the stress-migraine association, the exact role and the influence of psychopathological factors on the evolution of migraine also remains unclear (Guidetti et al., 1998). Some findings suggest that psychopathology precedes the onset of migraine (Merikangas et al., 1990), or that it may be the cause of it (Blanchard et al., 1989). Other findings suggest psychopathology to be the consequence of migraine. The association may also be bidirectional, with migraine predicting first-onset psychopathology and psychopathology predicting first-onset migraine (Breslau et al., 2000), perhaps reflecting a common (pathophysiological) predisposition to migraine and to (some) psychiatric disorders (Breslau and Davis, 1993; Glover et al., 1993; Brewerton and George, 1993; Haythornthwaite, 1993; Breslau et al., 1996).

In summary, results of recent research do not confirm migraine patients to possess specific personality characteristics. But they yielded strong evidence of an association between psychopathology and migraine, although the nature of this association is still a matter of dispute.

6. The burden of migraine

During the past decennium, it became clear that parameters other than the classical epidemiological indicators of morbidity and mortality were necessary to adequately evaluate the repercussion of chronic recurrent diseases like migraine. Hence attention has been focused on the Quality of Life (QoL) of migraine patients. A number of generic and migraine-specific self-administered questionnaires to measure QoL were developed and assessed for reliability and validity, e.g. the Nottingham Health Profile (NHP) (Hunt et al., 1980; Erdman et al., 1993), the Medical Outcomes Study Short Form (SF 36) (Stewart et al., 1988; Tarlov et al., 1989), the Headache Needs Assessment questionnaire (HANA) (Cramer et al., 2001), the 24-h Migraine-Specific Quality of Life Questionnaire (24-h MqoLQ) (Santanello et al., 1995; Hartmaier et al., 1995), and the migraine specific quality-of-life measure (MSQOL) (Bradley et al., 2000; Passchier et al., 2001). The migraine-specific measurements of QoL make it possible to quantify the burden of migraine and are responsive to changes in QoL secondary to migraine therapy. By using a generic instrument, the burden of migraineurs can be compared to that of patients with other chronic diseases and to that of the general population. Usage of these standardized instruments can increase awareness of the impact of migraine and can be useful to policy makers allocating health care resources. They can also be useful to individual practitioners, selecting the most appropriate migraine therapy, monitoring the course of illness and treatment outcomes. They also are usable by pharmacists, nurses and patients, and for research purposes (Osterhaus et al., 1994; Cavallini et al., 1995; Mannix and Solomon, 1998; Dowson, 2001). Two simple and brief tools were developed: the Migraine Disability Assessment (MIDAS) instrument and the Headache Impact Test (HIT). The MIDAS tool is a five-item questionnaire developed to determine a sufferer's level of

headache-related disability at the outset, and then match treatment accordingly. The score is based on answers to questions about time lost from the workplace, housework, and leisure activities. The reliability and internal consistency of the MIDAS score are high, evidenced by testing a population-based sample of headache sufferers (Stewart et al., 1999). The HIT was designed for greater accessibility (on the Internet at www.headachetest.com and www.amlhealthy.com), and as a paper-based form known as HIT-6. The HIT and HIT-6 are validated and reliable measures of the effect that headaches are having on patients (Pryse-Phillips, 2002). Both the MIDAS and the HIT tools facilitate the communication between physicians and patients to enable greater understanding of the impact of migraine (Dodick, 2002). Such a communication is essential for an effective therapy (Edmeads, 2002; Sheftell, 2002).

Findings of many studies indicate that migraine has a unique, significant quality of life burden. Compared to the general population and other populations with chronic illnesses, migraineurs exhibit an impaired quality of life during an attack (Dahlöf and Dimenäs, 1995; Cavallini et al., 1995; Solomon, 1997; Durham et al., 1998; Dowson and Jagger, 1999) and even between attacks (Osterhaus et al., 1994; Dahlöf and Dimenäs, 1995; Cavallini et al., 1995; van Roijen and Essink-Bot, 1995; Passchier et al., 1996), bearing in mind that various factors, cultural, environmental, and cognitive in nature, can greatly modify the impact of headache, even for the same subject at different times of his or her life (Micieli et al., 1995).

The broad areas usually investigated in the evaluation of the health-related quality of life of patients suffering from a chronic disease, include psychological, social and daily physical functioning.

6.1. Psychological functioning during migraine

The findings of the relatively few studies performed during a migraine attack demonstrate how almost all the aspects of the psychological status are impaired as compared to the migraine interval. Migraine patients have been found to show a significant reduction in activity, concentration, extraversion, self-confidence and mood and a significant increase in inactivity, fatigue, dizziness, introversion,

sensitivity, annoyance, timidity and depression, and to endure a high pain intensity before taking analgesic medication. In addition, patients reported feeling scared and lack of energy. They were also found to suffer from feelings of vulnerability, guilt, and shame (Göbel and Krapat, 1993; Cavallini et al., 1995; Haks et al., 1997; Passchier et al., 1998). Tiredness and sleep are prominent during the prodromal stages and during the attack (Blau and MacGregor, 1995). All these phenomena impede the patient's quality of life.

6.2. Social functioning during migraine

The effects of migraine attacks may severely interfere with, limit or totally prevent social engagements (sports, meeting friends), sexual relationships, leaving the house and/or taking care of families. It may lead to prejudices in the workplace. This tends to confirm that migraine may have deleterious effects on partners as well as on the underlying relationship (Kryst and Scherl, 1994; Dowson and Jagger, 1999),

6.3. Physical functioning during migraine

The study by Santanello et al. (1995) has shown that there are significant relations between subjects' 24-hour quality of life scores and activity limitation. As subjects reported decreasing ability to carry on with activities as a result of their migraine, quality of life scores in the domains 'work functioning', 'social functioning', and 'energy' decreased significantly. As activity became more limited, subjects reported feeling more upset, more physically uncomfortable, and more concerned regarding the capability of their migraine medication to relieve their migraine symptoms. As the limitation in daily activities during migraine significantly decreases work functioning, it thereby also determines another important impact of migraine: the economical costs of migraine. During the past ten years, studies were published on the effects on health care resources and lost labor cost, and the results of these studies all indicate that migraine results in significant economic costs (Micieli et al., 1995; Davies et al., 1999; Edmeads and Mackell, 2002). Dowson and Jagger reported that the effects of migraine attacks could severely limit or totally prevent

social engagements such as going to work. Forty percent were totally prevented, and an additional 23% were significantly prevented, from going to work. They concluded that migraine or migrainous headache leads to considerable work loss and reduced work performance, with an average of 1.1 work days lost per migraineur (over a three-month period), and a reduction in work effectiveness when working with a headache of 41% (Dowson and Jagger, 1999). So, migraine headache accounts for substantial economic cost, resulting in an estimated 3 million days spent bedridden each month in the United States (Hu et al. even report a total of 112 million bedridden days per year) and lost labor cost ranging from \$6.5 to \$17 billion per year (Osterhaus et al., 1994; Hu et al., 1999; Caro et al., 2000). Migraineurs generated 1.7 times more medical claims and 3.0 times more pharmacy claims and had 3.8 times more emergency room visits and 5.0 times more diagnostical procedures performed than an age and sex-matched control group (Osterhaus et al., 1994).

In 1995 van Roijen and Essink-Bot presented a comprehensive overview of the burden of migraine for The Netherlands in 1993. The baseline estimate of the total cost of migraine was NLG 675 million (309 million Euro) per year. Eighty percent of that cost was due to absenteeism and reduced productivity at work. Alternative practitioners were responsible for the main part of the cost of medical consumption (NLG 106.7 million or 48.5 million Euro) indicating that migraine patients often seek therapy outside established health care. Consequently, individuals with migraine, employers, and insurance companies all have an economic stake in reducing the migraine burden.

7. Migraine therapy

Therapies for migraine headaches may be divided in non-pharmacological and pharmacological prophylactic and abortive therapies. Non-pharmacological interventions include stress reduction behavioral modalities such as biofeedback, relaxation training, and brief cognitive behavioral therapy. These interventions can reduce migraine frequency on a long-term basis in a substantial percentage of patients. The patient's perception of emotional stress as a headache trigger seems

to be the essential element in successful treatment. Also presentation of diets and other complementary therapies may be given (Scopp, 1992a and 1992b; Pryse-Phillips et al., 1997; McGrath, 1999).

Pharmacological agents that may be used as a prophylactic include, beta blockers, calcium channel blockers, valproic acid, nonsteroidal anti-inflammatory drugs (NSAID's) and MAO inhibitors. Their effect in migraine was discovered by chance in clinical practice when these drugs were used for other purposes (Krymchantowski et al., 2002'. Prophylactic treatment is indicated if the patient has more than two migraine episodes per month, abortive/symptomatic medications fail or are contraindicated, or if a concurrent medical condition is present (Sharfman, 1998). Tricyclic antidepressants may be used when there are concomitant conditions such as sleep disturbance, depression, anxiety, or fibromyalgia (Cady, 1996). Abortive anti-migraine medications include: dopamine antagonists, serotonin agonists, opioids, local anesthetics, non-steroidal anti-inflammatory agents, and steroids (Peroutka, 1997; Ducharme, 1999). The serotonin agonists (the 'triptan' anti-migraine agents, e.g., sumatriptan, rizatriptan, zolmitriptan, naratriptan) were introduced more than a decade ago and represent a significant improvement in migraine therapy (Dulli, 1999). They have shown to act selectively, by causing vasoconstriction through 5-HT_{1B} receptors which are expressed in human intracranial arteries and by inhibiting nociceptive transmission through an action at 5-HT_{1D} receptors on peripheral trigeminal sensory nerve terminals in the meninges and central terminals in brain stem sensory nuclei. These three complementary sites of action underlie the clinical effectiveness of the 5-HT_{1B/1D} agonists against migraine headache and its associated symptoms (Hargreaves and Shepherd, 1999).

Previous research, however, has confirmed that between 40% and 66% of migraineurs do not consult a general practitioner, and that the reasons for this may be due to 'fatalistic expectations' relating to poor treatment options, unfavourable experiences with previous drug therapy, lack of physician empathy and nondiagnosis or misdiagnosis (Lipton et al., 1995; Young et al., 1997; Ferrari, 1998). Many papers point to the fact that migraine is an under-diagnosed and under-treated

condition, despite the high prevalence of known cases (Dowson and Jagger, 1999; Brandes, 2002). Despite the acknowledged severity of their condition, over half the sufferers were currently taking simple analgesics such as aspirin or paracetamol (Clarke et al., 1996; Dowson and Jagger, 1999). Therefore, it seems highly likely that significant proportions of sufferers are taking inadequate treatment (Lipton et al., 1995; Dowson and Jagger, 1999).

8. The rationale and scope of this thesis

The association between stress and migraine remains unclear, despite a large number of studies on this issue. This applies to the temporal relationship between the experience of stress and the beginning of a migraine attack; but also to a distinct psychological, cardiovascular or biochemical reaction to stress of migraineurs, and for the existence of a specific 'migraine personality' and its implications in migraine etiology.

As stated above, in previous studies methodological factors, such as the lack of (adequate) control groups, may be accountable for their inconsistent results. Therefore, in our study we compared the cardiovascular, serotonergic, and catecholaminergic responses of migraineurs with nonmigraineurs (both groups being treated in an outpatients' clinic) before, during, and after the induction of psychological stress. In addition to these parameters, temporalis pulse amplitude and frontalis muscle activity were studied because of their presumed specific role in the etiology of migraine attacks. Chapter 2 presents the results of this study. We also compared stress related personality traits of migraineurs with those of nonmigraineurs. In addition, we compared the psychological reactions to stress of these two groups. The results on these parameters are presented in Chapter 3.

Until now, the assessment of the burden of migraine has been based on subjective self-report measures. However, there may be a difference between what the patient reports and what he/she actually does. Therefore, it is important to investigate whether the outcome of subjective data can be substantiated by an objective, valid and reliable quantification of (the limitation of) daily functioning in the habitual environment of the patient. This is also important, because if such a

quantification is possible, then the burden of a migraine patient can be more objectively and reliably assessed, since the behavior of a migraine patient during an attack appears to be strongly related to relevant domains of this burden (work, social activities, energy) (Santanello 1995). Furthermore, the effects of anti-migraine therapies on this burden, on migraine-related disability and on daily functioning can then be determined more accurately as well as the relationships between psychological or psychophysiological parameters and parameters of overt behavior during a migraine attack. Progress in the technology of portable digital ambulatory recorders and the application of accelerometer sensors have recently made it possible to objectively, reliably and validly quantify (and discriminate between) different types of body postures and physical activities (Bussmann et al., 1995; Veltink et al., 1996; Bussmann et al., 1998a, 1998b, 1998c). In a feasibility study, we explored the conditions under which this so-called 'ambulatory accelerometry' can be used to objectively quantify the influence of a migraine attack. The results of this study are presented in Chapter 4.

As was shown in this feasibility study that ambulatory accelerometry can provide the objective behavioral effect parameters for the evaluation of migraine and as ambulatory accelerometry has also been proven to be sensitive enough to quantify the effects of (psycho)pharmacological manipulations on physical activities in healthy males (Tulen et al., 1997), we conducted a randomized, double blind, double dummy, cross-over study to assess the effects of acute treatment on daily functioning during two migraine attacks with oral administrations of a specific antimigraine drug (i.c. naratriptan - tablet 2.5 mg) and the nonspecific antimigraine drug naproxen (capsules 500 mg), a nonsteroidal anti-inflammatory agent. Measurements of 24-hour patterns of locomotor and physical activities and heart rate, as well as repeated subjective assessments of mood, level of functioning, presence and severity of headache, and sleepiness, were obtained during a headache-free baseline period (2-day period), as well as during and after the acute treatment of two migraine attacks with either naratriptan or naproxen. During and after each migraine attack, measurements were made for a maximal duration of two days. The psychological, heart rate and activity data of the headache free

period of the migraine patients were compared with the data obtained from a healthy control group (matched for age, gender, and occupation). The results of this comparison are presented in Chapter 5. In chapter 6 the results are presented of the ictal measurements, i.e. of the evaluation of the effect of naratriptan on objective measures of locomotor and physical activities and on subjective measures of clinical symptoms, mood, sleepiness, and level of functioning during the first six hours of treatment of a migraine attack in the habitual environment, in comparison with the effect of naproxen.

Finally, Chapter 7 presents a general discussion and concluding remarks on the content of the thesis.

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Chapter 2

Serotonergic, catecholaminergic, and cardiovascular reactions to mental stress in female migraine patients. A controlled study

Psychological stress evokes substantial increases in sympathoadrenomedullary system activity, resulting in increased plasma concentrations of epinephrine and norepinephrine and enhanced cardiovascular activity.^{1,2} The type and intensity of the responses depend upon the nature of the stressor,^{3,4} the emotional demands elicited,⁵ the coping style,⁶ the emotional state and personality of the subject as well as whether or not the subject is in control of the situation.⁵ Experimental, clinical and epidemiological research yields evidence that prolonged sympathoadrenomedullary activation due to psychological stress may adversely affect physical health and that it may be important in the etiology and maintenance of diseases such as affective disorders, anxiety disorders, or hypertension.^{1,2,5,7} In this respect, psychological stress also has often been mentioned as being a potent factor in the induction of a migraine attack.^{2,6,8,9}

Most investigators of the 'stress-migraine' association have tested whether patients suffering from these headache complaints, show 'symptom specificity', i.e., whether they have a dysregulation in the sympathoadrenomedullary system, which becomes most prominent in response to stress.^{3,10} Another hypothesis states that psychological stress induces abnormally high sympathetic responses in migraine patients. If so, this can explain why mental stress is often mentioned as a provoking factor for their attacks.^{2,6,10}

Many of the studies on the stress-headache association focused on the intracranial and extracranial vascular responses (mainly the temporal artery blood flow,^{3,10-14} and the frontalis muscle tension levels^{3,15}) whereas parameters such as electrodermal activity,^{11,13} heart rate and blood pressure were measured as responses reflecting general sympathetic nervous system activity.^{10,11,13,16} Although most of these studies found no differences between migraine patients and control subjects, neither in autonomic baseline levels^{3,11} nor in autonomic reactivity to stress^{3,8,10} nor regarding intracranial or extracranial vascular activity or frontalis muscle activity, their results are, nevertheless, inconsistent and confusing.^{3,10,11,17,18} Regarding plasma catecholamines, norepinephrine levels have been found to rise before¹⁹ or during^{20,21} migraine attacks, probably signifying the physiological stress patients experience as a result of headaches.²² However, the few studies on plasma levels and urinary excretion

patterns of catecholamines and their metabolites in relation to migraine allow little room for reaching firm conclusions on their role in the migraine disorder.^{22,23}

Many explanations for the divergent results of the autonomic responses to psychological stress are mentioned in the literature. Some concern the stressor employed in the experiment: (lack of) its ecological validity, the diversity of its nature, duration and (individual) psychological impact.¹³ Other explanations concern the methodology of the studies, eg, the use of various patient groups, the lack of neurologically acceptable diagnoses, of information on illness-related variables, of adequate control groups,^{15,24} of adequate time for adaptation before psychophysiological data collection begins,¹⁵ and of prospective longitudinal studies.^{3,8,10} For this reason, a definite conclusion about a specific autonomic response pattern of migraine patients to psychological stress cannot be drawn at this moment, neither about its presumed abnormalities nor about its etiological significance.

Apart from specific autonomic response patterns, there presently seems to be little doubt about a link between serotonin (5-HT) mechanisms and migraine.^{22,25-31} During migraine attacks without aura the concentration of 5-HT in platelets is significantly reduced compared to its level before and after the attack.^{23,32-34} During migraine attacks, with and without aura, platelet-free plasma levels of 5-HT are about twice as high as during the attack-free period, reaching control levels, while the 5-hydroxyindoleacetic (5-HIAA) concentration is reduced.^{23,32} Between attacks, migraine patients have significantly lower platelet-free levels of 5-HT in plasma and higher 5-HIAA levels in plasma than controls.³² Further evidence of the involvement of serotonin in migraine is provided by the fact that many effective migraine therapies interact with 5-HT receptors.^{28,30,31.}

To the present time, no investigations have been carried out on the combined assessment of serotonergic and sympathetic nervous system indices during the experience of stress by migrainous subjects.⁸

Therefore, the present study was set up to compare the cardiovascular, serotonergic, and catecholaminergic responses of migraineurs with nonmigraineurs before, during, and after the induction of psychological stress. In addition to these parameters, temporalis pulse amplitude and frontalis muscle activity were studied because

of their presumed specific role in the etiology of migraine attacks and tension headaches.

METHODS

Subjects.

Participants in the study included 23 patients with migraine, 7 without and 16 with aura (mean age 32.9; range 18 to 51); 18 patients with tension headache (mean age 34.3; range 18 to 55); and 22 healthy clinical controls (mean age 26.7; range 19 to 41), all women.

The group of patients with tension-type headache was included to avoid any effect that is specific for headache and not for migraine. All headache patients had been, or still were, under treatment by neurologists of the Department of Neurology of the University Hospital Rotterdam-Dijkzigt and were recruited by a neurologist of this Department. Diagnoses were made by the neurologist according to the criteria of the International Headache Society.³⁵ None of the patients were using prophylactic antiheadache medication. They had not experienced headache within 36 hours prior to the procedure, nor had they used antiheadache drugs in this period. In order to avoid a contamination, a control group was selected consisting of patients who were generally healthy, but who also visited the hospital. It has been shown that an anxiety-prone disposition plays an important role in making the decision to go see a doctor.³⁶ This means that the psychological makeup of the patient, instead of the physiological disposition, can explain abnormal physiological stress responses.

These control patients visited the outpatient clinic of the Dermatology Department of the University Hospital Rotterdam-Dijkzigt and had been treated for pityriasis rosea, verruca vulgaris, or nevus nevocellularis; disorders which had no consequences for the patient's long-term somatic condition and without any (known) psychological complications. As migraine is generally more prevalent in females than in males and to avoid any sex-specific effects, only women were asked to participate in this study. All participants were randomly selected.

Procedures.

The study was conducted at the University Hospital Rotterdam-Dijkzigt in Rotterdam, The Netherlands, and had received the approval of the hospital's Medical Ethics Committee.

During the first session, the patient was diagnosed by a neurologist who saw the patient in the polyclinic. The subjects were briefed by the experimenter (R.V.) on the procedure of the study and asked to sign an informed consent form. Written informed consent was obtained from all subjects. They were then asked to complete the trait anxiety scale of the State-Trait Anxiety Inventory.^{37,38} The subjects also solved some sample arithmetic problems to estimate their skills so that the experimenter was able to adjust the complexity level of the problems presented during the stress phase (see below).

Subjects were scheduled for the experiment in the second half of their menstrual cycle. They received instructions prior to the day of the experiment with respect to having a good night's sleep and a standardized breakfast (high in carbohydrates but without coffee, tea, alcohol or tyramine). They were asked not to take any alcohol or specific antimigraine drugs for 36 hours before the experiment. If a subject experienced any headache during a period of 36 hours prior to the experiment, she was asked to report this by telephone so that the experiment could be cancelled and a new appointment made. Subjects were informed that the experiment might cause them to experience stress and a headache. They were invited to bring some nonstressful literature of their own choice to read during the baseline and recovery phases of the experiment. Measurements were performed between 9 AM and 12 noon, while the subjects rested in a semirecumbent position on a bed in a study room (ambient temperature $22 \pm 1^\circ \text{C}$; sound level 36 dB(A)). The subjects were not allowed to eat, drink, or smoke during the procedures.

At the beginning of the experimental session, an intravenous cannula was placed in an antecubital vein of the non-dominant forearm in order to obtain blood samples for the biochemical assays at regular intervals during the experiment, and instruments to record heart rate, blood pressure, frontal EMG, and pulse amplitude from the frontal branch of the superficial temporal artery were attached to the subject. State aspects of

anxiety and presence of headache were assessed regularly by means of psychological self-report questionnaires. Psychological, physiological, and biochemical measurements were subsequently performed during the following procedures:

Baseline.- After a short adaptation period (15 minutes) for the subject to familiarize with the situation, baseline measurements were made for all variables.

The physiological responses registered during the last five minutes of a 10-minute baseline period were used to represent this period. Immediately after these 10 minutes, blood samples were taken for baseline measurement of the plasma catecholamines, epinephrine and norepinephrine, the 5-HT concentrations in plasma and platelets, and the 5-HIAA in plasma. Baseline state anxiety and headache intensity were assessed immediately after the blood sampling. The moments of these measurements are referred to as moment P1.

Stress.- Directly after the baseline measurements, patients were asked to perform the mental stress task. The mental arithmetic stressor consisted of performing subtractions between two numbers with a remainder higher than or equal to zero; the numbers were generated randomly by a program running on a personal computer. This procedure was adopted with modifications from Gannon et al³⁹ and Haynes et al.⁴⁰ The task was presented on the screen with both numbers on the same line. The subject was requested to enter the answers into the computer. The program was designed to adjust the level of complexity to the performance of the testee so that the problems would be neither too complex nor too simple. There were three levels of complexity, with subtractions involving numbers of 1, 2 or 3 digits, respectively. When the subject gave five correct answers in succession, the computer increased the complexity; when she gave five incorrect answers in succession, the level of complexity was decreased. If the subject did not respond within 15 seconds, she was given a new assignment. She was made aware of this time limit by a horizontal bar moving across the screen from the left to the right in 15 seconds. The subject had to do the subtractions mentally. This task was carried out for three 15-minute periods. During the interval between the second and third period, all subjects were told their performance was slipping, and were instructed to try to perform better. Actually, this was said to make the task more stressful.

While the physiological responses were recorded continuously, the first 2 minutes of the first mental stress period (referred to as moment P2) and the last 5 minutes of all three mental stress periods (referred to as the moments P3, P4 and P5) were analyzed. After each interval, during the moments P3, P4 and P5, the subject was asked whether she suffered from a headache and was asked to complete the questionnaire on state anxiety. She was instructed to have her answers reflect the last 15 minutes. Blood samples were also drawn for assay of plasma catecholamines, serotonin, and 5-HIAA. The duration of this experimental phase, including the measurement of the psychological parameters and the taking of the blood samples, was 60 minutes.

Recovery (20 Minutes).- Following the last arithmetic problem, the subject was informed that the experiment had ended and that she was allowed a 20-minute relaxation period. Recording of the heart rate, blood pressure, frontal EMG, and temporal artery continued. The physiological assessments during the first 5 minutes of this period (P6) and during the last 5 minutes (P7) were analyzed. After this relaxation period, a sample of blood was drawn for assay of plasma catecholamines, serotonin in plasma and in platelets, and 5-HIAA in plasma. The subject completed another state questionnaire and rated the presence and intensity of her headache (P7). After the last blood samples were obtained, the cannula, electrodes and sensors were removed from the subject and the subject was allowed to go home.

Measurement and Analysis.

Psychological.- State (Situational) Anxiety and Ttrait (Habitual) Anxiety were measured using a Dutch version of the State and Trait Anxiety Inventory presented by Spielberger.^{38,39} The presence and intensity of a headache was assessed by means of the 'Hoofdpijn Vragenlijst', a questionnaire designed for the purpose of this experiment, using the diagnostic criteria of the Headache Classification Committee.³⁵ The presence of a headache was assessed by asking the patient, "Do you experience a headache on this moment?" (yes/no). The intensity of a headache was assessed by means of a visual analogue scale (VAS), consisting of a horizontal line with the anchors 'no headache at all', and 'the worst headache I can imagine' on either side.

The patient was asked to indicate the intensity of a headache she experienced on that moment by drawing a vertical bar through the line. The lowest score was 0 and the highest 100.

Biochemical.- Plasma and platelet 5-HT concentrations. -The measurement of plasma and platelet 5-HT concentrations was based on a reversed-phase high-performance liquid chromatography (HPLC) method described by Bax et al. ⁴¹ Briefly, plasma proteins were removed with 4.2 % sulphosalicylic acid after addition of the internal standard, isoprenaline. Five-microliter samples were injected onto a reversed-phase column (Supelcosil LC-8-DB, 5 µm particle size, 250 x 3.2 mm; Supelco Inc, Bellefonte, Penn, USA.) which was protected by a 2-cm guard column packed with the same material. The HPLC apparatus consisted of an HP 1050 Series quaternary pump, on-line degasser, and autosampler (Hewlett-Packard (HP), Avondale, Penn, USA.). The mobile phase consisted of 80 mmol/L sodium acetate, 0.27 mmol/L disodium EDTA, 0.74 mmol/L heptaene sulphonic acid, and 15% methanol, pH 4.2. The flow rate was set at 0.4 mL/min and the column temperature was 45⁰ C. The effluent was monitored by an electrochemical detector consisting of a VT-03 flow cell (0.33 µL) equipped with a glassy carbon electrode and a CU-04 controller (Antec Leyden, Leiden, The Netherlands). The oxidation potential was maintained at 0.6 V (versus Ag/AgCl reference electrode), the sensitivity range was 0.2 nA/V and the time constant was set at 0.2 second. The detector was linked to an HP 3396A integrator (Hewlett Packard, Avondale, Penn, USA.) and quantification was done by measuring peak heights. The detection limit was 5 fmol at a signal to noise ratio of 3. The recoveries of 5-HT added to the samples were between 82% and 95%. Whole blood 5-HT was calculated using the platelet 5-HT and whole blood platelet count values. This method is valid since 99% of blood 5-HT is located in the platelets. ⁴²

Plasma catecholamines.- For determination of plasma catecholamines, blood (10 mL per sample) was collected in heparinized tubes containing 12 mg of glutathione. Blood samples were centrifuged (15 minutes at 3000g); and plasma was subsequently stored at -70⁰ C until assay. Plasma concentrations of norepinephrine and epinephrine were assayed by HPLC-FD after isolation from plasma by a specific liquid-liquid extraction method and derivatization with the selective fluorogenic agent, 1,2-

diphenylethylenediamine.⁴³

Physiological.- A Nihon Kohden polygraph was used to amplify and calibrate the physiological signals. All signals were monitored continuously on paper by means of a Nihon Kohden Neurofax electroencephalograph, and at the same time recorded analog on a multichannel FM-type analog recorder (Racal Store 14 DS, Sarasota, Fla, USA). The ECG was derived using a precordial lead. Blood pressure was recorded using a servoplethysmomanometer for continuous, noninvasive measurement of finger arterial blood pressure, employing the volume clamp technique of Penaz and colleagues^{44,45} (Finapres 2300 NIBP monitor, Ohmeda, Englewood, Colo, USA). The cuffed middle finger of the nondominant hand was kept at the level of the heart by means of a supportive armrest, in order to optimize the correspondence with intrabrachial pressure changes.⁴⁶ Forehead frontalis EMG was measured by means of two Ag/AgCl electrodes. The electrodes were placed vertically above each pupil at a distance of 2.5 cm above the eyebrow, while the subject fixated upon a distant point in front of her. Before electrode placement, the subject's forehead skin was cleaned with ethanol in order to reduce the electrode resistance below 10 k Ω . Temporal vasomotor activity was recorded using a reflectance photoelectric transducer positioned over the zygomaticofacial branch of the superficial temporal artery near the ear opening. The transducer was attached by means of two-sided tape and kept in position with an elastic strip around the subject's head.

