Pain, motion sickness and migraine: effect on symptoms and scalp blood flow

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DECLARATION

I declare that this thesis is my own account of my research and contains as its main content work which has not previously been submitted for a degree at any tertiary education institution

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ABSTRACT

Migraine, a neurovascular disorder, is associated with disturbances in brain stem activity during attacks. Interictal persistence of these disturbances might increase vulnerability to recurrent attacks of migraine. To explore this possibility, effects of motion sickness and pain on migrainous symptoms and extracranial vascular reponses were investigated in 27 migraine sufferers in the headache-free interval, and 23 healthy age/sex matched controls.

Symptoms of migraine and motion sickness are remarkably similar. As both maladies involve reflexes that relay in the brain stem, they most probably share the same neural circuitry. Furthermore, migraineurs are usually susceptible to motion sickness and, conversely, motion sickness-prone individuals commonly experience migraine. Participants in the present study were exposed to optokinetic stimulation (OKS), a well-established way of inducing symptoms of motion sickness in susceptible individuals.

Sensitivity to painful stimulation of the head and hand was also explored. Head pain is a hallmark of a migraine attack and cutaneous allodynia has been observed elsewhere in the body during attacks. The trigeminal nerve is associated with head pain in migraine, and trigeminal activity evokes reflexes that relay in the brain stem. To stimulate the trigeminal nerve, ice was applied to the temple. To stimulate nociceptors elsewhere in the body the participant immersed their fingers and palm in ice-water.

Procedures used in this study were physically stressful and probably psychologically stressful. The impact of stress in relation to the development of

symptomatic and vascular responses, particularly anticipatory stress-responses, was explored.

This research involved one central experiment that consisted of six experimental conditions. On separate occasions participants were exposed to optokinetic stimulation and painful stimulation of the head or limb, individually and in combination.

In migraine sufferers, symptomatic responses were enhanced during all procedures involving OKS and during temple pain after OKS, in the presence of residual motion sickness. During trigeminal stimulation independent of OKS, headache initially developed followed by nausea as the procedure progressed. In contrast, symptoms barely developed in controls during any of the six procedures except for slight dizziness, self-motion and visual-illusion during conditions involving OKS, and slight nausea when the temple was painfully stimulated during OKS and during OKS alone. Trigeminal stimulation during OKS intensified nausea and headache in migraine sufferers compared to during OKS alone or limb pain during OKS. However, the remaining symptomatic ratings were not affected by temple pain during OKS, suggesting a specific association between nausea and head pain. It may be that these cardinal symptoms compound one another during a migraine attack. Enhanced symptomatic responses in migraine sufferers during the headache interval may indicate activation of hypersensitive neural pathways that mediate symptoms of motion sickness or migraine. Migraineurs found procedures generally more unpleasant, and ice-induced pain ratings more intense and unpleasant, than controls, which may further indicate hyperexcitable nociception in this group, or a difference in their criterion of discomfort.

Vascular responses, particularly during OKS alone, and during painful stimulation independent of OKS, were greater in migraine sufferers than in controls. The added stress of painful stimulation during OKS appeared to boost facial blood flow in controls to approach levels obtained in migraine sufferers. Enhanced vasodilatation was observed in migraineurs prior to painful stimulation, presumably due to anticipatory anxiety.

For both groups ipsilateral vascular responses were greater than contralateral responses when the hand was painfully stimulated. During limb pain before OKS asymmetry was minimal in migraine sufferers but more apparent in controls. An enhanced stress response in migraineurs may have drawn ipsilateral and contralateral responses closer together.

The development of symptoms during the procedures of this study provides an insight into how symptoms might develop sequentially in a migraine attack. Once the headache is in motion, nausea and headache may mutually exacerbate one another. In turn, trigemino-vascular responses and stress appear to be associated with the migraine crisis. Given the interactive nature of symptomatic, vascular, and stress responses, it may be more effective to target multiple, rather than individual, symptoms, in prophylactic or acute chemical and psychological interventions.

Publications related to this thesis

Cuomo-Granston, A. (2009) Motion sickness, pain and migraine: effects on symptoms and scalp blood flow. Verlag VDM : Germany.

Cuomo-Granston, A. (2009) Living with migraine. Flourish, in press (due for publication Dec 2009).

Drummond, P.D. and Granston, A. (2003). Facilitation of extracranial vasodilation to limb pain in migraine sufferers, Neurology 61: 60-63.

Drummond P.D. and Granston, A. (2004) Facial pain increases nausea and headache during motion sickness in migraine sufferers. Brain 127: 526-534.

Drummond P.D. and Granston, A. (2005) Painful stimulation of the temple induces nausea, headache and extracranial vasodilatation in migraine sufferers. Cephalalgia 25: 16-22.

Granston, A. and Drummond, P.D. (2002) 14th Migaine Trust Platform presentations, abstracts: The association between nausea and head pain in migraine sufferers. Cephalalgia 22: 570-580, number 7.5, p.578.

Granston, A. and Drummond P.D. (2005) Painful stimulation of the temple during optokinetic stimulation triggers migraine-like attacks in migraine sufferers Cephalalgia 25: 219-224.

Part of this thesis was platform presented at an international conference in London, United Kingdom. Refer to publications related to this thesis, Granston and Drummond (2002), Appendix 14, page 443-444. Slides illustrating the content of this PowerPoint presentation are presented in Appendix 14, pages 459-464. *

Other publications in response to this thesis

Drummond P.D. and Granston, A. (2004). Facial pain increases nausea and headache during motion sickness in migraine sufferers (abstract); In Millson, D.S. and Tepper, S.T., Editors (2005) Abstracts and citations: migraine epidemiology, clinical features and natural history. Headache 45 (4): 399

Drummond, P.D. and Granston, A. (2004). Letters to the editor - Reply to: Conceptual divide between adaptive and pathogenetic phenomena in migraine: nausea and vomiting. Brain 127: E19.

Gupta, V.K. (2004). Letters to the editor – Conceptual divide between adaptive and pathogenic phenomena in migraine: nause and vomiting. . Brain 127: E18.

See Appendix 14, pages 418-464, for copies of publications *

*** Copies not available in the online digital version of this thesis**

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At the commencement of my candidature, I met with my supervisor, Professor Peter Drummond to discuss aspects of this forthcoming research. The pathophysiology of migraine, which in many ways despite the groundbreaking and promising research to date, still remains an enigma. The opportunity to contribute practically toward the knowledge-base in understanding this disease was an exciting challenge, which I eagerly looked forward to starting. I was also daunted at the mere thought of the research journey that lay ahead of me.

However, thanks to Professor Drummond's unfailing and expert guidance, and calming influence during times of pressure, my enthusiasm and excitement never waned. Learning to become a researcher has been the pinnacle of my career to date, and in many ways, now that my thesis has been submitted; I suspect that I will miss the whole researcher-experience terribly.

Professor Drummond is highly regarded internationally across disciplines and is a prolific contributor to the research literature. Consequently I feel privileged to have been under his tutorage, as my association with him has no doubt had a positive impact on my development as a researcher. Apart from being a prominent neuroscientist he is also an adept clinical psychologist and academic. His talents were formally recognized by Murdoch University when he was recently awarded the 'Vice-Chancellor's Excellence in Supervision Award'.

Professor Drummond was always accessible throughout my candidature regardless of how pressured was his timetable. He was consistently focused on the issues at hand, an impeccable critic, communicated his ideas clearly and encouraged lateral thinking. Professor Drummond encouraged me to present findings of this study to international and local audiences. He also encouraged me to contribute sections of my thesis findings for publication in various prestigious journals, which helped me to become increasingly familiar with my results, their interpretation, and how to communicate them orally and to a written publishable standard. From a personal viewpoint, my association with Professor Drummond these past years has instilled in me a desire for the pursuit of excellence, and taught me that a daunting task is only as big as the next manageable step ahead of you.

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No help from these two (Minx and Tim)

CHAPTER 1

INTRODUCTION

Living with migraine (*Maree, 2002: personal account of a chronic migraine sufferer)*

"Migraine has been my ultimate foe, merciless and efficient. It has destroyed my friendships, relationships, spontaneity, career, hobbies, social life, recreation, and my reliability as a person. It has derailed my dreams and goals. It has stolen from me over time – days, months, and now years. It has all but taken my life, not quite. Even when headache-free I live a constant nightmare that no day seems to follow ... in dread of that next attack."

The burden of migraine

Individual and community costs

Migraine is a common, chronic, sometimes progressive, and often incapacitating, neurovascular disorder (Lipton and Bigal, 2005; Goadsby, 2003; Silberstein, 2003). The above extract of a personal account from a chronic migraine sufferer demonstrates the extent to which migraine can disrupt an individual's life. Indeed the personal burden of this disease has been widely acknowledged (Lipton and Bigal, 2005; Holmes, MacGregor and Dodick, 2001). It is also accepted that many headache sufferers live with a fear of the next attack, which restricts their daily lives, and sometimes their ability to meet social commitments (Rasmussen, 2001). Even between attacks many migraine sufferers do not fully recover, reporting reduced general well being and negative repercussions on their quality of life (Linde, 2006; Linde and Dahlöf, 2004). As Jo Liddal, past director of the Migraine Action Association (previously the British Migraine

Association) aptly commented: "Migraine may not be life-threatening but it is certainly quality-of-life-threatening" (MacGregor, 1999, p.1).

Substantial socio-economic costs to the community are also well documented (Bigal, Rapoport, Bordini, Tepper, Sheftell and Speciali, 2003; Lafata, Moon, Leotta, Kolodner, Poisson and Lipton, 2004; Lipton and Bigal, 2005; Holmes, MacGregor and Dodick, 2001). Lost days because of severe headache can lead to both direct (e.g., lost wages, medical costs) and indirect (e.g., reduced productivity) costs. A large community based self-report survey in the United States in 1999 (29,727 respondents) indicated 53% of sufferers found that migraine headache either substantially disrupted routines/activities or required bed rest. Thirty-one percent missed at least 1 day of work or school because of migraine in a 3 month period, and productivity was decreased by about 50% in 51% of respondents (Lipton, Stewart, Diamond, Diamond and Reed, 2001). More recently, another large community-based survey in Norway (38,192 respondents) asked questions about headache (migraine and non-migrainous) and sick leave in the previous year (Fiane, Haugland, Stover, Zwart, Bovim and Hagen, 2006). The incidence of sick leave >8 weeks was greater than 3 times higher among those with headaches - more than 14 days per month (20%), compared to those without headache (6%). Elsewhere, a review of the literature (Celik, Ekuklu, Tokuc and Utku, 2005) confirmed that globally days of work lost because of migraine are substantial, ranging from 3.8 to 5.6 per year for every migraine sufferer. Not surprisingly, the financial cost of reduced productivity associated with migraine is substantial. Additionally, migraineurs have been found to use more medical care services and incur more associated medical costs than non-migraineurs (Edmeads and Mackell, 2002; Hu, Markson, Lipton, Stewart and Berger, 1999). Celik et al. (2005) point out that in the United States alone direct costs associated with migraine are approximately one billion dollars per year.

Furthermore, the persistent strain on interpersonal relationships, disruption to social/recreational activities, and the financial burdens (healthcare costs, lost wages), particularly incurred by chronic migraine sufferers, is also shared by significant others/carers (Liberman and Steiner, 2003). Additionally, they probably share to some degree the sense of helplessness that sufferers experience.

Prevalence

Migraine is the most prevalent of the headache disorders: worldwide, 46% of the adult population experience an active headache disorder, and of those 42% suffer with migraine (Stovner, Hagen, Jensen, Katsarava, Lipton, Scher, Steiner and Zwart, 2007). The World Health Organization ranks headache disorders in general as the 10th most disabling condition in comparison to other illnesses, for both genders, and the 5th most disabling for women (Stovner et al., 2007). Migraine specifically, in comparison to other illnesses, is a common, painful and disabling illness throughout the world, ranked 19th among all causes of years lived with disability (ICHD, 2004; Lipton, Bigal, Amatniek and Stewart, 2004; WHO, 2002, 2004).

The estimated prevalence of migraine across various European populations is variable but all agree with a female preponderance between 15-35% compared to 3-15% of males (Celic, Ekuklu, Tokuc and Utku, 2005; Rasmussen, 1995). American studies concur that migraine is a common disorder with a female predominance (Morillo, Alarcon, Aranaga, Aulet, Chapman, Conterno, Estevez, Garcia-Pedroza, Garrido, Macias-Islas, Monzillo, Nunez, Plascencia, Rodriguez and Takeuchi, 2005; Lipton, Stewart, Diamond, Diamond, and Reed, 2001; Lipton, Stewart and Simon, 1998). The female preponderance may be due to factors related to female hormones (Rasmussen, 1995). The implications of hormonal factors in relation to migraine susceptibility are considered later in this chapter. A population-based survey in the United States conducted in 1999 estimated that the prevalence of migraine was 18.2% among females and 6.5% among males (Lipton et al., 2001). These findings were compared to an identical national survey conducted a decade earlier and it was found that the prevalence and distribution of migraine had remained constant over time, proportionate to the growth of the population. This indicates that migraine is a consistently highly prevalent disorder.

Migraine usually peaks in the twenties or thirties, generally the most demanding years of life when family and career paths are being established, and starts to wane by age 50 (WHO, 2000; Gressor, 1992). Children and adolescents are also vulnerable and, depending on the frequency and severity of attacks, academic and social development may be hindered (Laurell, Larsson, Mattsson, and Eeg-Olofsson, 2006; Karwautz,

Wöber, Lang, Bock, Wagner-Ennsgraber, Vesely, Kienbacher and Wöber-Bingöl, 1999; Lipton, Stewart, Diamond, Diamond and Reed, 2001; Mazzone, Vitiello, Incorpora and Mazzone, 2005; Passchier and Orlebeke, 1985; Riva, Aggio, Vago, Nichelli, Andreucci, Paruta, Arrigo, Pantaleoni and Bulgheroni, 2006; Rossi, Cortinovis, Menegazzo, Menini and Carnelli, 2005; WHO, 2000), and perhaps self-confidence undermined.

The high prevalence and disabling consequences of migraine suggest it is indeed an important target for public health interventions (Lipton et al., 2001).

Other health related concerns

Needless to say, the personal burden of migraine and the toll of the accompanying mental/physical stress may render some individuals increasingly vulnerable to developing various stress related illnesses. Indeed, migraine has been linked with a number of psychiatric disorders including general anxiety, depression, bipolar disorder and social phobia (Dowson and Cady, 2002).

Physical health can also be threatened in cases of migraine-related stroke, with potentially lethal or permanently disabling consequences (Lampl and Marecek, 2006; Tietjen, Al-Qasmi, Gunda and Herial, 2005; Merikangas, Fenton, Cheng, Stolar and Risch, 1997; Buring, Herbert, Romero, Kittross, Cook, Manson, Peto and Hennekens, 1995). Some studies suggest that migraine may account for 10-27% of the probable causes of stroke in those under the age of 40 for both sexes combined (Sacquegna, Andreoli, Baldrati, Lamieri, Guttmann, de Carolis, Di Pasquale, Pinelli, Testa and Lugaresi, 1989; Spaccavento and Solomon, 1984), and up to 30-60% for women younger than 45, particularly those with migraine with aura who smoke or use oral contraceptives (Kurth, 2007; MacClellen, Giles, Cole, Wozniak, Stern, Mitchell and Kittner, 2007; Lampl and Marecek, 2006). The risk of comorbid stroke is clearly increased in migraine sufferers, particularly in certain subgroups.

Consistent with this, Welch, Brandes, Salerno and Brandes (2006) found that C-reactive protein, a sign of oxidative stress, inflammation, and stroke risk, were increased

in migraine sufferers with atypical (e.g., aura with complex features occurring late in the headache phase, marked hemiplegic or aphasic symptoms) and severe attacks. Furthermore, magnetic resonance imaging studies indicate that subclinical posterior circulation stroke, and diffuse white matter lesion loads, increase with regularity of migraine (Lampl and Marecek, 2006). Both types of brain injury: infarct (including subclinical posterior circulation stroke) and white matter lesions, are linked with increased risk of clinical stroke, physical limitations and cognitive impairment, including dementia (Longstreth, Manolio, Arnold, Burke, Bryan, Jungreis, Enright, O'Leary and Freid, 1996). Lampl and Marecek (2006) suggest that migraine may contribute to progressive damage to the brain; hence, it could be viewed as a chronic episodic and sometimes chronic progressive disorder. Evidence certainly suggests that migraine is a chronic episodic disorder that progresses in some individuals. Progression of migraine is characterized by gradual increase in migraine attack frequency, and sometimes constant pain (Bigal and Lipton, 2006; Lipton and Pan, 2004). This state is variously referred to as chronic migraine, a subtype of the chronic daily headaches (Bigal and Lipton, 2006; Silberstein, Lipton and Sliwinski, 1996), malignant migraine, transformed migraine (Lipton and Bigal, 2007) or probable chronic migraine with probable medication overuse (ICDH, 2004). Given the high prevalence of migraine, Lampl and Marecek (2006) thus recognize the importance of confirming whether migraine is indeed a possible risk factor for cerebral infarct or white matter lesions. Additionally, Lampl and Marecek recommend that a major goal of treatment should include preventing the accumulation of brain lesions, in addition to relieving pain and restoring the patient's ability to function (Diamond, Bigal, Silberstein, Loder, Reed and Lipton, 2006; Edwards, 2001).

Migraine has a long history with many questions that remain unanswered

Headache has troubled humankind since ancient times (Zayas, Mainardi, Maggioni and Zanchin, 2006; Rapoport and Edmeads, 2001; MacGregor, 1999). This long-association of headache and the human condition was accordingly encapsulated by John Ruskin Graham, MD, MACP (1909-1990) with his glib comment "Homo Sapiens Erectus has a headache" (cited in Spierings, 2001, p. 910). Headache generally, and migraineous type headache particularly, has been described in ancient literature along with an archaic understanding of head pain and associated treatments. Neolithic ancestors dating from 7000-BC apparently believed evil spirits were responsible for the pain of headache. Treatment included a primitive brain surgery referred to as 'trepanning', which involved removal of circular chunks of the skull thought to release evil spirits, which in turn cured the headache. Surprisingly many survived this operation as shown by bone regrowth around the holes of these skulls.

Migraine has also been mentioned in one of the oldest known medical manuscripts, the Ebers papyrus, discovered at Thebes, Egypt in the 1800's. It was described here as a "sickness of half of the head". Treatment from around 1200-BC involved the application of a ceramic crocodile, with herbs stuffed in the mouth, to the head of the patient which was believed to somehow cure the condition. Historians however, suggest that compression of the temples by the tie and/or the medicinal effect of the herbs may have helped relieve the pain (Lance and Goadsby, 2002; MacGregor, 1999). Clearly, migraine is an old and baffling condition.

The understanding of migraine today is thankfully more sophisticated but nonetheless the pathophysiology of the condition is still not completely understood (Knight, 2005). Current pharmacological treatment of migraine is aimed at relieving the acute attack and in some cases prophylactic medication is also required (Silberstein and Rosenerg, 2000). Non-pharmacological approaches to treatment include trigger avoidance, acupuncture, biofeedback, and stress management strategies, which may involve relaxation/meditation therapy and/or cognitive behaviour therapy (Linde, 2006; Rains, Penzien and Lipchik, 2006). Regular and frequent aerobic exercise has also been

suggested in the management of migraine (Köseoglu, Akboyraz, Soyuer and Ersoy, 2003; Locket and Campbell, 1992).

There is a paucity of treatment aimed at reducing the likelihood of recurring migraine attacks. Perhaps this is because attention to those migraineurs who may require preventive treatment is generally lacking (Diamond et al., 2006). In addition, little evidence is available on the effects of preventive treatments on the impact of migraine with regards to quality of life and activity limitations; whereas outcomes of acute treatments, particularly pharmacological, are more often explored (e.g., Amico, Solari, Usai, Santoro, Bernardoni, Frediani, De Marco, Massetto and Bussone, 2006; Linde, Mellberg and Dahlöf, 2006; Mushet, Miller, Clements, Pait and Gutterman, 1996; Santanello, Polis, Hartmaier, Kramer, Block and Silberstein, 1997; Dasbach, Carides, Gerth, Santanello, Pigeon and Kramer, 2000). If repeated attacks of migraine are to be reliably managed/treated, mechanisms underlying susceptibility to migraine need to be better understood in the first place. Therefore, more research aimed at deciphering mechanisms underlying susceptibility to migraine and associated preventative treatments is required.

Outcomes of treatments are variable in terms of relieving or reducing the frequency of attacks, and not all treatments are entirely harmless, particularly pharmacological interventions where adverse side effects are possible. Furthermore, if migraine headache is misdiagnosed and consequently mismanaged, inappropriate and unnecessary medication is likely to be administered. In turn, the haphazard use of medication may lead to overuse, which can exacerbate and complicate the clinical picture of headache (Rains, Lipchik and Penzien, 2006; Boes and Capobianco, 2005).

Aim of the book

Contemporary research indicates that migraine headache and associated symptoms are directly related to a disturbance in brain stem nuclei (Weiller, May, Limmroth, Jŭptner, Kaube, Schayck, Coenen and Diener, 1995). The present book aims to investigate whether this disturbance persists covertly interictally in migraine sufferers. To investigate this possibility people who suffer with recurring attacks of migraine were exposed to various sensory stimuli during the headache-free interval. Specifically, causal relationships between symptoms of migraine and extracranial vascular reactivity to various stimuli were explored. On separate occasions participants were exposed to optokinetic stimulation and painful stimulation of the head or limb, discretely and in combination.

Of further interest was the impact of stress in relation to the development of symptomatic and vascular responses. Procedures used in this study were physically stressful and most probably psychologically stressful. Hence, evidence of the stress-response, particularly anticipatory stress-responses, was explored.

In the susceptible individual it may be that brain stem nuclei are either hyperexcitable to sensory or trigeminal stimuli, or that neural mechanisms that normally inhibit the development of symptoms are compromised, which may increase vulnerability to attacks. Additionally, as stress is a commonly recognized trigger of migraine (Passchier, 1994; Reynolds and Hovanitz, 2000) it may be that an exaggerated stress-response influences the initiation and the development of attacks. It was hoped that findings might help clarify mechanisms that initiate migraine, and that these insights would assist the development of approaches to reduce susceptibility to recurring attacks of migraine.

Chapter outline

This chapter introduces migraine headache. The condition is defined, and physical and psychological changes that occur in the progression of a migraine attack are explained. The natural life course of migraine is also described. Triggers and risk factors linked with migraine, which may increase vulnerability to the condition, are discussed next. General characteristics that appear to be linked with vulnerability to migraine are described, including a possible genetic predisposition, biochemical and metabolic dysfunction, hormonal cycles, tendency to vestibular and autonomic instability, susceptiblility to motion sickness, and psychological ill-health/personality characteristics. Vascular, sensory and trigeminal responses of migraine sufferers between headaches are also reviewed. Stress, a commonly recognized migraine trigger, is also discussed. Following this, theories explaining mechanisms of a migraine attack are presented. In light of this knowledge, and the recognized characteristics peculiar to individuals vulnerable to migraine, proposed mechanisms that may increase vulnerablity to repeated migraine attacks are considered. This chapter concludes with a general overview of the book, and a list of key assumptions and hypotheses.

Diagnosis

Headache, *per se*, is a common symptom that signals numerous complaints. It may be a secondary symptom to an underlying complaint, e.g., sinusitis, hangover, fatigue, toothache, or illness (including flu, stroke, meningitis). Alternatively, headache may be the primary symptom of a headache disorder. Almost the entire population, 96% according to Dowson and Cady (2002), will experience headache at least some time in

their lives. In fact, MacGregor (1999) claims that fewer than 2% of individuals have never experienced a headache. The bulk of these complaints are primary headaches that resolve without the need of treatment. Only very few are sinister secondary headaches, e.g., those signaling brain tumor or stroke. Most of the headaches that present in primary care settings include migraine, tension-type headache, short, sharp headache, cluster headache, chronic daily headache, and sinus headache and other causes of facial pain (Dowson and Cady, 2002). Clear guidelines for the differential diagnosis of migraine and other headaches is crucial if headache is to be managed efficiently.

The International Headache Society (IHS) originally published standard diagnostic guidelines for migraine and other headache types in 1988 and updated these guidelines in 2002 (ICHD, 2004). The IHS classification system, initiated by Professor Jes Olesen, is a landmark in the scientific study of headaches. Prior to the introduction of these guidelines there was no basis for classifying headaches until the early 1960's. In 1962 the Ad-Hoc Committee of the National Institutes of Health published a glossary of definitions to help classify headache syndromes (Boes and Capobianco, 2005; Göbel, 2001). However, Göbel pointed out that from the start this glossary was not particularly reliable - it was not based on empirical findings and required subjective interpretation. In contrast, the IHS classification is empirically based. Furthermore, it is one of the most frequently cited texts and, since its introduction almost 2 decades ago, has inspired a surge of pathophysiological and epidemiological research into headache disorders. The World Health Organization (WHO), in recognition of the global burden of headache disorders, included the IHS classifications of headaches in its international classification ICD-10NA publication. The ICD-10NA codes and classifications are particularly important in clinical practice as all diseases are uniformly recorded using this system (Göbel, 2001).

Migraine manifests differently between individuals and also sometimes within individuals from attack to attack (Lance, 2000; Lance and Goadsby, 2002; Linde, Mellberg and Dahlöf, 2006; Lipton, Cady, Stewart, Wilks and Hall, 2002). Most migraine sufferers suffer from attacks without aura, one-third experience attacks with aura (Lance, 2000). Elsewhere the estimate of migraineurs with aura is even less, at most, one-fifth of migraine sufferers (Goadsby, 2001). Many of those who suffer attacks

with aura also experience attacks without aura (ICHD, 2004). The ICHD-II diagnostic criteria for migraine attacks with/without aura are presented in Tables 1.1 and 1.2, respectively.

Furthermore, migraine itself is not a homogenous condition, but instead encompasses a group of syndromes with specific aura features or uncommon courses (Evers, Áfra, Frese, Goadsby, Linde, May and Sándor, 2006; Linde, 2006). The ICHD-II diagnostic criteria of subclassifications of migraine and the WHO ICD-10NA codes are presented in Table 1.3.

Table 1.1. ICHD-II diagnostic criteria for migraine with aura

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Typical aura with migraine headache

A. At least two attacks fulfilling criteria B-D
B. Aura consisting of at least one of the following, but no motor weakness:
    1. Fully reversible visual symptoms including positive features (e.g., flickering lights, spots or lines) and/or negative features (i.e., loss of vision)
    2. Fully reversible sensory symptoms including positive features (e.g., pins and needles) and/or negative features (i.e., numbness)
    3. Fully reversible dysphasic speech disturbance

C. At least two of the following:
    1. Homonymous visual symptoms and/or unilateral sensory
    2. At least one aura symptom develops gradually over $\geq$5 min and/or different aura symptoms occur in succession over $\geq$5 min
    3. Each symptom lasts $\geq$5 min and $\leq$60 min

D. Headache fulfilling criteria B-D for migraine without aura begins during the aura or follows aura within 60 min

E. Not attributed to another disorder.

Table 1.2. ICHD-II diagnostic criteria for migraine without aura

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A. At least five attacks fulfilling B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
    1. Unilateral location
    2. Pulsating quality
    3. Moderate or severe pain intensity

D. During headache at least one of the following:
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia

E. Not attributed to another disorder

Table 1.3. ICHD-II diagnostic criteria of subclassifications of migraine and ICD-10NA codes

IHS ICHD-II code	WHO ICD-10NA code	Diagnosis
1.	G43	Migraine
1.1	G43.0	Migraine without aura
1.2	G43.1	Migraine with aura
1.2.1	G43.10	Typical aura with migraine headache
1.2.2	G43.10	Typical aura with non-migraine headache
1.2.3	G43.104	Typical aura without headache
1.2.4	G43.105	Familial hemiplegic migraine (FHM)
1.2.5	G43.105	Sporadic hemiplegic migraine
1.2.6	G43.103	Basilar-type migraine
1.3	G43.82	Childhood periodic syndromes that are commonly precursors of migraine
1.3.1	G43.82	Cyclical vomiting
1.3.2	G43.820	Abdominal migraine
1.3.3	G43.821	Benign paroxysmal vertigo of childhood
1.4	G43.81	Retinal migraine
1.5	G43.3	Complications of migraine
1.5.1	G43.3	Chronic migraine
1.5.2	G43.2	Status migrainosus
1.5.3	G43.3	Persistent aura without infarction
1.5.4	G43.3	Migrainous infarction
1.5.5	G43.3 + G40.x or G41.x[1]	Migraine-triggered seizure
1.6	G43.83	Probable migraine
1.6.1	G43.83	Probable migraine without aura
1.6.2	G43.83	Probable migraine with aura
1.6.5	G43.83	Probable chronic migraine

[1] The additional code specifies the type of seizure

Any individual may experience an isolated migrainous-like headache or even a few in a lifetime (Linde, 2006) but at least 5 lifetime attacks of migraine are required before it is regarded as a pathological disorder and a diagnosis of migraine is given. A cardinal feature of migraine, differentiating it from the majority of other headache syndromes, is prolonged (4-72 hours) often excruitiatingly painful headache. Another hallmark of an attack is nausea; around 90% experience nausea and 75% vomit (Lance and Goadsby, 2000). Nausea may be experienced at any point during the attack, and sometimes preceeds the headache by an hour or more (Lance, 1999; Lance and Goadsby, 2000), so understandably migraines are sometimes referred to as 'sick headaches' (Gressor, 1999; MacGregor, 1999). Dizziness/vertigo (Marano, Marcelli, Di Stasio, Bonuso, Vacca, Manganelli, Marciano and Perretti, 2005; Baloh, 1997; Cutrer and Baloh, 1992), drowsiness, and body temperature changes (fever, chills) are also commonly experienced during a typical attack (Gressor, 1999; Lance and Goadsby, 2000). In addition, intra- and extracranial vasodilatation is sometimes observed during attacks (Lance and Goadsby, 2000).

Clearly, symptomatic and vascular responses during attacks of migraine are pronounced and exposure to sensory stimuli have been found to accentuate responses, particularly headache (Linde, 2006; Linde, Mellberg andDahlöf, 2006). Linde et al. (2006) point out that hypersensitivity has also been demonstrated interictally and during the premonitory phase of an attack, i.e., photo- and phonophobia. Whether symptomatic and vascular responses to sensory stimuli are particularly reactive in migraine sufferers interictally, suggesting neural hypersensitivity which perhaps renders sufferers vulnerable to recurring migraine attacks, is the subject of this book. Specifically, the relationship between symptomatic and vascular changes in individuals vulnerable to migraine, following the activation of brainstem nuclei via stimulation of trigeminal nerve pathways, vestibular pathways, and painful stimulation away from the head, is investigated between headaches.

The natural life history of migraine and progression of a migraine attack

Natural history of migraine/prognosis

Migraine may first appear at any stage of life. However, for most individuals onset of migraine occurs between age 20-30. For some, the first signs of migrainous symptoms develop in childhood. Research suggests that 10-30% of children and adolescents experience weekly or daily headache, with migraine occurring in 3-15% of children (Mazzone et al., 2005). A long-term follow-up study found that 48.6% of adolescent females still had migraine after 6.6 $\pm$ 1.6 years (Kienbacher, Wöber, Zesch, Hafferl-Gattermayer, Posch, Karwautz, Zormann, Berger, Zebenholzer, Konrad and Wöber-Bingöl, 2006). Keinbacher et al. found that poor prognosis was partly related to delayed time between headache onset and first presentation/diagnosis, prompting the question whether early therapeutic intervention in children and adolescents with migraine may have a more favourable effect on the long-term prognosis.

Migrainous symptoms in very young children generally involve nausea, abdominal pain and vomiting, without headache. As the vulnerable child matures headache may accompany the gastrointestinal symptoms. Then at puberty, the headache may be announced by visual symptoms (aura). Most agree that during childhood males are equally as vulnerable to migrainous symptoms as females (Gressor, 1999; Lance and Goadsby, 2000; Lance, 1999; MacGregor, 1999). However, Lipton and Bigal (2005) in a review of the literature found that prior to puberty migraine is actually more common among boys than girls. The reverse is the case at puberty whereby females are predominantly more affected than males (Gressor, 1999; Lance and Goadsby, 2000; Lance, 1999; MacGregor, 1999). MacGregor (1999) points out that boys with childhood migraine are more likely to "grow out of migraine but girls grow into it", often worsening

during the menopause due to erratic oestrogen secretions. For some females (one-sixth), menarche heralds the onset of migraine attacks (Zacur, 2006). By adulthood three times as many females suffer migraine as males (Kemper, 2006). The influence of hormonal factors in relation to susceptibility to develop migraine is discussed later in this chapter (pages 46-47).

Prognostically, most individuals diagnosed with migraine will continue to suffer attacks throughout life to some degree. Bille (1981) found that 60% of a group of 73 children (age 7-13) with migraine went into remission by adolescence, but attacks started again in one-third of the remitters. When followed up some years later, Bille found that 60% of this original group of affected children were still suffering migraine attacks at age 30. A series of longitudinal studies related to Bille's 1981 study (including Bille, 1997) monitiored these migraine sufferers over 40 years. Bille found that the majority of sufferers (51%) still experienced migraine at the 40 year follow-up, then aged between 47-53 (Bille, 1997). Twenty-nine percent of these individuals suffered repeated attacks, at least annually without remission, 22% had migraine-free periods from 2 years up to 10 years on average. Forty-six percent were free of migraine, 23% free since puberty. The prognosis was poorer for females.

The frequency and intensity of migraine attacks in most cases wanes from around age 50 (Gressor, 1999; Lance, 1999). In one particular study (Whitty and Hockaday, 1968) occasional attacks were found to persist in 50% of adult migraine patients at 65 years of age. It was pointed out by Martins, Bordini, Bigal and Speciali (2006) that the incidence of migraine in the elderly may in actual fact be under recognized as symptoms in this cohort are less typical; consequently many seniors may be misdiagnosed.

These studies suggest that most individuals vulnerable to migraine can expect, following onset, to suffer with recurring attacks throughout life in differing forms and to differing degrees.

Natural progression of a migraine attack

A migraine attack involves a cascade of complex neurological changes that frequently start before and continue after the symptom of headache (Cady, Schreiber, Farmer and Sheftell, 2002). Blau in the 1990's established the terminology of the various stages of a migraine attack, identifying five distinct stages: the premonitory phase, aura, headache, resolution and postdrome - also sometimes referred to as recovery (Blau, 1992). Sometimes the resolution phase of an attack is not recognized as a phase in itself but is considered as the transition or bridge between the headache phase and postdrome of the attack (Linde, 2006; Griffin, Ruggiero, Lipton, Silberstein, Tvedskov, Olesen, Altman, Goadsby and Macrae, 2003; Quintela, Castillo, Muñoz and Pascual, 2006). Stages are fairly methodical but may vary for each migraine sufferer. Some phases may not necessarily occur and there is no distinct onset or end of each stage, apart from the aura. Commonly experienced symptoms during the progression of a complete/typical migraine attack are shown in figure 1.1. Figure 1.2 shows the average duration of each phase of a migraine attack.

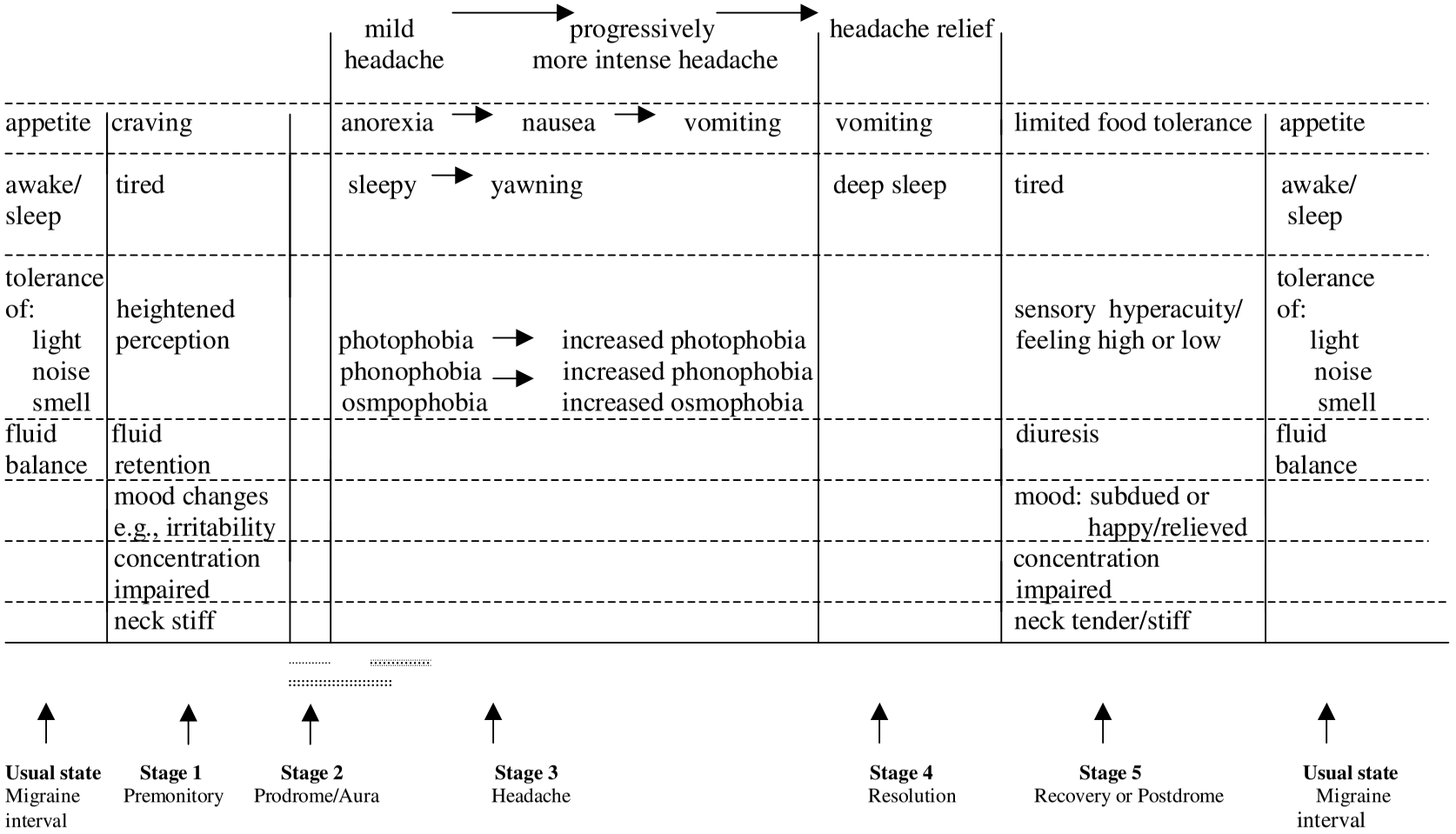


Figure 1.1. Common symptoms during the progression of a complete/typical migraine attack (Adapted from Blau, 1991,1992; Linde et al, 2006 and Quintela et al., 2006). Aura in relation to headache: ..... just before headache; ..... just before or simultaneously with headache; ..... after onset of headache (rarer) (Linde, 2006; Lance and Goadsby, 2000).

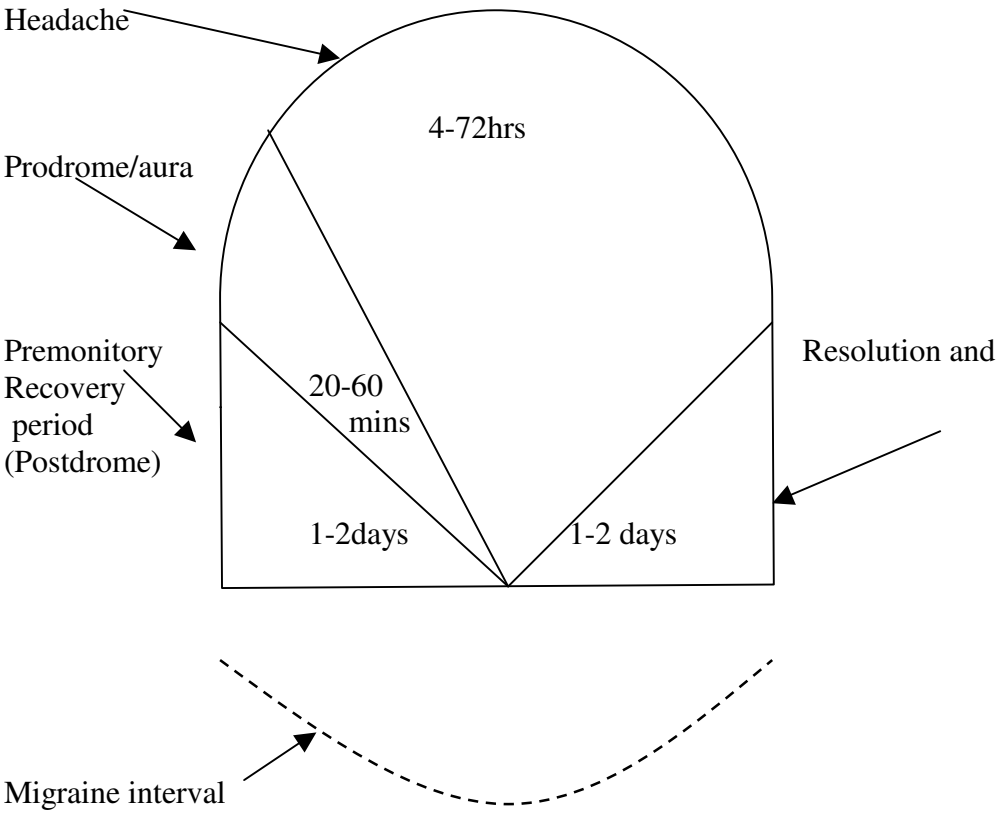


Figure 1.2. Average duration of each phase of a migraine attack (Adapted from ICHD, 2004; MacGregor, 1999; Lance and Goadsby, 2000)

The average duration of the headache phase of a migraine attack is variable (Stewart, Shechter and Lipton, 1994). The IHS estimate a migraine attack may last anywhere between 4-72 hours (see Table 1.2). However, in a review of the literature Stewart et al. found that the average duration of an attack varied depending on whether participants were IHS diagnostically categorized with migraine or were less strictly categorized. Studies based on IHS criteria indicated that the median duration of attacks ranged from 9-24 hours. In contrast, the usual duration of migraine headache tended to be shorter (<4 hours) in studies that had less strict diagnostic criteria that measured younger sufferers, particularly children and men.

The interval between attacks varies for each individual depending on the frequency of their attacks. Stewart et al. (1994) reviewed a number of studies measuring the frequency of migraine attacks. Comparing data between studies was

difficult as categories used to report frequency of attacks were variable, e.g., several per month vs one per month, <5-10 per year vs 0-52 per year. However, Stewart et al estimated, from studies where categories were mutually exclusive, the median number of attacks per month ranged between 0.4 per month to 1.5 per month. The median attack rate was greater for females than for males.

Dahlem and Podoll (2007) point out that the migraine interval is not seen as a phase itself. However, as cortical excitability has been observed interictally, suggesting migraine may be secondary to a genetic predisposition, the migraine interval should also be recognized as a distinct phase. This book further explores the possibility of an underlying persistent systemic vulnerablility to migraine.

Premonitory period

Most migraine sufferers experience premonitory symptoms (Amery, Waelkens and Vandenbergh, 1986; Dowson and Cady, 2002; Linde, 2006; Schoonman, Evers, Terwindt, van Dijk and Ferrari, 2006). Griffen et al. (2003) demonstrated that migraineurs, using an electronic diary system to record premonitory symptoms, successfully predicted the impending migraine headache with up to 72% accuracy. Dahlöf and Linde (2001) similarly found that patients were able to predict migraine headache from premonitory symptoms hours to days beforehand. Some premonitory symptoms, e.g., food cravings, heightened sensory acuity, and muscle tension, may be mistaken for migraine triggers. These misconceptions are probably, in part at least, a conditioned association due to the close proximity of the symptom to the headache phase of the attack. In reality exposure to supposed triggers does not always result in an attack. For some individuals certain triggers may play a role in the development of attacks but in general there is little evidence to support the claim that trigger factors, particularly foods, induce migraine. By and large research indicates that headache frequency is not different between those on restricted or normal diets (Dowson and Cady, 2002; Lance, 1999; MacGregor, 1999; Medina and Diamond, 1978). Trigger factors associated with migraine are reviewed later in this chapter (pages 62-69). In

fact most migraine attacks occur spontaneously. Therefore, premonitory symptoms are more likely part of the attack rather than triggers of the attack (Dowson and Cady, 2002).

Quintel et al. (2006) found that 83% of migraine sufferers reported experiencing premonitory symptoms, particularly anxiety, phono-/photophobia, irritability, unhappiness, yawning and concentration difficulties. Griffen et al. (2003) similarly demonstrated that migraineurs reported warning features prior to migraine headache including feeling weary (72%), experiencing impaired concentration (51%), neck stiffness (50%) photophobia (49%), phonophobia (38%), intolerance/irritablility (39%), yawning (28%) and feeling emotional (24%). Quintel et al. (2006) did not give participants the opportunity to report on the presence of muscular or neck tension/stiffness prior to an attack, which obviously accounted for the absence of this dimension as a potential premonitory symptom in their study.

Yawning can precede migraine or follow the attack, sometimes for hours (Drummond and Lance, 1984; Rasmussen and Olesen, 1992) and may well be related to tiredness also commonly reported during the premonitory period. Yawning is a motor response coordinated in the brainstem that generally signifies drowsiness and fatigue, but can also signal hunger or boredom (Argiolas, Melis and Gessa, 1987). Yawning in the premonitory phase of a migraine attack has been linked to dopamine release possibly involving brain stem nuclei (Griffen et al., 2003; Jacome, 2001). Interestingly, Jacome (2001) presented 3 case studies of migraine sufferers with persistent, isolated yawning in the absence of drowsiness prior to migraine headache. Perhaps the yawning in these cases was related to premonitory symptoms of hunger/craving, indicating hypothalamic disturbance (Waxman, 2003).

During the headache phase of an attack, drowsiness develops further, culminating in the urge to sleep (Jacome, 2001). Sleep and wakefulness, and degrees of tiredness/drowsiness between these levels of alertness, are regulated by reticular formation structures in the hypothalamus and brain stem. Nerve cells in the reticular formation of the pons begin to discharge just before sleep (Waxman, 2003).

Clearly, a number of cognitive and physical prodromal symptoms are experienced, suggesting that neurological changes start before the headache, perhaps mediated via hypothalamic and brain stem structures. Furthermore, as many prodromal symptoms continue throughout all three phases of a migraine attack (see figure 1.1), it appears that ongoing activity in these subcortical centers is somehow

involved in migraine. Therefore, headache is just one feature of the entire attack. These findings perhaps implicate migraine as an intermittent or episodic dysfunction of trigeminovascular regulation (Griffen et al., 2006), most likely mediated via brain stem structures (Weiller et al., 1995). In any case, prodromal symptoms are generally believed to arise from hypothalamic disturbance (Cady et al., 2002; Lance and Goadsby, 2000; MacGregor, 1999). The gradual development of prodromal symptoms most probably reflects neurochemical disruption (Dowson and Cady, 2002), as Lance and Goadsby (2000) propose, involving monoaminergic transmission in the hypothalamus culminating in migraine headache with/without aura. Cady et al. (2002) suggest that diffuse, non-specific alterations of supratentorial brain activity during the premonitory phase may underlie subsequent neural changes at the level of the brain stem.

The link between the prodromal and headache phases of a migraine attack may, in turn, have therapeutic potential for intervention in the management of migraine in the prodromal phase (Griffen et al., 2003). Most migraine sufferers, however, regard the headache phase as the worst feature of the attack (Linde et al., 2006). Hence, intervention, whether acute or preventative, is primarily focused on treating or diverting the headache phase (Griffen, 2003). In particular, pharmacological management of migraine involves treating the acute headache (medication may extend for days) or prophylactic daily treatment is taken. In either case, treatment does not always deflect attacks.

However, the frequency of attacks including premonitory symptoms may decrease in individuals on prophylactic anti-migraine medications. Also, in some cases premonitory symptoms following an attack have been found to be less prominent in those on preventatives. These findings imply that prophylactic medication not only reduces the headache phase of an attack but can also reduce the CNS activation occurring before the headache phase (Quintela et al., 2006).

Early adminstration of medication, preferably before the headache starts, is a key factor in migraine prevention (Waelkens, 1984). Griffen (2003) suggests that pre-emptive treatment during the premonitory period, at the brink of the headache phase, may not only more efficiently control the attack but also limit the amount of medication required. Pradel, Subedi, Varghese, Mullins and Weis (2005) confirm that early headache response/relief to eletriptan and sumatriptan in the acute treatment of migraine (by 0.5 hours) was associated with more rapid return to functioning

compared with patients who did not attain a headache response at 0.5 hours. However, as Linde et al. (2006) demonstrated, regardless of whether or not the acute attack was treated with various anti-migraine medications including sumatriptan, recurrence of headache was common (at least 1 in 3 attacks), necessitating re-medicating to manage symptoms.