Blood pressure, ECG, EMG, and temporal vasomotor activity were digitized at a sample frequency of 102,4 Hz on a personal computer (DELL Optiplex 466/L) connected to an analog/digital (A/D) converter (Advantech PC-Labcard, model PCL-718). Before A/D conversion, a Schmitt trigger was used to trigger the incidence of the R waves in the ECG; the output pulses of the trigger were fed into the converter for sampling. The time between the output pulses (interbeat interval) was measured with a resolution of 10 ms. Systolic and diastolic blood pressure were defined per RR interval of the ECG with a resolution of 0.2 mm Hg and were averaged per analysis period. Before A/D conversion, the raw EMG signal was integrated per second. Total integrated EMG per analysis period was expressed as percentage relative to the integrated maximal EMG, which was obtained during a 1-minute period before the

experimental procedures started by asking the subjects to contract the frontalis muscle as intensely as possible. Recording of the temporal pulse amplitude was also not always successful. Therefore, the number of valid cases with data on this variable was less than for the other physiological and psychological variables. Temporal pulse amplitude data was obtained for 13 control subjects, 12 in the migraine group, and 11 in the tension headache group. Data for the temporal pulse amplitude was calculated per RR interval of the ECG as the difference between maximum and minimum values of the pulse. Mean pulse amplitude per analysis period was expressed relative to the mean amplitude baseline period. Due to a large amount of movement artifacts and artifacts due to changes in sensor position and fixation in the temporal pulse signal, a correction procedure was applied to select reliable parts of the recordings, on the basis of visual inspection of the raw signal and predefined computer settings. Only the recordings on the moments P1 and P3, during which, on the basis of this correction procedure, more than 50% valid data were obtained, were used in the final analysis. Obtaining blood samples caused momentary increases in the physiological parameters and induced some movement artifacts; these periods were excluded from the analysis. The following periods were selected for the physiological analysis: (a) baseline (P1) 5-minute period preceding the stress task; (b) the first 2 minutes of the stress task, reflecting the initial response to the task (P2); (c) three 5-minute periods reflecting the sustained reaction to the stress task between 10 to 15 minutes (P3), between 25 to 30 minutes (P4), and between 40 to 45 minutes (P5) from the onset of the task; and (d) two 5-minute periods reflecting recovery the first 5 minutes after the stress task (P6), and the period between 10 to 15 minutes after the stress task (P7).

Statistical analysis.

A logarithmic transformation ($^{10} \log$) was applied to the parameters state anxiety, relative integrated frontalis EMG, plasma epinephrine and serotonin concentration, because of skewness of the distribution. A one-way analysis of variance (ANOVA) for the parameters age and trait anxiety was performed to detect a significant difference between the groups.

Differences between the three groups in proportion of subjects with headache during

the various phases of the experiment were tested with the Pearson chi-square statistic. Differences in mean psychological, physiological and biochemical parameters between groups and between the baseline, the experimental, and the recovery phase were analyzed with a multivariate repeated-measures design, using group (migraine, tension headache and the control group) and period (moment of measurement) as independent variables. Three moments of measurements were included in the analysis: baseline, the end of the first period of mental stress (P3) and the end of the recovery period (P7), except for serotonin in platelets, for which only samples from the baseline and the recovery period were assayed. Dependent variables were state anxiety and the averaged scores on the psychophysiological and biochemical parameters. To eliminate a possible confounding effect of headache on the responses, the analyses were also performed on those subjects of the migraine (n=12) and the control group (n=16) who did not experience a headache during the experiment. The tension headache patients were excluded from this analysis because approximately half of them experienced a headache during the experiment. The analyses were performed with the Statistical Package for the Social Sciences, version 4.0.1. ⁴⁷

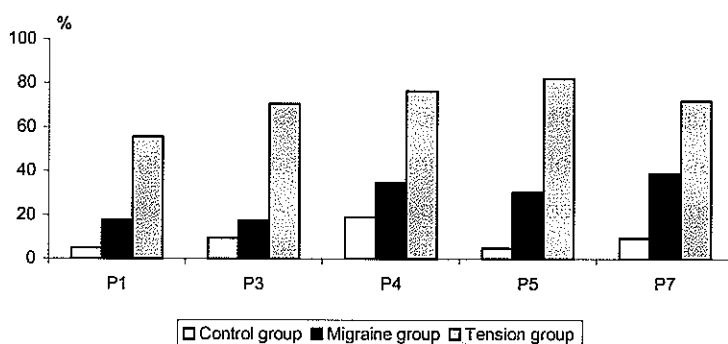
RESULTS

A one-way ANOVA revealed a significant difference in age between the groups ($F_{(2,59)} = 3.8$; $P = .028$). The control group was younger than the headache groups, which could lead to a contamination of age and group effects. Therefore, the relationship between the age of the participants and the dependent variables was analyzed. Only the plasma levels of epinephrine of P2 ($r = .53$; $P < .001$, two-tailed) and P4 ($r = .48$; $P < .001$, two-tailed) proved to be significantly correlated with age. Because of this relationship, the multivariate ANOVA of epinephrine was repeated, using age as a covariate.

Psychological parameters. - One-way ANOVA on trait anxiety did not reveal a significant difference between the groups, $F_{(2,57)} = 1.63$, $P = .20$, (Table 1). The proportion of subjects with headache during the experimental periods was consistently the highest for the tension headache group followed by the migraine and the control group (Figure

1). For all five moments of measurements depicted in Figure 1 the sample test statistic X^2 departed significantly from expectation under the hypothesis of no proportional differences between the groups (P was always less than .002). Mental arithmetic induced a significant increase in state anxiety and a subsequent decrease in state anxiety during recovery, but no differences between groups were observed (Tables 1 and 2).

Fig 1. Percentage of subjects with headache across time for all three groups



Biochemical parameters.-The drawing of a blood sample was not always successful. Therefore, the number of valid cases with data on the biochemical variables was smaller than those on the physiological and psychological variables. For the control group, there were 19 valid cases; for the migraine group, 23; and for the tension headache group, 16. Multivariate repeated ANOVA revealed a significant main effect of period for all biochemical variables, except for serotonin in platelets (Tables 1 and 2). Mean epinephrine and serotonin plasma levels increased during the first period of mental stress and subsequently decreased during the recovery period. Mean norepinephrine levels increased during recovery. Mean levels of 5-HIAA in plasma decreased during the periods of mental stress. Only for the migraine patients did the decrease continue during the recovery period (Figure 2). The MANOVAs failed to produce any significant group or interaction effects, although the mean norepinephrine levels of the control subjects appeared to be lower than those of both headache groups.

Psychophysiological parameters.- A Kruskal-Wallis one-way ANOVA on the pulse amplitude of the frontal branch of the superficial temporal artery measured during P3 relative to the baseline amplitude did not yield a significant difference between the three experimental groups, neither for all subjects ($\chi^2=.86$; $P=.65$ [Figure 3]) nor for the headache-free subjects ($\chi^2=.12$; $P=.94$). Significant period effects for the other four psychophysiological variables were found. Mean heart rate and mean levels of systolic and diastolic blood pressure were elevated during the first period of mental stress and dropped to baseline level during the recovery period. The levels of the frontalis EMG increased during both periods (Table 1, Figure 6). The MANOVAs on systolic blood pressure and on frontalis EMG produced a significant main effect of groups. Migraine patients show the highest systolic blood pressure (Figure 4). Analysis of the groups effect of the diastolic blood pressure showed a trend ($P<.10$): mean diastolic pressure levels of the migraine group tended to be higher than those of the tension headache and the control group (Figure 5). Also, the frontalis EMG levels for the migraine group were significantly higher than those for the other two groups (Table 1, Figure 6).

The analyses performed on the migraine and control subjects who did not experience a headache throughout the experiment were quite similar compared to those performed on all the subjects (Table 2).

Table 1.- Assessment of Serotonergic and Sympathetic Nervous System
Reactions Before, During, and After Induction of Mental Stress

Parameter and Group	Baseline (P1)	After 15 Minutes of Mental Stress (P3)	At the End of the Recovery Period (P7)
Trait anxiety			
Migraine	41 ± 8.9 [22]	-	-
Tension headache	45 ± 10.4 [16]	-	-
Controls	39 ± 10.5 [22]	-	-
State anxiety			
Migraine	16 ± 2.6 [23]	21 ± 3.6 [23]	18 ± 3.4 [23]
Tension headache	18 ± 3.9 [17]	23 ± 4.6 [17]	20 ± 3.5 [17]
Controls	17 ± 4.1 [21]	23 ± 5.3 [21]	17 ± 3.4 [21]
Norepinephrine (pg/ml)			
Migraine	249 ± 94 [23]	254 ± 113 [22]	273 ± 117 [22]
Tension headache	251 ± 122 [16]	246 ± 111 [16]	272 ± 126 [14]
Controls	200 ± 120 [19]	191 ± 85 [19]	213 ± 108 [19]
Epinephrine (pg/ml)			
Migraine	17 ± 9.1 [23]	30 ± 27.0* [22]	15 ± 9.7 [22]
Tension headache	15 ± 10.9 [16]	21 ± 13.3 [16]	18 ± 12.4 [14]
Controls	14 ± 14.1 [19]	18 ± 11.2 [19]	12 ± 5.9 [19]
Serotonin in plasma (nmol/l)			
Migraine	8.6 ± 9.5 [21]	11.5 ± 10.4 [19]	7.1 ± 8.9 [20]
Tension headache	6.0 ± 3.8 [14]	9.7 ± 7.0 [15]	4.6 ± 3.7 [13]
Controls	9.9 ± 10.6 [19]	15.2 ± 15.9 [17]	8.8 ± 8.0 [18]
Serotonin in platelets, nmol/10⁹ platelets			
Migraine	3.80 ± 1.7 [22]	-	3.42 ± 1.4 [22]
Tension headache	4.00 ± 1.5 [16]	-	4.06 ± 1.4 [14]
Controls	4.42 ± 1.3 [19]	-	4.23 ± 1.3 [19]
5-HIAA in plasma, nmol/L			
Migraine	42.38 ± 14.4 [21]	41.33 ± 11.6 [21]	35.65 ± 12.9 [20]
Tension headache	41.29 ± 13.1 [14]	38.27 ± 10.4 [15]	37.21 ± 15.3 [14]
Controls	47.47 ± 8.7 [19]	43.94 ± 8.9 [18]	40.94 ± 11.3 [18]
Heart rate, beats/min			
Migraine	71 ± 8.2 [23]	80 ± 14.5 [23]	70 ± 7.5 [23]
Tension headache	71 ± 10.7 [18]	75 ± 8.8 [18]	68 ± 9.0 [18]
Controls	71 ± 9.5 [22]	77 ± 13.8 [22]	68 ± 8.7 [22]

Table 1.- Continued

Parameter and Group	Baseline (P1)	After 15 Minutes of Mental Stress (P3)	At the End of the Recovery Period (P7)
Systolic blood pressure, mm Hg			
Migraine (whole group)	128 ± 12 [23]	143 ± 15 [23]	136 ± 17 [23]
Migraine without aura	139 ± 12* [7]	153 ± 8* [7]	148 ± 19* [7]
Migraine with aura	124 ± 10 [16]	139 ± 16 [16]	131 ± 13 [16]
Tension headache	118 ± 13 [18]	128 ± 15* [18]	127 ± 18 [17]
Controls	123 ± 15 [22]	139 ± 19 [22]	126 ± 15 [22]
Diastolic blood pressure, mm Hg			
Migraine (whole group)	73 ± 11 [23]	83 ± 12 [23]	80 ± 12* [23]
Migraine without aura	80 ± 9* [7]	90 ± 6* [7]	85 ± 8* [7]
Migraine with aura	69 ± 8 [16]	80 ± 12 [16]	77 ± 12 [16]
Tension headache	67 ± 13 [18]	75 ± 14 [18]	74 ± 16 [17]
Controls	66 ± 11 [22]	77 ± 14 [22]	70 ± 9 [22]
Frontalis EMG, arbitrary units			
Migraine	30.6 ± 21.5*	34.5 ± 31.1* [23]	35.4 ± 24.7* [23]
Tension headache	[23]	22.9 ± 8.9 [18]	26.1 ± 13.4 [18]
Controls	23.1 ± 11.4 [18]	19.9 ± 9.6 [22]	23.3 ± 11.6 [22]
	20.7 ± 13.1 [22]		

* Patients' mean which deviate significantly ($P < .05$) from that of control group (least significant difference test). All values given as mean ± SD, with sample size in brackets.

Fig 2. Mean 5-HIAA in plasma across time for all three groups

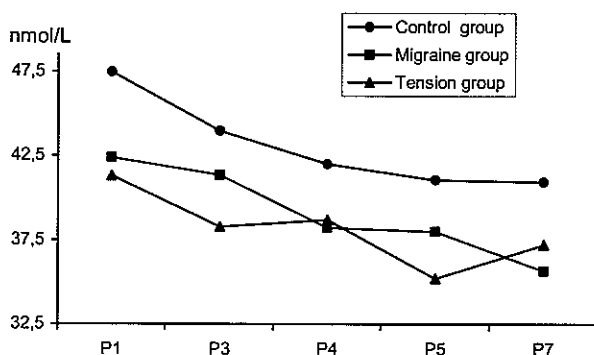


Table 2. - Outcome of MANOVA's on the parameters

Variable	Statistical outcome	
	All Subjects	Headache-Free Subjects
State anxiety		
Group	$F_{(2,59)}=1.26, P=.29$	$F_{(1,26)}=.21, P=.65$
Period	$F_{(2,116)}=62.24, P=.00$	$F_{(2,52)}=26.34, P=.00$
Group x period	$F_{(4,116)}=2.02, P=1.0$	$F_{(2,52)}=1.96, P=.15$
Norepinephrine, pg/mL		
Group	$F_{(2,52)}=1.86, P=.17$	$F_{(1,23)}=.02, P=.88$
Period	$F_{(2,104)}=3.6, P=.03$	$F_{(2,46)}=1.55, P=.22$
Group x period	$F_{(4,104)}=.23, P=.92$	$F_{(2,46)}=.10, P=.91$
Epinephrine, pg/mL		
Group	$F_{(2,52)}=1.43, P=.25$	$F_{(1,23)}=.01, P=.93$
Period	$F_{(2,104)}=15.74, P=.00$	$F_{(2,46)}=10.65, P=.00$
Group x period	$F_{(4,104)}=1.36, P=.25$	$F_{(2,46)}=.10, P=.91$
Epinephrine, pg/mL (age covariate)		
Group	$F_{(2,49)}=0.16, P=.85$	$F_{(1,22)}=.02, P=.89$
Period	$F_{(2,100)}=15.49, P=.00$	$F_{(2,46)}=10.65, P=.00$
Group x period	$F_{(4,100)}=1.28, P=.28$	$F_{(2,46)}=.10, P=.91$
Serotonin in plasma, nmol/L		
Group	$F_{(2,45)}=.68, P=.51$	$F_{(1,19)}=.32, P=.58$
Period	$F_{(2,90)}=20.72, P=.00$	$F_{(2,38)}=4.67, P=.02$
Group x period	$F_{(4,90)}=.36, P=.83$	$F_{(2,38)}=1.10, P=.34$
Serotonin in platelets, nmol/10 ⁹ platelets		
Group	$F_{(2,51)}=1.53, P=.23$	$F_{(1,22)}=3.52, P=.17$
Period	$F_{(1,51)}=1.10, P=.30$	$F_{(1,22)}=2.50, P=.13$
Group x period	$F_{(2,51)}=1.00, P=.38$	$F_{(1,22)}=.40, P=.53$
5-HIAA in plasma (nmol/l)		
Group	$F_{(2,45)}=1.63, P=.21$	$F_{(1,19)}=1.55, P=.23$
Period	$F_{(2,90)}=34.88, P=.00$	$F_{(2,38)}=22.99, P=.00$
Group x period	$F_{(4,90)}=.50, P=.74$	$F_{(2,38)}=1.98, P=.15$
Heart rate, beats/min		
Group	$F_{(2,60)}=.42, P=.66$	$F_{(1,26)}=.01, P=.92$
Period	$F_{(2,120)}=48.59, P=.00$	$F_{(2,52)}=16.66, P=.00$
Group x period	$F_{(4,120)}=1.84, P=.17$	$F_{(2,52)}=1.76, P=.18$

Table 2.- (continued)

Variable	Statistical outcome	
	All Subjects	Headache-Free Subjects
Systolic blood pressure, mm Hg		
Group	$F_{(2,59)}=3.37, P=.04$	$F_{(1,26)}=2.98, P=.10$
Period	$F_{(2,118)}=35.85, P=.00$	$F_{(2,52)}=24.74, P=.00$
Group x period	$F_{(4,118)}=2.09, P=.09$	$F_{(2,52)}=.80, P=.46$
Diastolic bloodpressure, mm Hg		
Group	$F_{(2,59)}=2.86, P=.07$	$F_{(1,26)}=2.49, P=.13$
Period	$F_{(2,118)}=45.23, P=.00$	$F_{(2,52)}=28.31, P=.00$
Group x period	$F_{(4,118)}=1.84, P=.13$	$F_{(2,52)}=1.40, P=.26$
Frontalis EMG, arbitrary units		
Group	$F_{(2,60)}=4.20, P=.02$	$F_{(1,26)}=3.97, P=.06$
Period	$F_{(2,120)}=5.87, P=.00$	$F_{(2,52)}=3.10, P=.05$
Group x period	$F_{(4,120)}=.86, P=.49$	$F_{(2,52)}=.05, P=.95$

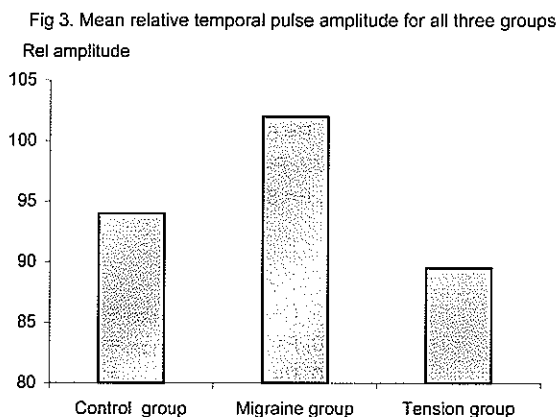


Fig 4. Mean systolic blood pressure across time for all three groups

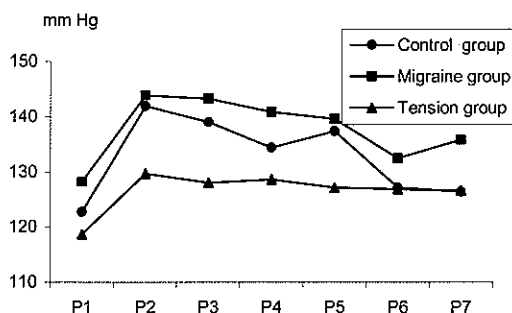
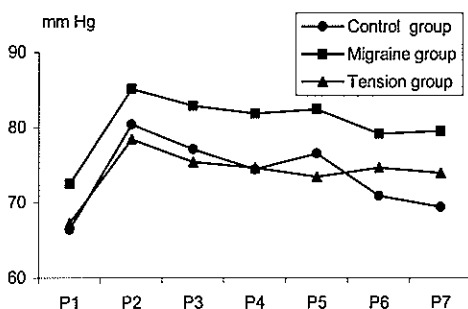


Table 3. – Assessment of Systolic Blood Pressure and Frontalis EMG in Headache-free Subjects Before, During, and After Induction of Mental Stress

Variable and Group	Baseline (P1)	After 15 Minutes of Mental Stress (P3)	At the end of the Recovery Period (P7)
Systolic blood pressure, mm Hg			
Migraine	132 ± 14	151 ± 12	143 ± 17
Controls	126 ± 14	143 ± 18	131 ± 13
Frontalis EMG, arbitrary units			
Migraine	30.1 ± 17.4	31.3 ± 18.9	35.1 ± 21.4
Controls	22.4 ± 15.2	21.4 ± 11.6	23.3 ± 11.1

All values given as mean ± SD.

Fig 5. Mean diastolic blood pressure across time for all three groups



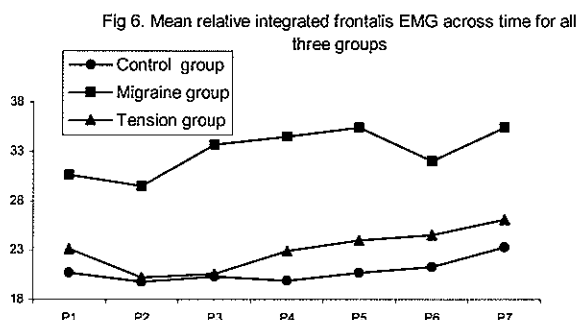


Table 4. Outcome of MANOVAs for the Patients Suffering From Classical and Common Migraine

Variable	Statistical outcome
Systolic blood pressure, mm Hg	
Group	$F_{(1,21)}=9.83, P=.005$
Period	$F_{(2,42)}=13.01, P=.000$
Group x period	$F_{(2,42)}=.13, P=.878$
Diastolic blood pressure, mm Hg	
Group	$F_{(1,21)}=5.64, P=.027$
Period	$F_{(2,42)}=13.79, P=.000$
Group x period	$F_{(2,42)}=.28, P=.754$

COMMENTS

Mental stress is often mentioned by migraine patients as a provoking factor for their attacks. This was the first study aimed at the combined assessment of the serotonergic and sympathetic nervous system reactions of migraine patients before, during, and after the induction of mental stress in order to detect the possible role of these reactions in inducing a migraine attack. For this purpose, these responses were compared with those from a tension headache group and a nonheadache clinical control group.

For all three experimental groups, increased activation of the sympathetic adreno-

medullary system was observed during the presentation of the stressor. This was apparent from the rise in heart rate, diastolic and systolic blood pressure, and mean plasma level of epinephrine following the presentation of a mental arithmetic task, as compared to their baseline values and to those during the recovery phase. Plasma concentration of serotonin, the frontalis EMG, and the subjective experience of anxiety exhibited also the same tendency. These results are indicative of the success of the stress induction.

For all the parameters, no significant group by period effects were found. These findings suggest that migraineurs do not respond differently to mental stress compared to nonmigraineurs. Although the result of the analysis of the amplitude of the superficial temporal artery pulsation must be interpreted with caution due to the many artifacts in the recordings, this variable also did not show a difference between the groups when the data collected after the first 15 minutes of mental stress and those of the baseline were compared. We found, however, a significant main effect of groups for the mean relative integrated frontalis EMG. The migraine patients consistently showed the highest mean values for this parameter during the experimental session. Because of the use of proportional EMG levels, ie, levels adjusted for the maximum contractibility of a muscle, it is conceivable that the subjects already suffering from a headache at baseline produced less maximum tension in the affected muscles because their muscles were painful, and they were afraid of increasing their pain level upon tensing.³ This, however, cannot be the explanation for the results of this study, since the difference was also present between the headache-free migraine patients and the control subjects (Table 3). Results from previous studies are inconclusive for that matter. In a number of studies, baseline frontalis EMG levels were elevated in patients with muscle contraction headaches as compared to nonheadache controls^{48,49,50} and in patients with migraine headache as compared to tension headache patients.^{51,52} We also found a significant main effect of groups for the systolic blood pressure, while the diastolic blood pressure showed a trend towards a group effect. Just as in the present study, Drummond found that throughout his experiment the diastolic blood pressure was approximately 5 mm Hg higher in migrainous patients compared to individuals who rarely or never suffered from headaches.¹⁴ The

elevated blood pressure appeared to occur independently of the stress task and, in this study, was not accompanied by a similar elevation in heart rate or plasma catecholamine concentrations.

Thus, although the effects were small, our experiment provided evidence of increased cardiovascular activity in migraine patients, although specific vascular hyperactivity to mental stress, as reflected in the temporal pulse amplitude, was not observed.

In previous research, the serotonergic response to stress in migraine patients has not been investigated during or immediately after the presentation of the stressor. Anthony et al measured the platelet serotonin level of 12 patients (9 of whom were not subject to vascular headaches) several days before and after various special medical procedures and found no consistent changes in the migrainous or non-migrainous patients. They concluded that a fall in platelet serotonin levels (often observed during a migraine attack) is not simply a nonspecific reaction to stress.²⁹

The results of the present study, however, indicate a slight, although not significant decrease in platelet 5-HT and a significant increase in plasma 5-HT levels as a consequence of mental stress.

In general, because of the absence of groups by period effects for the biochemical variables the assumption of nondifferential responding of migraineurs to stress as compared to nonmigraineurs can be extended to include the serotonergic and catecholaminergic reactions. Fifteen minutes after the start of the experiment (P1), more than half of the tension headache patients reported to have a headache, despite the exclusion criterium of not experiencing a headache for 36 hours prior to the procedure. Patients with tension-type headache may have been particularly susceptible for the development of tension due to the anticipation of the stress to be induced by the experiment and, as a consequence, developed a headache in the first 15 minutes of the trial. In our previous research, migraine patients took medication when the pain intensity was, on average, 55 on a 0 to 100 VAS. Taking this score as a cutoff for headaches with a clinically meaningful magnitude, in the present experiment, only patients with tension-type headache appeared to have a pain intensity of 55 or more; at the five moments of measurement, 2, 4, 3, 4, and 7 patients, respectively. Responses might have been influenced by the existence of a headache. Therefore,

the analyses were repeated, but only on those migraine and control subjects who did not suffer from a headache during the experiment. The results of these analyses only differed from those including all the subjects in that the systolic blood pressure and the frontalis EMG now showed a trend towards a group effect ($P < .10$). This is probably due to the loss of power of the statistical tests, since the differences between the experimental groups in the mean values on these variables were not smaller for the headache-free subjects than for those of all the subjects. Therefore, it seems justified to conclude that the recordings in this study were not influenced by the presence of a headache.

Post hoc analyses between patients with migraine with aura and those with migraine without aura did not reveal significant differences between these groups, except for blood pressure. Patients with migraine without aura showed a significantly higher diastolic and systolic blood pressure as compared to those with aura (Table 1 and 4). Clinical observations indicate that rather large proportions of patients with migraine have tension-type headache between their attacks. Studying exclusively subjects with pure migraine and subjects with pure tension-type headache, may result in nonrepresentative results due to a diagnostic purity bias.⁵³ Therefore, in this study a sample from the clinical population of migraine patients was studied, about half of whom also suffered from tension-type headache. Post hoc analyses on those patients suffering only from migraine and those with coexisting tension-type headache did not reveal significant differences on any parameter.