It is noteworthy that 28% of attacks are not preceded by premonitory symptoms (Griffen, 2003), so it appears that the nervous system sometimes recovers from the physiological process of migraine before the development of headache (Cady et al., 2002). In these instances pre-emptive medication may therefore be unnecessary.

Alternatively, it may be helpful to intervene prior to the premonitory phase as neurophysiological abnormalities have been observed interically (Judit, Sándor. and Schoenen, 2000; Evers, Quibeldey, Grotemeyer, Suhr and Husstedt, 1999). Electrophysiological studies measuring event-related potentials have demonstrated gradual reduction of cognitive habituation during the migraine interval, which abruptly normalizes on the first day of the attack, and is inversely related to levels of platelet serotonin (Evers et al., 1999). Other studies have shown normalization of visual and auditory evoked potentials just before and during migraine attacks in contrast to increasingly depressed interictal responses (Judit et al., 2000). The interictal abnormalities of cortical hyperexcitability demonstrated in these studies may be a neurophysiological sign of an impending attack and the increasing vulnerablity of the migrainous brain to precipitating stimuli (Griffen et al., 2003). As most migraine attacks occur spontaneously (Dowson and Cady, 2002), perhaps that 'next attack' is a time-bomb waiting to happen in a vulnerable system. It may be relevant to consider the premonitory phase as actually the earliest part of the entire attack, rather than a distinct phase in itself; headache would then represent the pinnacle of the temporal course of the attack. This being the case, it may be wiser to aim intervention at the migraine interval; hence, suppressing the premonitory phase altogether, before this earliest part of the attack is in motion.

The hypothalamus and brainstem may be involved in the generation of premonitory symptoms in migraine attacks (Cady et al., 2002; Lance and Goadsby, 2000; MacGregor, 1999) but whether these areas, particularly the hypothalamus, should be targeted in the development of prophylactic drug treatment, needs to be carefully considered. The hypothalamus is the chief region for the control and regulation of numerous bodily functions including endocrinal, cardiovascular,

respiratory, temperature, appetite and thirst. The hypothalamus also acts as a mediator of stressful, emotional and environmental influences on endocrine glands including the release of pituitary hormones. Hypothalamic mechanisms are complex, specialized and often interrelated (Venes, 2001; Bray et al., 1999). Hence, attempts to chemically manipulate this part of the brain may be problematic, bearing the risk of interfering with bodily homeostasis.

Prodrome/aura

Aura typically precedes the headache phase of an attack but can also occur simultaneously with the headache. In rare cases aura may appear hours or days after the onset of headache (Goadsby, 2001; Russell and Olesen, 1996). Many who experience migraine with aura commonly have attacks without aura but only a few patients have aura exclusively without headache (ICHD II, 2004). Migraine aura involves the gradual development of reversible neurological disturbances, e.g., visual (99% of auras), sensory (31% of auras), speech (18% of auras), and motor (6% of auras), discretely or in combination (Russell and Olesen, 1996). Symptoms of aura can take around 5-20 minutes to develop and can last up to 1 hour (Goadsby, 2001; Linde, 2006). There is generally an interval between the resolution of the aura and the onset of headache of up to 1 hour, in which disturbances similar to premonitory symptoms may be experienced, e.g., alterations of mood, speech, or a sense of detachment from the environment (MacGregor, 1999).

Aura symptoms can arise from anywhere in the cerebral cortex or brain stem (MacGregor, 1999). However, as visual symptoms are commonly experienced, the migraine aura is generally localized in the visual cortex of the occipital lobe (Lance and Goadsby, 2000). During the aura a transient oligemia spreads across the cortex (Lauritzen, 1994; Olesen, Larsen and Lauritzen, 1981). The underlying mechanism of the migraine aura is thought to be cortical spreading depression (CSD) as aura symptoms, particularly visual hallucinations, develop at a similar pace to the cortical spreading depression (Lauritzen, 1994; Russell and Olesen, 1996).

It has been suggested that the aura of migraine somehow generates the complete attack, particularly the component of pain (Goadsby, 2001). Goadsby explored this

premise, pointing out, that as only the minority of migraineurs experience aura, it seems unlikely that aura can account for headache in the majority of sufferers. In addition, aura does not necessarily precede an attack but can appear well after headache is established. Those convinced that aura may underly head pain suggest that 'clinically silent aura' may occur in migraine sufferers without aura (Goadsby, 2001; Ramadan and Welch, 1995). However, in attacks with aura in the absence of headache, implying that aura is independent of pain, the possiblility of a clinically silent aura underlying headache is challenged (Goadsby, 2001). Or, as Cady et al. (2002) suggest, as with the premonitory symptoms appearing independent of headache, it may be that the nervous system sometimes recuperates or aborts from the physiological process of migraine before the development of headache.

In an attempt to clarify the link between CSD and nociceptive activity, Ebersberger, Schaible, Averbeck and Richter (2001) recorded neuronal activity in anesthetized rats, from secondary sensory neurons in the trigeminal nucleus caudalis with input from the meninges and tested whether nociceptive neurons at this location could be activated as a consequence of cortical spreading depression. CSD was induced by the application of potassium chloride to the dura mater at levels normally seen during CSD. Plasma extravasation in the dura mater as a consequence of CSD was also explored. Ebersberger's findings suggest that CSD did not initiate headache (nociception) via neurogenic inflammation, at least in deeply located neurons of the trigeminal nucleus. Specifically, cortical spreading depression did not evoke plasma extravasation, and potassium levels seen during CSD did not alter the release of calcitonin gene-related peptide and prostaglandin E_2 from the dura.

In contrast to Ebersberger's findings, Supornsilpchai, Sanguanrangsirikul, Maneesri and Srikiatkhachorn (2006) discovered that CSD was indeed related to increased trigeminal nociceptive discharge. Specifically, serotonin depletion in rats enhanced CSD-induced trigeminal nociceptive discharge, cortical excitability increased, and trigeminal niociceptive sensitivity was enhanced. CSD was induced by the topical application of potassium chloride on the parietal cortex of anesthetized rats and serotonin depletion was achieved via administration of para-chlorophenylalanine, a tryptophan hydroxylase inhibitor. Cortical activity was monitored by electrocorticography. Trigeminal nociceptive activity was determined from the examination of concentrations of Fos-IR in various sites of the trigeminal nucleus

caudalis, the cervical spinal cord and from the caudal medulla. The concentrations of Fos-IR were greater in the low 5-HT group than in control rats.

According to Supornsilpchai et al., the effects of serotonin depletion on the development of CSD and trigeminal nociceptive activity has not previously been studied. On the other hand, it is widely accepted that pain modulation in a migraine attack is associated with low platelet/plasma serotonin levels (Ferrari, Odink, Tapparelli, van Kempen, Pennings and Bruyn, 1989; Lance and Goadsby, 2000; MacGregor, 1999). Other behaviours (e.g., sleep, feeding) are also linked to altered serotonin levels (Supornsilpchai et al., 2006). Supornsilpchai's recent novel findings shed light on the role that serotonin may play in the aura stage of a migraine attack which, in turn, may help to clarify the relationship between aura and head pain in migraine.

However, the literature generally asserts that CSD, or the aura of migraine, is not necessarily linked to trigeminovascular nociceptive activation (Goadsby, 2001). Instead, migraine aura and trigeminovascular nociceptive activity are more likely parallel processes (Goadsby, 2001; Silberstein, 1994). The pain of migraine may be more to do with 'the abnormal perception of the normal than the activation of nociceptive pathways in the classical way that pain is generated' (Goadsby, 2001, p.5) (e.g., photophobia is the exaggeration of normal light and phonophobia the exaggeration of normal sound, by the brain). Migraine may, in effect, be 'an episodic disorder of sensory sensitivity whose basic understanding and generation will be found in the brain and whose pathophysiological behaviour will not respect classical pain physiology' (Goadsby, 2001, p. 5.). Indeed, electrophysiological studies using evoked and event-related potentials demonstrate lack of habituation interictally, which normalizes during the headache stage of the attack (Gantenbein and Sándor, 2006; Evers et al., 1999; Judit et al., 2000; Wang and Schoenen, 1998), implying that abnormal cortical activity is ongoing.

It is clearly undecided whether CSD, the well-acknowledged neuronal process underlying visual aura, is required for migraine headache to develop (Wolthausen, Sternberg, Gerloff and May, 2009). Interestingly, findings from a recent study conducted by Wolthausen et al. may help resolve this intellectual stalemate. Wolthausen et al. treated 3 patients suffering migraine with (visual) aura with flunarize or topiramate for 4 months. Aura symptoms resolved completely in each case whereas headache persisted. For 1 patient, attack frequency increased. In all

patients aura returned once treatment ceased. Findings indicated that for these individuals at least, migraine headache developed without aura and presumably without CSD (the neurophysiological correlate of visual aura) – whether silent or not.

The Wolthausen group proposed that CSD, which involves cortical neuronal depolarization waves, single-handedly may not be prerequisite for migraine headache to develop, but instead CSD-related processes, occurring in isolation or together, could be to blame. CSD-related processes include haemodynamic changes, which involve the spread of vasodilatation along arterioles extending beyond CSD areas. Extensive intercellular changes are also associated with CSD involving astrocyte calcium waves associated with the release of neuromodulators of pain transmission. Wolthausen et al. suggest that these associated processes of CSD - haemodynamic changes and astrocyte calcium waves - rather than CSD itself, more likely determine whether headache develops together with aura or if aura develops in isolation of headache. With this in mind Wolthausen et al. speculated that cortical neuronal depolarization waves might not develop in migraine without aura, whereas aura without headache may be due to isolated cortical neuronal waves. However, all CSD-related processes may be involved in migraine with aura.

If this is the case it may shed light on why some drugs, as seen in Wolthausen's study, inhibit CSD without relieving headache (Wolthausen et al., 2009). Wolthausen recommends that future research exploring CSD-like phenomena in migraine without aura should investigate attacks as early as possible to avoid missing sometimes short-lasting early cortical propagating activity, to confirm or reject results. This may clarify whether a link does indeed exist between aura (silent or not) and the headache of migraine. However, if migraine with aura and aura without headache are derived from the interplay of CSD-related neural activity (Wolthausen et al., 2009), a neurophysiological relationship between aura (CSD) and headache might very well exist.

On the other hand aura may purely be part of the migraine process but is not necessarily linked to the pain of the condition. Headache sometimes follows, or is concomitant with aura, but is not necessarily part of the episodic-course of the attack.

Interestingly, Cady et al. (2002) challenged the view that aura is soley linked to migraine headache in the first place, which may have implications for early detection, diagnosis and management of migraine. In particular, when mild headache follows aura in the absence of associated migrainous symptoms (see Figure 1.1), the actual

headache resembles tension type headache rather than migraine headache (ICDH II, 2004). Also, curiously, aura has been described prior to the onset of cluster headache (Silberstein, Niknam, Rozen and Young, 2000). Cady et al. (2002) advise that atypical observations with regard to aura may require further investigation and revision. Nevertheless, these observations may indicate that primary headaches are more closely linked than otherwise supposed. Cady et al. proposed a "convergence hypothesis" of primary headaches, in contrast to the distinct diagnostic headache syndromes endorsed by the IHS, particularly with respect to a continuum for tension-type headache to migrainous headache to migraine headache. Furthermore, sinus headaches sometimes evolve to become migraine, suggesting that this headache syndrome may also be more closely associated that assumed. In an earlier study Drummond (1985) explored precipating, aggravating and relieving factors in different categories of headache, and similar to Cady et al. (2002), concluded that there may be a continuum between migraine, tension-vascular and tension headache. However, Drummond found that cluster headache emerged as a distinct entity with its own etiology.

Headache and Resolution

The first indication of migraine headache is typically a mild, dull, diffuse ache (Dowson and Cady, 2002; Lance and Goadsby, 2000; Lance, 2000; MacGregor, 1999). In about two-thirds of sufferers the pain is felt unilaterally and for the remainder, bilaterally. Pain may initially be felt deep behind the eye or can involve the frontotemporal region of the head, sometimes radiating to the back of the head and upper neck. Alternatively, the pain may begin at the occiput and/or upper neck, and radiate forward, developing into a band of pain surrounding the forehead and neck. In a few sufferers the pain is felt in the lower part of the face, typically unilaterally, involving the nostril, cheek and jaw/teeth, i.e., lower half head migraine, facial migraine (Lance and Goadsby, 2000).

The anatomical location of pain during migraine headache may indicate how pain is generated neurally in an attack. Neck pain in particular is a common feature of migraine so may be an important clue (Kaniecke, 2004). Kaniecke found that

neck pain, within an hour of the attack, was reported as frequently as was nausea or phono/photophobia (75%). Neck pain late in an attack, after headache has developed, may indicate central sensitization and cutaneous allodynia (Burstein, Cutre and Yarnitsky, 2000). It is less clear what the neck pain indicates earlier on in an attack. Kaniecke explored early and late onset of neck pain in relation to headache in an attack. Treating an attack with triptans at the first sign of neck pain in 50 sufferers who experienced neck pain first then headache, resulted in a better response rate than treating an attack when neck pain developed after headache in another 50 sufferers. Kaniecke suggested that early neck pain may represent referred pain, a trigger or premonitory symptoms. Perhaps treating the attack at the first sign of neck pain rather than headache (Kaniecke, 2004) aborts the migraine process before the sensitization of peripheral trigeminovascular neurons associated with headache (Burstein, 2004).

Within hours the initial dull headache intensifies to a throbbing quality of moderate to severe intensity (Lance and Goadsby, 2000). For some the pain has a different quality, in particular it is described as pressing or tightening (Kaniecke, 2004; Olesen, 1978). A state of constant pain may ensue, or alternatively pain may fluctuate between moderate to severe until the headache eventually resolves, in most cases, following sleep or vomiting (Blau, 1991, 1992; Lance and Goadsby, 2000; Linde et al., 2006; Olesen, 1978 and Quintela et al., 2006). Linde et al. (2006) found that the time of vomiting in relation to pain intensity influenced whether or not headache improved followed vomiting. When vomiting occurred before headache reached maximum intensity, improvement in headache followed. However, if vomiting appeared at the peak of pain intensity, headache did not necessarily decrease.

Migraine headache can manifest at any time of the day or night but its debut is commonly experienced as a mild headache on awakening (Linde, 2006; Linde et al., 2006). Sometimes the sufferer may awaken with a full-blown attack (see Table 1.2). In these cases the characteristic introductory mild head pain may have developed and progressed before the sufferer awakens (Olesen, 1978). Perhaps the premonitory and aura phases of the attack similarly develop unnoticed prior to awakening for some sufferers.

Symptoms typical of migraine headache (refer to Table 1.2) vary widely between sufferers, and even within sufferers from one attack to another (Linde et al., 2006).

However, in most cases symptoms other than headache progressively appear as head pain worsens. In turn, the headache may then become throbbing in quality as associated symptoms intensify (Olesen, 1978). More recently, Linde et al. (2006) charted the natural course of migraine attacks, treated and untreated. Linde et al. analysed data based on the hourly self-reports of 30 migraine sufferers during attacks, using a 100-point visual analogue scale. Despite inter- and intra-individual variability during attacks, or whether or not treatment was administered, symptoms of each attack generally followed the same temporal course – albeit with moderate variations. Acute medication, although effective, by and large only temporarily influenced the course of the attack. Headache recurred within 24 hours at least once in three attacks in 78% of sufferers, irrespective of whether attacks were treated with rizatriptan or left untreated. Usually a synchronized time-intensity course of phono/photophobia in proportion to headache intensity was observed. Compatible time-intensity courses between phono/photophobia and nausea were also seen. However, sometimes phono/photophobia did not develop at any stage, despite severe pain and nausea. Furthermore, nausea was sometimes absent despite severe pain and phono/photophobia. These observations demonstrate that IHS criteria for migraine are not always satisfied in each attack, particularly if the attack is treated early (Linde et al., 2006).

When typical features of attacks such as nausea or phono/photophobia appear before the pain, the notion that symptoms of migraine follows a predictable temporal course with head pain as the forerunner, is further challenged. Under these circumstances it appears that the attack as such may have started in the premonitory phase, implying that the driving force of the attack may take place in the hypothalamus or cerebral cortex rather than, as generally supposed, the trigeminal-somatosensory system (Griffen et al., 2003; Kelman, 2004; Schoonman, Evers, van Dijik and Ferrari, 2003).

This book is particularly interested in teasing-out causal relationships between symptoms of migraine. Specifically, symptoms normally experienced in a migraine attack were evoked in migraine sufferers interictally, in a sense simulating an attack. It was anticipated that experimentally controlled observations during the headache-free interval, of symptoms usually seen during an attack, may help clarify the contribution of a vulnerable nervous system in the manifestation of an attack; hence, providing further insights into understanding the pathophysiology of migraine.

Postdrome/Recovery

The postdrome refers to the period of symptoms experienced directly following the acute headache of a migraine attack, affecting some 68-94% of migraineurs (Blau, 1991; Kelman, 2005; Quintela et al., 2006). Symptoms commonly experienced include physical/mental tiredness, concentration difficulties, low-grade headache/head tenderness, and subdued or depressed mood, but a few individuals report feeling euphoria or relief. Gastrointestinal symptoms (e.g., anorexia), sensory hyperacuity (e.g., phono/photophobia) and neck pain/stiffness are occasionally reported. Symptoms generally last for around 24 hours but occasionally exhaustion and lethargy will linger for several days. Postdrome symptoms are more likely to occur following severe or more typical full-blown migraine attacks, i.e., those involving aura, headache, nausea, photo/phonophobia (Blau, 1991; Kelman, 2005; Quintela et al., 2006).

Curiously, pro- and postdrome symptoms affect more individuals, and last longer, than do aura symptoms, yet notably less attention has been paid to the early and late stages of the attack compared to the aura in terms of research (Blau, 1991; Quintela et al., 2006). This may be because the aura is so spectacular and, although debated, has been assumed to be the driving force of the entire attack (Goadsby, 2001). The dearth of attention given to the pro- and postdrome may also be because each of these phenomena is overshadowed by the headache phase of the attack, generally regarded as the worst feature of the condition (Linde et al., 2006).

Marginally more attention has been given to the prodrome than the postdrome, possibly because premonitory symptoms signal an unwelcome impending attack, so need to be taken seriously. On the other hand, the postdrome, despite uncomfortable and sometimes disabling symptoms, remains almost unstudied (Kelman, 2005; Quintela et al., 2006). It has been suggested that postdromal symptoms are merely after effects of the main attack, e.g., medications taken, extra time spent in bed, lack of food (Blau, 1991). However, Blau points out that analgesics typically do not have such prolonged effects and not all patients miss meals or remain in bed during attacks. Alternatively, the postdrome may be welcomed as a 'relative calm after the headache-storm', hence could be overlooked in terms of research as being somehow less

important than the acute headache. However, Selby (sited in Blau, 1991) referred to the postdrome as "the third act in the drama" of migraine episodes - an integral part of the condition. As headache recurrence is common within the first 24 hours following the acute headache (Linde et al., 2006), implying continued activation or disinhibition of neural pathways during the postdrome, the postdrome might indeed be considered part of the one process in the production of migraine headache. Therefore, the postdrome probably warrants as much attention as that given to the more prominent headache phase of the condition.

Consistent with the notion that the postdrome is an integral part of the migraine process, Shibata, Osawa and Iwata (1998) found abnormal visual evoked potentials to pattern reversals for several days after migraine attacks in migraineurs with aura and migraine without headache, indicating that hyperexcitability in visual pathways persists beyond the aura/headache phase of an attack. This abnormal electrophysiological dysfunction was found to gradually decrease but continued to some extent interictally, implying constant neural inhibitory deficits, which in turn may leave the individual vulnerable to the next attack.

The range of symptoms during the postdrome suggests that the entire brain is involved in the aftermath of a migraine attack (Kelman, 2005; Blau, 1991). Furthermore, given the striking similarity between symptoms of the pro- and postdrome, similar neural pathways or mechanisms may be common in the manifestation of both. Kelman (2005) described the pro- and postdrome as separate parts of the one process, interrupted or camouflaged by headache and associated symptoms. Perhaps then the driving force of the headache starts with generalized neural activity as seen in the prodrome stage of the attack. In turn, headache develops following subsequent trigeminovascular system involvement. Then, as Blau (1991) suggests, as the headache resolves postdromal symptoms may represent the slow decline of the migraine process involving the whole brain and associated abnormal neurotransmission or neural metabolic disturbances (Blau, 1991).

Headache interval

Abnormal brain activity has been detected in migraine sufferers during the interictal period (Gantenbein and Sándor, 2006; Aurora, Cao, Bowyer and Welch, 1999; Auror, Ahmad, Welch, Bhardhwaj and Ramadan, 1998; Wray, Mijovic-Prelec and Kosslyn, 1995; Dahlem and Podoll, 2007; Evers, Quibeldey, Grotemeyer, Suhr and Husstedt, 1999; Grosser, Oelkers, Hummei, Geisslinger, Brune, Kobal and Lőtsch, 2000; Judit, Sándor and Schoenen, 2000; Schoenen, 1996; Siniatchkin, Gerber, Kropp, Voznesenskaya and Vein, 2000; Wang and Schoenen, 1998). The abrupt normalization of interictal lack of habituation observed during an attack, using evoked and event-related potentials, suggests a possible role of increasing energy reserves in attack generation (Gantenbein and Sándor, 2006). Furthermore, migraine sufferers are more sensitive to sensory stimulation (light, sound, smell, pain) interictally than are healthy controls (Drummond, 1987; Drummond, 1986; Drummond and Woodhouse, 1993; Main, Dowson and Gross, 1997; Snyder and Drummond, 1997), which suggests that the nervous system in migraineurs is either constantly vigilant to incoming sensory stimuli or perhaps never fully recovers from persistent attacks. Whatever the case, the headache-free interval appears to be a vulnerable period. Certainly, migraine sufferers develop headache following stimulation of trigeminal and nociceptive pathways interictally (see publications related to this book, Granston and Drummond). Provocative visual stimuli during the headache-free interval also induced subsequent headache in migraine sufferers (Aurora et al., 1999; Cao, Welch, Aurora and Vikingstad, 1999).

The aim of preventative treatment, typically prophylactic medication, is to deflect the acute attack. Perhaps if the focus of preventative treatment was shifted to normalizing interictal malfunction, the threshold of the migrainous brain to provocative incoming stimuli may increase; hence, more robustly protecting the susceptible individual from attacks. Clearly, anti-nociceptive drugs act differently on trigeminal pain processing during and outside attacks. As Katsarava, Limmroth, Baykal, Akguen, Diener and Kaube (2004) demonstrated, anti-nocipetive drugs commonly used to treat acute migraine headache, i.e., acetylsalicylic acid and zolmitriptan, are more effective in suppressing nociceptive blink reflexes when administered during migraine attacks than interictally (Katsarava et al., 2004).

Therefore, use of pharmacological treatment interictally needs to be customized for optimal effect.

This book explored symptomatic and vascular responses in migraine sufferers between headaches. It was anticipated that observations during this particularly sensitive period might help further clarify the extent of interictal hypersensitivity in migraineurs. In turn, ways to more efficiently manage this common, relentless and unpredictable condition, may be realized.

Risk factors associated with increased vulnerability to migraine

Certain risk factors are thought to predispose the individual to migraine. This vulnerability in conjunction with some internal and/or external stimuli may then precipitate a migraine attack (Dowson and Cady, 2002; Lance and Goadsby, 2000; MacGregor, 1999). Numerous studies acknowledge the importance of identifying risk factors in order to control the progression of migraine, a well-recognized chronic-recurrent disorder, from evolving into transformed migraine, a subtype of the chronic daily headaches – a state sometimes leading to nearly constant pain (Bigal and Lipton, 2006; Lipton and Bigal, 2007). Bigal and Lipton (2006) categorized risk factors for migraine progression into two groups, non-remedial and remedial. Non-remedial or not readily modifiable risk factors include gender, age, race, head injury, and low education/socioeconomic status. Remedial or modifiable risk factors include attack frequency, obesity, medication overuse, stressful life events, caffeine overuse, and snoring. Bigal and Lipton also suggest that allodynia, pro-inflammatory states, other pain syndromes and pro-thrombotic states, render the individual more vulnerable for migraine progression.

The threshold of susceptibility probably depends on the degree of predisposition in conjunction with various triggering factors (Bigal and Lipton, 2006; Lance and Goadsby, 2000; MacGregor, 1999), which may explain why one particular trigger, e.g., missing a meal, flickering sunlight or lack of sleep, may not always trigger an

attack from one individual to the next or from one attack to another (MacGregor, 1999). MacGregor points out that if a potential trigger happens to coincide with hormonal changes during menstruation and/or a period of stressful life events, an attack is more likely to ensue than when exposure to triggers are in isolation.

Martin (2001) suggested that the tendency for migraine sufferers to avoid suspected triggers such as light might lead to the development of an insidious hypersensitivity to such stimuli, thus increasing headache frequency. Consistent with this idea Martin found that prolonged exposure to intense light was associated with a subsequent decrease in pain ratings in response to this stimulus. This reaction was not as clear for graded exposure to noise (Martin, Reese and Forsyth, 2006).

Dowson and Cady (2002) point out that proposed risk factors thought to predispose or precipitate migraine sufferers to migraine should be considered carefully as they may merely coexist coincidently. Nevertheless, research to date has produced some encouraging results with respect to the various contributing mechanisms that may render some individuals more likely to develop migraine than others. Predisposing and precipitating factors which may determine the migrainous threshold are discussed next.

Predisposing factors

Genetics

The majority of migraine sufferers participating in the research for this book reported a family history of migraine – 23 out of 27 participants (85.7%). In contrast, only 5 out of 23 healthy controls (21.7%) reported a similar history. The strong familial link with migraine suggests that migraine has a genetic link. There is 50% likelihood that a child will develop migraine if one parent is a migraine sufferer; 75% if both parents have the condition, and 20% if an extended family member has migraine (Larkin, 1997). Twin studies indicate a consistently greater co-incidence of migraine among monozygotic (identical) twins compared with dizygotic (fraternal)

twins, further suggesting that a genetic component underlies the disorder (Larkin, 1997; Svensson, Larsson, Waldenlind and Pedersen, 2003; Ziegler, Hur, Bouchard, Hassanein and Barter, 1998). The higher concurrent rates for migraine among monozygotic twins were found even among twins raised apart (Svensson et al., 2003; Ziegler et al., 1998), implying that genetic factors have more influence than environmental factors in determining who is likely to develop this disease.

In a large population based study of Finnish twins (monozygotic and dizygotic), structural equation techniques identified a strong genetic component in the etiology of migraine (Honkasalo, Kaprio,Winter, Heikkilä, Sillanpää and Koskenvuo, 1995). However, unshared environmental factors for twins raised apart were also found to play a role in the etiology of migraine. Honkasalo et al. suggested that environmental factors might account for much of the variability observed in migraine occurrence.

Understanding the basis for possible hereditary aspects of migraine is far from straightforward. There is no single gene that causes the disorder and only familial hemiplegic migraine has been found to have a strong genetic tendency (Gardner, 1999, 2006; Larkin, 1997; Peroutka, Wilhoit and Jones, 1997). This rare form of migraine appears to be transmitted by an autosomal dominant mode of inheritance linked to mutations in the calcium channel gene CACNA1A assigned to chromosome 19. This mutated calcium channel gene accounts for 50-55% of cases of familial hemiplegic migraine (Gardner, 1999, 2006; Ophoff, Terwindt, Vergouwe, van Eijk, Oefner, Hoffman, Lamerdin, Mohrenweiser, Bulman, Ferrari, Haan, Lindhout, van Ommen, Hofker, Ferrari and Frants, 1996; May, Ophoff, Terwindt, Urban, van Eijk, Haan, Diener, Lindhout, Frants, Sandkuijl and Ferrari, 1995). In some cases abnormalities have also been located on chromosome 1, in the sodium/potassium pump gene ATP1A2 (Ducros, Joutel, Vahedi, Cecillon, Ferreira, Bernard, Verier, Echenne, Demunain, Bousser and Tournierlasserve, 1997; Gardner, 1999, 2006). Mutations in CACNA1A lead to alterations of calcium activity in brain cells and, in turn, neurotransmission, which may explain brain excitability in individuals with migraine (Gardner, 2006). Furthermore, it is suggested that mutations in CACNA1A function may depress levels of serotonin via effects on ion homeostasis and gene expression (Estevez, 2006). Recent studies (Dichgans, Freilinger, Eckstein, Babinin, Lorenz-Depiereuz, Biskup, Ferrari, Herzog, van den Maagdenberg, Pusch and Strom, 2005; Jen, Wan, Palos, Howard and Baloh, 2005) have identified additional gene mutations linked to familial hemiplegic migraine in the genes SLC1A3 and SCN1A.

The latter gene has also been associated with epilepsy, suggesting molecular links between migraine and epilepsy (Dichgans et al., 2005).

It is thought that mutations on chromosome 19 may underlie susceptibility for the more usual forms of migraine including migraine with and without aura (May et al., 1995), but a genetic link has not been confirmed (Larkin, 1997). However, other susceptibility loci have recently been identified for common forms of migraine, in genome-wide screens and candidate-locus studies (Gardner, 2006). Data elsewhere has suggested the involvement of dopamine receptor and synthesis pathways in the manifestation of migraine, particularly migraine with aura (Peroutka et al., 1997).

Clearly the research demonstrates that migraine has a genetic component, but environmental factors also appear to play an important role in the etiology of this condition. All things considered, perhaps migraine results from the interaction of several genes with each other and/or environment factors. It may be that those who inherit a low threshold to migraine attacks are more vulnerable to migraine triggers (Larkin, 1997; MacGregor, 1999).

Dysfunction of the autonomic nervous system

Vascular and symptomatic responses of migraine sufferers to various stimuli including optokinetic stimulation and painful stimulation of the head and limbs were explored in this book. Presumably these stimuli would be considered stressful; hence activation of the autonomic nervous system might be expected. Research has shown instability of autonomic nervous system function in migraine sufferers during and outside migraine attacks, which has been hypothesized to predispose them to migraine (Dowson and Cady, 2002). It has been suggested that sympathovagal imbalance could explain systemic and central migraine phenomena including cranial vasculature changes and bowel motility. Also, associated symptoms of migraine, such as nausea and vomiting, as well as symptoms commonly experienced during the premonitory period including sensitivity to light, sound and smell, and irritability, could have an autonomic basis (Blau, 1992; Mosek, Novak,Opfer-Gehrking, Swanson and Low, 1999; Pogacnik, Sega, Pecnik and Klauta, 1993).

Autonomic dysfunction in migraine sufferers is well recognized but findings are inconsistent across studies as to the division of the autonomic nervous system affected and the direction and degree of instability. Autonomic impairment has mostly been attributed to sympathetic hypofunction (Havanka-Kanniainenm Tolonen and Myllylä, 1986, 1988; Fanciullacci, 1979; Mosek et al., 1999; Peroutka, 2004; Pogacnik, Sega, Pecnik and Klauta, 1993). However, sympathetic hyperfunction (Peroutka, 2004; Appel,Kuritzky,Zahavi, Zigelman and Askeirod, 1992; Zigelman, Appel, Davidovitch, Kuritzky, Zahave and Akseirod, 1994) has also been reported.

Unilateral autonomic symptoms such as lacrimation, conjunctival injection, eyelid oedema and nasal congestion - normally characteristic of trigeminal autonomic cephalalgias (e.g., cluster headache) - have been observed in up to almost 50% of migraineurs during attacks (Barbanti et al., 2002). The headache was more intense in migraine sufferers with unilateral autonomic symptoms than in those without. The presence of these symptoms suggests activation of the cranial parasympathetic system, specifically the activation of the trigeminal-autonomic reflex (Al-Din et al., 2005; Barbanti et al., 2002). Interestingly, Frese, Evers and May (2003) observed that autonomic activation such as lacrimation, conjunctival injection and nasal congestion was evoked in healthy controls following subcutaneous injection of capsaicin to the forehead, suggesting a normal response to trigeminal pain.

Consistent with parasympathetic involvement in migraine sufferers, during attacks with cranial autonomic symptoms, Goadsby, Edvinsson and Ekman (1990) found high levels of vasoactive intestinal polypeptide in the cranial venous circulation. Outside the cranial circulation, parasympathetic function in migraine sufferers was found to be normal compared to healthy controls when exposed to a battery of well-validated tests of autonomic function (Mosek et al., 1999).

An imbalance of the autonomic nervous system may indeed explain many of the clinical manifestations of migraine. Furthermore, autonomic instability may render the individual more vulnerable to the impact of external triggers in the migraine interval.

Moleculecular basis of migraine susceptibility

It has been suggested that migraine belongs to a functional, as opposed to structural, pathology (Bryn, 1980). A typical attack involves, with rare exceptions, reversible and transient autonomic, vascular and nociceptive dysfunction or changes. The absence of physical or structural changes (e.g., which may follow stroke or myocardial infartion) suggests that a migraine attack may be chemically induced.

Key molecular targets implicated in migraine pathophysiology which have been extensively studied, include:

- Mitochondria and magnesium (Barbirolli, Montagna, Cortelli, Fanicello, Iotti, Munari, Pierangeli, Zaniol and Lugarisi, 1992; Bigal, Bordini, Tepper and Speciali, 2002; Demirkaya, Vural, Dora and Topçuoğlu, 2001; Peikert, Wilimzig and Köhne-Volland, 1996; Schoenen, 1996; Welch and Ramadam, 1995;)
- Amino acids (Rajda, Tajti, Komoróczy, Seres, Klivényi and Vécsei, 1999; Martinez, Castillo, Rodriguez, Leira and Noya, 1993; Welch, Barkley, Tepley and Ramadam, 1993; Garlick, 2004; Schaumburg, Byck, Gerstl and Marshman, 1969; D'Andrea, Cananze, Joseph, Morra, Zamberlan, Milone, Grunfeld and Welch, 1991; Cananzi, D'Andrea, Perini, Zamberlan and Welch, 1995; Ferrari, Odink, Bos, Malessy and Bruyn, 1990)
- Calcitonin gene-related peptide (Ashina, Bendtsen, Jensen, Schifter and Olesen, 2000; Goadsby and Edvinsson, 1993; Kawasake, et al, 1988; Lassen, Haderslev, Jacobsen, Iversen, Sperling and Olesen, 2002; Moskowitz, 1993; Peitrobon, 2005)
- Endogenous opioids (Anselmi, Baldi, Casacci and Salmon, 1980; Bach, Jensen, Blegvad, Fenger, Jordal and Olesen, 1985; Baldi, Salmon, Anselmi, Spillantini, Cappelli, Brocchi and Sicuteri, 1982; Baskin and Hosobuchi, 1981; Facchinetti, Nappi, Savoldi and Genazzani, 1981; Fettes, Gawel, Kuzniak and Edmeads, 1985; ; Mosnaim, Diamond, Wolf, Puente and Freitag, 1989; Mosnaim, Wolf, Chevesich, Callaghan and Diamond, 1984; Sicuteri, 1981).

These findings are not directly related to the present study; hence their discussion is beyond the scope of this book. The reader is instead directed to the relevant bracketed references for more detailed debate. However, as physiological and symptomatic responses to stressful stimuli are of interest in the present study, biochemical aspects of migraine in relation to stress are discussed next. Stress is further discussed later in this chapter in the context of general migraine triggers (pages 62-69).

Stress and biochemical responses

Mitochondria and magnesium

Various biochemical and metabolic irregularities have been linked with migraine (Wang and Schoenen, 1998; Welch and Ramadam, 1995). Reduced levels of magnesium in the blood stream of migraine sufferers are proposed to alter mitochondrial energy metabolism (Welch and Ramadam, 1995). Subsequent biochemical/metabolic imbalance could culminate in a migraine attack. Mitochondrial irregularities may be directly due to low magnesium caused by systemic magnesium deficiency. Low systemic magnesium may be compromised further during acute stress, leading to additional decreases in systemic magnesium levels; thus tipping a threshold resulting in depleted brain magnesium (Welch and Ramadam, 1995). As procedures used in this study were stressful, the stress-response may potentially have compromised magnesium levels of participants and consequently influenced responses at a cellular level.

Magnesium is required for the aerobic stages of mitochondrial cell respiration, in particular for the synthesis of adenosine triphosphate (Venes, 2001). Adenosine triphosphate is the main source of cellular energy used for a host of metabolic processes, including transmission of nociceptive information within dorsal root ganglion neurons and the spinal cord (Hains, 2004). High brain adenosine triphosphate concentration was observed in migraine sufferers between attacks, which indicates unstable cerebral energy metabolism, most probably a sign of mitochondrial

dysfunction (Barbirolli, Montagna, Cortelli, Fanicello, Iotti, Munari, Pierangeli, Zaniol and Lugarisi, 1992). Magnesium deficit leads to increased cellular respiration and, in turn, decreased mitochondrial energy reserves (Welch and Ramadam, 1995).

Disruption of metabolic homeostasis and biochemical shifts are postulated to underlie activation of the trigeminovascular system, thus enabling the production of a migraine attack (Schoenen, 1996). Indeed, many migraine sufferers in the present thesis developed full-blown attacks following certain procedures (refer to publications related to book, Granston and Drummond, 2005), suggesting activation of trigeminovascular nuclei, possibly secondary to disrupted metabolic processes. It is not certain whether altered mitochondrial function is secondary to decreased brain magnesium or a primary fault. However, Welch and Ramadam (1995) suggest that magnesium deficiency or defects in mitochondrial metabolism, or both, may predispose the brain to spontaneous spreading depression, or at least its activation by migraine triggers.

The therapeutic benefits of magnesium supplementation (Bigal, Bordini, Tepper and Speciali, 2002; Demirkaya, Vural, Dora and Topçuoğlu, 2001; Peikert, Wilimzig and Köhne-Volland, 1996) support the idea that depleted magnesium plays a role in the pathogenesis of migraine. Administration of magnesium sulphate intravenously in the acute treatment of migraine (Bigal, Bordini, Tepper and Speciali, 2002; Demirkaya, Vural, Dora and Topçuoğlu, 2001), and oral magnesium prophylactically (Peikert, Wilimzig and Köhne-Volland, 1996), alleviates symptoms of migraine including aura, head pain, nausea, and phono/photophobia.

Endogenous Opioid peptides

Stress may be associated with fluctuating opioid levels observed during the migraine crisis (Anselmi et al., 1980). Anselmi et al. noted a decrease in cerebral spinal fluid enkephalin levels during migraine attacks and an increase in serum β-endorphin-like-immunoreactivity at the end of an attack. Hyperendorphinaemia at the end of an attack was thought to reflect the stress provoked by the attack. As stress has been shown to induce pituitary release of β-endorphins (among other related peptides and hormones), by implication, pituitary β-endorphin may play a role

in resolving migraine headache (a well acknowledged stressful event) and restoring a state of well-being.

It may be that lowered pain thresholds observed in migraine sufferers (Fernández-de-las-Peñas, Cuadrado, Arendt-Nielsen and Pareja, 2008; Giamberardino, Tafuri, Savini, Fabrizio, Affaitati, Lerza, Di lanni, Lapenna and Mezzetti, 2007; Kowacs, Piovesan, Werneck, Tatsui, Lange, Ribas and da Silva, 2001; Langemark, Jensen, Jensen and Olesen, 1989) may be, at least in part, due to a failure of the opiate receptor system to modulate sensitivity to pain (Mosnaim, Diamond, Wolf, Puente and Freitag, 1989; Sicuteri, 1981). In contrast, in schizophrenia, biochemical conditions compared to migraineurs are the reverse: cerebral spinal fluid is rich in enkephalins and endorphins. In these patients the pain threshold is particularly high, headache complaints are infrequent and monoamine receptor sensitivity is lowered. Hyperendorphinaemia is also seen during pregnancy which may explain the remission of pre-existent idiopathic headache, the increased pain threshold and the euphoric mood often reported in women during pregnancy (Anselmi et al., 1980).

Dysfunction of opiate receptor sites in the pain pathway of migraine sufferers may predispose them to migraine (Dowson and Cady, 2002; Lance and Goadsby, 2000). Endogenous opioid peptides are compounds made up of two or more linked amino acids found naturally in the body - in the brain, certain endocrine glands and the gastrointestinal tract. They have morphine-like analgesic properties, neurotransmitter and neuromodulator functions, and can influence behaviour (Venes, 2001), i.e, opioid-induced state of well-being (Anselmi, Baldi, Casacci and Salmon, 1980). Opioids that are produced exclusively in the brain include endorphins (polypeptides), enkephalins (pentapetides) and dynorphins. These inhibitory neurotransmitters interfere with the transmission of pain signals by binding to opiate receptor sites, preventing the release of substance P, thereby blocking the perception, transmission and sensation of pain (Venes, 2001). Other chemical substances such as gamma-aminobutyric acid cooperate with enkephalin to inhibit the response to pain. Enkephalin and gamma-aminobutyric acid help guard the nervous system from painful stimuli in accordance with information received from nerve pathways that descend from the midbrain to brain stem and spinal cord. In particular, the periaqueductal grey matter as well as the locus coeruleus, located in the brain stem, are important areas involved in modifying information transmitted through pain pathways. Descending pain control pathways regulate nociceptive impulses so that

the brain receives inhibitory or excitatory pain information, as required. The release of certain monoamines assists in the mediation of impulses from interneurons in the pain pathway, particularly serotonin from the periaqueductal grey matter and noradrenaline (also known as norepinephrine) from the locus coeruleus (Lance, 2000).

Sicuteri (1981) hypothesized that an opioid receptor hypofunction in migraine sufferers accounted for the absence of pain relief observed following morphine during a migraine attack, and the weak inhibition of the spasmogenic effect of serotonin on the dorsal vein in the hand. However, scientists are not all in agreement about plasma, cerebral spinal fluid or platelet methionine enkephalin and β-endorphin levels in migraine during or outside attacks (Anselmi et al., 1980; Bach, Jensen, Blegvad, Fenger, Jordal and Olesen, 1985; Baldi, Salmon, Anselmi, Spillantini, Cappelli, Brocchi and Sicuteri, 1982; Facchinetti, Nappi, Savoldi and Genazzani, 1981; Fettes, Gawel, Kuzniak and Edmeads, 1985; Mosnaim et al., 1989; Mosnaim, Wolf, Chevesich, Callaghan and Diamond, 1984). Bach et al. (1985) reported that plasma β-endorphins were comparable during and outside attacks. In contrast, Baldi et al. (1982) found that plasma β-endorphin levels were lower during attacks compared with the headache-free interval, and with controls. Additionally, plasma β-endorphin levels were significantly lower in daily headache sufferers than in controls. Another study (Fettes et al., 1985) found a difference in plasma β-endorphin levels between headache types. β-endorphin levels were found to be lower in classical migraine sufferers than in those with common migraine or chronic daily vascular headache, or the control group. Fettes et al. suggested that low levels of β-endorphin may play a role in the manifestation of the neurological dysfunction seen in the migraine aura. Interestingly, administration of naloxone, an opioid receptor antagonist used to treat addiction to opium-derived drugs (Venes, 2001), has been demonstrated to reverse migraine aura (Baskin and Hosobuchi, 1981) and cerebral ischaemia (Sicuteri, Boccuni, Fanciullacci and Gatto, 1983). These findings suggest that high opioid turnover is linked with migraine aura.

In the present study, exposure to stressful procedures during the headache-free interval most likely influenced physiological (Drummond, 1984, 1985b; Passchier, 1994; Peroutka et al., 1997) and symptomatic (Kowacs et al, 2001) responses. However, the influence of stress on circulating opiates in migraine sufferers interictally, and associated psychopyhsiological symptom development, was not explored in this book. Stress is clearly associated with fluctuating opioid levels

during the migraine crisis (Anselmi et al., 1980). Additionally, lowered opioid levels (Fettes et al., 1985), and atypical responses to stress have been observed during (Anselmi et al., 1980) and outside of attacks (Fettes et al., 1985). Perhaps opioid receptor sites in migraineurs are also insensitive to opioids released during stressful stimuli interictally. It may be that an exceptionally high level of stress is required to boost circulating opioids sufficiently for an impending attack to be aborted. This may be the case where migraine headache follows a period of intense stress (Kohler and Haimer, 1990; Levor, Cohen, Naliboff, McArthur and Heuser, 1986). Once the stress passes, opioid stores may drop to baseline levels, no longer sufficient to keep at bay the headache generated during the stressful period. In contrast the reverse may happen during the attack - hyperendorphinaemia as the headache subsides is thought to reflect the stress provoked by the attack, which may help to resolve the headache (Anselmi et al., 1980). Persistent dysfunction of opioid receptor sites may, to some degree, underlie susceptibility to migraine.

The migraine predisposition, biochemical and metabolic dysfunction, and stress: a synthesis

Genetic, biochemical and mitochondrial factors have been suggested to play important roles in the etiology of migraine. However, irrespective of any proposed candidate vying for the origin of migraine, it seems logical that responses to stress may variously, at least in part, explain why some individuals are more susceptible to developing a migraine attack than others. Indeed, stress is a commonly reported migraine trigger (Passcheir, 1994; Reynolds and Hovanitz, 2000). Stress is further discussed later in this chapter in the context of general migraine triggers (pages 62-69).

Hormones

Fifty to 68 percent of women migraineurs experience attacks associated with menstruation (Dzoljic, Sipetic, Vlajinac, Marinkovic, Brzakovic, Pokrajac and Kostic, 2002; Lance and Goadsby, 2000; MacGregor, 1999; Zacur, 2006), which suggests that hormonal factors may underlie the disorder. Additionally, the predominance of female migraine sufferers compared to male (3:1) (Kemper, 2006), further implicates female hormones, at least in part, in the etiology of migraine (Rasmussen, 1995). Female participants in the present study were tested between menstruation and outside the premenstrual phase, to minimize any hormonal influences.

The female life cycle involves a sequence of hormonal milestones: menarche, peri-menopause and menopause. Also, pregnancy, lactation, contraceptive use and the use of replacement sex hormones may be met in the course of the female lifespan (Fettes, 1999; Lipton, Stewart, Diamond, Diamond and Reed, 2001; Sances, Granella, Nappi, Fignon, Ghiotto, Polatti and Nappi, 2003; Silberstein and Merriam, 1999, 2000; Zacur, 2006). Cyclic sex hormone production over the female life span, including at different stages of the menstrual cycle, affects the clinical expression of migraine (Herzog, 2007; Loder, Rizzoli and Golub, 2007; MacGregor, Chia, Vohrah and Wilkinson, 1990; Martin, Wernke, Mandell, Ramadan, Kao, Bean, Liu, Zoma and Rebar, 2005; Newman, 2007).

A sudden decline in oestrogen and progesterone levels marks the onset of menstruation, the most vulnerable time for a migraine attack to develop. Some individuals are prone to migraine attacks mid-cycle (at ovulation), which is similarly marked by a sudden decline in oestrogen levels. The drop in oestrogen mid-cycle is followed by rapid restoration during the luteal phase in conjunction with an increase in progesterone levels (Silberstein and Merriam, 1999, 2000; Zacur, 2006). One migraine sufferer in the present study reported that in addition to premenstrual and menstrual migraine, an attack was also more likely at ovulation. Accordingly, this participant was tested during less vulnerable times of her cycle.

Studies confirm that hormone levels during the menstrual cycle in women who suffer menstrual migraine are comparable to those of controls (MacGregor, 1999). Evidently, migraineurs are more sensitive to the effects of normal hormonal fluctuations (Dzoljic et al., 2002; MacGregor, 1999).

Ovarian hormones have a major effect on the central nervous system and modulate several neurotransmitter systems including serotonergic, glutamatergic, gamma-aminobutyric acid (GABA)ergic; and opiatergic (Herzog, 2007; Martin and Behbehani, 2006a; Silberstein and Martin, 2000; Veith, Anderson, Slade, Thompson, Laugel and Getzlaf, 1984). All of these systems play a role in the pathophysiology of migraine headache, particularly in the pain modulation of this disorder (Herzog, 2007; Martin and Behbehani, 2006a; Silberstein and Martin, 2000). The risk for migraine headache during different phases of the menstrual cycle may therefore be due to changes in the balance of neurotransmitter systems (Martin and Behbehani, 2006a).

However, sex hormones may only be one of several factors acting together to trigger migraine in susceptible women (Gupta, 2004; Martin and Behbehani, 2006b; Zacur, 2006), or merely circumstantial (Gupta, 1994). Indeed, menstrual migraine is more likely to occur when hormonal triggers co-occur with other triggers, e.g., missed meals, physical or emotional stress, late nights (MacGregor, 1999). Nevertheless, in order to control for a possibly confounding variable, participants in this study were not tested during those times of the menstrual cycle when they were considered vulnerable to developing an attack.