In conclusion, the results of this study present no evidence of a specific serotonergic, sympathoadrenomedullary, or cerebrovascular response in migraine patients to mental stress as compared to nonmigraineurs. The overall moderately elevated blood pressure in patients with common migraine, as observed in this study, underlines the potential relevance of vascular hyperactivity in the pathogenesis of (common) migraine. These findings justify further research into the vascular activity of migraineurs before, during, and after a migraine attack, preferably employing a detailed spectral analysis of heart rate variability, which provides indicators of cardiac vagal tone^{1,16,54}.

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Chapter 3

Personality traits and psychological reactions to mental stress of female migraine patients

In many epidemiological and clinical studies, psychological stress is often mentioned as a potent factor that, in a hypothesized interaction with a dysregulated sympatho-adrenomedullary and serotonergic system, leads to an actual migraine attack (1-9). The type and intensity of the responses depend upon the nature of the stressor (10,11) and on the emotional demands elicited (12). However, because most of these studies have been conducted in a retrospective manner, the evidence may not be conclusive. Two in vitro studies, in which a prolonged cognitive stressor was used, yielded different results. The findings of Gannon et al. suggest that headaches of patients with tension-type headache and of migraineurs can result from these stressors and that they may be preceded by sustained physiological arousal (13). However, Leijdekkers et al. found no differences in physiological baseline levels and stress reactions between migraine patients and controls (14). In the last two decades the stress-migraine association has also been investigated in studies with a prospective design. The results are inconsistent and confusing, as some studies have reported more stress occurring on the day before a migraine attack than on days preceding a headache-free day (15-17) while others have found no association between increased stress and migraine (18,19).

The stress responses also depend on certain personality traits, traits that determine the way in which the subject copes with the stressor (2). Hence, the personality characteristics of migraineurs become important. So far, however, the causal relation between migraine and these stress inherent personality traits remains unclear. Does such a personality structure predispose to, or induce, the development of migraine (20,21)? Or is the psychological state a result of a process during years of suffering from migraine attacks (22)? Finally, the association may be bidirectional, i.e., personality traits may increase the risk for migraine and vice versa (23-25).

From 1930 to 1970, the opinion that disturbances of personality stimulate the expression of a migraine disposition was propagated. Migraineurs were characterized by difficulty in expressing hostility and resentment, of having obsessional characteristics and a tendency to be dependent and frustrated in various ways. Much credence to this position was given by Wolff's description of the rigid, emotionally inhibited, ambitious, perfectionist personality that he found in migraineurs (5). The weakness of this opinion

was that it was based on studies lacking the use of control groups (26). Moreover, the descriptions were mainly based on studies of clinical populations, which are not representative of the general population (27,28). Neither objective diagnostic criteria nor reliable and valid questionnaires were available or given sufficient consideration (10). Following this period, more internally and externally valid studies were performed. These studies reported higher levels of depression (21), of trait anxiety (21, 14, 29), and of the defense mechanism 'turning aggression on oneself' in patients with migraine compared to headache-free controls. Migraine patients also tended to show more repression of their emotions (30) than controls. However, in their study Blanchard et al. found higher levels of depression and habitual anxiety in tension headache patients than in migraineurs (21). It is important to note that these trait measures are different from those observed in psychiatric patients with anxiety and mood disorders. In the above mentioned studies, the scores on the personality traits still fell within the range of the normal population, while psychiatric patients score much higher.

Recent epidemiological studies reveal positive associations between migraine and psychiatric disorders, primarily major depression, anxiety disorders, and neuroticism (31-34). In addition, the presence of psychiatric disorders within the population of migraine patients seems rather high (1).

In summary, despite the abundance of investigations of both the stress-migraine association and the so-called migraine personality, results are diverse and inconsistent, reflecting methodological variability, i.e., methodological shortcomings involving the lack of a (proper) control group, the use of different designs, varying sample compositions, diagnostic criteria, and stressful stimuli. In particular, conclusions on migraine patients who deserve most scientific and clinical attention, i.e., those who visit a clinic for medical care, cannot be drawn due to the lack of an adequate control group. We therefore conducted a study trying to avoid the above-mentioned methodological flaws. We focused on the specificity of stress reactions and personality traits in migraine patients and compared these with tension headache and headache-free patients, all treated in an outpatient clinic. At present, no such study has been performed. Our purpose was twofold: (i) to compare stress-related personality traits of

migraineurs with those of nonmigraineurs, both groups being treated in an outpatient clinic; and (ii) to compare the psychological reactions to stress of these two groups, i.e. migraineurs and nonmigraineurs.

Methods

Subjects

Participants were 23 migraine patients, 7 without and 16 with aura (mean age 32.9; range 18-51), 18 patients with tension headache (mean age 34.3; range 18-55), and 22 dermatologically afflicted but otherwise healthy controls (mean age 26.7; range 19-41), all female.

The group of patients with tension-type headache was included to discern effects which are specific for both types of headache and not just migraine alone. All headache patients had been, or still were, under treatment in the outpatients' clinic of the Department of Neurology of the University Hospital Rotterdam-Dijkzigt and were recruited by a neurologist of this Department (GWHM). Diagnoses were made by the neurologist according to the criteria of the International Headache Society (35). None of the patients were using prophylactic antiheadache medication. They had not experienced headache within 36 hours prior to the procedure, nor had they used antiheadache drugs in this period.

It has been shown that an anxiety disposition plays an important role in the decision being made to go and see a doctor (36), which means that the psychological make-up of patients consulting a doctor can be biased. To stand comparison, a control group was selected consisting of patients who were generally healthy, but who also visited a hospital. The control group was selected from patients who visited the dermatology outpatients' clinic of the University Hospital Rotterdam-Dijkzigt and who had been treated for pityriasis rosea, verruca vulgaris or naevus naevocellularis; disorders which had no consequences for the patient's long-term somatic condition and were without any (known) psychological complications.

Only women were asked to participate in this study, as migraine is generally more prevalent in females than in males and to avoid any sex-specific effects. They were scheduled for the experiment in the second half of their menstrual cycle. All

participants were selected from those who visited the outpatients' clinic between January 1994 and March 1996.

Instruments

Personality or trait questionnaires. The trait anxiety scale of the State-Trait Anxiety Inventory (STAI) was used to measure the habitual level of anxiety (37). A Dutch version was prepared and validated by Van der Ploeg (38). The Beck Depression Inventory (BDI) was used to measure the habitual level of depression (39). The Defense Mechanism Inventory (DMI) (40) was used to measure the intensity of relative usage of five major groups of defenses: (1) Turning against a real or presumed external frustrating object (TAO). Identification-with-the-aggressor and displacement fall into this category; (2) Projection (PRO): attributing negative intent or characteristics to an external object without unequivocal evidence; (3) Principalization (INT): invoking a general principle that "splits off" affect from content and represses the former (defenses such as intellectualization, isolation and rationalization fall within this category); (4) Turning (aggression) against self (TAS), encompassing intrapunitive defenses; (5) Reversal (REV): responding in a positive or neutral fashion to a frustrating object which might be expected to evoke a negative reaction (defenses such as negation, denial, and reaction formation are subsumed under this category). Following Juni et al., we used a sixth scale for repression (REP) (41). This scale is made up by the subtraction of (TAO+PRO) from (INT+REV) in order to obtain a continuum in which a high score forms an indication for relative more internally focused defense. Passchier and Verhage demonstrated that the reliability and validity of the Dutch translation of the DMI are satisfactory for investigational purposes. For women, test-retest reliability coefficients over a 4-6 month period of the separate defense subscales ranged from 0.69 to 0.77 and correlations between defenses and personality measures indicated construct validity (42). The Utrecht Coping List (UCL) (43) was used to quantify behavior patterns and mental attitudes in confronting problems or unpleasant events. The UCL consists of 47 short descriptions of ways of dealing with problems or unpleasant events. The subject is asked to indicate for each

item whether he reacts this way seldom or never, sometimes, often or very often. The UCL has seven subscales: (i) Active problem solving (ACT): taking time to examine the situation; going about in a goal-oriented and confident manner; (ii) palliative coping (PAL): seeking distraction, trying to feel better by smoking, drinking or relaxation; (iii) delay and avoidance (DEL); (iv) seeking social support (SOC): asking for help, to have someone listen to one's problems; (v) depressive syndrome (DEP): being overpowered by the situation and unable to change things for the better; gloom, shrink into oneself; (vi) expression of emotions (EXP); (vii) comforting cognitions (COM): such as "every cloud has a silver lining", "everyone has bad luck once in a while" etc.; encouraging oneself. The psychometric qualities of validity and reliability are sufficient. Stability coefficients of the subscales ranged from 0.55 to 0.74. Correlations between subscales and personality measures indicated construct validity (44).

Finally, the Dutch Personality Questionnaire (DPQ), created by Luteijn (1975), was used. It consists of 133 statements, each describing an attitude towards different aspects of life. The subject is instructed to state her opinion about all 133 statements by checking one of three items for each statement: 'I agree', 'I don't agree' or '?' signifying indifference. The DPQ has seven subscales. On the basis of previous research demonstrating the relevance of specific traits for migraine (5, 45, 46), we chose three subscales: (i) Inadequacy (IN), covering vague physical complaints (but no clear-cut headache symptoms) ; (ii) social inadequacy (SI): avoidance of or uneasiness during social interactions; (iii) rigidity (RIG): the desire to see things happen as planned and a fondness for fixed habits and principles. Test-retest reliability coefficients of these subscales were respectively 0.86, 0.93, and 0.90. Construct validity, in view of the correlations between the subscales and several (subscales of) personality questionnaires turned out to be sufficient (47).

State questionnaires. The state anxiety scale of the State-Trait Anxiety Inventory (STAI) was used to measure the present level of anxiety (36). A Dutch version was prepared and validated by Van der Ploeg (37).

The Profile of Mood States (POMS) was used to measure depression, anger, fatigue, vigour and tension. The subscales consist of respectively 8, 7, 6, 5, and 6 items which

have to be rated on a 5-point Likert scale varying from 0 = not at all to 4 = extremely. Each item reflects a state of mood which might have occurred at the moment of rating. The total score of the subscales depression, anger, fatigue and tension, minus the score on vigour was used as an indication of the subject's general state of mood. This score will be referred to as POMS mood. Reliability and validity of the Dutch version proved to be sufficient (48).

Procedures

The study was conducted at the University Hospital Rotterdam-Dijkzigt in Rotterdam, the Netherlands, after receiving the approval of the hospital's Medical Ethics Committee.

In a first intake session, the subjects were briefed by the experimenter (RV) on the procedure of the study and asked to sign an informed consent form. Written informed consent was obtained from all subjects. The subjects were then asked to complete the personality or trait questionnaires, which took between 60 and 90 min.

The experimental session started with elaborate preparations for the psychophysiological and biochemical measurements. These included the positioning of an intravenous cannule in a forearm vein of the subject, and connecting instruments for recording heart rate, blood pressure, frontal electromyography (EMG) and arterial temporal pulse amplitude.

Baseline (10 minutes). After a short adaptation period (15 min) for the subject to familiarize with the situation, baseline measurements (measurement 1 (M1)) were made for state anxiety (STAI, state version) and mood (POMS).

Stress (45 minutes). The mental arithmetic stressor consisted of performing subtractions between two numbers with a remainder higher than or equal to zero; the numbers were generated randomly by a program running on a personal computer. This procedure was adopted with modifications from Gannon (1987) and Haynes (1990) (13, 49). The task was presented on screen with both numbers on the same

line. The subject was requested to enter the answers into the computer. The program was designed to adjust the level of complexity to the performance of the testee, such that the problems would be neither too complex nor too simple. There were three levels of complexity, with subtractions involving numbers of 1, 2 or 3 digits, respectively. When the subject gave 5 correct answers in succession, the computer increased the complexity; when she gave 5 incorrect answers in succession, the level of complexity was decreased. If the subject did not respond within 15 seconds, she was given a new assignment. The subject was made aware of this time limit by a horizontal bar moving across the screen from the left to the right in 15 seconds. The subject had to do the subtractions mentally.

Subjects carried out this task for 3 periods of 15 min. After all three stress tasks, the subject was asked to complete the questionnaires on state anxiety and mood again (measurements 2 (M2), 3 (M3), and 4 (M4)). She was instructed to have her answers reflect the last 15 min. To make the test more stressful, subjects were told after the second period that their performance was slipping and that they should try to perform better.

Recovery (20 minutes). Following the last arithmetic problem, the subject was informed that the experiment had ended and that she was allowed a 20 min relaxation period. At the end, the subject completed another set of the state questionnaires (measurement 5 (M5)). When the procedure was completed, all instruments were removed and the subject completed several short questionnaires about the procedure.

Statistical analysis

Trait parameters. Differences in mean scores between groups on the trait parameters, except for the mean score on trait depression, were analyzed with ANOVA's, using group (migraine, tension headache, and the control group) as the independent variable. Multiple post hoc comparison tests were performed with the Modified Least Significant Difference Test, to detect which pairs of the groups differed significantly from one another. Because of the skewness of the distribution of the scores on trait depression, these data were analyzed nonparametrically using the Kruskal-Wallis

oneway ANOVA; and in case of significance the latter were further analyzed by the Mann-Whitney U test, to detect which pairs of the groups differed significantly from one another.

State parameters. Differences in mean scores on state anxiety and on the six subscales of the POMS between the experimental groups (Group effect), between the mean scores on baseline, after the first period of mental stress, and after the recovery phase (Period effect), as well as the interactions between the groups and the moments of measurement (Group x Period effect), were analyzed using a multivariate repeated measures design, with group (migraine, tension headache, and the control group), and period (baseline, the first period of mental stress and the recovery period) as the independent variables. [Manova's require that each dependent variable entered into the analyses must be normally distributed. We nevertheless used this statistical model because in the Monte Carlo experiments it has been shown that even for leptokurtic, rectangular, moderately and markedly skewed, and J-shaped distributions and using sample sizes of 3 or 5, the empirically determined rejection region of the F-distribution would be no larger than $\alpha = .08$ when the usual 5% rejection region is used (Keppel G, 1973)].⁵⁰ These three periods were selected because we were primarily interested in the initial, not so much the sustained, effect of stress and in the recovery from it. The analyses were performed with the Statistical Package for the Social Sciences version 4.0.1. (51).

Results

A one-way analysis of variance revealed a significant difference in age between the groups ($F_{(2,59)} = 3.8$; $p = 0.028$). The control group was younger than the headache groups, which can lead to a contamination of age and group effects. Therefore, the relationship between the age of the participants and the dependent variables was analyzed. Only the score on UCLPAL (subscale of the UCL, $r = -0.41$; $p < 0.01$, 2-tailed) proved to be correlated significantly with age. Because of this association, the ANOVA on this variable was performed again, now using age as a covariate.

Trait measures.

Of the trait measures, the scores on depression, reversal, projection, repression, seeking social support, and rigidity revealed a significant difference between the groups (see Table 1).

Post hoc comparisons showed that the scores of the headache groups on reversal and the composite score on repression were significantly higher than those of the control group; those on projection were significantly lower than those of the control subjects. Migraineurs and tension headache patients scored significantly lower on the UCL subscale 'seeking social support' Than the control group. Subjects with tension headache exhibited significantly more rigidity and depression compared to control subjects. No significant differences between the migraine and the tension headache groups were found.

State measures.

The multivariate analyses of state anxiety and of the six subscales of the POMS revealed a significant period effect (see Table 2 - 4). Apart from vigour, mental arithmetic induced a significant increase in mean scores on these parameters , followed by a subsequent decrease during recovery. Vigour showed the opposite trend. The mean scores of these mood variables did not significantly differ between the experimental groups. Mean scores on depression, fatigue, and vigour showed a statistically significant interaction between group and period (see Table 3, Figure 1a - c).

Post hoc comparisons of this interaction effect in the various (aggregated) experimental groups yielded the following results (see Table 5). By comparing the migraine as well as the tension headache group with the control group either a statistical significant interaction effect was found or a trend towards an interaction for both the scores on depression and fatigue. Aggregation of both headache groups and comparing it with the control group revealed a significant interaction effect for these two variables. The post hoc MANOVA's on vigour produced a significant interaction effect between on the one hand the migraine group and on the other the tension headache group and

the aggregation of the tension headache and control group. A trend towards such an interaction effect was found comparing the migraine with the control group.

Discussion

In the present study, a range of personality traits of migraine patients was measured: depressive trait, trait anxiety, (social) inadequacy, rigidity, and the use of defense and coping mechanisms. During a mental stress experiment, changes in state anxiety and mood were assessed, too. The personality traits and reactions to mental stress of migraine patients were compared with those exhibited by tension headache patients, and dermatologically afflicted, though otherwise healthy, controls. For all three groups, mental arithmetic induced a significant increase in state anxiety and in adverse mood experience, in most cases followed by a subsequent decrease during recovery. We previously reported that participants showed an increased activation of the sympathoadrenomedullary system during the presentation of the stressor, as reflected in the increase in a number of physiological and biochemical parameters (52). Overall, the psychological, physiological and biochemical findings indicate the success of the stress induction.

Descriptions of migraine patients as neurotic, i.e. anxious, depressed, and hypochondriac, or as resentful, hostile, and rigid have been widely accepted, despite the fact that these descriptions were based on clinical samples with their potential for bias. Community-based epidemiologic studies have generally supported an association between migraine and neuroticism and provided evidence for increased rates of depression and anxiety disorders, as has a longitudinal study by Breslau et al (53). In contrast to these findings, however, in the present study migraine patients were found not to be more anxious, depressed, or rigid than tension headache patients or control subjects. These contradictory results may be partly due to the fact that many of these previous studies did not employ a (proper) control group. In this study, tension headache patients did show significant higher scores on rigidity and on depression than the control group. The latter result was also found by Ficek et al (54). Furthermore, both the migraine and the tension headache group were found to make more frequent use of internally focused defense mechanisms (more reversal and repression and less projection) than the control group. In addition, the headache

patients also exhibited a less strong tendency to seek social support as compared to the control subjects. Thus, no evidence was found for a specific personality profile of migraineurs. Consequently, there seems to be no reason to assume any association between personality traits as facilitating or causing a migraine attack or even as a consequence of the syndrome. Our findings rather suggest the existence of personality traits, characteristic of headache patients in general. Patients with a recurrent headache syndrome seem to be more inclined to the use of internal defenses and to seek less social support in coping with problems or unpleasant events. Due to the design of this study it cannot provide any evidence as to the etiological significance of these traits for a headache syndrome. However, the fact that the personality traits of two distinct groups of headache patients appear to differ in the same way from those of a control group could indicate that these traits develop as a consequence of frequently having a headache. The question arises whether repeated and frequent suffering from pain (despite its origin) induces such defenses and coping mechanisms.

This study does not provide strong evidence for a specific and distinct psychological reaction of migraineurs to mental stress as compared to nonmigraineurs. It provides, however, some evidence for a different reaction of both headache groups as compared to the control group. Suggestive for this conclusion is the fact that the post hoc comparisons of the interaction effect of experimental phase (period) and group found for the scores on depression and on fatigue, indicate that this interaction manifests itself between both headache groups and the control group. Visual inspection of Fig. 1A, B leads to the conclusion that the interaction effect is probably due to the fact that during recovery, the depression and fatigue scores of the headache patients decreased relatively less than those of the control patients. The recovery potential of these mood changes within the headache patients may be less than those of the controls. Also the results of the post hoc analysis and visual inspection of the scores on vigour are consistent with this interpretation as, in contrast to the headache patients, the vigour of the control subjects returns during the recovery phase to baseline level. (see Fig. 1C). The lesser tendency to seek social support and the above mentioned distinct mood reactions of the headache patients

may in some way be related to their different defense style, i.e. their autoplasic reactions to unpleasant emotions. Psychoanalytic authors state that individuals with a rigid conscience will punish themselves for aggressive impulses by directing those impulses towards themselves (1,55). This defense style may have led to the diminished recovery rate of depression, fatigue and vigour, while avoiding social support.

In summary, as the number of different statistical tests increases, the probability of at least one spurious significant result tends to increase as well. We nevertheless did not apply a (Bonferroni) correction for multiple comparisons, because in case of correlated hypotheses (like we have) these corrections would be unnecessarily conservative (56). Still, the results of this study should be interpreted with caution as the proportion of migraine patients with aura in the target group is much greater than in the general population. Our results provide no evidence for a specific migraine personality nor for a specific psychological reaction of migraineurs to mental stress. Compared to dermatologically afflicted control subjects, migraineurs show the same differences in personality traits or in reaction to mental stress as tension headache patients do. Migraine and tension headache patients appeared to make more frequently use of internally focused defense than the control group: they showed more reversal, more repression and less projection.

They also reported to have a lesser tendency to seek social support in coping with problems and a slower recovery from depressive feelings and from fatigue due to experienced mental stress. These differences in recovery between headache patients and controls may be associated with the use of relatively more internally focused defense mechanisms by headache patients. Inconsistent with this hypothesis seems to be the fact that the headache patients did not have significant lower scores on the UCL subscale 'expression of emotion'. However, in contrast to the items of the UCL, the items of the DMI inquire after the psychological reaction on concrete situations. These DMI-items may therefore have evoked the unconscious defenses more strongly than the items of The UCL did. Further research should be performed to understand the possible relation between the distinct psychological defense and coping style of patients with a recurrent headache syndrome and the frequency and intensity of their

headache attacks. If such a link exists, it might be recommendable for these patients to help them to learn to direct their unpleasant emotions less towards themselves, i.e. to express their feelings more overtly and to seek more social support when confronted with problems or unpleasant events.

Table 1. Mean, standard deviations (in parentheses) and test statistic of the trait parameters for each group

Parameter	Migraine	Tension headache	Controls	Test statistic
TRAIT ANXIETY	41 (8.9)	45 (10.4)	39 (10.5)	F=1.63
BDI	8 (6.4)	12 (8.6) [□]	6 (5.2) [□]	$\chi^2=6.48$ ¹⁾
DMIREV	41 (5.6) [□]	41 (5.9) [◇]	35 (7.6) ^{□◇}	F = 5.20 ²⁾
DMITAS	39 (6.9)	37 (5.9)	39 (7.0)	F = 0.48
DMIINT	46 (5.3)	47 (6.0)	46 (8.3)	F = 0.15
DMITAO	38 (6.3)	39 (8.7)	39 (8.6)	F = 0.07
DMIPRO	37 (5.7) [□]	37 (7.6) [◇]	42 (6.1) ^{□◇}	F = 4.38 ¹⁾
DMIREP	10 (15.9) [□]	18(20.5) [◇]	- 4 (21.8) ^{□◇}	F = 6.50 ²⁾
UCLACT	19 (3.9)	17 (3.4)	20 (3.2)	F = 3.05
UCLPAL	17 (4.1)	19 (4.0)	20 (27)	F = 1.65
UCLDEL	15 (4.4)	17 (2.9)	16 (3.7)	F = 0.95
UCLSOC	11 (4.1) [□]	13 (3.4) [◇]	16 (4.4) ^{□◇}	F = 6.92 ²⁾
UCLDEP	11 (3.7)	13 (4.0)	13 (3.7)	F = 1.69
UCLEXP	7 (1.7)	7 (1.9)	8 (1.6)	F = 1.46
UCLCOM	12 (3.6)	12 (1.8)	13 (2.0)	F = 1.59
DPQIN	14 (6.8)	16 (9.6)	13 (10.4)	F = 0.58
DPQSI	9 (7.6)	11 (7.5)	7 (6.8)	F = 1.18
DPQRG	26 (8.1)	30 (8.6) [□]	21 (9.9) [□]	F = 4.64 ¹⁾

¹⁾ p < 0.05; ²⁾ p < 0.01

^{□◇} Significant differences between the groups with the same superscript

Table 2. Twenty-fifth and 75th percentile of POMS subscales across time for all three groups

		Control group Percentile		Migraine group Percentile		Tension group Percentile	
		25	75	25	75	25	75
Depression	M1	0	2	0	1	0	1
	M2	0	2	0	1	0	3
	M5	0	1	0	0	0	1
Anger	M1	0	0	0	0	0	0
	M2	0	2	0	1	0	1
	M5	0	0	0	0	0	0
Fatigue	M1	0	2	0	1	0	3
	M2	0	4	0	1	0	2
	M5	0	4	0	4	1	6
Vigor	M1	6	12	10	15	3	14
	M2	7	11	8	12	3	11
	M5	5	11	6	12	4	13
Tension	M1	0	3	0	2	0	4
	M2	2	5	0	6	2	5
	M5	0	1	0	3	0	2
Mood	M1	5	12	3	10	7	16
	M2	8	27	7	13	10	23
	M5	5	16	6	12	7	19

Table 3. Mean, standard deviation (in parentheses) of state anxiety for each group during the conditions, and outcome of MANOVA.

	M1	M2	M5	Statistical outcome MANOVA	
Migraine	16 (2.6)	21 (3.6)	18 (3.4)	Group	F(1,58)=1.33; p=0.27
Tension headache	18 (3.9)	23 (4.6)	19 (3.5)	Period	F(2,116)=59.43; p=0.00
Controls	17 (4.1)	23 (5.3)	17 (3.4)	Group x period	F(4,116)=1.97; p=0.10

M1: Baseline; M2: After 15 min of mental stress; M5: At the end of the recovery period

Table 4. Outcome of MANOVA's on the subscales of the POMS.

Poms subscale	Group	Period	Group x period
Depression	F(2,58)=2.3	F(2,116)=6.66*	F(4,116)=2.56*
Anger	F(2,58)=.33	F(2,116)=15.8*	F(4,116)=1.5
Fatigue	F(2,58)=1.84	F(2,116)=18.04*	F(4,116)=2.44*
Vigour	F(2,59)=1.71	F(2,118)=9.8*	F(4,118)=2.84*
Tension	F(2,59)=0.1	F(2,118)=20.83*	F(4,118)=.50
Mood	F(2,589)=2.21	F(2,118)=12.59*	F(4,118)=0.90

*p<0.05.

Table 5. Outcome with p<0.10 of post-hoc MANOVA's on the POMS subscales.