The association between gastrointestinal disturbances and migraine

Early signs of gastrointestinal hypersensitivity

Eighty-two percent of children identified as having cyclic vomiting syndrome manifest symptoms typical of migraine. Interestingly, in children susceptible to migraine-associated cyclic vomiting, motion sickness was more likely to trigger vomiting/migrainous symptoms than in children with non-migraine cyclic vomiting - 10% *vs* 0% (Li, Murray, Heitlinger, Robbins and Hayes, 1999). Longitudinal studies found that children with a history of recurrent vomiting of unknown causes were at

increased risk of migraine in adulthood. Furthermore, children with a history of motion sickness, migraine/family history of migraine, were more likely to vomit after mild head injury (Jan, 1998; Jan, Camfield, Gordon and Camfield, 1997). The overlap between vomiting/migraine/motion sickness seen in childhood suggests hypersensitive gastrointestinal responses from an early age in vulnerable individuals. Perhaps these overlapping signs of vulnerability may be associated with inherited factors given that a family history of migraine is common in children prone to cyclic vomiting or vomiting after mild head injury.

The association between motion sickness and migraine

Motion sickness is associated with migraine in children (Barabas, Schempp Matthews and Ferrari, 1983; Jan, 1998) and adults (Cutre and Baloh, 1992; Kuritzky, Ziegler and Hassanein, 1981). Most migraine sufferers (about two-thirds) are prone to motion sickness (Baloh, 1997). Genetic factors may underlie the tendency to motion sickness (Reavley, Golding, Cherkas, Spector, MacGregor, 2006), just as neuro-otological symptoms common to migraine, have been linked to possible candidate genes (Baloh, 1997).

Bijveld, Bronstein, Golding and Gresty (2008) found that subjects exposed to visual motion while stationary developed headache more frequently than during off-vertical axis rotation with their eyes open or closed. Bijveld and colleagues suggested that mechanisms responsible for headache during visual motion alone may be similar to those of migraine.

Females are generally more prone to motion sickness (Golding, 2006; Grunfeld and Gresty, 1999), and are especially vulnerable during menstruation (Golding, Kadzere and Gresty 2005). Curiously, female predominance also applies to migraine (Celic, Ekuklu, Tokuc and Utku, 2005; Rasmussen, 1995; Lipton, Stewart, Diamond, Diamond, and Reed, 2001). Grunfeld and Gresty (1999) found an association between these female weighted maladies. Female yacht crew members who

experienced migraine reported greater susceptiblity to motion sickness than other crew members. Additionally, motion sickness and headache peaked during ovulatory or menstrual phases of the menstrual cycle, though migraine and motion sickness did not always occur together. Grunfeld and Gresty commented that as symptoms common to both of these disorders are remarkably similar, it is conceivable that some subjects may not have distinguished their symptoms.

Female sex hormones may, at least in part, predispose the susceptible individual to motion sickness (Golding, 2006) and migraine (Rasmussen, 1995). Hormonal influences in relation to migraine susceptibility were discussed earlier (pages 46-47). With respect to motion sickness, susceptibility onset commonly occurs in childhood around age seven. The appearance of motion sickness prior to puberty implies that sex hormones alone are not an explanation for the onset of the disorder. Additionally, susceptibility to motion sickness gradually declines into adulthood, which may indicate habituation to the ill-effects of motion over time (Golding, 2006).

Most individuals would probably find the disconcerting nature of motion sickness a stressful experience. Therefore, as Graaf and Gresty (1998) propose, stress and motion sickness may go hand in hand. Stress may influence the neurochemistry of motion sickness, and contribute to aspects of individual susceptibility to motion sickness. Stress is also a well-acknowledged trigger of migraine.

Vestibular instability

The essential mediator for motion sickness is the vestibular apparatus. This is indisputable, at least with respect to movement induced motion sickness, as animals and humans who have no functional vestibular apparatus do not develop motion sickness during rotation or when placed in unusual forced environments associated with the exploration of space (Crampton, 1990; Igarashi, 1990; Money, 1990). Movement-induced motion (boat/plane/car travel) or visually-induced perceived motion (optokinetic stimulation, wide-screen movies) that is incompatible with proprioceptive and vestibular cues (Drummond, 2005) stimulates central mechanisms

that induce symptoms of motion sickness. It may be that motion sickness is warning the body of the potential threat to homeostasis. The conflicting central sensory input evokes physiological disturbances and, as a precaution, nausea/vomiting occurs to expel potential toxins/poisons from the system; in much the same way as vomiting is triggered following absorbed toxins. This 'conflict theory of motion sickness' is consistent with Treisman's theory of conflicting sensory inputs leading to central disturbance (Money, 1990).

Migraine and motion sickness share many common symptoms including nausea, tiredness, dizziness, body temperature changes and headache (Marcus, Furman and Baleban, 2005). The presence of otoneurologic symptoms indicates activation of vestibular pathways. Dizziness and vertigo often accompany migraine attacks (von Brevern, Zeise, Neuhauser, Clarke and Lempert, 2005; Cutrer and Baloh, 1992; Lance, 2000) and are frequently reported during the headache-free interval (Kuritzy, Ziegler and Hassanein, 1981). A quarter of migraine sufferers experience episodes of vertigo. Additionally, phonophobia, the most common auditory symptom reported during attacks, sometimes involves fluctuating or permanent hearing deficits (Baloh, 1997).

Baloh proposed that a possible inherited mechanism, similar to that discovered in rare forms of migraine, may also account for otoneurologic symptoms that are experienced in the more common varieties of migraine, i.e., migraine with/without aura. Defective calcium channel genes and subunits have been isolated in familial hemiplegic migraine (Baloh, 1997; Gardner, 1999, 2006; Larkin, 1997; Peroutka, Wilhoit and Jones, 1997) and in families with episodic vertigo and ataxia (Baloh, 1997). In the case of the common varieties of migraine, auditory and vestibular symptoms may also be related to a defective calcium (ion) channel, primarily expressed in the brain and inner ear. This defect could lead to reversible hair cell depolarization (following calcium/potassium displacement) and, in turn, the otoneurologic symptoms experienced during, and outside, attacks. Perhaps genetic factors also underlie predisposition to motion sickness.

As motion sickness and migraine appear to share common pathways, the initiation of one malady may necessarily trigger the other - motion sickness or migraine – as a direct result of closely interconnected neural pathways that express either condition.

Vascular reactivity during and between attacks

Signs of intra- and extracranial vascular instability have been observed in migraine sufferers during and between attacks (Drummond, 1982a). Headache sufferers reported symptoms of vascular pulsatililty in the temples during stress (excitement or emotional upset) and othostatic symptoms (dizziness, flashing lights, black spots before the eyes on standing), which increased relative to the number of migrainous symptoms associated with headache. Drummond suggested that othostatic symptoms may be related to poor circulatory regulation in the intracranial blood vessels of the brainstem during changes of posture. The sensation of throbbing of the temples during stress (Drummond and Lance, 1981; Drummond, 1982b) and during migraine attacks (Drummond, 1983) may be a sign of extracranial vascular distention. The present study explored extracranial vascular responses in migraine sufferers interictally to a series of stressful stimuli. It was anticipated that findings may further clarify the role that the vasculature plays in those predisposed to migraine.

In a later experiment Drummond and Lance (1984b) assessed extracranial changes thermographically in relation to headache intensity, in response to the application of pressure over the superficial temporal and common carotid arteries. Heat loss was mostly observed on the affected side during attacks with unilateral pain, particularly in cases where pressure to the temporal vessel was associated with temporary pain relief. Asymmetric thermographic differences subsided as the headache improved. However, many migrainous-like headaches displayed no vascular component thermographically, or responded to vascular compression. In fact responses to vascular compression were inconsistent from one headache to the next in the same individual. It appeared, at best, that extracranial vascular changes happened erratically depending on the severity of pain and other associated migrainous features present during an attack.

A cerebral vasodilator response was provoked in migraine sufferers in response to 5% CO_2 inhalation but not in controls (Sakai and Meyer, 1979). Furthermore, cerebral blood flow showed greater responsiveness to CO_2 in the hemisphere corresponding to the usual side of head pain during an attack than the non-headache

hemisphere. Sakai and Meyer suggest that the asymmetry of the vascular response may indicate different types of abnormality in cerebrovascular receptor sites; therefore, one region of the brain may be more disordered than another.

Overall, this series of studies indicates that intra-and extracranial vascular instability is evident in migraine sufferers during and outside attacks. Migraine headache is attributed to neurovascular mechanisms (Edvinsson and Uddman, 2005; Moskowitz, 1993). Thus, it is conceivable that the increased vascular reactivity also observed outside attacks in migraine sufferers (Drummond, 1982) may render the susceptible individual vulnerable to recurring attacks. Perhaps, a low threshold to triggers, such as excess stress (Drummond, 1981; Drummond, 1982b; Hassinger, Semenchuk and O'Brien, 1999), potentiates neurovascular mechanisms involved in the development of migraine headache.

Sensory hyperacuitity

Symptoms typically experienced during migraine headache, and to some extent between attacks, such as phono/photophobia, nausea, hyperalgesia and dizziness, demonstrate activation of the somatosensory system. Four different types of sensation are encoded by the somatosensory system (Waxman, 2003):

i superficial - touch, pain
ii deep - muscle/joint position (proprioception), deep muscle pain
iii visceral - hunger, thirst, nausea, visceral pain
iv special - smell, vision, hearing, taste, and balance

Symptoms of migraine, *per se*, suggest that each of these sensations is involved in attacks. Sensory irregularities also occur in the headache-free interval. The present study compared symptomatic responses of migraine sufferers interictally to healthy controls, in relation to a series of stressful sensory stimuli. It was anticipated that findings might further clarify the extent to which sensory hyperacuity in those predisposed to migraine may render them vulnerable to attacks.

Studies of evoked and event-related potentials (visual, auditory, cortical, olfactory and trigeminal) suggest interictal brain abnormalities (Gantenbein and Sándor, 2006; Aurora, Cao, Bowyer and Welch, 1999; Auror, Ahmad, Welch, Bhardhwaj and Ramadan, 1998; Wray, Mijovic-Prelec and Kosslyn, 1995; Dahlem and Podoll, 2007; Evers, Quibeldey, Grotemeyer, Suhr and Husstedt, 1999; Grosser, Oelkers, Hummei, Geisslinger, Brune, Kobal and Lőtsch, 2000; Judit, Sándor. and Schoenen, 2000; Schoenen, 1996; Siniatchkin, Gerber, Kropp, Voznesenskaya and Vein, 2000; Wang and Schoenen, 1998); while somatosensory evoked potentials have demonstrated delayed latency and nerve conduction velocity, particularly along the arm, compared to tension headache sufferers (Montagna, Zucconi, Zappia and Liguori, 1985). Perhaps the slow nerve conduction detected by somatosensory tests is a signal that neurotransmission/ neuromodulation (Firenze, Del Gatto, Mazzotta and Gallai, 1988) is generally compromised in individuals prone to migraine; thus, increasing susceptibility to migraine. It has been suggested that trigeminal somatosensory evoked potentials may provide important information about the functional integrity of trigeminal sensory pathways from the peripheral nerve up to, and including, the sensory cortex during and outside attacks (van Vliet, Vein, le Cessie, Ferrari and van Dijk, 2002). Superficial, deep and visceral sensations in migraine sufferers are discussed in detail in the general discussion later in this book. The special senses are discussed next.

The special senses are conveyed by cranial nerves, and almost all cranial nerve nuclei are situated in the brain stem (Waxman, 2003), an area of focal activity in the development of migraine attacks (Weiller, May, Limmroth, Juptner, Schayck, Coenen and Diener, 1995). Migraine sufferers commonly experience exaggerated sensitivity to even innocuous sensory stimulation during attacks (Goadsby, 2001). Heightened sensitivity to light, sound, smell (Lance and Goadsby, 2000), balance (Kuritzy et al., 1981), and to some extent, taste (Debney, 1984) have been documented. Up to 80% of migraineurs find light and sound uncomfortable (Lance and Goadsby, 2000; Kayan and Hood, 1984). Additionally, sense of smell is frequently sharper at this time (Kayan and Hood, 1984; Snyder and Drummond, 1997).

During the interictal period hypersensitivity of the special senses may persist. Migraine sufferers are more sensitive to light between attacks than controls (Drummond, 1986; Main, Dowson and Cady, 1997; Woodhouse and Drummond, 1993; Vanagaite, Pareja, Støren, White, Sanc and Stovner, 1997), particularly to glare

following exposure to dull and bright light (Drummond, 1986). Headache sufferers also report that bright light is painful. Drummond concluded that glare probably demonstrates a general hypersensitivity of the special senses in migraine sufferers. Exposure to bright light seems to exacerbate pain during an attack, possibly due to trigeminal pain pathway activation. The pain of migraine may be more to do with the abnormal perception of the normal rather than the activation of pain processing pathways in the usual way that pain is generated, e.g. photophobia is the exaggeration of normal light and phonophobia the exaggeration of normal sound, by the brain (Goadsby, 2001).

Main et al. (1997) found that phonophobia also persisted interictally. This finding was in contrast to Woodhouse and Drummond (1993), who discovered that while the auditory discomfort threshold was lower during headache, interictally it did not differ from healthy controls. Main et al. (1997) suggested that the discrepancy between these studies was probably due to the larger sample size in their study.

Contradictory findings have similarly been reported in olfaction of migraineurs between attacks. Snyder and Drummond (1997) found that olfactory thresholds to vanillin were lower than in contols. This hyperosmia also applied to acetone thresholds - particularly in the case of migraineurs usually hypersensitive to odours during attacks. In contrast, Hirsch (1992) found that 18% of migraine sufferers, when given pyridine odour threshold tests, were hyposmic or anosmic. In contrast, only 1% of the population of the United States is hyposmic or anosmic. Snyder and Drummond (1997) suggested that the difference in findings between these studies may have been due to the lack of standardized controls, adaptation, and the use of a trigeminal rather than olfactory stimulus, in Hirsch's (1992) study.

Light, sound and smell have been reported to trigger attacks in some individuals (Blau and Solomon, 1985; Debney, 1984; Scharff, Turk and Marcus, 1995). Indeed, provocative visual stimuli during the headache-free interval induced subsequent headache in migraine sufferers (Aurora et al., 1999; Cao, Welch, Aurora and Vikingstad, 1999).

Collectively, these studies imply that the headache-free interval in migraineurs appears to be a vulnerable time. Hyperacuity of the special senses appears to persist between attacks, which may increase susceptibility to migraine.

Hyperalgesia

Normal pain *vs* migraine pain

Under normal circumstances pain serves a functional purpose. Primarily, the somatosensory system guards against any overt threat impinging on the body (Waxman, 2003). However, migraine pain is felt spontaneously rather than functionally, which suggests that the pain-control system is not working as it predictably should (Lance, 2000; Woolf, 2004).

Nociceptive pain alerts the body to potentially damaging sensory stimuli. Nociception involves the 'transduction' of information received from the periphery, in the form of electrical activity from primary afferents, to the central nervous system. This information is then sent to the central nervous system by a process referred to as 'conduction' (Woolf, 2004). Electrical messages conducted via nerve fibres converge on nerve cells, which then chemically transmit the message, i.e., neurotransmission (Lance, 2000). Following this, information is carried from primary sensory neurons to central projection neurons by a process known as 'transmission' (Woolf, 2004). Finally, information is transferred to the cerebral cortex, which is responsible for pain perception, and so the sensory experience of pain transpires (Lance, 2000; Woolf, 2004). Impulses then descend from the pain control pathways in the midbrain (the periaqueductal grey matter and locus coeruleus), and brain stem to the spinal cord. Pain control pathways regulate the transmission of pain via the release of various chemical messengers (Lance, 2000).

In cases where early warning nociceptive pain is overwhelmed, such as during acute severe pain/trauma, an inflammatory response ensues. A feature of inflammatory pain is hypersensitivity to innocuous stimuli due to the production of inflammatory mediators that alter the properties of high-threshold primary-sensory neurons. Inflammatory pain is associated with peripheral sensitization, which involves changes in the chemical properties and function of neurons in the nervous system. Peripheral sensitization leads to an increase in the excitability of neurons within the central nervous system; hence, central sensitization results. Some

pathological conditions, such as rheumatoid arthritis, are associated with severe pain and ongoing inflammation (Woolf, 2004).

The present study investigated vascular and symptomatic responses associated with pain processing in migraine sufferers. Migraineurs were exposed to painful stimulation of the head (trigeminal sensitivity) and limb (general pain processing) in a series of experimental conditions.

Pain processing in migraine sufferers during and outside attacks are discussed next. Following this pain thresholds in migraine sufferers are considered.

Ictal pain

Woolf (2004) classifies migraine pain as a very distinct category of pain, which has features that resemble inflammatory pain. Certainly, inflammatory mediators (Moskowitz, 1993) within the cortex appear to act on meningeal sensory fibres. A key mechanism operating in the manifestation of migraine pain appears to involve changes in sensory terminals that innervate blood vessels in the meninges (Moskowitz, 1993; Woolf, 2004). It is suggested that migraine headache is initiated following activation of peripheral sensory fibers which appear to innervate intracranial blood vessels and the dura; activation of descending pathways that facilitate processing of pain impulses by spinal cord neurons; and restraint of descending pathways that inhibit processing of these pain impulses in the spinal cord (Burstein, 2001). Vasodilatation and scalp muscle contraction are commonly associated with migraine headache; these mechanisms do not cause pain in headache-free controls (Sicuteri, 1981b). Another process operating in migraine pain appears to be the alteration of excitability of central pain processing neurons and the development of central sensitization (Burstein, 2001; Woolf, 2004).

Woolf distinguishes migraine from functional pain syndromes such as tension-type headache and fibromyalgia, which similarly have features of inflammatory pain. However, functional pain syndromes also have characteristics of neuropathic pain, which have underlying physiological mechanisms that generate pain, e.g., the compression of the median nerve in carpal tunnel syndrome. With respect to

migraine, there is typically an absence of organic lesions in pain-affected areas (Sicuteri, 1981b).

Despite the difference between functional syndromes and migraine, certain features are common to both - specifically, the involvement of altered sensitivity of the pain system: central sensitization, hyperexcitability of somatosensory pathways, and also altered modulation of nociceptive discharge (Woolf, 2004).

Interictal pain

Hypersensitivity to painful stimuli has also been observed in migraine sufferers during the headache-free interval (Drummond, 2002; Drummond, 1987; Kowacs, Piovesan, Werneck, Tatsui, Lange, Ribas and da Silva, 2001). Drummond (1987) found that migraine sufferers who experienced frequent headaches reported that tenderness of the forehead and temples persisted interictally; raising the question of whether scalp tenderness might somehow be linked to susceptibility to recurring attacks. More recently, Drummond (2002) found that scalp tenderness developed during optokinetic stimulation-induced motion sickness, particularly in the most nauseated subjects. Furthermore, migraine sufferers were more prone to nausea than healthy controls. Additionally, pain in the fingertips increased more so in migraine sufferers than controls, after optokinetic stimulation. Based on these findings Drummond proposed that brain stem disturbances responsible for nausea may also sensitize central trigeminal nociceptive nuclei. Alternatively, inhibitory controls on the discharge of trigeminal neurons may be lost. The tendency to develop nausea, and for sensitization to develop in pain pathways, may increase an individual's susceptibility to migraine (Drummond, 2002).

Lance and Goadsby (2000) suggested that hypersensitivity of the face and scalp, commonly observed in migraine sufferers, may involve mechanisms similar to those responsible for the increased acuity of the special senses. Kowacs et al. (2001) found that pain perception thresholds in migraine sufferers interictally, measured by pressure algometries to a series of trigeminal and cervical sites, persistently dropped following exposure to progressively intense light stimulation. Controls tolerated procedures. Kowacs et al. concluded that light might influence trigeminal and cervical pain tolerance thresholds in migraineurs. Conversely, light pain increased

following painful stimulation of the forehead and face in migraine sufferers interictally (Drummond, 1997; Drummond and Woodhouse, 1993), suggesting that pain and visual pathways may be functionally interconnected. Perhaps then, headache and photophobia increase and compound one another during an attack (Drummond, 1997).

Elsewhere, the association between muscle contraction and hyperalgesia in migraine has been explored during and between headaches (Bakal and Kaganov, 1977; Tfelt-Hansen, Lous and Olesen, 1981). Electromyogram activity in frontal and neck muscles was greater in migraine sufferers during and outside attacks compared to controls and tension headache sufferers. Perhaps these findings indicate that muscle contraction mechanisms are linked to predisposition to migraine (Bakal and Kaganov, 1977), at least in part.

Altered pain thresholds in migraine sufferers

Trigeminal pain pathways (Goadsby, Lipton and Ferrari, 2002) and pericranial musculature (Drummond, 1987; Giamberardino, Tafuri, Savini, Fabrizio, Affaitati, Lerza, Di lanni, Lapenna and Mezzetti, 2007; Fernández-de-las-Peñas, Cuadrado, Arendt-Nielsen and Pareja, 2008) are particularly sensitive in migraine sufferers. Migraine sufferers, interictally, were found to have lower pain thresholds in pericranial musculature than controls, in response to mechanical (Drummond, 1987; Fernández-de-las-Peñas et al., 2008), heat (Langemark, Jensen, Jensen and Olesen, 1989) and electrical (Giamberardino et al., 2007) stimulation. Pain perception thresholds distant from the head were also observed to be lower in migraine sufferers interictally than in controls (Nicloldi, Sicuteri, Coppola, Greco, Pietrini and Sicuteri, 1994). Over-distension of the hand-forearm veins following pressure-cuff inflation induced more local pain in migraine sufferers than controls. Also, injection of hypertonic saline into the anticubital vein during restricted circulation (ischemia) from pressure-cuff inflation to the arm, provoked moderate to unbearable local pain in migraineurs but not in controls (Nicloldi et al., 1994).

Research elsewhere (Göbel, Weigle, Kropp and Soyka, 1992; Metsahonkala, Anttila, Laimi, Aromaa, Helenius, Mikkelsson, Jäppilä, Viander, Siianpää and Salminen, 2006) has not detected lowered pain perception in migraine sufferers. Göbel et al. (1992) found that pericranial pain sensitivity in migraineurs, tension headache sufferers and healthy controls, was generally comparable in response to mechanical pressure - although migraine and tension-headache sufferers tended to have lower thresholds than controls. Furthermore, Göbel et al. found that electromyogenic (EMG) activity increased in all three groups following experimental pain. Scores were significantly higher in tension headache sufferers than in migraineurs at high experimental pain levels. It was suggested that increases in EMG scores may have been partly due to facial movement, possibly reflecting an emotional reaction to pain induction procedures. Indeed, psychophysiological stressors have provoked increased muscular activity in both muscle contraction headache sufferers and migraineurs (Bakal and Kaganov, 1977; Feuerstein, Bush and Corbisiero, 1982). However, in Göbel's study, psychological measures did not differ between individuals within groups with lower or higher pain sensitivity scores, implying that motor components of pain, rather than affective components, were responsible for differences in EMG scores.

Metshonkala et al. (2006) also found that interictal extracephalic pain perception thresholds did not differ between children with migraine or episodic tension headache. However, children with migraine reported more non-headache pains (gastric and limb) than those children with episodic tension headache.

Drummond (1986) found that migraine sufferers experienced more light-induced pain and glare in the headache-free interval than controls. Based on these findings Drummond suggested that the threshold to stimulation of the special senses is lower in migraineurs, perhaps due to poor inhibitory controls. In a later experiment (Drummond and Woodhouse, 1993), painful stimulation of the forehead increased glare and photophobia in migraineurs between headaches. Drummond and Woodhouse (1993) suggested that migraine-related glare may reflect hyperexcitable visual afferences, and that migraine-related photophobia may be due to activation of trigeminal pathways. This notion is consistent with Vanagaite, Pareja, Støren, White, Sand and Stovner's (1997) suggestion that visual and trigeminal neural pathways may converge at the thalamus. Alternatively, attenuation of inhibitory mechanisms may account for atypical responses (Drummond, 1986). Furthermore, while migraine

sufferers display lower thresholds to light than controls do, visual discomfort in both groups diminishes with repeated stimulation - perhaps demonstrating a general adaptation to light or 'central fatigue' in response to previous stimuli (Vangaite et al., 1997).