POMS subscale	Groups compared	Groups x period
Depression	Migraine with the control group	F(2,85)=3.15; p=0.048
	Tension headache group with the control group	F(2,72)=2.55; p=0.085
	Both headache groups aggregated with the control group	F(2,118)=3.09; p=0.049
Fatigue	Migraine with the control group	F(2,84)=2.84; p=0.64
	Tension headache group with the control group	F(2,72)=5.12; p=0.008
	Both headache groups aggregated with the control group	F(2,118)=4.16; p=0.018
Vigor	Migraine with the control group	F(2,84)=2.43; p=0.94
	Migraine with the tension headache group	F(2,78)=3.98; p=0.023
	Tension and control group aggregated with the migraine group	F(2,120)=3.43; p=0.035

Fig. 1a. Mean POMS depression across time for all three groups

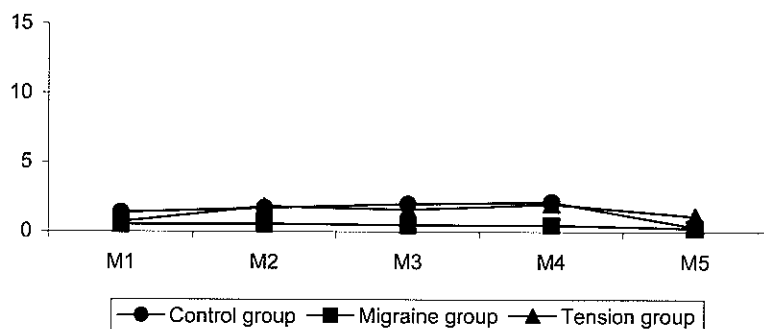


Fig. 1b. Mean POMS fatigue across time for all three groups

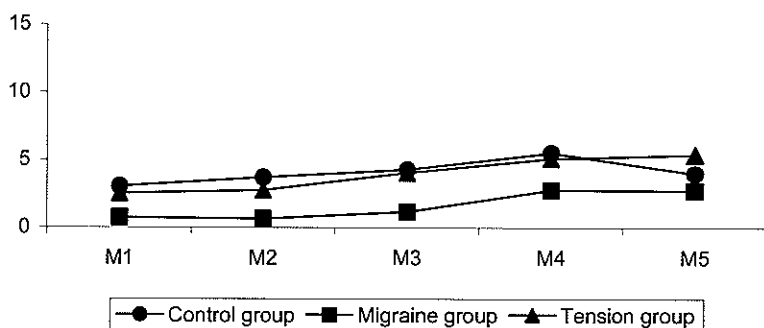
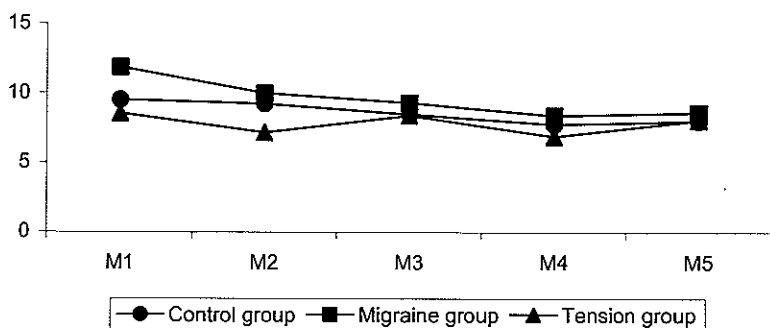


Fig. 1c. Mean POMS vigour across time for all three groups



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Chapter 4

Towards an objective quantitative assessment of daily functioning in migraine: a feasibility study

1. Introduction

Migraine is a chronic disabling disorder, with paroxysmal attacks of unilateral, pulsating headache associated with symptoms such as nausea, vomiting, photophobia and phonophobia, which sometimes can be preceded by an aura (Headache Classification Committee of the International Headache Society, 1988). In Western countries, population-based studies have estimated that approximately 15-18% of women and 6% of men suffer from migraine headaches (Rasmussen et al., 1991; Stewart et al., 1992; Henry et al., 1992; Lipton & Stewart, 1994). The repeated recurrence of migraine attacks significantly reduces quality of life and leads to impaired functioning (physically, socially, emotionally) both at home and at work, dependent upon the intensity of pain, the duration of the migraine episode and the associated symptoms (Passchier et al., 1993, 1996); Kryst & Scherl, 1994; Stewart et al., 1994). Although intensity of pain is an important factor for the individual patient (Edmeads et al., 1993), the degree of disability induced by migraine has been assumed to be a major determinant of the economical costs of this illness. Measures of disability ideally should comprise the psychological, social, and behavioral effects of a diminished level of functioning of the patient during the migraine episodes and may also be indicative of the financial losses that the patient, the employer or the society may suffer as a consequence. In their review, Stewart et al. (1994) demonstrated that disability measures are usually restricted to the number of workdays lost. They claimed this measure to be inadequate because most migraineurs attempt to function on the job while experiencing a headache; the number of workdays lost does not reflect impairment at work nor does it show the impact of migraine on other domains of daily functioning such as family and social activities. In a recent study, Hu et al. (1999) estimated the direct and indirect migraine-related costs using population-based estimates of bedridden days/year, health care resource use, economic loss due to missed workdays, and economic loss due to reduced productivity. They found that, for the American population, migraineurs required 3.8 bed rest days for men and 5.6 days for women each year. On the basis of their computations Hu et al. (1999) concluded that the economical burden of migraine predominantly falls on patients and their employers in the form

of bedridden days and lost productivity (about \$13 billion/year); these costs by far exceed the direct medical care costs (about \$1 billion/year). Similar findings regarding differences between indirect and direct costs have previously been reported for The Netherlands (van Rooyen et al., 1995).

The migraine disability assessment (MIDAS) score was developed to obtain a more general measure of migraine-induced disability (Stewart et al., 1999); the MIDAS is a short self-administered questionnaire that captures aspects of time lost from work for pay, housework or chores, and leisure activities, whereby the MIDAS score consists of the sum of the number of days lost in these three domains. With the MIDAS and other self-report measures of illness severity or disability, the patients are usually requested to provide a general impression of their headache-related functioning within a certain time period (for instance, 1 year) in order to nullify the effects of intra-individual variation in headache severity and duration (e.g., Osterhaus et al., 1994; Stewart et al., 1998; Stewart et al., 1999). However, since the behavior of the patient during a migraine episode appears to be such a relevant characteristic of disability, it is important (a) to investigate whether these subjective reports about alterations in the level of functioning can be substantiated by objective and reliable indices related to the behavioral aspects of daily functioning (e.g. daily activities such as lying, sitting, standing, physical activities and locomotion), and (b) to study the responses to individual migraine attacks. Intra-individual variations in attack severity and their implications for daily functioning are relevant to consider when the effects of anti-migraine therapies on the psychophysiological condition of the patient are evaluated.

When searching for tools to quantify behavior during migraine one is confronted by at least two challenges: (1) migraine attacks are by nature episodic - what are the conditions (or restrictions) needed to obtain behavioral measurements during a migraine episode? and (2) what tool can be used to reliably quantify the time spent in different body positions and physical activities under ambulatory conditions in the habitual environment of the patient? Progression in the technology of portable digital ambulatory recorders and the application of accelerometer sensors for quantification of kinematic processes in humans recently have led to the

development of an activity monitor (Bussmann et al., 1995; Veltink et al., 1996; Bussmann, 1998). By combining the signals of four uni-axial piezo-resistive accelerometer sensors on the trunk and the upper legs, it proved to be feasible to reliably discriminate different types of body postures (e.g. lying, sitting, standing) and different types of physical activities (e.g. walking, cycling, climbing stairs) in ambulatory situations. Validation studies in healthy subjects, amputees, and patients after failed back surgery showed high percentages of agreement (85-90%) between the automatic computer classification of the ambulatory accelerometry signals and the visual analysis of simultaneously recorded videotapes (Bussmann et al., 1998a,b,c). The method also has proved to be sensitive enough to quantify the effects of (psycho)pharmacological manipulations on physical activities in healthy males (Tulen et al., 1997). Furthermore, ambulatory accelerometry by means of four body mounted sensors has several advantages over current subjective and objective methods to assess aspects of daily activities: (1) in comparison with the use of daily logs and/or questionnaires, it has the advantage of being more reliable and accurate (Patterson et al., 1993), and (2) in comparison with quantification of overall 24-h motor activity patterns by means of wrist actigraphy (which has proved to be a clinically relevant tool, e.g. Raoux et al. (1994)), it has the advantage of being able to study details of posture-related behavioral activities.

In this feasibility study, we explored the conditions under which ambulatory accelerometry can be used as a method to quantify the influence of a migraine attack on normal daily physical activities by recording eight migraine attacks and subsequent recovery periods of six patients in their habitual environment. In order to quantify the influence of a migraine episode on daily activities, we also performed measurements during a headache-free baseline period of the same patients. As such, the present study is the first to explore the changes in objective measures of daily functioning that are related to migraine attacks in real life situations of adult patients.

2. Methods

2.1. Patients

Six female migraine patients (mean age 39.8 years, range 29 – 49 years) participated in this study; the patients were recruited by means of advertisements and all lived in or around Rotterdam. Selection was focused on obtaining a patient sample that comprised both treated and untreated migraine attacks of moderate or severe intensity. The diagnosis of 'migraine', according to the criteria of the International Headache Society (Headache Classification Committee of the International Headache Society, 1988), was confirmed by a neurologist of the University Hospital Rotterdam-Dijkzigt. Patients with a positive history of drug abuse or psychiatric illness, or current medical illness other than migraine, were excluded from the study. The patients used their habitual medication for the acute treatment of migraine (see Table 1 for the attack characteristics), but did not use prophylactic anti-headache medication during the study; two patients used no medication during their migraine attack (patients 1 and 3). The study was approved by the Medical Ethical Committee of the University Hospital Dijkzigt – Rotterdam. The patients provided written informed consent and were paid for their participation in the study.

2.2. Procedures

Repeated measurements of 24-h patterns of locomotor and physical activities, as well as repeated subjective assessments of pain, mood, level of functioning, and subjective sedation, were obtained during a headache-free baseline period, as well as during and after a migraine attack in the habitual environment of the patients.

2.2.1. Daily functioning during a 2-day headache-free baseline period

Dependent on the frequency and occurrence of the headache attacks in time for each patient, a headache-free period was defined during which baseline measures were obtained. On the morning of the first day (between 7:00 and 10:00 h, dependent upon the activity pattern of the patient), the procedures were explained,

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Table 1
Migraine characteristics for each patient

Patient	Anti-migraine drug	Severity of attack Onset	2 h	4 h	Recording time elapsed before improvement (h)
1	none	severe	mild	mild	4
2	ibuprofen 400 mg (one tablet)	moderate	mild	mild	4
3	none	severe	severe	severe	10
4	sumatriptan 20 mg (nasal spray)	moderate	mild	mild	2
5	sumatriptan 6 mg (injection)	severe	mild	mild	1
6a ^a	paracetamol (two tablets), ergotamine (one suppository)	severe	moderate	mild	4
6b	paracetamol (two tablets)	moderate	moderate	'Asleep' ^b	5
6c	ergotamine (one suppository) paracetamol (two tablets)	moderate	moderate	mild	4

^a Patient 6 was recorded during three attacks (a-c).

^b Assessments could not be made because the patient was asleep.

the sensors were attached and tested, the ambulatory recorder was placed in a small bag around the waist of the patient, and a brief calibration procedure of the signals in the sitting and standing posture was performed. Instructions were provided regarding use of the equipment, including practical advice for handling the recorder and sensors during the sleep periods. The daily log was explained and the patient was instructed regarding the documentation of relevant events in time (start sleep period, end sleep period, special types of physical activities or psychological events, naps, means of transportation); furthermore, the type of day (workday, weekend) was also indicated. The daily log included brief questionnaires regarding sleep quality, sleepiness during daytime, level of functioning and mood. The sleep quality scale was filled in every morning at breakfast; the other scales were filled in four times during the day (breakfast, lunch, dinner, before going to sleep) during all days of the protocol (this required about 3-5 min/assessment). The patients were instructed to perform their normal daily activities during the measurement period, to keep a regular sleep/wake pattern and to avoid abnormal physical and mental exertions. The presence of sensors and recorder did not allow the patients to take a bath or go swimming.

2.2.2. Daily functioning during and after a spontaneous migraine attack

The moment the patient sensed the development of a migraine attack the investigator was informed, who proceeded as fast as possible to the patient's home to start the measurements as defined above. During the migraine attack and the 2 consecutive days after the migraine attack, physical activities were recorded and the daily log was completed; in addition, during the first 4 h of recording, the patients filled in a headache diary in which assessments of severity of headache and pain were made just before medication intake and after 2 and 4 h of medication intake. The instant of medication intake was documented on file by means of a marker device attached to the recorder. After 1 day of measurement, the investigator visited the patient to change the flashdisk and batteries of the recorder and check the sensors; this procedure also allowed the patient to take a shower/bath.

2.3. Measurements and analysis

2.3.1. Accelerometer signals

Data acquisition was done by means of a portable digital recorder (VitaportTM System; TEMEC Instruments, Kerkrade, The Netherlands; dimensions 15 x 9 x 4.5 cm, 700 g) that was carried on a belt around the waist. Definition of the sample rate and preprocessing settings of the acceleration signals and transfer of the Vitaport data to a PC occurred by means of VitagraphTM software (TEMEC Instruments, Kerkrade, The Netherlands). Four IC-3031 uni-axial piezo-resistive accelerometers were employed to quantify activities (see Fig. 1). The accelerometer signals are a mixture of a component of the gravitational force (giving absolute angle information) and a component of the actual acceleration of the sensor (Veltink et al., 1996). Two sensors were attached to the skin over the sternum: in the upright standing position, one sensor being sensitive parallel to the field of gravity (the longitudinal- or Y-axis) and one sensor was attached perpendicular to the Y-axis sensor, sensitive along the sagittal- or X-axis (combined dimensions of sensors 2.0 x 1.1 x 0.9 cm). The two sensors on the upper legs (dimensions for each sensor 1.9 x 1.9 x 0.7 cm), placed approximately halfway along the spina iliaca anterior superior and the upper side of the patella, were sensitive along the sagittal- or X-axis (according to Bussmann et al., 1995; Bussmann, 1998). The accelerometer signals were stored digitally on the flashdisk of the Vitaport recorder at a sample frequency of 32 Hz.

2.3.2. Analysis of accelerometer signal

All four accelerometer signals were employed for the classification of body postures and physical activities. From each of the four accelerometer signals, additional feature signals were derived: (a) a low-pass filtered signal (finite impulse response (FIR) filter 0.3 Hz), which was subsequently converted to represent

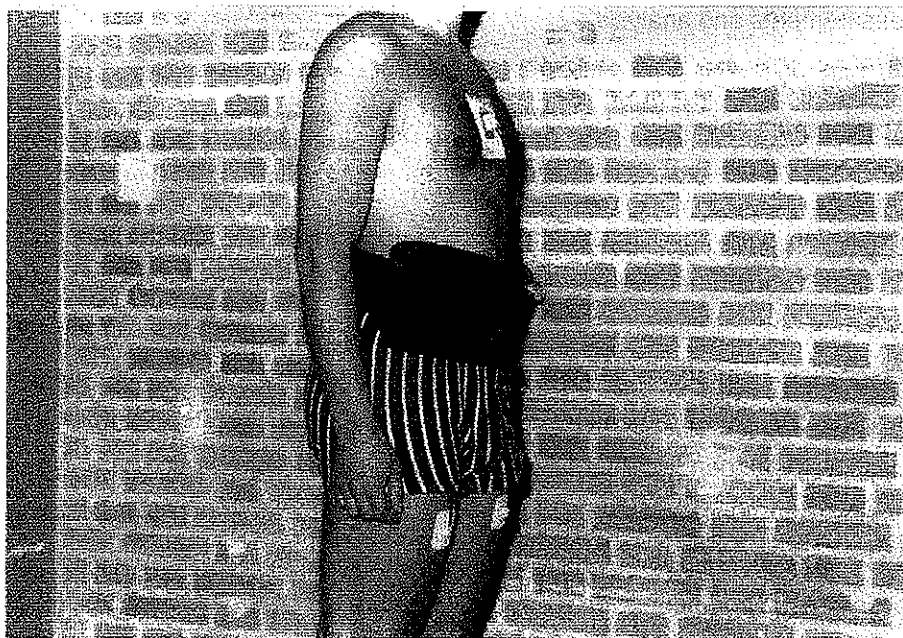


Fig. 1. Placement of accelerometer sensors on trunk and upper legs.

angular information (-90 to $+90^0$); (b) a high-pass filtered (FIR) filter 0.3 Hz), rectified and smoothed signal (HRF signal) - this signal reflects the variability of the measured signal, or 'acceleration energy', and was used to compute an index of motility; and (c) a band-pass filtered signal (FIR filter 0.3-2 Hz for the legs and 0.6-4 Hz for the trunk sensors) - this signal was further analysed by means of an instantaneous frequency analysis method (Martens, 1992) to determine various cyclic movements. Twenty-three activity subcategories were defined (e.g., walking fast, walking slow, standing upright, standing with the trunk flexed). For each subcategory, a minimum and maximum value was pre-set for each feature channel in an activity detection knowledge base (which was developed on the basis of the validation studies). The output signal of the computerized activity detection (according to Bussmann, 1998) was processed to obtain the following categories: (a) the body postures lying back, lying side, lying prone, sitting, and standing; and (b) the dynamic activity categories walking, cycling, climbing stairs, and unspecified non-cyclic movements. Short-lasting activities (< 5 s) were discarded. Typical examples of the raw accelerometer signals, motility signals and the output of the

activity monitor during different body postures and physical activities are shown in Fig. 2. For each patient, the following output parameters were computed for each relevant 'migraine period' (i.e. the period from medication intake, or in case of no medication the onset of measurement, until the moment the patient indicated a 'noticeable' reduction of the symptoms of the migraine attack) and for each corresponding time period of the second day of the headache-free baseline recording (first day was considered a habituation period): the total time spent in each posture (lying, sitting, standing) or as movement (summation of time spent as walking, cycling, climbing stairs, or as unspecified movements), the total number of transitions between lying, sitting and standing; and a total motility index. The motility index was based on the mean of the HRF acceleration signals within a certain analysis period; the mean of the motility values of the four sensors was used to reflect total body motility. For each analysis period, the time spent in the different body postures or as movement was expressed in minutes; total motility was expressed in arbitrary units/s, whereas the total number of transitions during the periods was counted.

Because of the exploratory nature of the study, the activity patterns of several patients are presented graphically in order to illustrate the influence of a migraine attack on body posture and physical activities. Furthermore, the effect of migraine on the behavioral parameters was studied in relation to the duration of the 'migraine period'; this procedure emphasises behavioral differences (in absolute number of minutes) between the patients in relation to the duration of the attack. For each patient, we computed for each 'migraine period' the difference in time spent in each activity category versus the corresponding time period of the baseline recording; these data represent a quantitative description of the influence of migraine on the activity categories within a relevant time period for the patient.

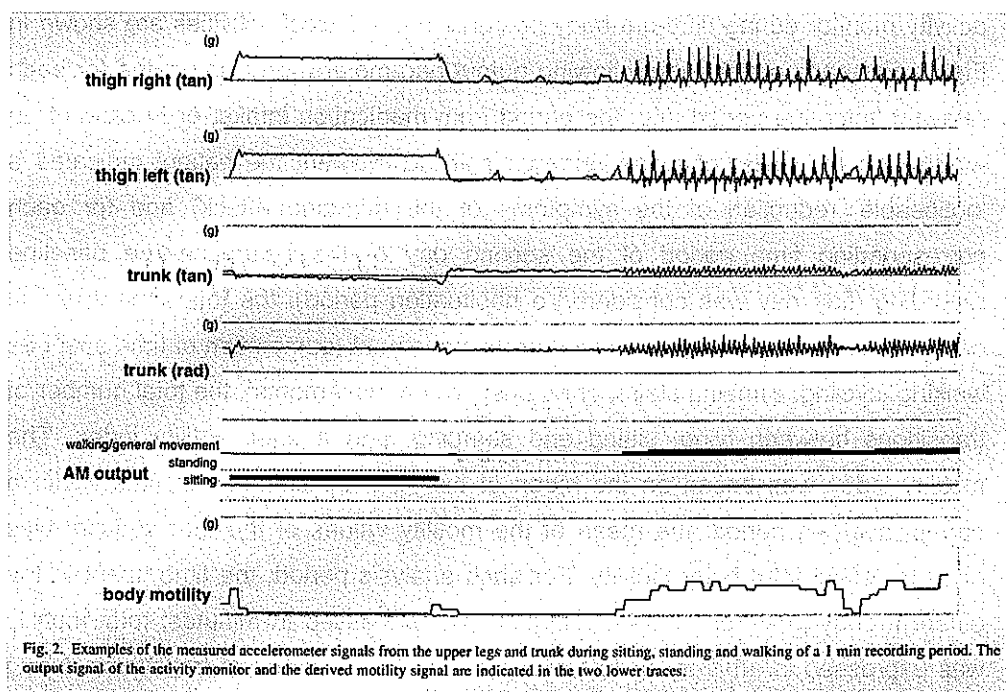


Fig. 2. Examples of the measured accelerometer signals from the upper legs and trunk during sitting, standing and walking of a 1 min recording period. The output signal of the activity monitor and the derived motility signal are indicated in the two lower traces.

3. Results

3.1. Feasibility of procedures and measurements

For each measurement, 20-30 min were required to attach the sensors and to check the ambulatory equipment and provide instructions. The patients reported that wearing the recorder and sensors did not limit them in performing their normal daily activities, including going to work or perform activities such as cycling or sleeping. Because the headache-free measurements were performed first, the patients were familiar with the procedures, recordings and daily logs during the actual migraine attack. The time required to travel to the patient, after the patient informed the investigator by phone of the development of a migraine attack, varied in these six patients between 30 and 45 min. When we add the time required to attach the sensors, the patients in this study suffered for 60 to 75 min from a migraine attack before the recordings started and before they were allowed to take their anti-migraine medication. Overall, the ambulatory measurements during the

headache-free, the migraine, and the recovery period were well tolerated by all patients. Attachment of sensors during the actual migraine attack introduced some discomfort in the patients, but once the sensors were attached, wearing the recorder and sensors proved to be possible without causing distress. Also, keeping the daily log during the headache-free, the migraine, and the recovery period was performed well by the patients.

3.2. Severity and duration of migraine attacks

Patient 6 suffered from frequent migraine attacks. Three migraine attacks were recorded of this patient (a-c); attacks b and c developed while already recording and could therefore be monitored from start until recovery.

The migraine attacks of the six patients varied in severity at the onset of measurements between moderate (patients 2, 4, 6b, and 6c) and severe (patients 1, 3, 5, and 6a) (table 1). Although the migraine attack of patient 1 at starting point was reported to be severe, the patient used no anti-migraine medication because almost immediately after starting the recording it reduced to mild intensity; the patient reported a significant improvement of this mild headache after 4 h. An untreated severe attack (patient 3) lasted 10 h before a significant improvement was observed; treatment of a severe attack with sumatriptan (injection; patient 5) resulted in a significant improvement after 1 h, treatment of a moderate attack with sumatriptan (nasal spray; patient 4) reduced migraine complaints after 2 h, whereas treatment of moderate or severe attacks with ibuprofen or ergotamine (preceded by paracetamol) (patients 2 and 6) resulted in improvements after 4 or 5 h (Table 1). In patient 4, the migraine attack developed in the late evening at a time point when she usually went to bed ('migraine period' between 23:00 and 01:00 h); all other migraine attacks ('migraine periods') developed and were monitored during daytime.

3.3. Migraine and daily activities : examples

Patient 3 (aged 29 years) suffered from a severe, menstrually associated, migraine attack (with severe nausea and vomiting, photophobia and phonophobia) that

lasted 2 days. She never used medication for the treatment of her migraine attacks. Migraine developed at the end of the morning; from 13:45 h onwards it was recorded. A significant improvement was reported after 10 h of recording, but a substantial part of the first recovery day was also spent in bed, still with complaints of vomiting and photophobia and phonophobia. Fig. 3 shows the temporal distribution of her normal daily activities during the 12-h period that corresponded with the first 12 h of recording of the migraine attack. During the first recovery day, the activity pattern showed some normalization, but lying down still dominated the pattern.

Complete patterns of two of the three migraine attacks of patient 6 (aged 49 years; attacks b and c) were obtained because they occurred during the recordings. Attack b (Fig. 4, upper part) developed in the early morning due to psychological factors ("worrying"), was of moderate intensity and was accompanied by moderate complaints of photophobia and phonophobia; the arrows mark the time points that she took paracetamol (two tablets) and ergotamine (one suppository). After a period of bed rest, she reported a significant improvement at about 14:30 h, after which an increase in postural changes and physical activities was observed. The period of lying down around 18:30-19:00 h was customary for her. Attack c (Fig. 4, lower part) developed after awakening in the morning at 06:40 h, it was also moderate of intensity and accompanied by moderate complaints of photophobia: at this time point the patient took two paracetamol tablets. At about 8:15 h, she rose from her bed because she intended to go to work; at 10:40 h she reported a significant improvement of her attack, after which she went to work for the rest of the day. Fig. 4 subsequently illustrates her dynamic activity pattern during daytime, corresponding with her active work as a groupleader for children.

3.4. Quantitative comparisons between migraine and the headache-free period

3.4.1. Time spent in activity categories and number of postural transitions (Table 2)

Patients 1 and 2 required no bed rest during their relatively light attacks. As a result, no change in time spent as lying down was observed versus the headache-

free period (values < 2 min, Table 2). The changes in number of postural transitions, or the changes in number of minutes spent sitting, standing, or as movements versus the headache-free period were variable in these patients. In patient 2, who was able to continue her work as a secretary during migraine, the time spent in the standing position and as dynamic movements was higher during her migraine period, as compared with her baseline period (Table 2). The increase in movement time (+19 min, Table 2) was due to an increase in the time spent as walking (+22.5 min) combined with a small decrease of time spent as non-cyclic movements (-3.5 min).

Patients 3, 5 and 6 did require bed rest during their attack. With the exception of the time spent in the sitting position, patients 3, 5 and 6 (all attacks) responded in an unequivocal manner to migraine; the number of postural transitions decreased, the time spent in the lying position increased and the time spent in the standing position or as movement decreased, in comparison with the headache-free period. The time spent in the sitting position showed variable changes versus the headache-free period; both increases and decreases were observed (Table 2). Of these patients, patient 3 (severe untreated attack, migraine period 10 h) showed the largest behavioral changes (in absolute number of minutes) versus the headache-free period, and patient 5 (severe attack, sumatriptan injection, migraine period 1 h) showed the smallest. The three migraine attacks of patient 6 showed an intermediate pattern between patients 3 and 5 (possibly due to the slower effectivity of paracetamol and ergotamine in comparison with sumatriptan injection).

Patient 4 only showed minor changes versus the baseline period because of the late occurrence of her 'migraine period' (between 23:00 and 01:00 h); although the migraine attack was sufficiently severe to require bed rest, during the comparable time period of the headache-free recording she already slept for a large part of the time.

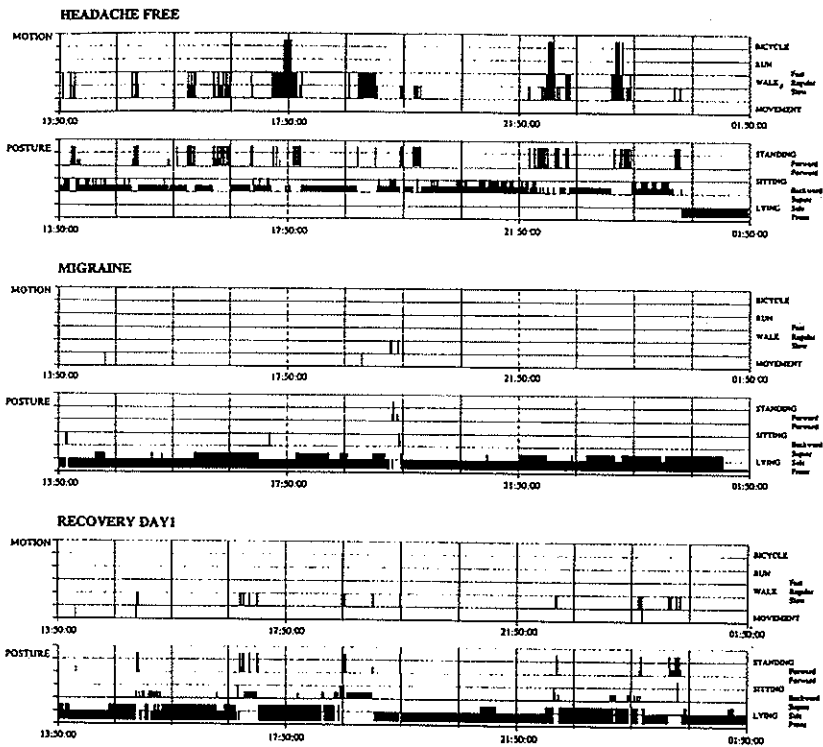


Fig. 3. Temporal distributions of the activity patterns of three corresponding 12-h periods of patient 3: the headache-free baseline period (upper curves), the migraine period (middle curves), and recovery day 1 (lower curves). The lower part of each graph depicts the postural changes (lying, sitting, standing), the upper part the dynamic activities (general non-cyclic movement, walking, running, cycling). Subcategories are presented for the postural activities and walking. The displayed data are based on the output signal of the activity monitor which has a resolution of 1 s; of each 30 s period, the classification that occurred most frequently is graphically presented.

3.4.2. Motility

Total body motility was expressed in arbitrary units/s and was therefore independent of the length of the 'migraine period'. Motility during migraine was reduced in all patients, also in those who did not require bed rest (patients 1 and 2) (Fig. 5A). It was remarkable that in patient 2 an increase in dynamic movements (walking) also corresponded with a decrease in overall motility. Post-hoc analyses revealed that motility during walking in the 'migraine period' was 12% lower compared to walking in the baseline period. Also in patient 4, who spent most of her 'migraine period' and corresponding baseline period in bed, a reduction in motility level was observed. Percentage-wise, the reduction in motility versus the

baseline period was much larger in the patients who required bed rest (patients 3-6, between 50 and 93% reduction) than in those who did not (patients 1 and 2, 30 and 15% reduction, respectively) (Fig. 5B). Because patient 5 spent most of her migraine period (1 h) in the lying position (the first 49 min), percentage-wise, the reduction in motility (-90%) resembled that of patient 3, who also spent most of her migraine period (10 h) in bed (-93%). Even though motility of patient 4 during the baseline period was already low due to the fact that she spent most of this time asleep in bed, her migraine induced a further reduction of 75%.

4. Discussion

Ambulatory accelerometry was evaluated as an objective method to quantify behavioral activities in the habitual environment of migraine patients when they were headache-free, as well as during and after an actual migraine attack.

4.1. Feasibility of procedures and measurements

Two 24-h periods were recorded when the patients were headache-free; the first day was used as a habituation period for wearing the recorder and sensors, the second day was used for analyses of the baseline activity patterns. Within the context of the time required to travel to the patient and attach the sensors (approximately 60-75 min), the migraine attacks and recovery periods were monitored. Overall, the procedures functioned well, indicating that ambulatory accelerometry measurements before, during and after a migraine attack are feasible to perform. However, in order to record as much as possible of each migraine attack and also to record as soon as possible, it was essential to emphasise to the patients the need to contact the researcher the instant they sensed the development of a migraine attack.



Fig. 4. Temporal distributions of the activity patterns of two 12-h periods of patient 6 during which migraine attacks occurred. Migraine attack b (upper curves): the arrows indicate the time point of intake of paracetamol (first) and ergotamine (second). Migraine attack c (lower curves): the arrow indicates the time point of intake of paracetamol (see also legend to Fig. 3).

4.2. Activity parameters

All recorded migraine attacks influenced daily physical activities as quantified by means of ambulatory accelerometry. A moderate or severe migraine attack requiring bed rest showed the following behavioral changes. The number of postural transitions and the time spent in the standing position or as movement were reduced, whereas the time spent in the lying position was increased, versus a headache-free baseline period. Total motility was always reduced during migraine, including in those patients who were able to continue their daily activities. Overall, these data suggest that migraine always influences behavior by reducing motility and that, dependent upon the severity of the attack, the effectiveness of acute treatment, and the time of day, the time spent in various body positions, dynamic activities, and the number of postural transitions are affected. This also corresponds with patients reports in general, indicating that they avoid active activities or fast movements to avoid an increase in their pain.

4.3. Quantification of behavior in migraine

Many factors influence behavior during an actual migraine attack; apart from the severity and duration of the headache, the severity of associated symptoms, the time of day, job requirements, home activities and chores, social obligations and leisure activities, sleep/wake patterns, habits and experience with the disease, mood, and effectiveness of anti-migraine therapies all may determine the extent to which daily activities are affected. Population-based studies have shown that there may be a threshold for headache-related pain intensity; below this threshold, pain appears not to be associated with disability (Stewart et al., 1994).

We have provided an objective method to quantify behavior in the habitual environment of patients in terms of time spent in different body postures and physical activities and general level of motility. Our (limited) data thus far show that behavior is always affected by migraine, although severity and duration of pain may play a crucial role in determining the extent to which it is affected. Because migraine is by nature episodic and thus unpredictable in its occurrence, with our approach the patients will always suffer from headache for a certain period of time before measurements can take place. However, with this limitation kept in mind,

the advantages of the method manifest themselves particularly in two domains of research. (1) Ambulatory accelerometry can be used as a valid and objective tool to quantify the daily activities during interictal periods. It is relevant to establish whether migraine patients differ from controls (matched for age, gender and type of job) regarding daily activities and how these differences interact with the psychophysiological condition of migraine patients during interictal periods. This may, for instance, help to clarify issues regarding chronobiological and autonomic nervous system disturbances in migraine (e.g. Takeshima et al., 1997). (2) When using ambulatory accelerometry during migraine episodes, the main advantage is the possibility to evaluate the behavioral changes from headache till full recovery; this provides an interesting opportunity to monitor the time-dependent effects of acute treatments of migraine on daily functioning in relation to variations observed in severity of the illness, changes in mood, and subjective level of functioning.

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Table 2

For each patient, for each migraine attack, the time spent in different body positions and dynamic activities as well as the number of postural transitions during the migraine period and the difference with the corresponding time period of the baseline day^a

Patient	Migraine period (min)	Lying		Sitting		Standing		Movement		Transitions (n)	
		Migraine	Diff ^b	Migraine	Diff	Migraine	Diff	Migraine	Diff	Migraine	Diff
1	240	0 (0)	-0 (-0)	47 (20)	+32 (+13)	173 (72)	-21 (-9)	20 (8)	-11 (-5)	19	+1
2	240	2 (1)	+1 (+0)	123 (51)	-43 (-18)	66 (28)	+24 (+10)	50 (21)	+19 (+8)	108	-5
3	600	584 (97)	+584 (+97)	5 (1)	-441 (-74)	5 (1)	-63 (-11)	5 (1)	-91 (-15)	15	-55
4	120	118 (98)	+11 (+9)	1 (1)	-6 (-5)	0 (0)	-4 (-3)	1 (1)	-2 (-2)	4	0
5	60	49 (82)	+49 (+82)	8 (13)	-23 (-38)	2 (3)	-16 (-27)	1 (2)	-9 (-15)	4	-12
6a	240	21 (9)	+21 (+9)	137 (57)	+48 (+20)	44 (18)	-37 (-15)	38 (16)	-33 (-14)	27	-16
6b	300	121 (40)	+121 (+40)	143 (48)	+21 (+7)	15 (5)	-75 (-25)	21 (7)	-67 (-22)	23	-37
6c	240	119 (50)	+119 (+50)	63 (26)	-26 (-11)	31 (13)	-50 (-21)	26 (11)	-46 (-19)	30	-13

^a Values are given as the absolute number of minutes, with the percentage of the duration of the migraine period in parentheses.

^b Diff, difference between the migraine period and the corresponding time period of the baseline day; a positive value implies more time spent in that position/activity during migraine, a minus sign implies less time spent in that position/activity during migraine.

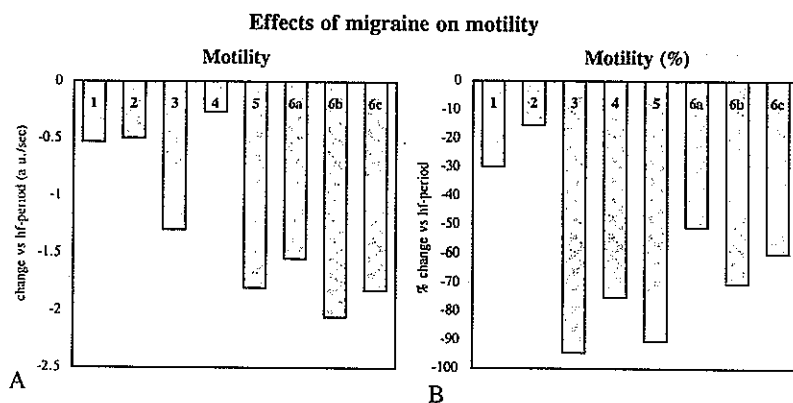


Fig. 5. Effects of migraine on motility. (A) Difference in motility level between the migraine period and the baseline period expressed in arbitrary units/s. (B) The motility data during migraine expressed as percentage of change versus the values of the baseline period.

Complete monitoring of the recovery phase of the migraine attack is feasible particularly when starting with acute treatment after the sensors are attached. Further studies are required to assess the sensitivity of our method to differentiate between the behavioral effects of various anti-migraine treatments. At present, in clinical trials the headache response from moderate/severe to mild/no headache is still mostly used as the primary end point (Goadsby, 1998). Although the emphasis on pain as a target parameter is plausible, from the perspective of both the patient and the society it is almost equally relevant to monitor the effects of anti-migraine drugs on headache-related disability and behavior during and after acute treatment of migraine attacks, in order to relate drug efficacy to improved daily functioning. Quantification of the patient's actual behavior in relation to their subjective perspective of the level of functioning before, during, and after a migraine attack can provide a better understanding of the relationships between mobility, migraine and (costs)effectiveness of therapeutic interventions. Our data showed that ambulatory accelerometry can provide the objective behavioral effect parameters for the evaluation of these processes in the habitual environment of migraine patients.

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Chapter 5

Interictal daily functioning in migraine

During the last ten years it became increasingly clear that pain indices (the pattern of symptoms, the frequency and severity of attacks) alone provide incomplete information about the impact of migraine on the patient. To adequately describe and evaluate this impact, information about the psychological, social, and behavioral effects on the level of functioning during the attack is also needed. Hence, disability scales and Health-related Quality of Life (HRQoL) instruments that promised to provide this additional information came into use, enabling clinicians to distinguish between the less and more disabled patient, to tailor treatment and measure its effect. The resulting information was also useful to policy makers allocating health care resources (1,2,3). Findings of many studies utilizing these questionnaires indicate that, compared to the general population and other populations with chronic illnesses, during an attack migraineurs are disabled and exhibit an impaired quality of life. They report emotional disturbances, difficulty or limitation in performing daily activities, interference with social and sexual activities (4,5,6,7). Migraine not only causes suffering for individuals. It also has an impact on the society. This collective impact of migraine is measured by assessing the direct and indirect costs for society. Direct costs encompass the costs of diagnosing and treating; indirect costs include the economic effects on productivity at work, at home and in other roles. Studies on both direct and indirect costs reveal that the collective burden of migraine is substantial (for the USA about \$13 billion a year; for The Netherlands about 300 million Euro a year) and illustrate the need for improved strategies to target migraine treatment (3,6,8,9,10,11,12,13).

Recently, it was recognized that the individual burden of migraine extends beyond the episodes of attacks. The results of several studies showed that migraine also induces an impaired HRQoL between attacks (5,9,14,15,16). Co-morbidity can only partly explain this impaired status (17). Compared to controls, migraine patients were found to perceive more symptoms and greater emotional distress as well as disturbed contentment, vitality and sleep (18). There is an enduring disposition to attacks and there may be changes in behavior and mood, long-term adoption of the sick-role with disruption at work, school, and in social roles and sexual relationships (5,19). Therefore, in many cases, migraine should be considered a

chronic rather than an episodic illness (16). These chronic aspects are characterized by how the condition changes an individual's behavior and induces disability between attacks. It therefore is important to assess the interictal behavior and mood changes. All the more, because a significant relationship may exist between the interictal (limitation of) activity of the patient and the concurrent quality of life – as such a relationship was established during migraine attacks (20,21).

Until now research related to interictal mood and daily functioning has been based on subjective reports only (4,14,17,18,22,23,24). In our study, however, the daily functioning was also recorded using ambulatory accelerometry. In a previous study we have shown that this method, which provides an objective, reliable and valid quantification and classification of the behavioral aspects of daily functioning (such as lying, sitting, standing, physical activities and locomotion) (25,26,27,28,29), is feasible to perform before, during and after a migraine attack (21).

The possible involvement of the autonomic nervous system in migraine mechanisms has long been a subject of interest. Autonomic dysfunction in migraine patients outside attacks usually was studied *in vitro* (30,31,32). These studies, including those on heart rate fluctuations, have produced contradictory results. Thomsen et al. observed a mild parasympathetic interictal hypofunctioning with preserved sympathetic functioning (33). Cortelli et al. found no impairment of the autonomic control of the cardiovascular system in migraine without aura in the headache-free interval (34), whereas Pogacnik et al. concluded that the sympathetic function is impaired (35). Results of *in vivo* studies monitoring the ambulatory heart rate of migraineurs suggested a hypofunction of the parasympathetic nervous system during normal daily activity in the headache-free period (36) or a clear sympathetic instability (32). Heart rate is influenced by changes in postures and movements. By using ambulatory accelerometry it becomes possible to control for the effect of body postures and physical activities on heart rate variability. Therefore, in addition to the parameters mentioned above, we also recorded the ambulatory ECG of the subjects.

The aims of the present study were:

- (1) to quantify the normal daily interictal activities of patients with migraine in their habitual environment;
- (2) to determine the ambulatory recorded interictal mean heart rate of migraineurs, during the various body postures and physical activities;
- (3) to assess interictal subjective symptoms reflecting mood, sleepiness, and level of functioning, in patients with migraine in their habitual environment;
- (4) to compare the outcome of all these parameters with that of a control group which had been matched for age, gender and occupation.

Methods

Subjects

Twenty-four migraine patients participated in this study. They were recruited by means of advertisements in the area in and around Rotterdam. These subjects were diagnosed by a neurologist of the Ikazia Hospital Rotterdam (LJMMM) as having migraine (18 patients without aura, 4 with aura, 2 with both forms) according to the criteria of the Headache Classification Committee of the International Headache Society (37). For eligibility of the patients, reference is made to the in- and exclusion criteria listed in Table 1. A control group of 24 subjects, matched with the migraine patients for gender, age was recruited. They were also matched for occupation, on the basis of the inherent general level of daily activity any occupation entails. Fourteen were recruited from faculty members and students of the Erasmus University Rotterdam, in addition to 10 persons who responded to local advertisements. They were in good physical and mental health and free from drugs during the study and at least two months prior to it. If they had a history of chronic headache complaints, of psychiatric illness or of alcohol abuse, then they were excluded from the study. So were those who experienced recent circadian shifts, including working at night. The study was conducted at the Erasmus Medical Centre in Rotterdam, The Netherlands, and had received the approval of the

Table 1. Inclusion and exclusion criteria

Patients were included, if they

1. were between 18 and 65 years of age at the beginning of the study;
2. had experienced one to six moderate or severe migraine attacks per month for at least two months prior to entry to the study;
3. did not experience more than 6 days of tension-type headache per month;
4. had the ability to distinguish migraine headaches from other headache types (e.g. tension-type headache) early in the onset of a migraine attack;
5. had no more than six days of tension-type headache per month.

Subjects were excluded, if they

1. had a history of drug or alcohol abuse or a positive history of psychiatric illness;
 2. had a current illness, other than migraine, interfering with locomotion and physical activities;
 3. used prophylactic anti-migraine medication or other medication that could influence the subjective and/or objective outcome measures;
 4. had experienced recent circadian shifts, including working at night;
 5. had a history of cardio-vascular and/or neurological disease.
-

Medical Ethics Committee. All subjects provided written informed consent once they understood the nature and scope of the study.

Procedures and measurements

During a migraine-free two-day period, measurements were obtained in the habitual environment of the participant. On the morning of the first day the procedure was explained and the sensors attached. Instructions were given regarding the use of the equipment and the daily log was explained. The following measurements were made:

Accelerometer signals: Four uni-axial piezo-resistive accelerometers were employed to classify static and dynamic activity. The data-acquisition of the accelerometer signals was done by means of a portable digital recorder (VitaportTM System; TEMEC Instruments, The Netherlands) which was carried on a belt around the waist. For a detailed description of this method of data-acquisition, see our previous publication (21). The static activities comprised three different body postures: lying, sitting, and standing; the dynamic activity three types of

movements: general movement (unspecified non-cyclic movements), walking (including climbing stairs), and cycling. The accelerometers were also employed to quantify the time spent in the different body postures or as movements. Furthermore, an index of the motility¹ of the body during these different postures (static motility) and movements (dynamic motility) was calculated. The number of postural transitions between lying, sitting, standing was calculated as well.

ECG signal: ECG was recorded from a precordial lead by means of adhesive disposable Ag/AgCl electrodes. The ECG signal was stored at a sample rate of 128 Hz on the Vitaport recorder. In order to analyze heart rate, interbeat-interval (IBI) time series were obtained from the R-R waves of the raw ECG signal. The IBI series were checked for presence of movement artefacts and incidental R-wave detection failures, which were corrected by means of linear interpolation techniques. IBI series were converted to heart rate series; mean heart rate levels were computed of the different classes of body postures and physical activities.

The daily log: during the measurement period, the subjects kept a daily log in order to document relevant events (start sleep period; end sleep period; special types of physical activities or psychological events). The daily log included four brief questionnaires: (1) Subjective Sleep Quality Scale (SSQ): an 11 true-false item questionnaire to assess subjective sleep quality, to be filled in at breakfast (39); (2) Stanford Sleepiness Scale (SSS, Dutch translation): the SSS consists of a 7-point scale with items ranging from 'feeling active, alert' to 'cannot stay awake, sleep onset appears imminent', to be filled in at breakfast, lunch, dinner, and before sleep (40). Subjects were instructed to have their scores at breakfast reflect the period between rising out of bed and taking their breakfast; the other moments of measurement had to reflect the previous period of the day, i.e. morning, afternoon and evening. (3) Level of Functioning (LOF). The LOF is an ad hoc constructed, short Guttman Scale on daily functioning with seven items ranging from 'is only capable of lying on bed' to 'is capable to perform heavy physical activities'. The subjects were asked to fill in the LOF questionnaire at the same points in time as the SSS; and (4) Profile Of Mood States (POMS; validated Dutch version) (41). It

¹ Motility is defined as 'the intensity of body segment movements measured with accelerometry' (38)

was used to measure depression, anger, fatigue, vigor and tension. Reliability and validity of the Dutch version proved to be sufficient (41). The POMS was also filled in at the same points in time as the SSS.

The participants were instructed to perform their normal daily activities and to follow their habitual pattern of eating, smoking and drinking during the measurement period, and to avoid abnormal physical and mental exertions.

Data analysis

Because the first day of measurement was considered as a habituation period, the data collected on the second day were used for analysis.

In order to analyze the kinematic parameters, this second day was divided into three intervals: (a) from rising up in the morning till noon; (b) from noon till 6.00 pm; (c) from 6.00 pm till going to sleep. Because the first and third period varied in duration, the proportion of time spent in a posture (summation of lying, sitting or standing) and as movement (summation of walking, cycling or as unspecified movements) during the three periods were computed. To quantify the motility during sitting and standing, the periods spent in these postures while using public or private transport were not included.

Statistical analysis

Differences between the migraine and the control group on variables with a normal distribution were tested with the independent-samples T test; those with a skewed distribution with the Mann-Whitney U test. Differences between migraine and control subjects were further analyzed using binary logistic regression analysis. Predictor variables entered into the regression equation were those variables, which revealed a significant difference between the experimental groups at any moment of measurement, namely sleepiness, vigor, level of functioning, relative duration of dynamic activity (the proportion of time spent during dynamic activity), static and dynamic motility, and relative duration of lying down. To reduce the number of tests performed and to improve interpretation of findings, the predictors

entered into the regression equation were based on variables reflecting the whole daytime period. The model was estimated using the backward stepwise selection method (Backward: LR). The alpha of the tests was set at 0.05. The analyses were performed with the Statistical Package for the Social Sciences (SPSS for Windows, version 9.0).

Results

Control subjects and patients did not differ in age ($p=0.84$) and in male-female ratio. They were also comparable regarding their occupation (see Table 2)

Body postures and physical activities

The recording of the kinematic parameters and of heart rate of one patient was not successful. Therefore, the number of valid cases with data on these variables was 23 and those with data on the subjective variables 24.

The statistical tests revealed that the relative duration of dynamic activity (summation of time spent as walking, cycling, or as unspecified movements) of the migraineurs was significantly shorter during the afternoon ($p=0.018$) and during the evening ($p=0.006$) (see Figure 1). (As the relative duration of body postures is linear dependent on the relative duration of dynamic activity, scores on this parameter also showed a significant difference between the groups in the same daily periods). The dynamic motility of the patients with migraine was significantly lower during all three daily periods than that of the control subjects; during the morning: $p=0.047$, during the afternoon: $p=0.016$, and during the evening: $p=0.025$ (see Figure 2). Compared to controls, migraine patients were also found to spent a significantly larger part of their afternoon lying down; in the evening, the motility of their body during lying, sitting, and standing (static motility) was significantly lower (see Table 3).

Heart rate

For all daily periods, no significant differences regarding mean heart rate levels were observed during lying, sitting, standing, or during dynamic activities (see

Table 2. Demographic characteristics of the subjects

	Patient group N=24	Control group N=24
<u>Age</u>		
Mean	39.8	39.6
Std deviation	10.1	10.5
Range	18-59	21-57
<u>Sexe (N)</u>		
Female	23	23
Male	1	1
<u>Occupation</u>		
Housewife	3	6
Student	3	2
PhD student	1	1
Secretary	2	2
Nurse	3	3
Teacher	1	2
Analytical chemist	2	1
Psychotherapist	2	0
Groupleader	0	1
Researcher	2	0
Co-ordinator reports	0	1
Co-operator restaurant	2	0
Glazier	0	1
Co-operator day nursery	0	1
Care for the elderly/ handicapped	1	1
Hairdresser	0	1
Clerical post	1	0
Librarian	1	0

Fig 1. Proportion of time spent during dynamic activity per daily period

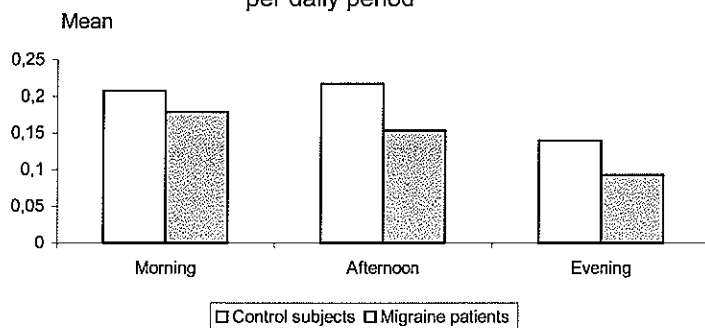


Fig 2. Dynamic motility per daily period

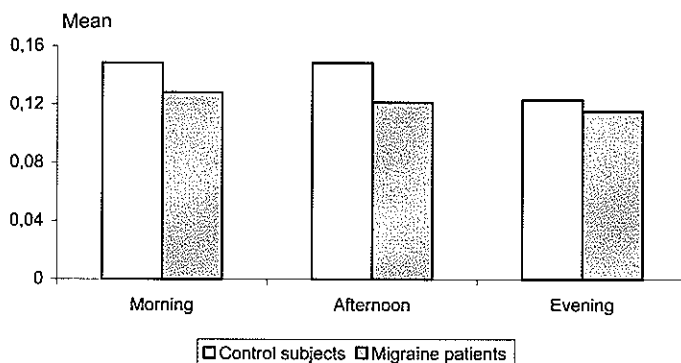


Table 4. Also during the night the migraineurs did not significantly differ from the controls on this parameter (mean heart rate of the migraineurs was 66.7 bpm (sd: 7.52) and that of the controls 65.1 bpm (sd: 6.44))

Subjective daily log parameters

Compared to controls, patients with migraine reported significantly higher levels of sleepiness (during the morning and the evening) and a trend towards a higher level at breakfast. In addition, they reported significant lower realizable levels of functioning (during the morning, afternoon, and the evening) and of vigor (during the whole day) (see Table 5). No significant differences were observed regarding the other subscales of the POMS.

Logistic regression analysis

The binary logistic regression analysis resulted in a linear combination of the level of sleepiness (coefficient B of this covariate was 1.1902; $p=.007$) and the relative duration of dynamic activity ($B=-14.8806$; $p=.006$), both variables reflecting the whole daytime period. Entering these covariates into the regression equation resulted in a postdiction of the subject's group classification with an overall accuracy of 75,5% (Control subjects with an accuracy of 75%, patients with 76%).

Table 3. Mean (sd) of physical activity parameters per daily period, for controls and migraine patients

Interictal activities	Morning		Afternoon		Evening	
	Control	Migraine	Control	Migraine	Control	Migraine
Postural trans. (n)	33 (24)	38 (23)	54 (37)	46 (24)	46 (31) ¹	32 (14)
Lying (rel.)	.00 (.01)	.03 (.10)	.02 (.04) *	.05 (.16)	.11 (.15)	.20 (.24)
Standing (rel.)	.29 (.14)	.34 (.17)	.24 (.08)	.29 (.16)	.18 (.08)	.16 (.10)
Sitting (rel.)	.50 (.20)	.45 (.20)	.52 (.16)	.51 (.18)	.57 (.17)	.55 (.20)
Static motility	.0165 (.0072)	.0164 (.0064)	.0158 (.0065)	.0142 (.0057)	.0120 * (.0038)	.0094 (.0034)

Trans.: transitions; rel.: relative duration; *) significant difference between the experimental groups;

¹) p=.052

Discussion

Although interictal chronobiological data are now being collected more frequently in headache research (33), the results of the vast majority of ambulatory studies on interictal impact of migraine are based on subjective self-reports. They indicate that the impact of migraine is not restricted to the episode in which the patient suffers from an attack. The current study using the objective, reliable, and valid method of ambulatory accelerometry to classify and quantify overt behavior, confirms this finding, as it indicates an interference of migraine with interictal physical activity. Compared to healthy controls, migraine patients spent relatively less time being active (summation of time spent as walking, cycling, or as unspecified movements). Moreover, if active, the motility of the body was found to be lower than that of the control subjects, i.e., migraineurs appeared to move more calmly and more prudently. Because the level of motility differed between the three types of movement (general movement, walking, and cycling), the aforementioned result could be caused by a difference between both groups in the proportion of time spent during the three modi of movement within the daily periods. Posthoc analysis, however, did not reveal such differences. The relevance of kinematic parameters in differentiating migraineurs from healthy controls is also apparent

Table 4. Mean (sd) of heart rate per activity category, per daily period and for controls and migraine patients separately

Interictal Heart rate	Morning		Afternoon		Evening	
	Control	Migraine	Control	Migraine	Control	Migraine
Lying	81.9 (8.9)	86.1 (8.9)	78.5 (3.9)	74.4 (11.4)	73.7 (13.8)	73.3 (8.8)
Sitting	77.5 (8.8)	82.5 (11.0)	78.7 (9.1)	81.4 (12.4)	77.7 (9.1)	78.6 (9.7)
Standing	91.2 (10.0)	95.2 (12.6)	90.4 (9.5)	92.1 (13.8)	91.2 (11.7)	90.4 (9.6)
GMove	96.1 (9.0)	97.3 (10.4)	96.3 (8.4)	94.6 (14.2)	95.2 (9.8)	92.7 (9.2)
Walking	100.3 (10.6)	100.6 (12.1)	99.6 (9.8)	99.4 (13.5)	99.1 (12.0)	95.7 (9.8)
Cycling	129.0 (16.8)	128.2 (26.6)	116.5 (20.6)	130.0 (19.6)	115.0 (24.5)	116.4 (.)