Kowacs, Piovesan, Werneck, Tatsui, Lange, Ribas and da Silva (2001) explored the influence of light on trigeminal and cervical pain thresholds. Pressure algometries were performed on the supraorbital, infraorbital, mental and occipital nerves, and temporal muscles. Response to progressively uncomfortable light stimulation was compared immediately after, then ten minutes following the second algometric procedure. Pain perception thresholds were observed to consistently diminish (similar to Vanagaite's 1997 findings for visual discomfort) at all sites in migraineurs; however, a slight but non-significant increase in pain perception thresholds was observed over muscle sites ten minutes following the second algometric procedure. Kowac's findings suggest that light influenced both trigeminal and cervical pain thresholds - further implying that there is an interplay or convergence of visual afferences (sensory circuits) on trigeminal (Vanagaite et al., 1997), as well as cervical nociception.

Interestingly, pain sensitivity of the pericranial musculature was not only found to vary over the course of the day in pain-free volunteers, but women were twice as sensitive as men to painful stimuli (Göbel and Cordes, 1990). Göbel and Cordes applied varying pressure over the superficial temporal and occipital vessels of participants by inflating a cuff around the head at 0200, 0600, 1000, 1400, 1800 and 2200 hours. Diurnal differences in pain sensitivity were not detected at low levels of pain intensity. However, at high levels of pain, sensitivity was greatest at 0200 hours. Given the female preponderance in migraine (Rasmussen, 1995), and that many migraineurs awaken with headache in the morning (Linde, 2006; Linde et al., 2006), Göbel and Cordes' (1990) findings may be relevant in understanding migraine pathophysiology.

While hereditary factors have not been conclusively linked with pain sensitivity, Norbury, MacGregor, Urwin, Spector and McMahon (2007) found that pain sensitivity may indeed have a genetic component. Ninety-eight healthy pairs of twins (51 monozygotic, 47 dizygotic) were exposed to thermal, mechanical and chemical pain-producing stimuli. Sensory scores were then compared using structural equation modeling to provide an estimate of heritability between monozygotic and dizygotic

pairs. Responses to the majority of pain-producing stimuli showed strong genetic components (22 - 55%). Norbury et al. concluded that genetic factors may be important, at least in determining human experimental pain sensitivity. Moreover, as pain sensitivity has been associated with pathological pain, genetic factors, with respect to pain sensitivity, may underlie clinical pain states (Norbury et al., 2007) including migraine headache.

This research compared pain processing in migraine sufferers, interictally, in response to painful stimulation of the head and limb. The aim was to determine the extent of sensitivity of pain pathways in this vulnerable group, and to clarify the roles of trigeminal and general pain mechanisms in the recruitment of vascular and symptomatic responses.

Precipitating factors

Triggers in general

Migraine triggers (or precipitants) are factors alleged to induce headache attacks in predisposed individuals; distinct from predisposing factors, regarded as constitutional, initiating or causal agents (Rasmussen, 1995). Numerous migraine precipitants have been reported (Dowson and Cady, 2002; Lance and Goadsby, 2000; MacGregor, 1999; Perkins and Hartje, 1983; Sandler, Li, Jarrett and Glover, 1995; Seltzer, 1982; Weiss, Stern and Goldberg, 1991) including:

- stress/emotional triggers: anxiety, tension, excitement, depression, shock, frustration
- relaxation after stress
- various foods/irregular meals
- exposure to vasodilators: alcohol, heat, strenuous exercise
- odours, light and noise
- weather/temperature changes, barometric pressure
- insufficient/excessive sleep
- head/neck pain, illness
- trauma to the head
- hormonal changes

It has been suggested that crying may be a commonly underrecognised trigger, particularly when associated with emotional upset (Blau, 1995; Evans, 1998). Emotional crying would presumably be considered stressful and, indeed, stress is a commonly acknowledged migraine precipitant (Passchier,1994; Reynolds and Hovanitz, 2000). Another underrecognised trigger may be water deprivation (Blau, 2005), which is apparently not acknowledged by the medical profession. Blau pointed out that too little or too much of diverse stimuli are reported to provoke headache such as insufficient or prolonged sleep, and during or after stress.

Additionally, variable body temperature (Blau, 2005) and serum glucose levels (Blau, 1966, 2005; Lance and Goadsby, 2000; Perkins and Hartje, 1983; Seltzer, 1982) are also implicated in migraine.

Ice-cream or cold drink has also been reported to trigger migraine (Raskin and Knittle, 1976). Many individuals experience 'ice-cream' headaches, which typically last for twenty to thirty seconds. The swift onset suggests that the pain results from a reflex response triggered by stimulation of the trigeminal nerve (Cheshire and Ott, 2001). Raskin and Knittle (1976) found that ice cream or cold drink resulted in headache in 93% of migaine sufferers compared with 31% of the general population. Drummond and Lance (1984) found that about one-third of migraine sufferers who experience ice-cream headache feel the pain on the same side as their usual migraine headache, suggesting that involved pain pathways are very sensitive in migraine sufferers. Migraine sufferers with typically more severe headache were more likely to to be prone to ice-cream headache.

Dowson and Cady (2002) acknowledge the role that trigger factors play in the genesis of some individual's attacks, but caution that research findings are open to debate. Conclusions are conflicting, particularly regarding diet-induced migraine, and are often based on poorly designed studies. For instance, investigations related to food allergies have been both positive (Egger, Carter, Wilson and Turner, 1983; Garlick, 2004; Monro, Brostoff, Carini and Zilkha, 1980; Peatfield, 1994; Peatfield, Littlewood, Glover, Sandler and Clifford Rose, 1983; Speer, 1971; Schaumburg, Byck, Gerstl and Marshman, 1969) and negative (Medina and Diamond, 1976, 1978; Moffett, Swash and Scott, 1972, 1974). Trigger factors associated with the development of migraine headache were not investigated in the present study; therefore, research dealing with migraine triggers will not be further addressed in this book. The reader is directed to the bracketed references (pages 62-63) for more detailed debate on this somewhat contentious topic. However, stress, a commonly reported migraine trigger, was of interest in this research, so will be discussed next in light of the relevant literature.

Stress: a commonly reported migraine trigger

Headache triggers are generally determined via retrospective self-report questionnaires or are monitored prospectively by diary (Passcheir, 1994). Particular triggers are implicated more frequently than others. Robbins (1994) found that stress (62%) was reported most often, followed by weather changes (43%), missing meals (40%), and bright sunlight (38%). Van den Bergh, Amery and Waelkens (1987) also found that stress (48.8%) was commonly reported in addition to alcohol (51.6%), menstruation (48%) and selected foods (44.7%). Stress is a frequently reported potent factor associated with an imminent migraine attack (Passcheir, 1994; Reynolds and Hovanitz, 2000).

The stress-response has also been measured physiologically in the laboratory involving the measurement of extracranial vasomotor responses in response to stressful stimuli. Facial blood flow was found to increase in migraine sufferers in the temporal artery in response to stress (Drummond, 1984, 1985b). Sympathetic/parasympathetic activity such as heart rate, blood pressure, skin conductance, and stress hormones have also been measured in response to stressful stimuli (Passchier, 1994). Stress hormones have been observed in the blood stream following stressful stimuli (Peroutka et al., 1997). Passchier (1994) cautioned that laboratory data assessing the link between stress and headache may only be relevant in those cases where migraine headache follows shortly after provocative testing (up to 24 hours). However, Passchier (1994) acknowledged that data from migraine sufferers who do not develop headache after experimental conditions may still provide useful subclinical information about abnormal reactions to stress.

Retrospective self-report questionnaire data may not be as useful as prospective diarised data (Köhler and Haimer, 1990; Passchier, 1994). Self-report data is obviously subjective and therefore possibly influenced by individual attributional tendencies. Additionally, as attacks tend to start after the cessation of stress, retrospective data may miss these connections because of the passage of time. An attack might have occurred anyway and stress was wrongly held responsible for its onset (Kohler and Haimer, 1990).

Kohler and Haimer (1990) analysed the diaries of migraine sufferers who recorded headache and stressful events over a six month period. Headache was found to frequently occur on the day of stressful events or the day after. Attacks

rarely occurred three or four days after the cessation of stress. Similarly, Levor, Cohen, Naliboff, McArthur and Heuser (1986) analysed the diaries of migraine sufferers kept for a month, and found that stressful events were greater on headache days than headache-free days. However, unlike Kohler and Haimer (1990), Levor et al. also found that the quality/presence of stressful events for three days before a headache differed to corresponding days before headache-free days. Migraine sufferers in Levor's study experienced more headaches per month (10.71) than in Kohler and Haimer's study (2.4 per month of 1 day duration). As clusters of stressful days appeared to be pathogenic for Levor's (1986) group, perhaps acute stress plays a more prominent role in migraine sufferers with more chronic or frequent attacks.

Clearly, emotional factors, distress, or relaxation after stress, may precipitate migraine attacks. Van den Bergh et al. (1987) suggest that this is probably related to somatic factors associated with the excitation of the autonomic nervous system. Interestingly, migraine sufferers in Van den Bergh's study reported several trigger factors in conjunction with stress, which may be relevant as they may serve as compounding stressors. Together these triggers may tip the migraine-threshold necessary for an attack to ensue (MacGregor, 1996). Alternatively, stress may simply be an early prodromal sign wrongly blamed as being a trigger (Griffen et al., 2003;Van den Berg et al., 1987). If this is the case, perhaps more subtle prodromal signs were overlooked by the more prominent associated anticipatory anxiety in the wake of an impending attack.

Personality traits, psychiatric disorders and stress

Although stress in relation to personality/psychiatric factors were not studied in this book, symptomatic and vascular aspects of the stress-response were explored. Thus, the degree of reactivity to stress following painful/uncomfortable procedures in this study may shed some light on the psychological influences of coping/pain thresholds in migraine sufferers. Indeed, psychological factors have been associated with atypical reactions to various life stressors, particularly with respect to a given

quantity and quality of stress (Henryk-Gutt and Rees, 1973). Personality/psychiatric characteristics in migraine sufferers in relation to stress, are discussed next.

Henryk-Gutt and Rees proposed that certain personality traits may predispose migraine sufferers to experience a greater than average reaction to stressful life events. Stress indeed appears to be a potent migraine precipitant (Passchier, 1994; Reynolds and Hovanitz, 2000). Furthermore, as migraine sufferers and controls experience comparable emotional stressors over the course of their lives, it appears that autonomic hyper-reactivity to stressors in migraineurs may be a factor that predisposes them to attacks (Henryk-Gutt and Rees, 1977). Perhaps atypical autonomic wiring is also associated with vulnerability to develop certain personality traits. Henryk-Gutt and Rees identified several personality traits in migraine sufferers including increased neuroticism (Eysenck Personality Inventory), anxiety and somatisation (Minnesota Multiphasic Personality Inventory), hostility (Buss Scale), and emotionality/psychological symptoms. Certain personality/psychological tendencies found in those predisposed to migraine may further indicate that this group is neurally programmed to experience a greater than average reaction to stressful events (Henryk-Gutt and Rees, 1977). Consistent with these findings, research elsewhere has found that migraine correlates positively with major psychiatric conditions such as depression and anxiety, often in a reciprocal manner (Baskin, Lipchik and Smitherman, 2006; Breslau, Davis and Andreski, 1991; Hamelsky and Lipton, 2006). Additionally, obsessive-compulsive disorder (Baskin, Lipchik and Smitherman, 2006), borderline personality disorder (Saper and Lake, 2002), and personality traits including hostility, suppressed anger and rigidity (Bag, Hacihasanoglu and Tufekci, 2005; Lanzi, Zambrino, Ferrari-Ginevra, Termine, D'Arrigo, Vercelli, Silvestri and Guglielmino, 2001; Passchier, Schouten, van der Donk and van Romunde, 1991), are associated with migraine. Attachment problems have also been linked with migraine (Rossi, Di Lorenzo, Malpezzi, Di Lorenzo, Cesarino, Faroni, Siracusano and Troisi, 2005). Furthermore, there may be a genetic link between certain psychological conditions (e.g., borderline personality disorder) and hemiplegic migraine (Castro, Nunes, de Vries, Lemos, Vanmolkot, van den Heuvel, Temudo, Barros, Sequeiros, Frants, Koenderink, Pereira-Monteiro and van den Maagdenberg, 2008).

Abnormalities of serotonergic, noradrenergic and dopaminergic pathways are implicated in a wide variety of disorders including anxiety, depression, psychosis,

sexual functioning, sleep, cognition, eating, and migraine (Naughton, Mulrooney and Leonard, 2000; Silberstein, 1994). The Tridimensional Personality Questionnaire, designed to measure discrete traits associated with aminergic activity, found that migraine sufferers and tension headache sufferers had higher harm avoidance scores (related to serotonergic activity) than controls. Additionally, migraine sufferers had lower novelty seeking scores (dopaminergic-dependent) and higher persistence scores (glutamine-dependent) than other groups. It was concluded that personality traits associated with dysfunction in serotonergic transmission are common to migraine sufferers and tension headache sufferers. Dysfunction of dopaminergic and glutaminergic tone is specific to migraine (Di Piero, Bruti, Venturi, Talamonti, Biondi, Di Legge and Lenzi, 2001). Boz, Velioglu, Ozmenoglu, Sayar, Alioglu, Yalman and Topbas (2004) used a similar psychometric tool – The Temperament and Character Inventory - but migraine sufferers were not found to deviate from normal in relation to personality dimensions. Since migraine is thought to be a disorder related to abnormal serotonergic tone, somewhat unexpectedly, Boz et al. found that only tension headache sufferers demonstrated higher serotonergic activity related to increased harm avoidance scores.

Other scientists have also found that migraine sufferers have normal personality profiles (Cuypers, Altenkirch and Bunge, 1981; Wise, Mann, Jani and Jani, 1994). The inconsistent research denotes that the psychological correlates of migraine are unclear. However, it is well recognized that headaches generally occur in relation to emotional/psychological stress – albeit that the cause-effect relationship is not certain (Bag et al., 2005). To illustrate this, Merikangas and Merikangas (1993) draw attention to two opposing explanations with regard to the association between migraine and anxiety/depression: either the same etiologic factors are shared in both conditions or, alternatively, that migraine causes anxiety/depression (or vice versa).

Triggers in perspective

The conflicting research/lack of substantial findings, challenges the notion of a firm role for triggers in migraine (Dowson and Cady, 2002). Nevertheless, 85% of migraine sufferers attribute their attacks to various internal and external triggers (Van den Bergh et al., 1987). Triggers differ between individuals and even across attacks in the same individual (MacGregor, 1999; Rasmussen, 1995; Turner, Molgaard, Gardner, Rothrock and and Stang, 1995; Van den Bergh et al., 1987). Most migraine sufferers report that several triggers in unison, rather than in isolation, are linked to migraine onset, such as high stress levels and alcohol consumption during menstruation (Robbins, 1994; Van den Bergh et al., 1987). Perhaps a combination of genetic, internal and precipitating factors are needed to challenge the migraine threshold before an attack can ensue (MacGregor, 1996; Van den Bergh et al., 1987).

Precipitants generally change over the lifespan, e.g., missed meals and late nights when young, neck and dental problems later in life (MacGregor, 1999). Furthermore, Van den Bergh et al. (1987) found that the prevalence of triggers tended to increase proportionally to aging and duration of illness. This trend was attributed to greater familiarity with triggers due to increasing exposure to attacks over time. However, as it may be difficult to differentiate suspected triggers from prodromal symptoms, such as food cravings or photophobia, suspected triggers may simply be an early migraine symptom (Dowson and Cady, 2002; MacGregor, 1999) mistakenly assigned as a trigger. Alternatively, the emotional impact of an associated trigger may lead to a conditioned response (Lance and Goadsby, 2000). Hence, the mere sight or thought of a supposed trigger, even if harmless, is ascribed an offensive role and declared a trigger.

The variability of reported migraine triggers - between individuals and from attack to attack in the same individual - suggests that migraine sufferers have varying sensitivities to environment changes, which may be based on varying individual responses/neurochemistry. Specifically, environmental changes may initiate a 'neural shift' or neurochemical response which manifests as a key trigger factor in vulnerable individuals (Turner et al., 1995).

Indeed, migraine frequently occurs spontaneously without any obvious trigger (Dowson and Cady, 2002; Lance and Goadsby, 2000). Additionally, the cyclical regularity and pattern of attacks, e.g., migraine on awakening, has prompted the

notion that an internal mechanism may be involved akin to a 'biological' or 'circadian' clock (Lance and Goadsby, 2000). Despite the apparent constitutional (Rasmussen, 1995) nature of migraine, Lance and Goadsby (2000) recommend that trigger factors need to be explored in the patient's history as their avoidance may reduce the frequency and severity of migraine headache. However, some scientists disagree with the concept of avoiding triggers; instead insisting that avoidance of precipitants may serve to heighten sensitivity to triggers (Martin, 1999, 2001; Martin, Reece and Forsyth, 2006). In this case greater exposure to the offending agent is recommended to desensitize the susceptible individual to the trigger in much the same way that phobias are treated in anxiety disorders (Andrews, Crino, Hunt, Lampe and Page, 1995).

Medina and Diamond (1978) suggested that some triggers, at best, may set the pace for headaches, but it is doubtful that they produce new ones. This notion was based on findings that alcohol, chocolate or fasting occasionally triggered headaches, whereas headache frequency remained constant despite dietary manipulations. However, Drummond (1985) found that frequency of migraine, tension-vascular, and tension headache, was associated with certain precipitating factors. Specifically, psychological factors (social problems, depression) and symptoms of muscular contraction (frowning, neck pain) were more often associated with constant headache than episodically-recurring headache. Jaw clenching or teeth grinding was only reported by migraine patients.

Chabriat, Danchot, Michel, Joire and Henry (1999) found that frequently reported precipitating factors, particularly fatigue/sleep, stress, diet, menstruation, temperature/weather changes, and illness were identical in migraineurs and non-migraineurs. However, all these factors, except illness, were reported more frequently in migraine sufferers, indicating that the degree of sensitivity to these triggers differed between groups. Maybe, as Drummond (1985) proposed, there is a continuum between migraine and tension headache, and those closer to the migraine end of the headache spectrum are more sensitive to certain precipitants.

Mechanism of migraine

Brain stem involvement

Brain stem and hypothalamic disturbance often precede migraine, and focal brain stem activity develops during attacks (Weiller et al., 1995). Weiller et al. explored neuronal activity during migraine attacks using positron emission tomography to examine regional cerebral blood flow as a reference. Increased blood flow was found in brain stem regions corresponding to the dorsal raphe nuclei and locus coeruleus, suggesting increased neural activity in this area. This finding led to the concept that the brain stem may in fact be the migraine "generator". Specifically, it was proposed that in migraine sufferers an abnormality might lead to an imbalance in brain stem regulation of the normal control of cerebral blood vessels and pain. Furthermore, brain stem dysregulation seems specific to migraine, since it was not observed during cluster headache (Bahra, Matharu, Buchel, Frackowiak and Goadsby, 2001; May, 2003).

The trigeminovascular system and migraine

There is considerable evidence that migraine headache is associated with trigeminal nerve activation (Williamson and Hargreaves, 2001). This nerve contains sensory and motor components but the sensory division, in particular, appears to be associated with migraine pathophysiology (Borsook, Burstein, Moutlton and Becerra, 2006).

The trigeminal nerve, the fifth and largest of the cranial nerves, has three divisions: the ophthalmic, maxillary and mandibular. The central fibres of all three divisions enter the brain stem, and project to the pons or medulla, or enter the spinal trigeminal tract. Sensory information from the face and forehead, including pain, thermal and tactile sensations, are conveyed to higher brain centers via this nerve. Cerebral blood vessels and dura mater are innervated by branches of the trigeminal nerve. Specifically, the trigeminovascular system - a collection of specific cell bodies

located in the trigeminal ganglion of the trigeminal nerve - regulates vascular activity. The trigeminal ganglion houses bipolar nerve cells, as well as synaptic links from the periphery to blood vessels including the pain-producing large cranial vessels and dura mater. Centrally projecting fibres synapsing in the caudal brain or upper cervical cord (C_2, C_3) are also contained in the trigeminal ganglion (May and Goadsby, 1999). The trigeminal nerve regulates the vasculature of the pia mater (Mayberg, Langer, Zervas and Moskowitz, 1981), forebrain and the rostral basilar artery (Arbab, Wiklund and Svendgaard, 1986). Additionally, the cerebral (middle cerebral artery) and extracerebral (middle meningeal artery) circulation is influenced by the trigeminal nerve (O'Conner and van der Kooy, 1986). Nerve fibres that project from peripheral and central arms of the trigeminovascular system provide pathways for the transmission of pain signals from cranial vessels to brain centers involved in pain sensation (Borsook, et al., 2006).

Migraine has long been considered a vascular headache (Lance, 1993; Williamson and Hargreaves, 2006). Consistent with this notion, elevated levels of the vasodilator calcitonin gene-related peptide were identified during the headache phase of migraine, which was assumed to be released from activated trigeminal nerve fibres (Goadsby et al., 1990). The finding that calcitonin gene-related peptide has a powerful effect on cranial blood vessels (Edvinsson, Ekman, Jansen, McCulloch and Uddman, 1987) indeed supported the belief that migraine may be a disorder characterized by distention of cerebral blood vessels. Additionally, the throbbing quality of migraine headache, the sometimes conspicuous dilatation of extracranial vessels, and the recognized pain sensitivity of cranial blood vessels, further implied that migraine may be linked to trigeminovascular mechanisms (Lance, 1993). Lance proposed that an unstable trigeminovascular reflex, in conjunction with a fault within pain control pathways, may underlie the pathogenesis of migraine.

Susceptibility to migraine, in the first place, is presumedly due an underlying innate 'migrainous threshold', delicately balanced depending on excitation or inhibition within the nervous system. Given this vulnerability, a number of key players in the brain are then implicated in the generation of migraine headache. The cerebral cortex responds to stressful stimuli and the thalamus to afferent stimuli such as glare or noise. The hypothalamus detects changes within the body and the internal/external carotid blood vessels respond to vasodilators. The nucleus raphe dorsalis and the locus coeruleus communicate with the cortex via serotonergic and

noradrenergic neurochemical pathways. Additionally, the nucleus raphe dorsalis and the locus coeruleus regulate the internal/external carotid circulation via parasympathetic efferent pathways shared by the facial nerve (seventh cranial nerve) and the trigeminal nerve, to increase blood flow in both circulations. The pain control pathway extends from the periaqueductal gray matter of the mid brain and incorporates the serotonergic nucleus raphe magnus in the medulla and locus coeruleus in the pons (Lance, 1999). Stimulation of the locus coeruleus leads to the discharge of norepineprine from the adrenal medulla (Goadsby, 1985), which may be a catalyst for the discharge of serotonin systemically (Lance, 1999). Lance suggests that these mechanisms may explain brain and vascular activity responsible for the aura and headache of migraine.

Despite the appealing logic of increased cerebral blood flow resulting in migraine headache, vasodilatation does not necessarily equate to headache. For example, the headache of migraine with aura frequently begins while blood flow is restricted (Olesen, Friberg, Skyhøj Olsen, Iversen, Lassen, Andersen and Karle, 1990). Furthermore, severe headache has also been observed during vasoconstriction following subarachnoid haemorrhage (Macfarlane, 1993). Macfarlane suggests that vasodilatation is more likely to be an 'epiphenomenon' to nociceptive or sensory nerve activation, rather than the cause of it. Stimulation of trigeminovascular axons evokes a neurogenic inflammatory response within cephalic tissue involving the release of the vasoactive neruopeptides substance P, neurokinin A, and calcitonin gene-related peptide, from perivascular axons. Vasodilatation, plasma protein extravasation and pain ensue (Moskowitz, 1993). Moskowitz points out that triggers of the trigeminovascular reflex are unclear but probably involve neurochemicals which develop within brain parenchyma. After the provoking stimulus is removed, the sensitization of sensory nerve endings, a result of the inflammatory reponse, may perpetuate pain (Macfarlane, 1993).

Sensory and trigeminal stimuli

During the aura, sensory and trigeminal stimuli appear to provoke reflexes that relay in the brain stem and initiate a brain stem disturbance in migraine sufferers. In

particular, sensory stimuli increase intensity of headache and other symptoms of migraine during (Linde, 2006) and outside attacks (Kowacs et al., 2001), and also trigger attacks (Debney, 1984; Scharff et al., 1995; publication related to this book, Granston and Drummond, 2005). Additionally, head pain increases discomfort to sensory stimulation (Drummond and Woodhouse, 1993; Woodhouse and Drummond, 1993). Even seemingly innocuous visual and auditory stimulation is commonly associated with migraine headache (Goadsby, 2001), which supports further the notion of an underlying brain stem disturbance in migraine sufferers. Drummond (1997) suggests that hypersensitivity of the special senses during migraine attacks may be due to the loss of normal inhibitory controls, resulting in increased sensory discomfort and aggravation of headache.

It is well documented that migraine headache can be triggered by physiological and psychological factors. The initiation of migraine is thought to involve activation of peripheral sensory fibres, which, in turn, initiate changes in cranial blood vessels and dura mater. Alternatively, the initiation of attacks may reflect mechanisms involving the activation of descending pathways in the brain that facilitate pain signals, or the suppression of descending pathways that inhibit pain processing in the spinal cord (Edvinsson and Uddman, 2005).

Influence of the stress-response

Stress, a commonly recognized trigger of migraine (Passchier,1994; Reynolds and Hovanitz, 2000), may also contribute to the quality of the attack once in motion. Brain stem mechanisms associated with migraine headache may, in part, be triggered from the cerebral cortex in response to stress (Lance, 1993).

The brain itself is largely insensitive to pain (Lance, 2000); therefore, intracranial pain is probably generated from intracranial blood vessels. Blood vessels are supplied with nuclei in ganglia that form part of the sympathetic, parasympathetic and the sensory nervous systems (Edvinsson and Uddman, 2005). This neuroanatomy, particularly the presence of autonomic receptors in blood vessels, implies that the stress-response in migraine most likely has a role in the disorder - be it in the initiation of an attack, or its perpetuation. For example, it has been

suggested that intense activation of central pain pathways may involve the superior salivatory nucleus leading to parasympathetic activation, thus resulting in the release of the parasympathetic neuropeptide vasoactive intestinal peptide and the manifestation of facial symptoms such as flushing or lacrimation, observed in cluster headache and migraine (Edvinsson and Uddman, 2005; Knight, 2005).

Lance (1993) proposed that an unstable pain control system in migraine sufferers may render them vulnerable to recurring attacks. Stimulation from higher brain centers, such as the cortex or hypothalamus during stress or emotion, or excessive afferent input from the special senses, or cerebral or extracranial vessels, may provoke defective discharge of the pain control system in individuals vulnerable to migraine.

Characteristics peculiar to those vulnerable to migraine

Atypical hyperexcitable vascular and sensory reactivity has been observed in migraine sufferers between attacks, which may underlie susceptibility to recurring attacks. Furthermore, migraine sufferers share several characteristics, which may also render them vulnerable to the disorder. Characteristics peculiar to those susceptible to migraine include:

- motion sick prone - evidence of brain stem disturbance in motion sickness
- persistence of photo/phonophobia
- persistence of scalp tenderness– hyperalgesia/allodynia
- altered pain thresholds
- exaggerated stress-response

These characteristics were previously discussed, pages 35-69 of this chapter. The caveat to these findings is that it is not certain what is cause or effect in terms of what predisposes one to migraine or whether these features are purely symptoms of the migrainous brain/predisposition. Either way these factors may predispose the susceptible person to repeated attacks.

Indeed, painful stimulation of the face/head in migraine sufferers interictally, increased photophobia and trigemino-parasympathetic reflexes such as extracranial vasodilatation (Drummond, 1992; Drummond, 1997; Drummond and Woodhouse, 1993); symptoms typically observed during migraine attacks. Sometimes a full-blown migraine attack can even follow provocative procedures such as painful stimulation of the trigeminal nerve (see publication related to this book, Appendix 14, pages 445). Furthermore, hyperalgesia and photophobia followed optokinetic stimulation-induced motion sickness (Drummond, 2002). Optokinetic stimulation and painful stimulation might well be considered stressful events; therefore, the stress-response probably played a role in evoking vascular and sensory responses observed during these procedures. It appears that once the head hurts, other symptoms follow, e.g., photophobia or nausea. On the other hand, the presence of motion sickness further challenges responses to sensory stimuli (Drummond, 2002).

Proposed mechanisms underlying susceptibility to recurring attacks of migraine in migraine sufferers

Mechanisms underlying susceptibility to recurring attacks of migraine probably involve the following components:

- Sensitization of brain stem nuclei, or disruption to brain stem mechanisms that normally inhibit sensations of head pain, increases headache and sensory discomfort.
- Sensory stimuli most likely intensify sensitization of brain stem nuclei.
- Trigeminovascular reflexes probably aggravate brain stem disturbances responsible for some of the symptoms of migraine.

Whether this reciprocal vascular and neurochemical cascade in the brain stem is externally or internally triggered, or is simply a spontaneous discharge based on a persistent subclinical or a cyclical brain stem disturbance, is not certain. However, it

seems likely that the stress-response influences the initiation and development of symptoms of migraine.

Neural pathways that generate symptoms of migraine may be shared with those responsible for motion sickness. Migraine headache begins with a disturbance in the brain that resembles the effects of motion sickness, and symptoms of migraine and motion sickness are remarkably similar. Therefore, in the susceptible individual, activation of these pathways, regardless of the condition, may explain the recruitment of analogous symptoms.

General overview of this book

This book investigated cause-effect relationships between symptoms of migraine and extracranial vascular reactivity to various stimuli in one central experiment comprised of six experimental conditions. Migraine sufferers were tested in the headache-free interval and compared to healthy controls who rarely experience headache. Participants were exposed to optokinetic stimulation and painful stimulation of the temple or non-dominant hand, individually and in combination. Each condition was investigated independently, and findings were then compared across conditions. The purpose of each condition and the rationale for selected condition comparisons are presented in the introductory text of the results/discussion chapters for each condition (refer to Chapters 5 to 12). Specific hypotheses and expectations are also presented in the introductory section of these chapters.

The key assumptions and hypotheses that underlie this book are as follows:

- A cyclical covert brainstem disturbance between episodes of migraine increases sensitivity to recurrent attacks.
- Brainstem disturbances, sensory stimulation, and inflammation of tissue surrounding blood vessels, mutually interact to reinforce one another. This interaction may trigger attacks of migraine and might also underlie a vicious-circle of escalating headache and other migrainous symptoms during attacks.

- The physiological disturbances that underlie motion sickness are similar to those of migraine.
- Anticipating stressful stimuli will provoke physiological responses that may be accentuated in migraine sufferers.
- Pain processing may be compromised in migraine sufferers.

CHAPTER 2

METHODOLOGICAL CONSIDERATIONS

Questionnaire

Participants were asked to complete a questionnaire ('confidential details form') where they detailed features of their headaches including triggers, and also motion sickness susceptibility. Appendix 2 (page 276) has a copy of the questionnaire.

Headache triggers

Participants were asked to consult a checklist about their headache triggers. The compilation of this checklist was based on some key references (Chabriat, Danchot, Michel, Joire and Henry, 1999; Debney 1984; Evans 1998; Martin and Seneviratne 1998; Medina and Diamond 1978; Perkin and Hartje, 1983; Seltzer, 1982).

Motion sickness items

Questions about motion sickness susceptibility were adapted from Golding's (1998) Motion Sickness Susceptibility Questionnaire Revised (MSSQ-R). Golding reported that the internal reliability of the whole scale was high (Cronbach's standardised item alpha of 0.86) and the split-half reliability was 0.77. Correlations across several studies showed the validity of the scale in predicting tolerance to motion sickness exposure averaged r = 0.45 (range, 0.14-0.72). Only the adult section of the MSSQ-R was used in this study, and 3 additional items were added (omni theatre, simulators, reading in the car

The nature and duration of motion sickness after exposure was also investigated. Symptoms experienced, their intensity (0 = not present, 10 = extremely intense), how long symptoms persisted, and frequency of vomiting, was noted. The participant was also asked if they experienced vertigo or dizziness independent of headache. Cutrer and Baloh (1992) found that nearly 50% of migraineurs (with and without aura, and

recurrent aura without headaches) reported that episodes of dizziness would linger for more than 24 hours, and that many of these episodes were independent of headache. Elsewhere, vertigo not associated with headache was reported more often in migraine (in particular, with aura) patients than in controls (Kuritzky, Dewey, Ziegler and Hassanein, 1981). These researchers also found that motion sickness during headache-free periods was significantly more frequent in migraine with aura patients (42%), and in a high percentage (25%) of those without aura when compared with controls (17%). They concluded that the migraine with aura group probably have an especially sensitive vestibular system, while those without aura showed a tendency to vestibular impairment.

Subjective measures

Participants were asked to rate their experience of motion sickness during each procedure. Five symptoms were rated. These included what Harm (1990) referred to as the two cardinal symptoms of the syndrome, nausea and change in body temperature. The other symptoms rated were those Harm called 'associated' or more variable in their occurrence and time course: dizziness, drowsiness and headache. Participants were also asked to rate how 'unpleasant' the symptoms felt. They also rated the 'intensity' and 'unpleasantness' of pain eliciting tasks using ice as the stimuli. Physiological correlates describing motion sickness (Reason and Brand, 1975) and pain (Melzack and Wall, 1988) are well accepted. Emotional distress and the role this plays in pain perception has also been acknowledged (Bishop, Holm, Borowiak and Wilson, 2001), as have individual characteristics (i.e., level of anxiety, previous experience) in mediating motion sickness (Grunfeld and Gresty, 1998). Hence, the rating scales in the present study included physiological and emotional ('unpleasantness') indicators for motion sickness and pain. All items on the rating scales required a response between 0 (not noticed) to 10 (extreme).

Methods used, including time intervals between reports for obtaining subjective ratings of pain, vary widely (Loftin, Zeichner and Given, 1998), and the same might be suspected of self-report ratings generally. The present study required the participant report on between 8 to 10 items (nausea, body temperature, dizziness, drowsiness, headache, self-motion, visual illusion, unpleasantness, ice intensity, ice

unpleasantness) at one time, depending on the condition being tested. It was decided, based on earlier trials in the laboratory, self-report at 2 minute intervals would allow enough time for the person to concentrate on the task at hand and not be distracted by too frequent self-reporting. It was also estimated that this time would be sufficient to pick up gradual changes throughout the testing period.

Optokinetic Stimulation

This study involved observing reactions to optokinetic stimulation. Exposure to the optokinetic drum is a well-established way of inducing symptoms of motion sickness in susceptible individuals (Cheung and Vaitkus, 1998). The neurophysiology of motion sickness is extremely complex and has been described in several reviews (Crampton, 1990; Harm, 1990; Yates, Miller and Lucot, 1998). Numerous structures, pathways and mechanisms are implicated and the brain stem plays an essential as well as coordinating role in the circuitry. Stern, Koch, Leibowitz, Lindblad, Shupert, and Stewart (1985) claim that the optokinetic drum induced symptoms of motion sickness in approximately 60% of healthy subjects. In a later study (Stern, Koch, Stewart and Lindblad, 1987) 66% of healthy subjects were affected.

Nociceptive stimuli: ice

Mechanical and electrical stimuli have been used effectively to evoke pain experimentally. Additionally, the cold pressor procedure has shown validity as a laboratory pain analogue (Melzack, 1983). In this study, the pain stimulus was ice.

To stimulate the trigeminal nerve, ice was applied to the temple. The trigeminal nerve is associated with head pain in migraine and involves reflexes that relay in the brain stem (Lance, 1993; Macfarlane, 1993; Moskowitz, 1993; Weiller, May, Limmroth, Jŭptner, Kaube, Schayck, Coenen and Diener, 1995).

To stimulate nociceptors elsewhere in the body the participant immersed their fingers and palm in ice-water. These experiments involved observing reactions to painful stimulation in the body (non-specific pain) away from the trigeminal area. Burstein, Cutrer, and Yarnitsky (2000) found cutaneous allodynia away from the

referred pain area of the head during a migraine attack. They found that allodynia developed gradually and extended from the head to the forearms. They suggested that central sensitisation and cutaneous allodynia developed 1-2 hours after the activation of peripheral nociceptors in the trigeminal-vascular pain pathway. This activation was then thought to have resulted in intracranial hypersensitivity, which led to the activation of nearby second-order neurons and then third-order neurons. This state, they hypothesised, was the precursor to the development of cutaneous allodynia. Drummond (2002) reported increased pain ratings in the fingertips of migraineurs during the headache-free interval compared to controls, directly after optokinetic stimulation. Allodynia was not related to the intensity of nausea or headache during motion sickness so the mechanism of this non-cranial pain was unclear. However, Drummond speculated that mechanisms to account for allodynia beyond the referred pain area in migraineurs could be due to faulty central-pain modulating mechanisms. The present study was interested in further observing sensitivity to pain in the body away from the trigeminal area during the headache-free interval in migraine sufferers. The plan was to compare findings between the trigeminal stimulation tests and the non-specific painful stimulation tests, independently and in relation to optokinetic stimulation.

CHAPTER 3

METHOD

Participants

A total of 50 individuals, 27 migraineurs and 23 healthy controls of similar age and sex distribution, participated after giving informed written consent. The University Human Ethics Committee approved the study. The migraine group consisted of 22 women and 5 men (mean age 40.7 + 11.2 years; range, 20 to 59 years) who met the International Headache Society (I.H.S.) (1988, 2004) criteria for migraine. Three participants had migraine with aura and 24 had migraine without aura. Participants were screened for absence of other medical problems and were not taking ongoing medication for migraine. Headache frequency was on average 2 per month. To relieve attacks 5 individuals took imigran and 2 ergodryl, but the majority took analgesic, anti-inflammatory, or caffeine based remedies. Some supplemented with anti-emetics. Twenty-three from this group reported a family history of migraine; the remainder did not. The control group consisted of 17 women and 6 men (mean age 39.7 + 11.8 years; range, 18 to 62 years) who reported less than 12 headaches per year that did not meet the diagnostic criteria for migraine. All but 6 controls reported experiencing occasional mild headache. The other 6 controls reported experiencing 1 to 3 more intense headaches per year. These more intense headaches were described as lasting from 20 minutes to an hour, predominantly associated with tension or sinusitis and generally resolved without treatment. Analgesics, when used, included paracetamol or aspirin, which relieved the headache within 20 minutes. Only 5 individuals in the control group reported a family history of migraine. Participants were enlisted by public advertisement (local and state newspapers), from the Migraine Support Group and the university population. Each participant was invited to take part in 3 separate sessions spaced, on average, a month apart. They were paid in total $35 for their assistance ($10 session 1, $10 session 2, $15 session 3).

Experiments were carried out when individuals were headache-free for at least 4 days, and medication and alcohol free for at least 24 hours. One migraineur, prior to her second testing session, commenced a course of celecoxib for an inflamed knee joint, then diclofenac for the same problem prior to her last testing session. Before these sessions she withheld taking the drug for 72 hours to ensure they cleared from her system. Participants were also required to fast for 2 hours prior to testing and to avoid cigarettes for this period. Females were tested between menstrual periods. As procedures used in this study had the potential to trigger a headache in susceptible individuals, migraineurs were advised to bring their medication to testing sessions. If required, the service of the University Health Centre was available: 2 migraineurs made use of this service once. Transport home was available for those not well enough to drive but this facility was not used.

Five participants did not complete the 3 testing sessions (4 migraineurs, 1 control) and withdrew after session 1. Two from the migraine group commenced prophylactic anti-migraine medication, which meant they no longer met inclusion criteria. The remaining 2 migraineurs withdrew due to experiencing unabated nausea and headache after testing for up to a week. The control subject discontinued because of time restraints from personal and work commitments.

Appendix 1 (page 275) has a copy of the consent form given to participants.

Apparatus

Questionnaire

Participants were asked to give details about their headaches including triggers, and also about motion sickness susceptibility. The experimenter interviewed and guided each participant through the questionnaire. General medical status including history was

established. Migraineurs indicated if their migraine was previously diagnosed but all subjects, including controls, were reviewed about the quality of their headaches according to the I.H.S. criteria. Participants were also questioned on frequency, intensity, duration and location of their headaches and about family history of migraine. Medication used to treat headache, and use generally, was investigated to ensure individuals met inclusion criteria (no prophylactic medication).

All participants were asked about their headache triggers; and migraineurs, whether they observed a difference between headache and migraine triggers. Triggers were presented in checklist form, grouped under: 'psychological', 'physiological', 'external', and 'others' (not mentioned in the checklist). Responses required either: 'yes', 'no' or 'unsure'; and relevant details were noted against particular triggers.

Appendix 2 (page 276) has a copy of the questionnaire given to participants.

Headache Diary

Both groups were instructed to record details of their headaches between each testing session, and for 1 week after the final session. They were supplied with a 'headache diary' and 'headache details form' booklet to fill out daily for this purpose. Even if they were headache-free this was still noted in the diary. The 'headache diary' asked participants to note the time, intensity (0 = no headache, 10 = extremely intense), headache trigger, and treatment for the attack. If a headache was more than mild (>3) they were asked to complete the 'headache detail forms' booklet, where they supplied more detail about the attack. In this book they recorded the location of head pain, signs and symptoms and the intensity every 8 hours until the headache resolved. To address signs and symptoms they were asked to consult a checklist which included: sensitivity to light and sound, nausea, vomiting, sweating or increase in body temperature, dizziness, drowsiness, headache, and aura. Individuals noted any additional signs or symptoms not on the list.

Appendix 3 (pages 284-290) has copies of the 2 booklets given to participants for recording headache occurrence. The diaries between sessions covered 32 days to allow for the required 3-4 week interim between testing sessions. The booklets also covered a 7-day period after the final session.

Subjective measures

Participants were asked to rate their experience of motion sickness during each procedure. Five symptoms were rated including nausea, body temperature, dizziness, drowsiness and headache. Participants were also asked to rate how 'unpleasant' the symptoms were. Additionally, they rated the 'intensity' and 'unpleasantness' of pain eliciting tasks using ice as the stimuli. All items on the rating scales required a response between 0 (not noticed) to 10 (extreme).

Circular vection was assessed during optokinetic stimulation by having the participant report on 'self-motion' (sensation of self-rotation though stationary) and 'visual illusion' (visual change in the stripes inside the drum). Reponses required either 'none', 'some', or 'complete'.

Subjective ratings were recorded at 2-minute intervals and the researcher recorded responses on a series of forms.

Appendix 4 (pages 291-295) has a copy of the rating scales given to participants and forms used by the researcher to record participant self-ratings during the experiment.

Nociceptive stimuli

To stimulate the trigeminal nerve, an ice block 3.5 centimetres square held by a short stick, was applied to the temple. To stimulate nociceptors elsewhere in the body the participant immersed the fingers and palm of their non-dominant hand in a foam box (24 cm long, 14 cm wide, and 14 cm high) containing a mixture of 8 cups of crushed ice to 8 cups of tap water, giving a temperature of 2 degrees Celsius. The participant alternated the placement of this hand between the ice-water and an identical container of water at *32*

degrees Celsius. The purpose of placing the hand into the warm water was to standardise hand temperature prior to being placed in the ice-water. The temperature in the second container was obtained by mixing 9 cups of tap water with 2 cups of boiling water. This testing session entailed 2 testing blocks of approximately 25 minutes each and over each block the water temperature dropped gradually by about 2 degrees in the second container. In the ice-water container, the temperature remained at 2 degrees Celsius over this time. Both foam boxes, however, were rejuvenated at the commencement of the second testing block. A thermometer remained in each container throughout testing to monitor the temperatures.

Optokinetic Drum

The drum consisted of a metal cylinder 50 centimetres in diameter and 70 centimetres in height. The interior was covered with alternate black and white vertical stripes 3.3 centimetres wide. The participant sat still on a chair with their head and shoulders inside the drum, which rotated 10 times per minute.

Appendix 5 (page 296) illustrates the optokinetic drum and positioning of the participant.

Physiological Equipment

Pulse volume was detected via a Polygraph Data Recording System (Grass Instrument Model 79E, Quincy, U.S.A.). Physiological information was transferred to a BIOPAC Systems Analogue/Digital Channel Receptor and MacPacq, MP100, 16 Bit (BIOPAC Systems, U.S.A.). Data was then sent to a personal computer and the AcqKnowledge (version 3.01, BIOPAC Systems, U.S.A.) computer programme recorded input. The BIOPAC System and the acqKnowledge programme were prepared to obtain 2 channels (A1 = right pulse volume; A2 = left pulse volume) at 100 samples per second

for 45 minutes. The AcqKnowledge version 3.71 programme was later used to transform and analyse output.

Pulse Volume

Pulse volume was estimated by measuring blood flow close to the surface of the skin of the temples via pulse transducers. Before the transducers were attached, the skin was cleaned with an alcohol swab. A photoelectric pulse transducer (photo plethysmograph, Grass Instrument, Quincy, U.S.A.) was attached with a double-stick disc (MEDITEC) approximately 4.5 centimetres above the top of both ears and 8.5 centimetres forward of this point over the vicinity of the anterior branches of the superficial temporal blood vessels (see Figure 3.1). A black lightproof headband was placed over the transducers to ensure light emitted via the transducer reflected back into the instrument when blood moved through the skin, and was not affected by outside light.

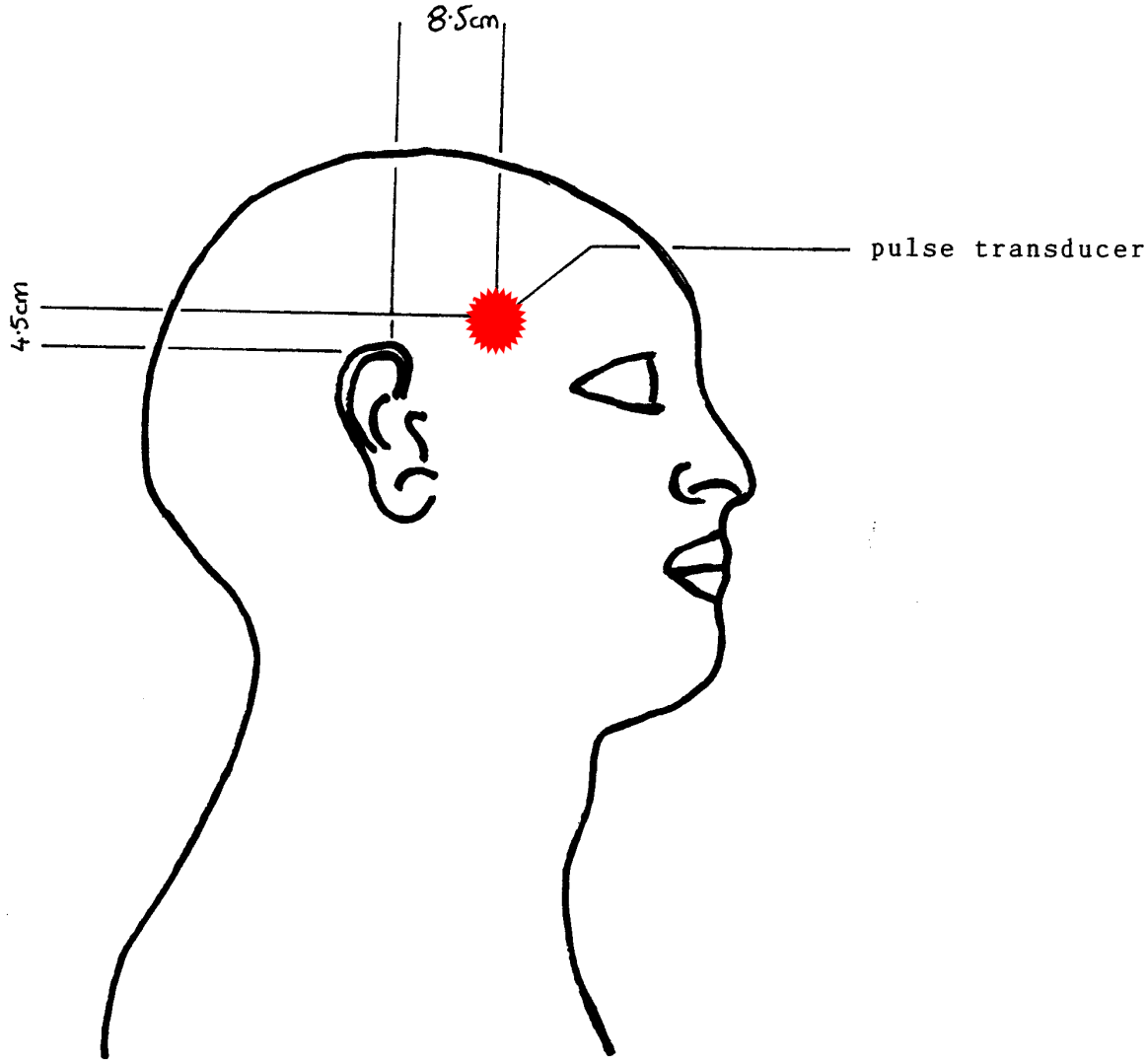


Figure 3.1. Positioning of pulse transducers on the temples

Testing Area

The participant was tested in a small electrically shielded room (1.6m x 1.5m) to reduce the effects of interference from extraneous electrical artifacts on physiological signals. The optokinetic drum and the sensors for the pulse transducers were housed in this room. The experimenter and remaining physiological recording equipment were positioned next

to the participant's room. Communication between rooms was via a small earplug and a microphone clipped to the collar. A stopwatch was used to time recordings throughout testing.