GMove: general movements

from the results of the binary logistic regression analysis. The relative duration of dynamic activity during the day turned out to be one of the two important variables on the basis of which the participant's membership of either the control or patient group could be postdicted. Interpretation of the results on the kinematic parameters is challenging, because they can not be compared to those of previous studies, as these parameters have not been measured before (in the same way). All subjects were medication-free and not on any prophylactic treatment during the 48-hour period of measurement. Therefore effects of medication can not explain the difference in dynamic activity and dynamic motility. Nor can it be attributed to a difference in concomitant feelings of depression or tension - symptoms of depression and anxiety have been claimed to be more frequent among migraine sufferers -, because the experimental groups did not differ on these parameters (see Table 5). As a certain level of physical activity is required to exercise a particular profession, the participants of both groups were pairwise matched for occupation in order to level the physical activity of both groups. Moreover, the relative duration of dynamic activities of the control group within the twenty-four hours of the day used for analysis, was 12%. This figure is consistent with those of reference groups configuring in previous research using ambulatory accelerometer (42,43). Therefore, methodological shortcomings in representativeness of the experimental groups or the comparability between them also can not be

Interictal daily functioning in migraine

Table 5. Median (interquartile distance) of subjective parameters per daily period, for controls and migraine patients separately.

	Breakfast		Morning		Afternoon		Evening	
	Control	Migraine	Control	Migraine	Control	Migraine	Control	Migraine
Vigor	13 (9;15)*	7 (4;10)	15 (13;16)*	11 (6;14)	13 (11;15)*	10 (4;14)	10 (9;15)*	5 (2;12)
Depression	0 (0;0)	0 (0;1)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;1)	0 (0;0)	0 (0;0)
Tension	0 (0;1)	0 (0;2)	0 (0;1)	0 (0;1)	0 (0;1)	0 (0;1)	0 (0;0)	0 (0;0)
Sleepiness	2 (1;2) ^a	2 (1;4)	1 (1;1)*	2 (1;2)	1 (1;2)	2 (1;4)	2 (2;3)*	3 (2;4)
LOF	28 (21;28)	28 (21;18)	28 (28;28)*	28 (21;28)	28 (28;28)*	28 (15;28)	28 (21;28) ^b	21 (7;28)
LOF: Level of Functioning								

*) Significant difference between control subjects and migraine patients

^a) p=0.06; ^b) p=0.09

accountable for the observed difference in dynamic activity and dynamic motility between the groups.

But a change in the patients' behavior, i.e., an over the years of suffering acquired habit to anticipate an acute attack might offer an explanation (14). As the aggravation of headache by physical activity is a discriminative feature of a migraine attack (37), migraineurs might try to avoid the aggravation by moving less and more carefully, explaining the observed reduced ictal dynamic activity and dynamic motility compared to an interictal period (21). Furthermore, the results of this study show that during headache-free periods the level of dynamic activity and dynamic motility of migraineurs is still lower than that of healthy controls. So, the ictal behavioral pattern of activity and motility might have been generalized to the interictal periods and have become a (learned) habit, now serving the purpose of avoiding an acute attack. This explanation is in accordance with the results of the study by Cavallini et al. (1995), who conclude that many headache patients experience distress from the imminence of attacks in the intervals between them. This distress pushes them to take the precautions necessary to avoid an attack (5). The lower level of motility of the patients during physical activity might, however, also originate in a difference in central nervous system functioning. The finding that migraineurs reported to be more sleepy and less vigorous and only to be able to function at a lower level of activity during daytime (periods) than controls did and the fact that these results can not be explained by differences in subjective fatigue (there were no significant differences in fatigue between controls and patients) or by the effects of medication, adds to the plausibility of this assumption. Future research might aim at clarifying this issue, by investigating a possible relation between the length of history of migraine and the kinematic and subjective parameters.

Mean heart rate levels during static activity (lying, sitting, and standing) controlled for body posture and movement, did not differ between the experimental groups. They also did not differ during dynamic activity (general movement, walking, and cycling). In our study mean R-R intervals were analyzed, while in many of the studies referred to, spectral analyses of the beat-to-beat variations were

performed. Therefore, although the results of the current study do not confirm previous findings indicating autonomic dysfunction at the cardiac level in migraineurs during headache-free periods, they also do not necessarily contradict them, because of the difference between the current and the aforementioned studies in analyzing the ECG.

Because the duration of time since the last migraine attack and that until the next one has not been recorded in this study, the influence of either of these attacks on the results can not be excluded. However, during the explanation of the study procedure none of the migraine patients reported a recent attack in the past 48 hrs. Moreover, although not reported here, the current investigation also consisted of the measurement of two migraine attacks. The measurement in the headache-free period always preceded the ictal measurements. The time elapsed between the interictal and the first ictal measurement varied between a week and four months. Consequently, the influence of the prodromes of an imminent attack is unlikely as well. As is the influence of a headache on the recorded data: only one patient developed a headache during the evening, scoring 6.7 on a 10-centimeter visual analogue scale.

Finally, the large number of statistical tests conducted in this study without a corresponding correction of alpha might be a cause of concern. However, as we wanted to assess each parameter in its own right, Bonferroni adjustments were not appropriate and hence not performed (44).

In summary, during a substantial part of an interictal day, migraineurs were significantly less physically active than healthy controls. Moreover, when active, the motility of their body was reduced. They also subjectively reported a lower level of realizable activity and of vigor and a higher level of sleepiness. These phenomena might be conceptualized as consequences of a migraine-specific CNS functioning. Alternatively, they may be interpreted as acquired habits to anticipate and / or avoid a migraine attack; particularly with reference to the overt, physical behavior. Despite the various studies indicating an interictal autonomic impairment, the results of this study did not confirm this position based on heart rate evaluations.

The observed migraine-specific interictal phenomena constitute an important part of the individual and collective impact of migraine. Migraine leads both objectively and subjectively to a limitation in physical activities, also outside attacks. This may result in a reduction of the productivity at work, in school, and in other roles and consequently in an increase of the indirect costs to society. If so, the interictal behavioral and psychological characteristics migraine patients exhibit, contribute to the individual, as well as to the collective burden of migraine, confirming the chronic impact of this disease.

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Chapter 6

Effects of naratriptan and naproxen on daily functioning in the acute treatment of migraine

Migraine is a common disorder with paroxysmal attacks of unilateral, pulsating headache associated with symptoms such as nausea, vomiting, photophobia, and phonophobia (1). Its lifetime prevalence is as high as 18% among women and 6% among men (2).

Results of several studies indicate that migraine patients are disabled and quality of life is seriously affected during an attack. Migraine patients report psychological problems, difficulty or limitation in performing daily activities and interference with social and sexual activities (3-12). The psychological problems include a significant reduction in mental concentration, extraversion, self-confidence and positive mood and a significant increase in fatigue, dizziness, introversion, anxiousness, and depression (4,7,9).

Besides headache, the aforementioned disability in carrying out normal daily activities may be an essential problem of a migraine attack. Passchier et al. (13) found that, although pain relief was the main motive for taking medication for the majority (57%) of the patients, a considerable proportion of the patients (about 43%) took medication in the first place to be able to continue their activities. The importance of daily activities is also supported by the existence of a significant inverse relationship between the limitation in activity during a migraine attack and the concurrent quality of life of the patient. Santanello et al.(6) found that, as subjects reported an increasing inability to carry on with activities as a result of their migraine, the 24-Hour Migraine Quality of Life Questionnaire (MQoLQ) scores on the domains of work functioning, social functioning and energy/vitality decreased significantly. They also found that as the activity became more limited, migraine patients reported feeling more upset, more physically uncomfortable, and more concerned regarding the ability of their migraine medication to relieve their migraine symptoms.

In addition, the limitation in activity during an attack leads to substantial economic effects on productivity at work, at home and in other roles (8,14-18). Van Roijen et al. (19) estimated in 1995 that the collective economic burden of migraine to

the Dutch society with about 16 million inhabitants is about 307 million euro a year, including the costs of diagnosing and treating.

Therefore, from the perspective of both the patient and the society it is relevant to monitor the effects of treatment of migraine attacks on the behavioral functioning of the patient. Until now the effect studies of ictal behavioral functioning were limited to subjective reports of the outcome measure (4,6). Subjectively reported daily functioning, however, may be different from the actual daily functioning based on physical activities performed. Therefore, in our study the daily functioning is also evaluated using ambulatory accelerometry. This method provides an objective, reliable and valid quantification and classification of the behavioral aspects of daily functioning (such as lying, sitting, standing, physical activities and locomotion) (20-24). In an earlier study we have shown that this method of ambulatory accelerometry is feasible to be used before, during and after a migraine attack (11). Most pharmacological studies into the effects of drugs on the acute treatment of migraine focus on the clinical symptoms of the attack. As the effects of pharmacological drugs on mood and behavioral parameters in the acute treatment of migraine have not received much attention, we set up a study to evaluate these effects using both a nonspecific anti-migraine drug and a specific anti-migraine drug. We chose as nonspecific anti-migraine drug the NSAID naproxen, because it has been found to be superior to placebo and to standard reference drugs (anti-emetics, ergotamine tartrate, and analgesics like paracetamol and acetylsalicylic acid) in the treatment of migraine in double-blind trials (25-31). As specific anti-migraine drug we used the 5-HT_{1B/1D} agonist naratriptan, introduced in many countries in 1997. Naratriptan tablets 2.5 mg differ from other triptans on the basis of their high tolerability, their long elimination half-life of two hours and high bioavailability of 74% (32-34).

To summarize, the objective of this study was to evaluate the effect of naratriptan on objective measures of locomotor and physical activities and on subjective measures of clinical symptoms, mood, sleepiness, and level of functioning during

the first six hours of treatment of a migraine attack in the habitual environment, in comparison with the effect of naproxen.

METHODS

Patients. - Twelve migraine patients, 11 without aura and 1 with aura, with a mean age of 42.2 years (s.d. 9.8; range 20-59) were recruited from the neurological outpatient service of the Ikazia Hospital Rotterdam in the order of their admission, or by means of advertisements in the area in and around Rotterdam. The diagnosis migraine was made by a neurologist (LM) of the Ikazia Hospital Rotterdam according to the criteria of the International Headache Society (1). For eligibility of the patients, reference is made to the in- and exclusion criteria listed in Table 1. The study received the approval of the Medical Ethics Committee. All subjects provided written informed consent before admission to the study.

Design, procedure and measurements.- In this randomized, double-blind, double-dummy, crossover study, the migraine patients were instructed to treat two migraine attacks with either naratriptan (tablet 2.5 mg) or naproxen (capsule 500 mg) in accordance with a randomization by means of the Latin-square approach. The procedure started the moment the patient sensed the development of a migraine attack. The researcher (DLS) was informed and proceeded to the patient's home to start the protocol. During the two spontaneous migraine attacks ambulatory measurement of the following parameters were made in the patient's habitual environment:

Behavioral parameters. - Before the taking of the study medication, four uni-axial piezo-resistive accelerometers were attached to the patient's body to record the static and dynamic activity. The continuous data-acquisition of the accelerometer signals was done by means of a portable digital recorder (VitaportTM System; TEMEC Instruments, The Netherlands) which was attached to a belt around the waist. For a detailed description of this method of data-acquisition, reference is made to our earlier publications (11,24). The static activities comprised three

Table 1. Inclusion and exclusion criteria

Subjects were included, if they

1. were between 18 and 65 years of age at the beginning of the study;
2. had experienced one to six moderate or severe migraine attacks per month for at least two months prior to entry to the study;
3. did not experience more than 6 days of tension-type headache per month;
4. had not used 5HT₁ agonists or naproxen during the last year in the treatment of acute migraine, with the exception of their use when participating in a double blind study;
5. had the ability to distinguish migraine headaches from other headache types (e.g. tension-type headache) early in the onset of a migraine attack;
6. had no more than six days of tension-type headache per month.

Subjects were excluded, if they

1. had a history of drug or alcohol abuse or a positive history of psychiatric illness;
 2. had a current illness, other than migraine, interfering with locomotion and physical activities;
 3. used prophylactic anti-migraine medication or other medication that could influence the subjective and/or objective outcome measures;
 4. had experienced recent circadian shifts, including working at night;
 5. were contra-indicated for a treatment with naratriptan or naproxen according to the local instruction sheets;
 6. were, in the opinion of the investigator, unsuitable for treatment with a 5HT₁ agonist;
 7. had a history of cardiovascular and/or neurological disease.
-

different body postures: lying, sitting, and standing; the dynamic activity three types of movements: general movement (unspecified non-cyclic movements), walking (including climbing stairs), and cycling. The accelerometers were utilized to quantify the time spent in the different body postures or as movements. Furthermore, an index of the body's motility¹ during these different postures (static motility) and movements (dynamic motility) was calculated. The number of postural transitions between lying, sitting, standing was calculated as well. Measurements of these parameters were computed for three consecutive standardized periods of two hours (0-2 hrs; 2-4 hrs; 4-6 hrs) after taking the study medication.

¹ Motility is defined as 'the intensity of body segment movements, measured by means of accelerometry' (37).

Ambulatory monitoring of physical activities, in addition to the headache diary, took place during the migraine attack and ended 48 hours after the intake of the study medication. In order to accurately analyze the effects of naratriptan and naproxen on daily functioning during the first six hours post dose, six hours of behavior had to be monitored before the patient went to sleep at night. In practice this meant that migraine attacks that developed after approximately 16.00 hours were not included in the trial.

Clinical parameters.- The subjects kept a daily log during the measurement period. In this daily log, patients rated on a 10-centimeter visual analogue scale (VAS) the intensity of their migraine symptoms: headache, nausea, vomiting, photo- and phonophobia.

Patients were asked to complete the daily log just prior to taking the study medication and 2, 4, and 6 hours post dose. At these last-mentioned points in time, the patients were also asked whether a noticeable difference² in the migraine had occurred during the past two hours.

Mood, sleepiness and subjective level of functioning. - The subjects were also asked to complete the following questionnaires just prior to taking the study medication and 2, 4, and 6 hours post dose: (1) Profile Of Mood States (POMS; validated Dutch version) (35); the sum of the subscales depression, anger, fatigue and tension, minus the score on vigor was used as an indication of the subject's general state of mood, which will be referred to as Total Mood Disturbance (TMD). Reliability and the validity of the Dutch version proved to be sufficient (35); (2) the Stanford Sleepiness Scale (SSS, Dutch translation version); this questionnaire consists of a 7-point scale with items ranging from 'feeling active, alert' to 'cannot stay awake, sleep onset appears imminent' (36); (3) the Level of Functioning (LOF). The LOF is an ad hoc constructed, short Guttman Scale on daily functioning with seven items ranging from 'is only capable of lying on bed' to 'is capable to perform heavy physical activities'. So, this questionnaire measured the highest

² A noticeable difference was defined as a major subjective relief of the migraine symptoms as a result of which some daily activities could be resumed

level of activity of which the patient considered herself to be able to perform, whereas by means of the accelerometers the actual overt behavior of the patients was recorded

Medication. - The study medications were manufactured in tablet form (naratriptan) and capsule (naproxen), active drug and corresponding placebo looking identical. The naratriptan 2.5 mg tablets and corresponding placebo's were made available by Glaxo Wellcome BV.

The patients were allowed to take rescue medication (the patients could take their own medication with the exception of 5HT₁ agonists or medications containing dihydroergotamine or ergotamine, due to the use of naratriptan in this study) for intolerable headache beginning four hrs after taking the study medication. The type and time point of taking the medication had to be recorded in the daily log. The patients were allowed to follow their habitual pattern of coffee, tea, alcohol and tobacco consumption. Concomitant medication other than the study medication or the rescue medication was not allowed during the measurements. The subjects were instructed not to use prophylactic anti-headache medication. During two migraine attacks, they took their double blind, double dummy study medication at the start of the recording period. The researcher was present during this procedure in order to verify the administration of both tablet and capsule. In the case of severe vomiting, the patient was allowed to use 20 mg metoclopramide (suppository) 30 minutes before taking the study medication.

Data analysis. - In order to analyze the objective kinematic parameters the six hour post dose interval was divided into three periods of two hours each. To quantify the motility during sitting and standing, the periods spent in these postures while using public or private transportation were not included. The clinical and subjective variables (mood, sleepiness and level of functioning) were measured just before taking the study medication (baseline) and two, four and six hours post dose.

Statistical analysis. - Differences between the two conditions in baseline level of the clinical and subjective parameters were tested by means of the Paired-Samples T Test ; the skewed distributed variable "vomiting" was tested using the Wilcoxon Signed Ranks Test , as was the - also skewed - variable "time till noticeable difference". Differences in mean of the normally distributed clinical, subjective and objective parameters between the naratriptan and naproxen condition and between the moments of measurements as well as the interactions between the conditions and the moments of measurement (Medication x Time effect) were analyzed by means of a multivariate repeated-measures design for paired samples, using Medication (naratriptan and naproxen) and Time (moment of measurement) as independent variables. Also the skewed distributed variable "vomiting" was analyzed using this statistical model, given the robustness of analysis of variance (38)³ . The alpha of the tests was set at the traditional 0.05 level. The analyses were performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 9.0).

RESULTS

Baseline scores of the clinical variables and of mood, sleepiness and level of functioning did not significantly differ between the two conditions (see Table 1).

Clinical parameters. - Within the first six hours post dose, the severity of the headache, nausea, and the photo- and phonophobia showed a significant reduction in both the naratriptan and the naproxen condition. Only vomiting was not significantly reduced after six hours. Naratriptan was significantly more effective than naproxen in reducing the severity of headache, nausea, and vomiting. No difference was found between naratriptan and naproxen in the effect on photo- and phonophobia (see Table 2). The time till noticeable difference was significantly

³ Manova's require that each dependent variable entered into the analyses must be normally distributed. We nevertheless used this statistical model because it has been shown in the Monte Carlo experiments that even markely skewed distributions the empirically determined rejection region of the F-distribution would be no larger than $\alpha = .08$ when the usual five percent rejection region is used (38) .

shorter in the naratriptan condition compared with the naproxen condition ($p < 0.02$) (see Figure 1). Rescue medication was not used during the first six hours post dose.

Mood, sleepiness, and level of functioning. - Except for sleepiness, the multi-variate analyses of variance revealed a significant main effect of time for these variables. During the six hours post dose period the total mood disturbance decreased significantly, whereas the level of functioning significantly increased. No significant difference was found between both medications in their effect on these variables (see Table 2).

Behavioral parameters. - During the first six hours post dose, no significant differences between the naratriptan and naproxen condition were found, neither in the effect on the relative duration of the static and dynamic activity of the patients nor on their motility during these activities (see Table 3).

COMMENTS

Previous studies, based on subjective reports of patients, have shown that the behavioral component, particularly pertaining to the (in)ability to carry out daily activities, is an essential aspect of a the patient during a migraine attack, both from the perspective of the patients themselves and of the society. As subjectively reported effects may differ from the actual behavioral ones, we set up this pharmacological intervention study, for the first time focusing on the objective measurement of these effects. For this purpose, ambulatory accelerometry as an objective, reliable and valid method of quantifying locomotor and kinematic activities was used. In addition, the core clinical symptoms of migraine, i.e., headache, nausea, vomiting, photo-and phonophobia, as well as the effects on mood, sleepiness, and subjective level of functioning were measured. As treatment, two widely used anti-migraine drugs were used, ie. naproxen (500 mg;

capsule) as a representative of the NSAIDs and naratriptan (2.5 mg; tablet) as a representative of the 5-HT_{1b/1d} receptor agonists (the triptans).

The results of this study showed that the intensity and the duration of daily activities did not significantly change over the six hour post dose period. Both treatments also did not significantly differ in their effect on these parameters. This result is not confounded by a possible circadian trend in activity level, because the time of the intake of the study medication did not significantly differ between both conditions ($p=0.859$, Wilcoxon Signed Ranks Test).

In a previous study we found that for migraine patients the mean relative duration of dynamic activity during waking hours of a headache free day is about 14% (43). So, compared to a headache free period, the relative duration of dynamic activity during the first six hours of a treated migraine attack is reduced to approximately 8%, a reduction by about 43% (see Table 3). This result indicates that the recovery to the actual level of daily activity occurs later in the ictal period.

In accordance with the findings of previous studies, the current study demonstrated that within the period of six hours post dose both the intake of naproxen and naratriptan resulted in a significant reduction of headache, nausea, photo- and phonophobia (25,34,39-41). Compared to naproxen, naratriptan was found to be superior in reducing the migraine related symptoms of headache, nausea, and vomiting. In view of the fact that only patients with moderate to severe migraine attacks were included in the current study and in view of their mean baseline level of moderate headache severity obtained therein, this result confirms the fact that patients with moderate or severe migraine are known to respond better to specific agents (triptans, dihydroergotamine (DHE), ergotamine) than to NSAIDs and should be treated accordingly (42).

In agreement with previous findings, nausea, phono- and photophobia, and disturbance of mood significantly decreased and level of functioning significantly increased over the six hour post dose period in both conditions (4,25,32,33). Although naratriptan turned out to be superior compared with naproxen in reducing pain, nausea, and vomiting, the drugs did not differ in their effects on the other clinical and subjective parameters. In contrast to the significant decrease in the

clinical symptoms of migraine and in mood disturbance and the significant increase in the in the subjectively reported highest attainable level of activity, the intensity and duration of the actual daily activities did not significantly change over the six hour post dose period. Evidently, during the first hours of a migraine attack, the changes in the subjectively reported pain and pain equivalents (headache, nausea, photo- and phonophobia, mood) are not accompanied by changes in the objective, overt behavioral activity of the patient. Interestingly, this discrepancy also exists between the subjectively reported attainable level of activity (level of functioning (LOF) together with the sensing of a the ability to resume some daily activities ('noticeable difference') and the actual behavioral level of daily activity. Apparently, in the course of the first hours of a treated migraine attack patients feel themselves capable of a higher level of activity than they actually perform. As the aggravation of headache by physical activity is a discriminative feature of a migraine attack (1), a possible explanation of this discrepancy might be, that migraine patients (by experience) try to avoid the aggravation of pain by moving less and more carefully, even when experiencing relief of their pain and an increasing ability to perform their daily activities. This explanation would consequently lead to a consistent interpretation of the overt behavior of migraine patients, as we in the same way accounted for our observation, that the relative duration of dynamic activity of migraineurs during the interictal periods is significantly reduced, compared to healthy controls (43).

Nevertheless, the observed asynchronicity between the subjective and objective recorded measures is in line with the conception of pain as a multi-dimensional event that also includes subjective and objective behavioral components. Vendrig and Lousberg (44) found no association between the ratings of chronic pain patients of their pain intensity and activity level. In addition, Fordyce et al. (45) interpreted the results of their study with chronic pain patients, to suggest that there may be a questionable relationship between what people say about their pain and what they actually do. It would also be in accordance with Holroyd et al. (46), who concluded that pain and disability are separable dimensions of headache impact, that may be altered in different ways by different therapies.

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Table 2. Mean (sd) of the clinical and subjective variables and outcome of MANOVA's (p-values)

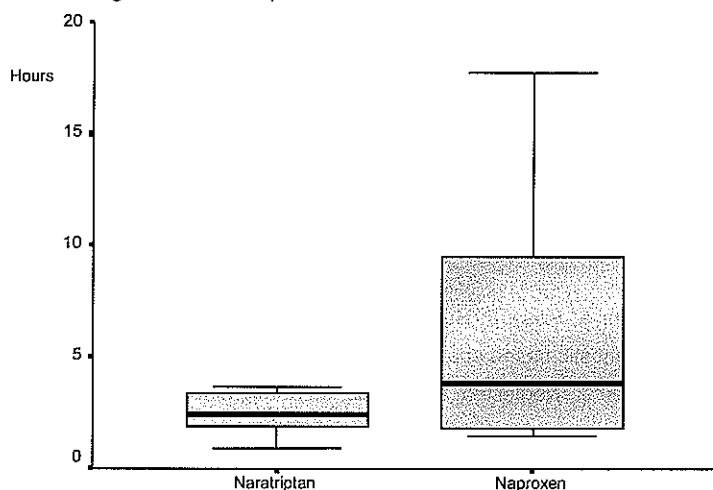
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Effects of naratriptan and naproxen on daily functioning
in the acute treatment of migraine

Table 3. Mean (sd) of the behavioral parameters and outcome of MANOVA's (p-values)

	0-2 hours post dose			2-4 hours		post dose		4-6 hours	post dose		Ptime	Pmed	Ptime x Pmed
	Naratriptan	Naproxen		Naratriptan		Naproxen		Naratriptan	Naproxen				
Number of transitions	6.6	5.0		4.9		7.4		6.6	5.7		.69	.63	.26
<u>Relative duration</u>													
Static activity	0.92 (.08)	0.90 (.12)		0.93 (.08)		0.92 (.10)		0.92 (.09)	0.91 (.09)		.80	.45	.95
Dynamic activity	0.08 (.08)	0.10 (.12)		0.07 (.08)		0.08 (.10)		0.08 (.09)	0.09 (.09)		.80	.45	.95
<u>Motility</u>													
Static activity (E-03)	6.66 (3.88)	7.52 (5.13)		7.79 (5.13)		7.56 (5.36)		7.97 (4.57)	7.26 (5.98)		.78	.98	.80
Dynamic activity (E-02)	11.57 (1.88)	10.91 (1.91)		12.61 (2.26)		10.58 (1.77)		12.13 (1.58)	11.02 (2.14)		.75	.28	.93

Figure 1. Time elapsed till noticeable difference



A criticism on our study might be the limited number of subjects included. However, this study was not a clinical efficacy study and our within subjects design, having each patient as her own control, is an asset for having enough power.

So, since the limitation of daily activities during a migraine attack poses a major problem for both the patient and for the society, it would be justified to consider not only the migraine-related clinical and subjective phenomena, but also the objective physical activities as an important determinant of the efficacy of the treatment of a migraine attack. Consequently, we recommend to include the effects on (overt) behavioral functioning in the evaluation of the general efficacy of anti-migraine drugs in the acute treatment of a migraine attack.

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Chapter 7

Summary and concluding remarks

Chapter 1.

Migraine is a disease with episodic exacerbations, which are characterized by a moderate to severe, unilateral, pulsating or throbbing headache, which is aggravated by routine physical activity and may be accompanied by photophobia, phonophobia, nausea and sometimes vomiting (Headache Classification Committee of the International Headache Society, 1988). Recent studies using the International Headache Society (IHS) diagnostic criteria have given relatively consistent estimates of migraine prevalence in the industrialized Western world (about 15-18% of women and 6% of men) and indicate that migraine occurs most commonly in men and women aged 25-55 years (Rasmussen et al., 1991; Henry et al., 1992; Stewart et al., 1992; Lipton and Stewart, 1994; Russell and Olesen, 1996; Dowson and Jagger, 1999).

Concerning the pathogenesis of migraine, for centuries migraine pain experts believed this disorder to be caused by swollen blood vessels in the head (Graham and Wolff, 1938; Schumacher and Wolff, 1941). However, research within several medical disciplines performed during the last fifteen years strongly indicates that migraine is a brain disorder. Current theories emphasize the interaction between vessels and nerves and propose that the primary dysfunction is located within the central nervous system (CNS). Hence, they are called neurovascular theories. Neural impulses are assumed to produce changes in the trigeminovascular system resulting in headache. Whether cortical, midbrain or brain stem centers generate the attack, is still a matter of debate (Buzzi and Pelligrino, 1995; Diener and May, 1996; Welch, 1997 and 1999). Although blood vessels do ultimately become involved, they are assumed to play a secondary role.

Migraine has an ever-expanding therapeutic armamentarium. Pharmacological agents that may be used as a prophylactic include beta blockers, calcium channel blockers, valproic acid, nonsteroidal anti-inflammatory drugs (NSAID's) and MAO inhibitors. Abortive antimigraine medications include: dopamine antagonists, serotonin agonists, opioids, local anesthetics, non-steroidal anti-inflammatory agents, and steroids. The first serotonin agonist (the 'triptan' anti-migraine agent sumatriptan) was introduced more than a decade ago. Since then, several other

triptans have been introduced, namely rizatriptan, zolmitriptan, naratriptan, eletriptan, almotriptan, frovatriptan. They represent a significant improvement in migraine therapy (Dulli, 1999). Non-pharmacological interventions include stress reduction behavioral modalities such as biofeedback, relaxation training, and brief cognitive behavioral therapy.

This thesis is composed of a series of articles on two main relevant aspects of the migraine syndrome. The first aspect is psychological stress as an antecedent of a migraine attack. As an often mentioned external provoking factor, psychological stress may trigger the pathophysiological mechanisms that lead to an attack (Feuerstein et al., 1983; Passchier, 1985; Sorbi and Tellegen, 1988; Passchier, 1994). Comparing the psychophysiological, biochemical, and psychological reactions of migraine patients to mental stress with those of people not suffering from migraine can help finding the pathological mechanism of migraine or enable the testing of current pathological theories. It may also provide clues for improving pharmacological and behavioral treatments. We, therefore, performed an experiment in which we subjected migraine patients and controls to mental stress and measured physiological systems which are related to migraine pathology.

The second main aspect in this thesis concerns the daily physical functioning of migraine patients as a consequent of (a) migraine (attack). Research yields evidence that, although pain relief is the main motive for taking medication for the majority (57%) of the patients, a considerable proportion of the patients (about 43%) take medication in the first place to be able to continue their daily activities (Passchier et al., 1998). The importance of daily activities is also supported by the existence of a significant inverse relationship between the limitation in activity during a migraine attack and the concurrent quality of life of the patient (Santanello et al., 1995). The limitation of activity also leads to substantial economical costs for the society (Stang et al., 1993; van Roijen et al., 1995; Solomon and Price, 1997; Ferrari, 1998; Von Korff et al., 1998; Hu et al., 1999). Until now the evidence of limitation of ictal and also of interictal behavioral functioning is based on subjective reports only (Göbel and Krapat, 1993; Kryst and Scherl, 1994; Osterhaus et al.,

1994; Essink-Bot et al., 1995; Dahlöf and Dimenäs, 1995; Dahlöf and Solomon, 1998; Lipton et al., 2000; Terwindt et al., 2000). Therefore, we have quantified the ictal and interictal overt behavior of migraine patients, using the objective, reliable and valid method of ambulatory accelerometry. In addition to subjective parameters, we monitored the effect of two representative anti-migraine drugs on headache-related disability and behavior during an attack, using the recording method of ambulatory accelerometry mentioned above.

Chapter 2.

The precipitating factors of an actual migraine attack most frequently mentioned in the literature are mental and emotional stress, consumption of alcoholic beverages (particularly red wine), and the menstrual cycle (Wolff, 1937; Henryk-Gutt and Rees, 1973; Lance, 1975; Blau, 1985; Sorbi and Tellegen, 1988; Brandt et al., 1990; Passchier and Andrasik, 1993). Two lines of inquiry into the 'stress-migraine association' have been pursued. The first line is based on the fact that psychological stress evokes substantial increases in sympathoadrenomedullary system activity (Passchier, 1985; Tulen, 1993) and on the assumption of a dysregulation of this system in migraine patients, resulting in the development of a migraine attack in these patients and not in healthy controls (Flor and Turk, 1989; Passchier and Andrasik, 1993). The results of the studies performed until now, however, are inconsistent and confusing, due to methodological variability, e.g. the use of different study designs, varying sample compositions, the lack of a (proper) control group, and the employment of different stressors (Flor and Turk, 1989; Lichstein et al., 1991; Passchier et al., 1993; Passchier, 1994; Wittrock et al., 1996). Making allowance for these methodological considerations, we carried out an investigation to compare the cardiovascular, serotonergic and catecholaminergic responses of migrainous subjects with nonmigraineurs before, during, and after the experience of mental stress. In addition to these parameters, temporalis pulse amplitude and frontalis muscle activity were studied because of their presumed specific role in the etiology of migraine attacks and tension headaches (Drummond, 1982; McCaffrey et al., 1986; Flor and Turk, 1989;

Leijdekkers and Passchier, 1990; Passchier et al., 1993; Passchier and Andrasik, 1993). Up to now, such a combined assessment has not been performed. Participants in the study included 23 patients with migraine (7 without aura and 16 with aura) and 18 patients with tension headache. All headache patients had been, or still were, under treatment by neurologists of the Department of Neurology of the Erasmus MC Rotterdam. It has been shown that an anxiety-prone disposition plays an important role in making the decision to go see a doctor (Packard, 1979). This means that the psychological makeup, rather than the physiological disposition of the headache patients could explain their abnormal physiological stress response. To avoid this contamination, a control group was added consisting of subjects ($n = 22$) who were generally healthy, but who also visited the outpatient clinic of the Dermatology Department of the hospital and had been treated for disorders which had no consequences for their long-term somatic condition and without any (known) psychological complications. Measurements were made in a standardized experimental room. During the intake session, the participants were asked to complete the trait anxiety scale of the State-Trait Anxiety Inventory. The beginning of the experiment consisted of a short adaptation period (15 min) for the subject to familiarize with the situation. During this period baseline measurements were made of the subject's heart rate (HR), blood pressure (BP), frontalis EMG (FEMG), and pulse amplitude from the frontal branch of the superficial tempory artery (TPA). In addition to these parameters, during the last five minutes of the baseline period, blood samples were drawn for assay of the plasma catecholamines epinephrine and norepinephrine, of 5-HT concentrations in plasma and platelets, and of 5-HIAA in plasma. Also headache intensity was assessed. Directly after the baseline measurements patients were asked to perform a mental stress task. Subjects were asked to carry out this task for 3 sequential periods of 15 minutes. The physiological responses were recorded continuously, while in the interval between the mental stress periods new blood samples were collected for the analysis of the biochemical variables. In addition the headache intensity was measured. Following the last arithmetic problem, the subject was allowed a 20 minutes recovery period, while physiological registration continued. After this relaxation period headache

intensity was assessed and a last sample of blood was drawn. Activation of the sympatho-adrenomedullary system due to mental stress was successfully induced in the subjects of the three experimental groups. We found an overall moderately increased blood pressure in patients with migraine without aura as compared to migraine patients with aura, and to nonmigraineurs. However, no evidence was found of specific serotonergic, sympathoadrenomedullary or cerebrovascular responses of migraine patients to mental stress as compared to nonmigraineurs.

Chapter 3.

A second line of inquiry is based on the notion that many variables determine whether or not and to what extent an aversive stimulus will cause a stress reaction. These variables encompass the nature of the stressor, the emotional demands elicited and personality traits that determine the way in which the subject copes with the stressor (Flor and Turk, 1989; Allen and Cromwell, 1989; Steptoe, 1991). During the last decennia, many investigations were performed hypothesizing differences between migraine patients and nonmigraineurs in these stress-regulating variables. These studies reported higher levels of depression (Blanchard et al., 1989), and trait anxiety (Blanchard et al., 1989; Leijdekkers and Passchier, 1990; Leijdekkers et al., 1990) in patients with migraine compared to headache-free controls. Migraine patients also tended to show more repression of their emotions than controls (Passchier et al., 1988). Recent epidemiological studies revealed positive associations between migraine and psychiatric disorders, particularly major depression, anxiety disorders, and neuroticism (Merikangas et al., 1988; Breslau and Davis, 1992; Breslau and Andreski, 1995). The results of this second line of research are also inconsistent and inconclusive, mainly due to the methodological variability in the studies, i.e., methodological shortcomings involving the lack of a (proper) control group, the use of different designs, varying sample compositions, diagnostic criteria and stressors. Therefore, in our study outlined in Chapter 2, we also incorporated the comparison of stress related personality traits and the psychological responses of migraine patients with those of nonmigraineurs. The results of this part of the study showed that migraine

patients do not have a higher disposition for anxiety, depression or rigidity than tension headache patients or controls. Between the headache groups no differences in the use of defense and coping mechanisms were found. Compared to the control group, however, both migraine patients and tension headache patients were on the one hand more inclined to use the defense mechanisms 'reversal' and 'repression' and on the other hand less inclined to use 'projection' as a defense mechanism and to seek social support when confronted with a problem. The psychological reaction of migraine patients to mental stress hardly differed from tension headache and control subjects. Compared to the control subjects however, both groups of headache patients exhibited a diminished recovery from feelings of vigour, depression and fatigue due to the stress induced. It is suggested, that this distinct psychological recovery from stress of headache patients versus healthy control subjects is related to the aforementioned defense style of the headache sufferers. Thus, in contrast to the results of previous studies, our study does not present evidence of a migraine personality. It is suggested that the specific personality characteristics develop as a consequence of suffering from episodic headache.

Chapter 4.

Apart from the antecedents of (a) migraine (attack), the findings of many studies on its consequents reveal that during an attack migraine patients suffer from an impaired quality of life, compared to the general population and other populations with chronic illnesses. They report disturbances in the broad areas of psychological, social and daily physical functioning, i.e., a decreasing ability to carry on with their usual daily activities (Kryst and Scherl, 1994; Cavallini et al., 1995; Micieli et al., 1995; Dowson and Jagger, 1999). Research findings have shown that there are significant relations between subjects' 24-hour quality of life scores during and just after an attack and this latter aspect of activity limitation. As subjects reported decreasing ability to carry on with activities as a result of their migraine, quality of life scores in the domains 'work functioning', 'social functioning', and 'energy' decreased significantly. As activity became more limited,

subjects reported feeling more upset, more physically uncomfortable, and more concerned regarding the capability of their migraine medication to relieve their migraine symptoms (Santanello et al., (1995). Until now the alterations in the level of behavioral functioning are based on subjective reports only (Osterhaus et al., 1994; Stewart et al., 1998; Stewart et al., 1999). However, since this behavioral functioning of the patient appears to be such a relevant characteristic and determinant of their disability and concurrent quality of life, we set up a study to determine whether the subjective reports can be substantiated by objective, valid and reliable quantifications of the behavioral daily functioning. To this end we applied the recently developed technology of portable digital ambulatory recorders and accelerometer sensors. Validation studies in healthy subjects, amputees and patients after failed back surgery have shown high percentages of agreement between the automatic computer classification of the ambulatory accelerometry signals and the visual analysis of simultaneously recorded videotapes (Bussmann et al., 1998a,b,c). In a feasibility study we explored the conditions under which ambulatory accelerometry can be used to quantify the physical activities of migraine patients before, during, and after an acute migraine attack in their habitual environment. Six female migraine patients participated in this study. Repeated measurements of the 24-h patterns of locomotor and physical activities, as well as repeated subjective assessments of pain, mood, level of functioning, and subjective sedation were obtained during a headache-free baseline period, as well as during and after a migraine attack in the habitual environment of the patient. The results indicated that in all three phases ambulatory accelerometry is feasible to perform. Furthermore, our data revealed that migraine influences behavior, generally by reducing overall body motility, dynamic activities, and the number of postural transitions. Ambulatory accelerometry was found to be able to provide the objective behavioral effect parameters for the evaluation of migraine and its treatment on daily functioning in the habitual environment of migraine patients.

and sleepiness, all the clinical and subjective parameters showed a significant reduction within the six hour period during both treatments. Evidently, consciously perceived clinical and subjective symptoms do not run synchronically to their behavioral equivalents.

Recommendations for future research

1. *Stress as an antecedent of (a) migraine (attack)*

The aims of this first aspect of our inquiry into the migraine syndrome were twofold. Firstly, the potential role of the serotonergic, sympathoadrenomedullary, and cerebrovascular system of migraineurs in the genesis of (a) migraine (attack) was investigated by comparing the responses of these systems to mental stress with those of a group of patients with tension headache and with a group of healthy controls. The results of this study present no explicit evidence of a specific dysregulation in these systems in migraine patients. However, although no differences in heart rate and temporal pulse amplitude were observed, the overall moderately elevated blood pressure of migraine patients without aura emphasizes the potential relevance of vascular hyperactivity in the pathogenesis of migraine without aura. Therefore, we recommend further research into the vascular activity of migraineurs before, during and after a migraine attack, preferably employing spectral analysis of heart rate and blood pressure variability. This analysis of beat-to-beat fluctuations can be used as a sensitive non-invasive probe of cardiovascular autonomic control. Studies have revealed that different branches of autonomic control (sympathetic and parasympathetic) contribute to the power spectrum of heart rate and blood pressure in different, well defined frequency bands. This frequency specificity is very important in enabling an evaluation of the sympathetic versus the parasympathetic balance (Sayers, 1973; Akselrod et al., 1981; Task Force, 1996).

Secondly, whether a stressor elicits a stress response and to what extent depends, amongst others, on specific stress-regulating personality traits that determine the way a subject copes with a stressor. For decennia the opinion was propagated, that migraineurs exhibit such specific stress-related personality traits. Therefore,

this opinion was put to an empirical test. For this purpose, we incorporated into the study mentioned above (i) a comparison of stress-regulating personality characteristics of migraineurs with those of the patients with tension headache and with healthy controls, and (ii) a comparison of the psychological reactions to stress of these groups. The results of this comparisons neither indicated the existence of a specific 'migraine personality', nor did they suggest strong evidence for a specific psychological reaction of migraineurs to stress. Therefore, our study could not provide any evidence as to the etiological significance of these traits for the migraine syndrome. Our findings rather indicate the existence of certain personality traits, that are characteristic of headache patients in general when compared to healthy controls, i.e., the inclination to utilize more frequently the defense mechanisms 'reversal' and 'repression' and less frequently 'projection' and to seeking less social support in coping with unpleasant events. The question is raised whether repeated and frequent suffering from (head)pain (despite its origin) induces such defenses and coping mechanisms. Future research should be performed to understand the causal relation between the distinct psychological defense and coping style of patients with a recurrent headache syndrome by investigating the correlations between these psychological phenomena on the one hand and the length of time of their suffering from the headache syndrome, the frequency and the intensity of their headache attacks on the other.

2. *Daily physical functioning of migraine patients as a consequent of (a) migraine (attack)*

This second aspect of the migraine syndrome has been studied by recording of the interictal and ictal daily activities of migraineurs, using the method of ambulatory accelerometry. In addition, we monitored heart rate continuously and measured the following subjective parameters: sleep quality, sleepiness, highest realizable level of physical functioning, and mood. This study has yielded objective evidence of a significant interictal reduction in daily activities of migraine patients when compared to healthy controls. Cavallini et al. (1995) concluded that many headache patients experience distress from the imminence of attacks in the

intervals between them. So, the interference of migraine with the ictal physical behavior of migraine patients might, in course of time, have been generalized to their interictal behavior as the result of a chronic fear of developing an attack. Again, no significant differences in mean heart rate levels were observed between the migraine patients and the control subjects. Patients, however, reported higher levels of sleepiness, and lower levels of subjective realizable levels of functioning, and of vigour. This underlines the above mentioned relevance to study in the future the causal association between pain indices (the length of time a patient suffers from migraine, the frequency, duration and intensity of the pain attacks) and the use of defenses and coping style, now also including objective parameters of interictal daily functioning of migraine patients and subjective parameters of their concurrent level of sleepiness, highest realizable level of functioning, and mood.

In addition, our results provide a rationale for psychological interventions which aim at diminishing the aforementioned fear of developing a migraine attack (preferably in combination with an attempt to increase the patients' insight into their defense style and social support seeking-behavior) and, through that, reduce the impact of migraine on interictal physical behavior. It might (also) directly aim at this behavior by administering behavioral therapy. This might result in a reduction of the individual and collective impact of migraine, i.e., an improved functioning at home, at work, at school, in other social roles and in improved sexual relationships. Research into the beneficial effects on the quality of life of psychological interventions, which aim (directly) at the increase of the interictal activities of migraine patients, seems therefore to be justified.

Our second line of inquiry also included the recording of the daily functioning during acute treatment of a migraine attack. We evaluated the effect of two representative pharmacological migraine treatments (naratriptan versus naproxen) on daily functioning and on subjective measures of clinical symptoms, mood, sleepiness, and highest realizable level of physical functioning during the first six hours of treatment. In both the naratriptan and the naproxen condition the severity of the clinical symptoms headache, nausea, and photo- and phonophobia decreased significantly during that period. Naratriptan, however, was significantly

more effective than naproxen in reducing the severity of the headache, nausea, and vomiting. The total mood disturbance decreased significantly, whereas the level of highest realizable functioning increased. Interestingly, no significant differences between the two pharmacological agents were found in their effect on daily activities. Evidently, consciously perceived clinical and subjective symptoms do not run synchronically to their behavioral equivalents, at least not during the first six hours of treatment. This phenomenon is in line with the conception of pain as a multi-dimensional event that also includes subjective and objective behavioral components. Vendrig and Lousberg (1997) found no association between the ratings of chronic pain patients of their pain intensity and activity level. Fordyce et al. (1984) suggested that there may be a questionable relationship between what people say about their pain and what they actually do, whereas Holroyd et al. (1999) concluded that pain and disability are separable dimensions of headache impact, that may be altered in different ways by different therapies. Bearing also in mind that the limitation in performing habitual daily activities constitutes a major problem for both the patient and for the society, we therefore recommend to include in future studies not only the migraine-related clinical and subjective phenomena, but also the objectively measured physical activities in the evaluation of the general efficacy of (non)pharmacological therapy of migraine, in acute treatment of attacks and in the periods between them. In future research, the clinical, subjective and objective parameters might be pursued during a longer period of time after the start of pharmacological anti-migraine therapy, establishing the (different) durations of time required for these parameters to return to baseline levels. Such a procedure might not only offer clues for understanding their nonsynchronicity during the first hours after treatment, but it also might yield measures regarding the various anti-migraine drugs of their efficacy in restoring the clinical, subjective and objective repercussions of an acute migraine attack.

Chapter 5.

The results of several recent studies showed that migraine induces an impaired quality of life even between attacks. Compared to controls, migraine patients were found to perceive more symptoms and greater emotional distress as well as disturbed contentment, vitality and sleep. There is an enduring disposition to attacks, long-term adoption of the sick-role with disruption at work, school, and in social roles and sexual relationships and there may be changes in mood and in behavior (Osterhaus et al., 1994; Cavallini et al., 1995; Van Roijen et al., 1995; Passchier et al., 1996; Steiner, 2000). Migraine therefore should be considered a chronic rather than an episodic illness. These chronic aspects are characterized by how the condition changes an individual's behavior and induces disability between attacks. It therefore is important to assess the interictal behavior and mood changes. All the more, because a significant relationship may exist between the interictal (limitation of) activity of the patient and the concurrent quality of life – analogous to an already observed relationship during migraine attacks. Also the research related to interictal daily functioning has until now been based on subjective reports only (Kryst and Scherl, 1994; Osterhaus et al., 1994; Essink-Bott et al., 1995; Dahlöf and Dimenäs, 1995; Dahlöf and Solomon, 1998; Lipton et al., 2000; Terwindt et al., 2000). Our previous study had shown that, using ambulatory accelerometry, the quantification and classification of behavioral aspects of daily functioning of migraine patients is feasible to perform during interictal periods as well as during migraine attacks. Based on this finding, a next study was set up to quantify the normal daily interictal activities using this method and to assess interictal subjective symptoms reflecting mood, sleepiness, and level of functioning of patients with migraine ($n = 24$) in their habitual environment. We also recorded the ambulatory ECG of the subjects. By using ambulatory accelerometry it became possible to control for the effect of body postures and physical activities on heart rate variability.

Compared to healthy controls, migraine patients spent relatively less time being active. Moreover, if active, the motility of the body was found to be lower than that of the control subjects, i.e., migraineurs appeared to move more calmly and more

prudently. A fear and/or habit to anticipate an acute attack, that has been acquired over the years of suffering, might offer an explanation. Patients with migraine also reported significantly higher levels of sleepiness and significant lower realizable levels of functioning and of vigour. No significant differences regarding mean heart rate levels were observed. We concluded that migraine leads both objectively and subjectively to a limitation in interictal physical activities. This may result in a reduction of the productivity at work, in school, and in other roles and consequently in an increase of the costs to society. If so, the interictal behavioral and psychological characteristics migraine patients exhibit, contribute to the individual, as well as to the collective burden of migraine, confirming the chronic impact of this disease.

Chapter 6.

Until now research into the effects of pharmacological drugs on normal daily functioning in the acute treatment of migraine has also been based on subjective reports only. So, in addition to the interictal parameters, we evaluated the effect of acute treatment on this outcome parameter of the migraine patients ($n = 12$) participating in the above mentioned study, using the method of ambulatory accelerometry. For this purpose we used both a nonspecific anti-migraine drug (the NSAID naproxen) and a specific anti-migraine drug (the 5-HT_{1B/1D} agonist naratriptan). In summary, in a randomized, double-blind, double-dummy, crossover study, we evaluated the effect of naratriptan on objective measures of locomotor and physical activities and on subjective measures of clinical symptoms (headache, nausea, vomiting, photo- and phonophobia), mood, sleepiness, and level of functioning during the first six hours of treatment of a migraine attack in the habitual environment, in comparison with the effect of naproxen. During the first six hours after intake of the study medication, the objective behavioral parameters showed no significant effect of time and no significant differences between naproxen and naratriptan. However, naratriptan was significantly more efficacious than naproxen on the relief of headache, nausea and vomiting. Except for vomiting

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Hoofdstuk 1.

Migraine is een ziekte, die gekenmerkt wordt door herhaalde aanvallen van matig tot ernstig, unilaterale, pulserende of kloppende hoofdpijn, die verergerd worden door routinematige lichamelijke activiteit en vergezeld kunnen gaan van overgevoeligheid voor licht (fotofobie) en geluid (fonofobie), misselijkheid en soms van overgeven (Headache Classification Committee of the International Headache Society, 1988). Recent onderzoek, dat gebruik maakte van de door de International Headache Society (IHS) opgestelde diagnostische criteria, leverde relatief consistente schattingen op van de prevalentie van migraine in de Westerse geïndustrialiseerde landen (15-18% van de vrouwen en 6% van de mannen) en het feit dat migraine het meest voorkomt bij mannen en vrouwen in de leeftijd tussen 25 en 55 jaar (Rasmussen et al., 1991; Henry et al., 1992; Stewart et al., 1992; Lipton and Stewart, 1994; Russell and Olesen, 1996; Dowson and Jagger, 1999).

Eeuwenlang dachten migraine-experts dat de aandoening veroorzaakt werd door gedilateerde bloedvaten in het hoofd (Graham and Wolff, 1938; Schumacher and Wolff, 1941). Onderzoek gedurende de afgelopen vijftien jaar vanuit verschillende medische disciplines verricht wijst echter in de richting van een hersenstoornis. Vigerende neurovasculaire theorieën benadrukken de interactie tussen bloedvaten en zenuwen en stellen dat de primaire disfunctie gelokaliseerd is in het centraal zenuwstelsel (CZS). Neurale impulsen worden verondersteld veranderingen in het trigeminovasculaire systeem te veroorzaken, met hoofdpijn als gevolg. De bloedvaten spelen hierbij een secundaire rol. Of zenuwcentra in de cortex, in de middenhersenen dan wel in de hersenstam een migraine aanval genereren is nog niet duidelijk (Buzzi and Pelligrino, 1995; Diener and May, 1996; Welch, 1997 and 1999).

Het therapeutisch arsenaal van migraine breidt zich steeds verder uit. Tot de profylactische farmacologische middelen die gebruikt worden behoren bètablokkers, calciumkanaal blokkers, niet-steroïde anti-inflammatoire geneesmiddelen (NSAID's) en MAO-remmers. Onder de abortieve medicamenteuze behandeling vallen: dopamine antagonisten, serotonine agonisten, opioïden en steroïden. De

eerste serotonine agonist (de triptan 'sumatriptan') werd in 1991 in Nederland geïntroduceerd. Sindsdien zijn er ook andere triptanen beschikbaar gekomen, zoals rizatriptan, zolmitriptan, naratriptan, eletriptan, almotriptan en frovatriptan. Ze betekenen een significante verbetering van de migraine therapie (Dulli, 1999). Niet-farmacologische interventies omvatten stressreducerende psychologische interventies, zoals biofeedback, ontspanningsoefeningen en korte cognitieve gedragstherapie.

Dit proefschrift is gebaseerd op vijf artikelen handelend over twee belangrijke aspecten van het migrainesyndroom.

Het eerste aspect betreft psychologische stress als een vaak genoemde potentiële antecedent van een aanval. Vergelijking van de psychofysiologische, biochemische en psychologische reactie van migrainepatiënten op mentale stress met die van mensen die geen migraine hebben, kan leiden tot een beter begrip van de pathologische mechanismen van migraine en maakt de toetsing van hypothesen over deze mechanismen mogelijk. Ook kan het aanwijzingen opleveren voor de verbetering van medicamenteuze en psychologische behandeling van migraine. Daarom hebben wij een onderzoek verricht, waarin migrainepatiënten en controle personen aan mentale stress werden bloot gesteld en hun fysiologische reacties gemeten. Het betrof die fysiologische reacties, die verondersteld worden gerelateerd te zijn aan de pathologie van migraine.

Het tweede aspect betreft de consequentie van (een) migraine (aanval) voor het dagelijks functioneren van de patiënt. De relevantie van dit aspect blijkt uit het navolgende. Onderzoek toonde aan, dat verlichting van de pijn de belangrijkste reden voor inname van medicatie voor een meerderheid van de migrainepatiënten (57%) is; de resterende 43% vermeldde echter als voornaamste reden de wens tot continuering van hun dagelijkse bezigheden (Passchier et al., 1998). De relevantie voor migrainepatiënten van (de mogelijkheid tot voortzetting van) hun dagelijkse activiteiten wordt mede ondersteund door de significante negatieve correlatie tussen de beperking van deze activiteit tijdens een migraine aanval en de kwaliteit van leven, die ze op dat moment bezitten (Santanello et al., 1995). De beperking

van activiteit leidt bovendien tot substantiële economische kosten voor de maatschappij (Stang et al., 1993; van Roijen et al., 1995; Solomon and Price, 1997; Ferrari, 1998; Von Korff et al., 1998; Hu et al., 1999). De bevinding van de beperking van ictaal, maar ook van interictaal gedrag is tot nu uitsluitend gebaseerd op subjectieve metingen (Göbel and Krapat, 1993; Kryst and Scherl, 1994; Osterhaus et al., 1994; Essink-Bot et al., 1995; Dahlöf and Dimenäs, 1995; Dahlöf and Solomon, 1998; Lipton et al., 2000; Terwindt et al., 2000). Daarom hebben wij de interictale fysieke activiteiten van migrainepatiënten gekwantificeerd met behulp van de objectieve, betrouwbare en valide methode van de ambulante accelerometrie. Daarnaast hebben we met behulp van deze techniek ook de effecten van twee representatieve antimigraine middelen op het ictale gedrag gemeten in combinatie met subjectieve metingen van hun effecten op de klinische symptomen, op de stemming, de sedatie en het maximaal haalbare fysieke activiteitsniveau (MHFA).

Hoofdstuk 2.

De in de literatuur meest frequent genoemde uitlokkende, c.q. bevorderende factoren van een migraine aanval zijn mentale en emotionele stress, consumptie van alcoholische dranken (met name rode wijn) en de menstruele cyclus (Wolff, 1937; Henryk-Gutt and Rees, 1973; Lance, 1975; Blau, 1985; Sorbi and Tellegen, 1988; Brandt et al., 1990; Passchier and Andrasik, 1993).

Twee lijnen van onderzoek naar deze 'stress-migraine associatie' zijn te onderscheiden. De eerste lijn is gebaseerd op het feit dat stress substantiële verhoging van de activiteit van het sympathoadrenomedullaire systeem tot gevolg heeft (Passchier, 1985; Tulen, 1993) en op de assumptie van een disregulatie van dit systeem bij migrainepatiënten, resulterend in de ontwikkeling van een aanval bij hen en niet bij gezonde controle personen (Flor and Turk, 1989; Passchier and Andrasik, 1993). De resultaten van onderzoek dat hiernaar is gedaan zijn echter inconsistent en verwarrend, mede als gevolg van de methodologische variabiliteit in de studies (het gebruik van verschillende studiedesigns, het ontbreken van een (adequate) controlegroep en het aanwenden van verschillende stressoren) (Flor

and Turk, 1989; Lichstein et al., 1991; Passchier et al., 1993; Passchier, 1994; Wittrock et al., 1996). Rekening houdend met deze methodologische overwegingen hebben wij de cardiovasculaire, serotonerge en catecholaminerge responsen van migraine patiënten voor, tijdens en na de inductie van mentale stress vergeleken met die van personen, niet lijdend aan migraine. Tevens zijn de temporale pulsamplitude en de activiteit van de musculus frontalis onderzocht, vanwege hun veronderstelde rol in de etiologie van migraine aanvallen en spanningshoofdpijn (Drummond, 1982; McCaffrey et al., 1986; Flor and Turk, 1989; Leijdekkers and Passchier, 1990; Passchier et al., 1993; Passchier and Andrasik, 1993). Onderzoek met een zodanige combinatie van uitkomstparameters is tot nu toe niet verricht. Drieëntwintig migrainepatiënten (7 met aura en 16 zonder aura) en 18 patiënten met spanningshoofdpijn namen aan dit onderzoek deel. Alle hoofdpijnpatiënten waren onder behandeling van een neuroloog van de afdeling Neurologie van het Erasmus MC (geweest). Packard heeft aangetoond dat een angst dispositie een rol speelt bij de beslissing een arts te raadplegen (Packard, 1979). Dit betekent dat de psychologische, eerder of meer dan de fysiologische gesteldheid van de hoofdpijnpatiënten, hun afwijkende fysiologische respons zou kunnen verklaren. Om deze contaminatie te vermijden werd aan het onderzoek een controlegroep (n = 22) toegevoegd, bestaande uit personen die de polikliniek van de afdeling Dermatologie van het Erasmus MC bezocht hadden en onder behandeling waren geweest voor aandoeningen die geen consequenties hadden voor hun lichamelijke en psychische gezondheid op lange termijn.

De metingen werden verricht in een gestandaardiseerde experimentele ruimte. Tijdens de intake werd de participanten gevraagd de angstschaal van de State Trait Anxiety Inventory in te vullen. Het onderzoek begon met een korte adaptatie periode (15 min), zodat de persoon vertrouwd kon raken met de onderzoeks-situatie. Gedurende deze baselineperiode werden metingen verricht van de hartfrequentie (HF), de bloeddruk (BD), de activiteit van de musculus frontalis (FEMG) en de pulse amplitude van de voorste tak van de arteria temporalis superficialis (TPA). Tijdens de laatste vijf minuten van deze periode werden bloedmonsters afgenomen ter bepaling van de plasma concentratie van 5-HIAA en

de catecholaminen epinefrine en norepinefrine en van de concentratie 5-HT in plasma en in plaatjes. Tevens werd de intensiteit van de mogelijk aanwezige hoofdpijn bepaald. Direct na de baseline periode werd de proefpersoon gevraagd om tijdens drie sequentiële perioden van 15 minuten een rekentaak uit te voeren onder mentale stress. De fysiologische reacties werden continu geregistreerd, terwijl tijdens de intervallen tussen de perioden met mentale stress, nieuwe bloed monsters werden verzameld ten behoeve van de analyse van de biochemische parameters. Ook werd de ernst van de hoofdpijn weer gemeten. Na de laatste rekentaak kreeg de persoon twintig minuten rust. Tijdens deze herstelperiode werd de meting van de fysiologische responses gecontinueerd. Hierna werd andermaal de hoofdpijntensiteit gemeten en werd een laatste bloedmonster afgenomen.

De geïnduceerde stress leidde bij de personen uit alle drie experimentele groepen tot activatie van het sympathoadrenomedullaire systeem. Vergeleken met de niet-migrainepatiënten en met de patiënten met migraine met aura, vertoonden de patiënten met migraine zonder aura over de gehele onderzoeksperiode een matig verhoogde bloeddruk. De onderzoeksresultaten wezen echter niet op een specifieke serotonerge, sympathoadrenomedullaire of cerebrovasculaire reactie van migraine patiënten op mentale stress.

Hoofdstuk 3.

Of, en de mate waarin, een aversieve stimulus tot een stressreactie leidt, wordt door vele factoren bepaald. Op dit inzicht is de tweede lijn van onderzoek naar de 'stressmigraine associatie' gebaseerd. Deze factoren omvatten de aard van de stressor, het emotionele beroep dat deze op de persoon doet en persoonlijkheidsfactoren, die de wijze bepalen waarop het individu de stressor het hoofd biedt (Flor and Turk, 1989; Allen and Cromwell, 1989; Steptoe, 1991). De afgelopen decennia is veel onderzoek gedaan naar deze stressregulerende factoren. Vergeleken met hoofdpijnvrije controles, vertoonden migrainepatiënten meer depressieve gevoelens (Blanchard et al., 1989) en meer habituele angst (Blanchard et al., 1989; Leijdekkers and Passchier, 1990; Leijdekkers et al., 1990). Ook vertoonden ze een grotere tendens tot repressie van hun emoties (Passschier et

al., 1988). Uit recente epidemiologische studies bleek een positieve samenhang tussen migraine en psychologische stoornissen, i.c. depressie, angststoornissen en neuroticisme (Merikangas et al., 1988; Breslau and Davis, 1992; Breslau and Andreski, 1995).

De resultaten van deze tweede lijn van onderzoek zijn echter ook inconsistent en weinig overtuigend, voornamelijk ten gevolge van de methodologische variabiliteit in de studies: het al dan niet gebruik maken van een (adequate) controle groep, het gebruik van verschillende designs, van wisselende steekproefsamenstellingen, uiteenlopende diagnostische criteria en stressoren. Vandaar dat wij in het in hoofdstuk 2 beschreven onderzoek tevens stressgerelateerde persoonlijkheidstrekken van migrainepatiënten en hun psychologische responses op de mentale stressor vergeleken hebben met die van de proefpersonen zonder migraine.

De resultaten van dit onderdeel van het onderzoek tonen niet aan dat migrainepatiënten een grotere dispositie voor angst, depressie of rigiditeit bezitten dan patiënten met spanningshoofdpijn of controles. Zowel de patiënten met migraine als die met spanningshoofdpijn bleken in vergelijking met de controles significant meer geneigd te zijn tot het gebruik van de afweermechanismen verdringing en herbenoemen en minder tot het gebruik van projectie. Ook verschilde hun copingstijl: ze waren, indien geconfronteerd met een probleem, significant minder geneigd tot het zoeken van sociale steun. De psychologische reactie van migrainepatiënten op mentale stress verschilde nauwelijks van die van de beide andere groepen. Vergeleken met de gezonde controle proefpersonen, vertoonden de hoofdpijnpatiënten een trager herstel van depressieve gevoelens, van energie (vigour) en van vermoeidheid. Mogelijk is dit verschil in snelheid van psychologisch herstel na mentale stress gerelateerd aan hun bovengenoemde specifieke afweerstijl.

Dus, in tegenstelling tot de resultaten van voorafgaand onderzoek, levert ons onderzoek geen evidentie op voor het bestaan van een specifieke migraine-persoonlijkheid.

Hoofdstuk 4.

De vele studies naar de gevolgen van (een) migraine (aanval) tonen aan dat, in vergelijking met de algemene populatie en met de populaties met chronische aandoeningen, migrainepatiënten tijdens een aanval een mindere kwaliteit van leven hebben. Ze rapporteren verstoringen op het terrein van hun psychologisch, sociaal en fysiek functioneren, zich uitend in een verminderd in staat zijn hun dagelijkse bezigheden te continueren (Kryst and Scherl, 1994; Cavallini et al., 1995; Miceli et al., 1995; Dowson and Jagger, 1999). Onderzoek heeft aangetoond dat er een significante relatie bestaat tussen de scores op de 24-Hour Migraine Quality of Life Questionnaire (MQoLQ) van migrainepatiënten tijdens en direct na een aanval en de genoemde beperking van activiteit. Naar gelang de patiënten een afnemende mogelijkheid tot voorzetting van hun activiteiten ervoeren, daalden de scores op de (MQoLQ) op de terreinen 'functioneren op het werk', 'sociaal functioneren' en 'energie' significant. Hoe groter de ervaren beperking van activiteit, hoe meer ze zich ontredderd en fysiek oncomfortabel voelden en ze zich meer zorgen maakten over de potentie van de medicatie tot verlichting van hun migrainesymptomen (Santanello et al., 1995). De veranderingen in het niveau van activiteit zijn tot nu toe uitsluitend gebaseerd op subjectieve metingen (Osterhaus et al., 1994; Stewart et al., 1998; Stewart et al., 1999). Aangezien het dagelijks functioneren van migrainepatiënten kennelijk een belangrijke determinant is van hun actuele kwaliteit van leven, hebben we een onderzoek opgezet om vast te stellen in hoeverre de subjectieve bevindingen door objectieve, betrouwbare en valide kwantificering van hun fysieke activiteit kunnen worden bevestigd. Hiertoe hebben we gebruik gemaakt van de recent ontwikkelde Activiteiten Monitor: een instrument dat het langdurig ambulant meten van lichamelijke activiteit mogelijk maakt en gebruik maakt van een draagbare, digitale recorder en accelerometers. Na beëindiging van de registratie wordt een gecomputeriseerde classificatie uitgevoerd van de signalen van de accelerometers in statische activiteit (houdingen), dynamische activiteit (bewegingen), transitities (houdingsovergangen) en motiliteit (intensiteit van de bewegingen binnen de statische of dynamische activiteit). Validatieonderzoeken met gezonde

proefpersonen, met personen met een onderbeenprothese en met patiënten na failed back surgery, vertoonden hoge percentages overeenstemming tussen de automatische, gecomputeriseerde classificatie van de accelerometersignalen en de visuele analyse van de gelijktijdig opgenomen videobanden (Busmann et al., 1998a,b,c). In een haalbaarheidsstudie hebben wij de condities onderzocht, waaronder deze techniek van de ambulante accelerometrie kan worden gebruikt om de activiteit te kwantificeren van migrainepatiënten voor, tijdens en na een acute aanval in hun normale dagelijkse omgeving. Zes vrouwelijke migrainepatiënten participeerden in deze studie. Herhaalde 24-uurs ambulante activiteitenregistraties, als ook herhaalde subjectieve metingen van pijn, stemming, MHFA en sedatie werden verricht tijdens een hoofdpijnvrije (baseline) periode en tijdens en na een migraine aanval. De resultaten van dit haalbaarheidsonderzoek wezen uit dat ambulante accelerometrie in alle genoemde perioden uitvoerbaar is. Voorts bleek migraine de activiteit van de patiënt te beïnvloeden door een verlaging van de motiliteit, een vermindering van de dynamische activiteit en van het aantal transitities. Ambulante accelerometrie bleek de objectieve gedragsparameters te kunnen genereren om het effect vast te stellen van migraine en haar behandeling op het dagelijks fysiek functioneren van de patiënt in zijn / haar eigen omgeving.

Hoofdstuk 5.

De resultaten van verschillende recente studies tonen aan dat migraine een verminderde kwaliteit van leven tot gevolg heeft, zelfs in de perioden tussen aanvallen. Vergeleken met controles, bleken migrainepatiënten meer symptomen te ondervinden als ook een verminderde tevredenheid, vitaliteit en slaap. Er kan een aanhoudende angst voor het ontwikkelen van een aanval bestaan, er kan sprake zijn van het aannemen van een ziekenrol met negatieve gevolgen voor de seksuele relatie, het functioneren op het werk, in de school, in andere (sociale) omgevingen en er kunnen veranderingen optreden in de stemming en het gedrag (Osterhaus et al., 1994; Cavallini et al., 1995; Van Roijen et al., 1995; Passchier et al., 1996; Steiner, 2000). Daarom zou migraine veeleer als een chronische dan als

een episodische aandoening moeten worden beschouwd. Het is daarom belangrijk het interictale gedrag en de zich in die perioden manifesterende verandering van de stemming vast te stellen. Temeer, omdat de interictale (beperking van de) activiteit en de actuele kwaliteit van leven aan elkaar gerelateerd kunnen zijn – analoog aan de gevonden relatie tussen beide tijdens migraine aanvallen. Ook het onderzoek met betrekking tot het interictale dagelijks fysiek functioneren is tot op heden uitsluitend gebaseerd op subjectieve mededelingen (Kryst and Scherl, 1994; Osterhaus et al., 1994; Essink-Bott et al., 1995; Dahlöf and Dimenäs, 1995; Dahlöf and Solomon, 1998; Lipton et al., 2000; Terwindt et al., 2000). Op grond van de bevindingen uit ons voorgaande onderzoek, hebben we een onderzoek opgezet bij migrainepatiënten ($n = 24$) om, met behulp van de ambulante accelerometrie, de normale dagelijkse interictale activiteiten te kwantificeren en tevens interictale subjectieve metingen van de stemming, de sedatie en MHFA te verrichten. Ook werd het ambulante ECG geregistreerd. Doordat gebruik gemaakt werd van de Activiteiten Monitor werd het mogelijk om te controleren voor het effect van lichaamshouding en -activiteit op de hartfrequentie variabiliteit.

Uit de resultaten van dit onderzoek bleek dat migrainepatiënten, vergeleken met gezonde controles, een geringer deel van hun tijd (gemeten per tijdsinterval) fysiek actief doorbrachten. Bovendien bleek de motiliteit van hun lichaam tijdens deze activiteit geringer te zijn, d.w.z. migrainepatiënten bewogen zich kalmer en voorzichtiger. Een gedurende jaren van migrainelijden ontwikkelde vrees voor een acute aanval, of een gewoonte hierop te anticiperen, zou hiervoor een verklaring kunnen bieden. Migrainepatiënten rapporteerden bovendien een significant hoger sedatieniveau en een significant lagere maximaal haalbaar activiteitsniveau (MHFA). Er werden geen verschillen gevonden in gemiddelde hartfrequentie tussen de beide onderzoeksgroepen. Geconcludeerd werd dat migraine leidt tot een beperking van interictale fysieke activiteit, zowel blijkend uit de objectieve metingen als de subjectieve ervaring van de patiënten. Deze activiteitsbeperking kan resulteren in een vermindering van de productiviteit op het werk, in de school of in andere maatschappelijke domeinen en daarmee in een verhoging van de economische kosten voor de gemeenschap. Alsdan dragen de psychologische en

gedragsskarakteristieken van migraine bij aan de individuele, als ook aan de collectieve impact van migraine, hiermee de chronische invloed van deze aandoening bevestigend.

Hoofdstuk 6.

Ook voor het tot nu toe verrichtte onderzoek naar de effecten van acute medicamenteuze behandeling van migraine op de dagelijkse fysieke activiteiten geldt, dat de resultaten ervan uitsluitend op subjectieve metingen zijn gebaseerd. Vandaar dat wij bij een deel van de patiënten ($n = 12$), die participeerden in het boven beschreven onderzoek, tevens deze effecten hebben onderzocht, hiertoe weer gebruik makend van de ambulante accelerometrie. Voor dit doel hebben we zowel een specifiek antimigraine middel (de 5-HT_{1B/1D} agonist naratriptan) als een niet-specifiek middel (de NSAID naproxen) aangewend. In een gerandomiseerde, dubbelblinde, dubbel dummy, cross-over studie hebben we het effect van naratriptan op de objectieve maten voor fysieke activiteiten en op de subjectieve maten voor klinische symptomen (hoofdpijn, misselijkheid, overgeven en overgevoeligheid voor licht en geluid), op de stemming, de sedatie en het maximaal haalbare niveau van fysiek functioneren, vergeleken met het effect van naproxen. Ook nu weer betrof het ambulante metingen in de eigen omgeving van de patiënt. Slechts de eerste zes uren na inname van de studiemedicatie zijn geëvalueerd. Beide middelen hadden in dit tijdsinterval geen significant effect op de objectief gemeten fysieke activiteit. En (dus) ook was hun effect onderling niet significant verschillend. Naratriptan had echter, vergeleken met naproxen, een significant groter verlichtend effect op de hoofdpijn, de misselijkheid en het overgeven. Met uitzondering van misselijkheid en sedatie, leidden de beide behandelingen tot een significante verbetering voor alle klinische en subjectieve parameters.

Kennelijk loopt de beleving van de (ernst van de) klinische en subjectieve symptomen van een migraine aanval niet parallel met hun objectieve gedragsequivalenten.

Aanbevelingen voor vervolgonderzoek.**1. *Stress als antecedent van (een) migraine (aanval)***

Het doel van dit eerste aspect van onze studies naar het migrainesyndroom was tweeledig. Als eerste werd de potentiële rol van het serotonerge, sympathoadrenomedullaire en cerebrovasculaire systeem in de ontwikkeling van (een) migraine (aanval) onderzocht. Hiertoe werden de responses van deze systemen op mentale stress van migrainepatiënten vergeleken met die van spanningshoofdpijn patiënten en met die van gezonde controles. De resultaten leverden geen expliciete aanwijzing op voor een specifieke disregulatie van deze systemen bij migrainepatiënten. Echter, hoewel geen significante verschillen in hart frequentie en temporale pulse amplitude werden gevonden, benadrukt de significant gematigd verhoogde bloeddruk van migrainepatiënten zonder aura, de potentiële relevantie van vasculaire hyperactiviteit voor de pathogenese van migraine zonder aura. Aanbevolen wordt daarom om vervolgonderzoek te verrichten naar de vasculaire activiteit van migrainepatiënten voor, tijdens en na een aanval. Bij voorkeur wordt dan gebruik gemaakt van spectraalanalyse van de hartfrequentie en de bloeddruk variabiliteit. Deze analyse van R-R interval fluctuaties kan worden aangewend als een sensitieve, noninvasieve techniek voor onderzoek van de autonome cardiovasculaire regulering. Onderzoek heeft aangetoond dat zowel sympathische als parasympathische autonome controle bijdraagt aan het vermogensspectrum van de hartfrequentie en van de bloeddruk in verschillende en goed gedefinieerde frequentiedomeinen. Om de sympathische versus de parasympathische balans te kunnen evalueren, is deze frequentie specificiteit zeer belangrijk (Sayers, 1973; Akselrod et al., 1981; Task Force, 1996).

Ten tweede: of en in welke mate een stressor een stressreactie oproept, hangt onder meer af van specifieke, stressregulerende persoonlijkheidstrekken, die bepalend zijn voor de wijze waarop de persoon met een stressor omgaat. Decennia lang is de stelling gepropageerd, dat migrainepatiënten zulke specifieke persoonlijkheidstrekken bezitten. Wij hebben daarom deze visie empirisch getoetst. Hiertoe hebben we in boven omschreven onderzoek tevens (1) een aantal stressregulerende persoonlijkheidstrekken van de migrainepatiënten

gemeten en ze vergeleken met die van de spanningshoofdpijnpatiënten en die van de controles en (2) de psychologische reactie op de mentale stressor van deze onderzoeksgroepen met elkaar vergeleken. De resultaten duiden niet op het bestaan van een specifieke 'migrainepersoonlijkheid'; ook leveren ze geen duidelijke evidentie voor een specifieke psychologische stressreactie van migrainepatiënten. Ons onderzoek verschaftte daarom geen evidentie voor een etiologische relevantie van deze factoren voor het migrainesyndroom. De resultaten wijzen veeleer op het bestaan van bepaalde persoonlijkheidstrekken, die karakteristiek zijn voor hoofdpijnpatiënten in het algemeen, namelijk de geneigdheid tot het gebruik van bepaalde afweermechanismen en het, in vergelijking met gezonde controles, in mindere mate zoeken van sociale steun bij het omgaan met onplezierige gebeurtenissen. De vraag wordt gesteld, in hoeverre het frequent hebben van hoofdpijn (los van haar oorzaak) op den duur tot het ontwikkelen van deze afweer- en copingstijl kan leiden. Vervolgonderzoek zou zich kunnen richten op de causale richting van het verband tussen het hanteren van een bepaalde psychologische afweer- en copingstijl en het bekend zijn met recidiverende hoofdpijn. Hiertoe is het mogelijk om de correlaties te onderzoeken tussen deze psychologische fenomenen enerzijds en de ziekteduur, de frequentie, de duur en de ernst van de hoofdpijn(aanvallen), anderzijds.

2. Het dagelijkse fysieke functioneren van migrainepatiënten als gevolg van (een) migraine (aanval)

Dit tweede aspect van het migrainesyndroom werd onderzocht door de interictale en ictale dagelijkse activiteiten van migrainepatiënten te meten met behulp van de ambulante accelerometrie. Tevens werd hun hartfrequentie en de volgende subjectieve parameters gemeten: de kwaliteit van de slaap, sedatie, de maximaal haalbare fysieke activiteit en de stemming. Dit onderzoek leverde objectieve evidentie voor een interictale geringere dagelijkse activiteit van migrainepatiënten vergeleken met gezonde controles. Cavallini et al., (1995) concludeerden uit hun onderzoek, dat veel hoofdpijnpatiënten in de interictale perioden gespannen zijn

door de continue dreiging van een aanval. Het is daarom mogelijk, dat het ictale gedrag, gekenmerkt als het is door een beperking van de fysieke activiteit, in de loop der tijd gegeneraliseerd is naar de interictale perioden, ten gevolge van een chronische angst voor een aanval. Zoals vermeld, zijn er geen significante verschillen in hartfrequentie tussen migrainepatiënten en controles gevonden. Wel rapporteerden patiënten echter een hoger niveau van sedatie en een lager niveau van maximaal haalbare fysieke activiteit en van energie (vigour). Deze bevindingen ondersteunen de hierboven genoemde relevantie van een (longitudinale) vervolgstudie naar het causale verband tussen pijnindices (de duur van de ziekte; de frequentie, duur en intensiteit van de pijnaanvallen) en het gebruik van afweer- en copingstijlen. De objectief te meten interictale fysieke activiteit en subjectieve parameters, als het niveau van sedatie, het maximaal haalbare niveau van fysieke activiteit en de stemming, zouden in de vervolgstudie kunnen worden geïncorporeerd.

De resultaten van ons onderzoek leveren ook een rationale voor psychologische interventies, die hierboven genoemde angst voor een aanval verminderen, bij voorkeur in combinatie met een verbetering van het inzicht van de patiënt in zijn of haar afweerstijl en in de wijze van zoeken van sociale steun. Hierdoor zou de invloed van migraine op het interictale gedrag kunnen worden beperkt. Met behulp van technieken voor gedragsmodificatie zou de interventie ook meer direct op het interictale gedrag gericht kunnen worden. Deze psychologische behandelingen zouden dan moeten leiden tot een vermindering van de individuele en collectieve invloed van migraine, d.w.z. tot een verbeterd functioneren in de thuissituatie, op het werk, op school en in andere sociale posities en in een verbeterde seksuele relatie. Onderzoek naar de verbetering van de kwaliteit van leven door psychologische interventies, die zich (direct) richten op de interictale fysieke activiteiten van migrainepatiënten, lijkt hierdoor gerechtvaardigd.

De tweede lijn van ons onderzoek sloot tevens het registreren van de fysieke activiteiten tijdens acute medicamenteuze behandeling van een aanval in. We onderzochten het effect van twee representatieve farmacologische behandelingen van migraine (naratriptan en naproxen) op de dagelijkse activiteiten en op de

klinische symptomen, op de stemming, sedatie en het maximaal haalbare fysieke activiteitsniveau. In zowel de naratriptan als de naproxen conditie trad er in genoemd tijdsinterval een significante verbetering op van de meeste subjectieve maten. De hoofdpijn, de misselijkheid en de foto- en fonofobie verminderden significant, terwijl de stemming en de MHFA een significante verbetering liet zien. Naratriptan bleek significant meer effectief in het reduceren van de hoofdpijn, de misselijkheid en het overgeven. Interessant is, dat in deze eerste zes uren, in beide therapeutische condities geen verandering in de fysieke activiteit van de patiënten optreedt. Kennelijk is er geen sprake van synchroniciteit tussen de beleving van de klinische en andere subjectieve symptomen en hun gedragsequivalenten. Althans niet tijdens de eerste zes uren van de behandeling. Deze constatering stemt overeen met de conceptie van pijn als een multi-dimensioneel verschijnsel, dat ook subjectieve en objectieve gedragscomponenten insluit. Vendrig en Lousberg (1997) vonden geen relatie tussen de pijnscores van chronische pijnpatiënten en hun activiteitsniveau. Fordyce et al., (1984) gewagen van een twijfelachtig verband tussen wat mensen over hun pijn zeggen en wat ze feitelijk doen; Holroyd et al., (1999) concluderen dat pijn en 'disability' twee te scheiden dimensies van de invloed van hoofdpijn zijn, die beide op verschillende wijze en door verschillende therapieën kunnen worden beïnvloed.

De beperking van het uitvoeren van de dagelijkse activiteiten vormt een belangrijk individueel en collectief probleem. Daarom bevelen we aan om in vervolgonderzoek naar de effectiviteit van (niet)medicamenteuze (inter)ictale behandeling van migraine niet alleen de meting van de aan migraine gerelateerde klinische en andere subjectieve fenomenen te includeren, maar ook de objectief te meten fysieke activiteiten. Het beloop van deze variabelen zou gedurende een langer tijdsinterval kunnen worden gevolgd, waardoor de (verschillende) benodigde tijd voor deze parameters om terug te keren op baseline niveau, kan worden vastgesteld. Een dergelijke onderzoeksprocedure zou aanwijzingen kunnen verschaffen voor de verklaring van hun non-synchroniciteit. Bovendien kan het een maat opleveren van de effectiviteit van de verschillende antimigraine middelen in

het opheffen van de klinische, subjectieve en objectieve repercussies van een acute migraine aanval.

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Appendix

Migraine without aura (MO) diagnostic criteria *)

A. At least five headache attacks lasting 4 - 72 hours (untreated or unsuccessfully treated), which has at least two of the four following characteristics:

1. Unilateral location
2. Pulsating quality
3. Moderate or severe intensity (inhibits or prohibits daily activities)
4. Aggravated by walking stairs or similar routine physical activity

B. During headache at least one of the two following symptoms occur:

1. Phonophobia and photophobia
2. Nausea and/or vomiting

Migraine with aura (MA) diagnostic criteria

A. At least two attacks fulfilling with at least three of the following:

1. One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem functions
2. At least one aura symptom develops gradually over more than four minutes, or two or more symptoms occur in succession
3. No aura symptom lasts more than 60 minutes; if more than one aura symptom is present, accepted duration is proportionally increased
4. Headache follows aura with free interval of at least 60 minutes (it may also simultaneously begin with the aura)

B. At least one of the following aura features establishes a diagnosis of migraine with typical aura:

1. Homonymous visual disturbance
2. Unilateral paresthesias and/or numbness
3. Unilateral weakness
4. Aphasia or unclassifiable speech difficulty

*) Headache Classification Committee of The International Headache Society, 1988

Dankwoord
Curriculum Vitae
List of publications

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Curriculum Vitea

Dirk Leendert Stronks werd op 23 juli 1950 geboren te Aalten. Na de middelbare school ging hij in 1966 studeren aan de Pedagogische Academie te Doetinchem. Hierna studeerde hij psychologie aan de Vrije Universiteit te Amsterdam. In 1979 voltooide hij deze studie met het doctoraal examen in de hoofdrichting Klinische Psychologie. Daarna volgde een aanstelling als leraar psychologie, sociologie en statistiek aan de HBO-opleiding Diëtetiek te Groningen. Vanaf 1988 was hij als wetenschappelijk onderzoeker enkele jaren verbonden aan de afdeling Geriatrie en later aan de afdeling Medische Psychologie en Psychotherapie van het Erasmus MC. In 1999 volgde een aanstelling aan de afdeling Psychiatrie. Momenteel werkt hij als medisch psycholoog en statisticus bij het Pijnkenniscentrum van het Erasmus MC.

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