Research Design and Analysis

This was a factorial experiment as the effects of more than 2 independent variables were studied simultaneously. Participants were exposed to 6 separate experimental conditions. Statistical analysis was performed using the Statistical Package for the Social Sciences 11.5 for Windows. Within-subjects and between-subjects factors were investigated by mixed analyses of variance, the general linear model for repeated measures statistic. Post hoc tests were performed using paired t-tests to compare responses within groups and independent t-tests to compare those between groups. The within-subjects design minimizes error variance (Grimm, 1993; Kerlinger, 1986) and strengthens power (Grimm, 1993). To reduce adaptation effects the 3 sessions were spaced 3 to 4 weeks apart. This break also allowed for the time between menses required for female participants. To minimize order effects participants were equally allocated to 1 of 6 combinations of test orders in the 3 sessions. Table 3.1 shows the number of migraine sufferers and controls in each of the 6 testing orders. Each session involved 2 testing parts (see figures 3.2, 3.3 and 3.4).

Quantifiable subjective data was collected at 2-minute intervals for all experimental conditions, and physiological data was recorded continuously. The AcqKnowledge programme version 3.71 was used to transform physiological data. Pulse amplitude was calculated as the mean difference between the peak and trough of the pulse wave using acqKnowledge software.

Test Order	Sessions			N	
	1	2	3	Migraineurs	Controls
1	1 + 2	3 + 4	5 + 6	4	4
2	1 + 2	5 + 6	3 + 4	4	5
3	3 + 4	1 + 2	5 + 6	4	3
4	3 + 4	5 + 6	1 + 2	5	4
5	5 + 6	1 + 2	3 + 4	4	4
6	5 + 6	3 + 4	1 + 2	4	3

Table 3.1. Number of participants in each testing order

Key: 1 = OKS alone
2 = ice to temple after OKS
3 = ice to temple before OKS
4 = OKS + ice to temple
5 = hand ice-water before OKS
6 = OKS + hand ice-water

Procedure

At the first testing session the participant was asked to fill out the questionnaire on headache details including triggers, and motion sickness susceptibility. They were guided through this form with the experimenter. Following this they were tested according to the session and conditions they were allotted. After testing, and prior to leaving, they were given the headache diary and the headache details booklet and instructed how to fill them in. They were advised that a summary of the instructions given in this session was on the inside cover of each booklet. Subsequent sessions involved the researcher initially going through the returned diary with participants to ensure information was adequately recorded. The booklets were reissued at the end of each of the next 2 sessions, and in the last session a reply paid envelope was given to participants not on campus, so they could return the diary.

Prior to each testing condition the self-rating scales were explained to the participant. Participants with mobile phones were asked to turn them off as they may interfere with physiological recording during testing. The pulse transducers were placed on the temples. Finally, the communication headset was placed on the individual.

The same researcher carried out procedures and recordings throughout the study in a laboratory maintained at a temperature of 22 degrees Celsius ($\pm$ 1.5^{o} C). Participants

were encouraged to complete all 3 testing sessions although they were free to withdraw at any time. Testing sessions were 3 to 4 weeks apart, although a few participants (particularly migraineurs) had longer breaks between sessions due to not meeting pre-testing requirements. Each session comprised 2 testing conditions of approximately 25 minutes each. The gap between the end of the first condition and commencement of the next was 8-10 minutes. This period allowed for preparation of the pending condition (eg. moving in or out of drum, setting up pain eliciting apparatus).

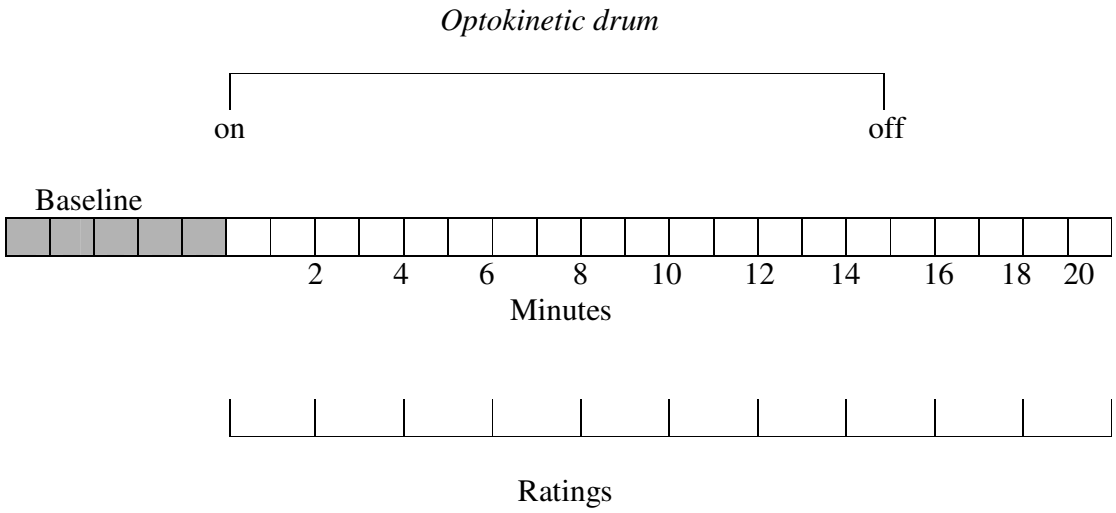
Optokinetic stimulation

The participant was instructed to sit still with their head and shoulders inside the optokinetic drum. They were told that once the drum began revolving to look straight ahead and were asked to keep their eyes open. They were asked to look beyond the stripes and to avoid changing focus or tracking the stripes. They were advised the drum would revolve for a maximum of 15 minutes but if they felt they were about to vomit they should tell the experimenter and the drum would be turned off. They were also requested not to speak during testing, apart from reporting to the experimenter as instructed.

For the first 5 minutes a baseline was recorded while the participant sat still in the non-revolving drum. During this period they were asked to rate the 5 symptoms of motion sickness and unpleasantness. At the completion of baseline recording they were reminded that the drum was about to start. After the drum started, self-ratings continued at minutes 2, 4, 6, 8, 10, 12, and 14, and they also rated self-motion and visual illusion. The drum was turned off at minute 15. The participant was advised of this beforehand to avoid being startled. They remained seated inside the drum for a further 5 minutes while self-ratings (excluding self-motion and visual illusion) continued for minutes 16, 18, and 20. The participant then withdrew from the drum, and the pulse sensors were checked in readiness for the following condition.

Figure 3.2.A demonstrates the timing of the optokinetic stimulation procedure.

A. Optokinetic stimulation



B. Trigeminal stimulation after optokinetic stimulation

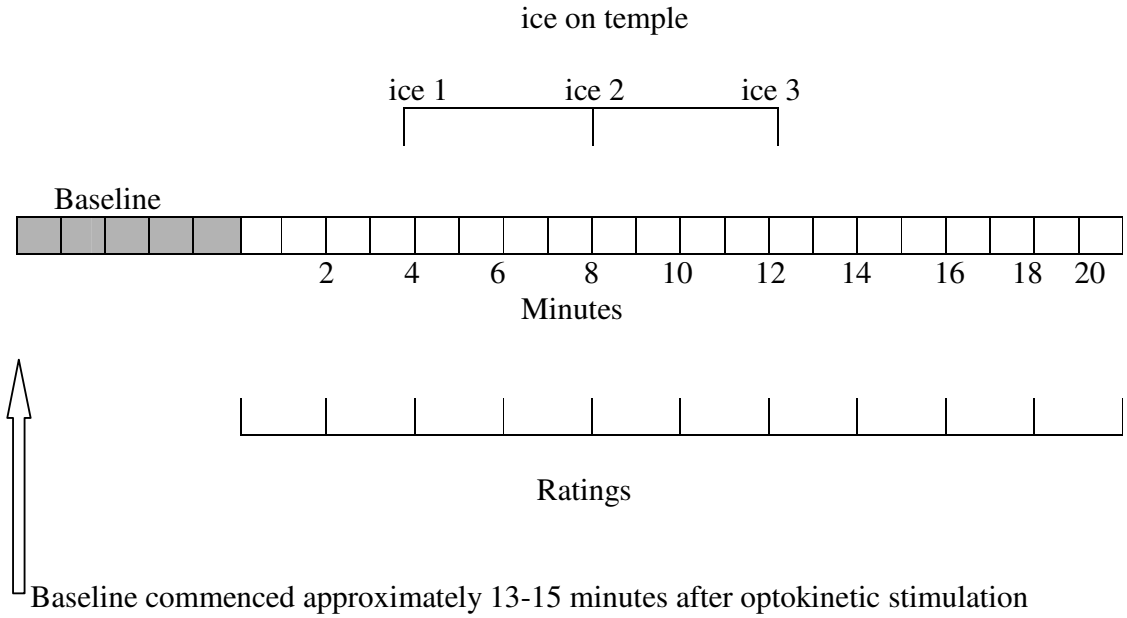


Figure 3.2. Optokinetic stimulation (top) and trigeminal stimulation after optokinetic stimulation (bottom)

Trigeminal stimulation after optokinetic stimulation

To evoke this stimulation the participant was instructed to apply ice to their temple. Migraineurs used the side of the head usually most painful during migraine and controls selected either side. The side selected was used in all testing conditions requiring ice on the temple. Before beginning this condition participants were given the ice block on a stick and instructed how to apply the ice when prompted during the test. When not in use the ice block was placed in a nearby cup. To absorb any drips from the ice, a small towel was placed on the participant's shoulder.

Initially a 5-minute baseline recording was taken which involved the participant sitting still and when prompted, they rated their motion sickness symptoms and unpleasantness. Two minutes later they were asked to rate these items again, and then in another 2 minutes (minute 4) they were instructed to pick up the ice and place it firmly side on to their temple for the first time. The instant they made contact they said 'on' and the experimenter timed the placement of ice for 30 seconds. Immediately following this, the experimenter said 'off' at which the participant removed the ice and placed it back into the cup ready for the next placement. A second application of ice was at minute 8 and a third placement at minute 12. The procedure was identical for each ice placement. Each time the ice was removed the subject was prompted to recall what their self-ratings were at the time the ice was on. Minutes 4, 8 and 12 were the only times the participant was required to recall when giving self-ratings. All other ratings fell on the timed 2-minute interval (baseline, then at minutes 2, 6, 10, 14, 16, 18, 20). Ratings from minute 4 onwards included ice intensity and unpleasantness in addition to motion sickness symptoms and unpleasantness.

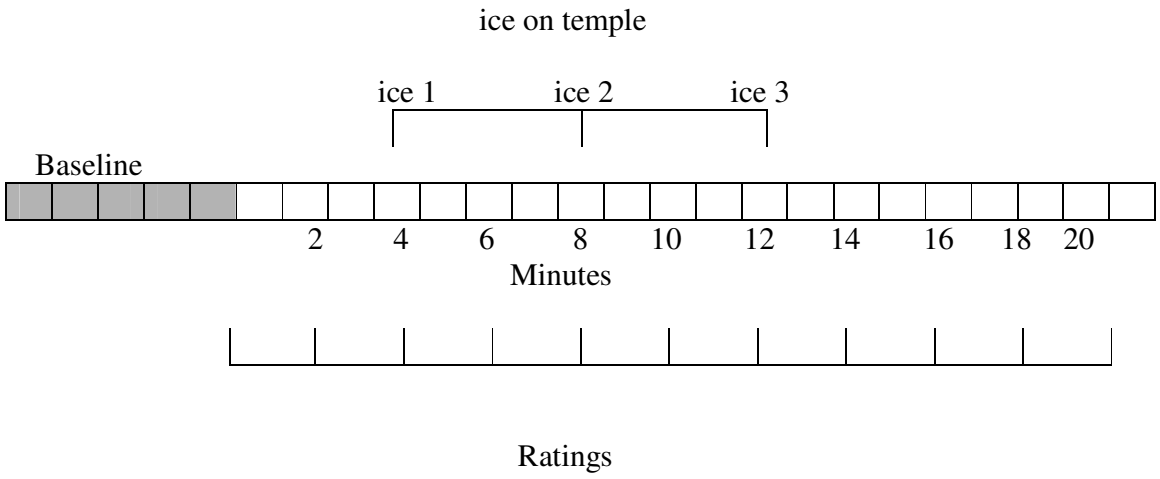
Figure 3.2.B demonstrates the timing of the trigeminal stimulation after optokinetic stimulation procedure.

Trigeminal stimulation before optokinetic stimulation

The procedure for this condition was the same as that described for trigeminal stimulation after optokinetic stimulation (see figure 3.3.A). The intention this time was to observe effects of trigeminal stimulation independent of optokinetic stimulation.

A. Trigeminal stimulation before optokinetic stimulation

A. Trigeminal stimulation before optokinetic stimulation



B. Trigeminal stimulation during optokinetic stimulation

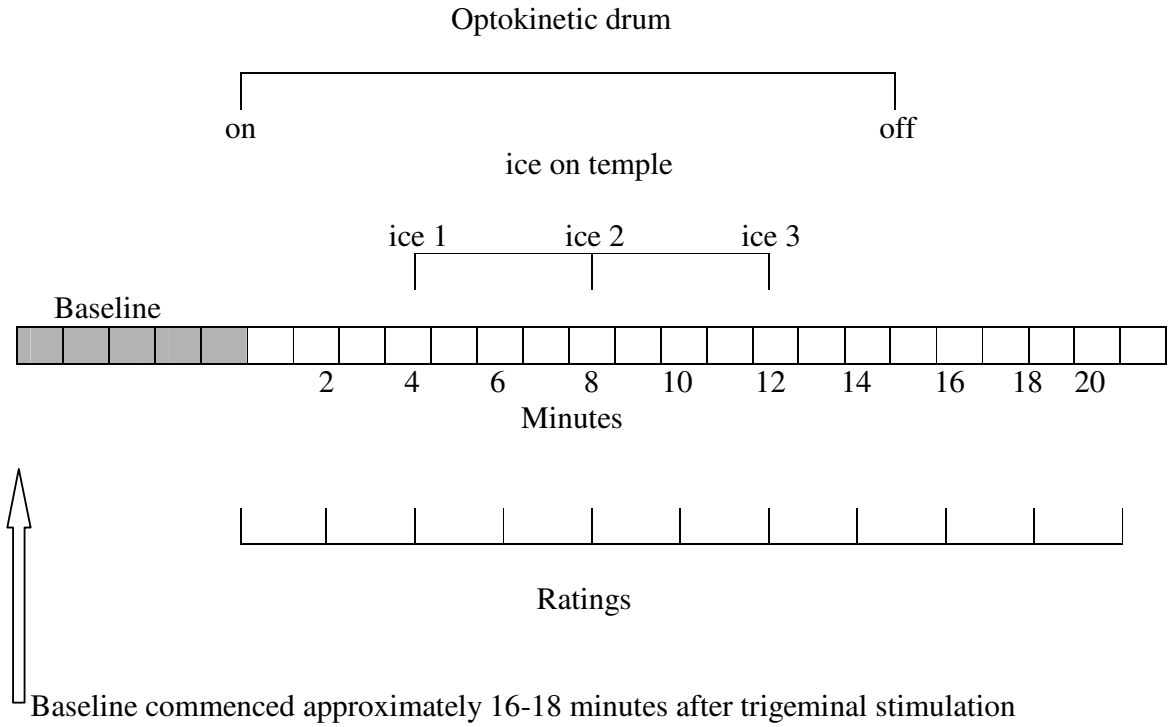


Figure 3.3. Trigeminal stimulation before optokinetic stimulation (top) and, trigeminal stimulation during optokinetic stimulation (bottom)

Trigeminal stimulation during optokinetic stimulation

This test involved observing reactions to trigeminal stimulation during optokinetic stimulation. The participant sat in the optokinetic drum, as described in the optokinetic stimulation condition. This time however, they were given additional directions concerning the placement of ice on their temple while under the drum. A cup holding the ice apparatus was placed on the participant's lap. It was placed on a towel to ensure the individual did not sense coldness, which would be distracting. They were told that placement of the ice was identical to the previous condition but now the task would be performed in the rotating drum. They were asked to orientate themselves to where the ice block was on their lap and that when prompted they should place the ice on their temple. They were told that this task would be performed without looking at the ice block or without breaking their gaze from the rotating drum.

As in condition 1, baseline recording involved the participant sitting still in the stationary drum and when prompted they rated motion sickness symptoms and unpleasantness. Ice was not placed on their temple at this stage but they were still prompted to rate ice intensity and unpleasantness. This particular rating was based on the after-effects from ice received before optokinetic stimulation. All these ratings were prompted again 2 minutes into the rotating drum, and they also rated 'self-motion' and 'visual illusion'. After 4 minutes in the rotating drum the participant was directed to place ice on their temple for the first time. The second application of ice was at minute 8 and the third at minute 12. As in the other ice conditions, each time the ice was removed the subject was prompted to recall their self-ratings at the time the ice was on. Minutes 4, 8 and 12, as before, were the only times the participant was required to recall when giving self-ratings. All other ratings fell on the timed 2-minute interval (baseline, then at minutes 2, 6, 10, 14, 16, 18, 20). Ratings after the rotating drum until the end of the experiment (minutes 16, 18, &20), excluded self-motion and visual illusion.

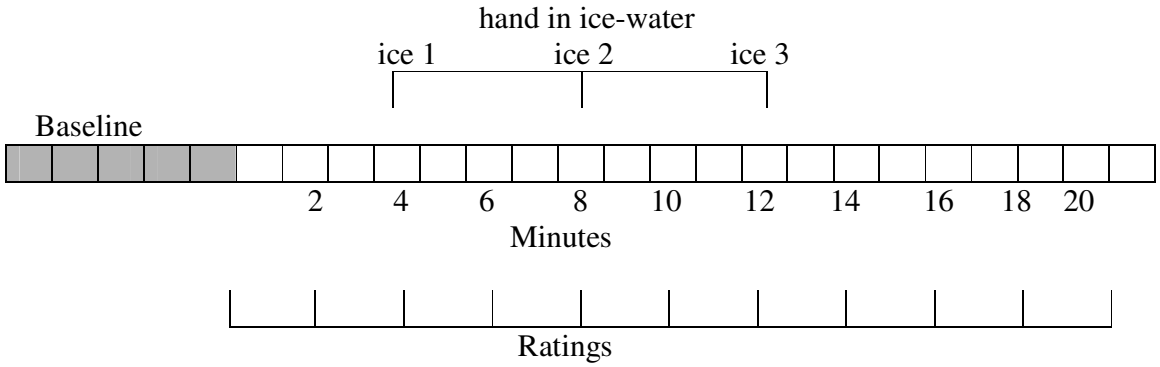
Figure 3.3.B demonstrates the timing of the trigeminal stimulation and optokinetic stimulation procedure.

Non-specific painful stimulation

To evoke non-specific painful stimulation the participant was instructed to immerse the fingers and palm (excluding thumb) of their non-dominant hand in ice-water. The same timing was used for the ice-water immersion as application of ice to the temple. Items and timing of subjective ratings also matched that used in the application of ice to the temple. Figure 3.4.A demonstrates timing of ice-water placement and self-ratings. The foam boxes filled with ice-water and warm water were positioned on a table next to the participant's chair. The participant was instructed how to place their hand in the warm and ice-water.

Two minutes after the participant's self-report at baseline they were asked to rate these items again and to place their hand in the warm water. The instant it was immersed they said 'in' and the experimenter timed the placement for 2 minutes. Then they were instructed to remove their hand from the warm water and say 'out' when it was removed. They were then instructed to place it in the ice-water for the first time and say 'in', on immersion. The hand, with fingers splayed, was continually swirled while in the ice-water. The experimenter timed this placement for 30 seconds and then said 'out' at which the participant removed their hand and placed it back in the warm water. Other than when prompted for ice-water placement, the participant's hand remained in the warm water until the end of the test.

A. Non-specific painful stimulation



B. Non-specific painful stimulation during optokinetic stimulation

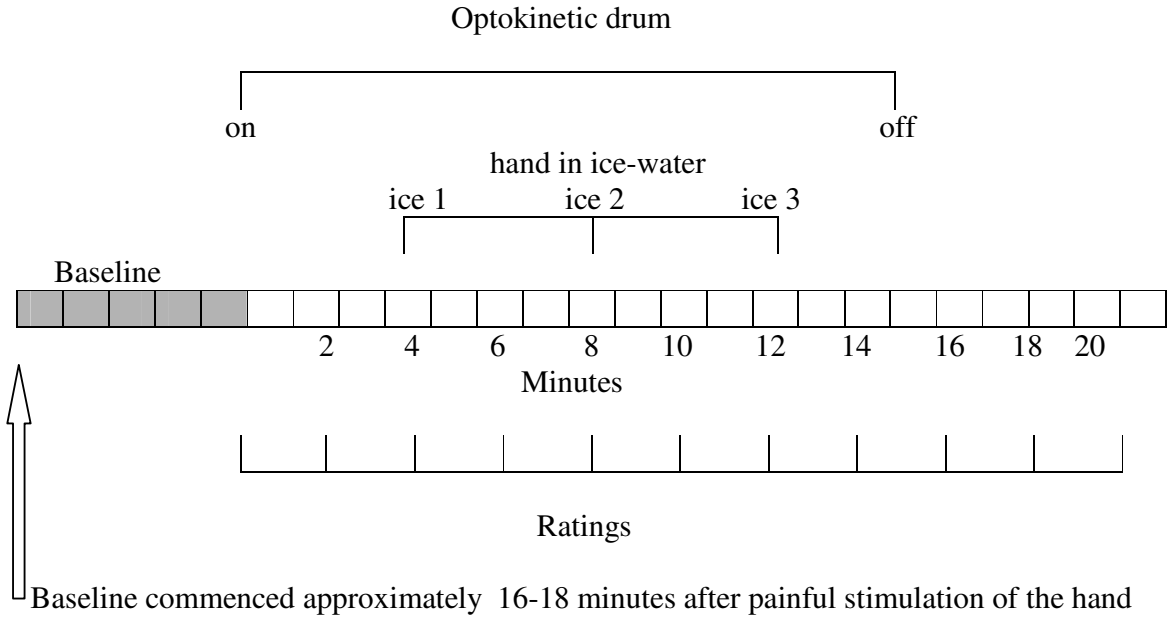


Figure 3.4. Non-specific painful stimulation (top) and, non-specific painful stimulation during optokinetic stimulation (bottom)

Non-specific painful stimulation during optokinetic stimulation

This test involved observing reactions during non-specific painful stimulation and optokinetic stimulation. The participant was instructed to sit in the optokinetic drum, as described during the optokinetic stimulation condition. Items and timing of subjective ratings were the same as those used during trigeminal stimulation and optokinetic stimulation. The participant was given additional directions concerning the placement of their hand in the warm and ice-water while in the rotating drum. They were positioned in the drum with the foam boxes on the table next to their chair. They were asked to orientate themselves to where the foam boxes were and when prompted to alternate their hand between the warm and ice-water. They were instructed that these tasks would be performed without looking at the boxes or breaking their gaze from the drum. Two minutes into the optokinetic stimulation they were told to place their hand in the warm water for the first time. Thereafter, whilst in the rotating drum, they placed their hand alternately between the warm and ice-water in the same way as in the previous condition.

Figure 3.4.B demonstrates the timing of the non-specific painful stimulation and optokinetic stimulation procedure.

CHAPTER 4

QUANTIFICATION OF DATA

Statistical approach for each condition

Symptom ratings

Migrainous symptoms were analyzed in a 2 (group: migraineurs, controls) x 11 (time: every 2 minutes from baseline to minute 20) repeated-measures analysis of variance (ANOVA) with simple contrasts between baseline and each subsequent point. Self-motion and visual-illusion were analyzed in a 2 (group: migraineurs, controls) x 7 (time: every 2 minutes during OKS) repeated-measures ANOVA and ice-induced pain intensity and unpleasantness in a 2 (group: migraineurs, controls) x 9 (time: every 2 minutes from the first application of ice) repeated-measures ANOVA. Where appropriate, simple contrast analyses were used to explore each time point in relation to baseline within each group. The multivariate solution is reported for Time and the Time x Group interaction. ANOVA results (main effects, interactions) are presented in tables in the following chapters. Means, standard deviations and simple contrasts are presented in supplementary tables in Appendix 6 to 11.

Pulse Amplitude

As condition 1 (OKS) did not involve painful stimulation, responses were analyzed in a 2 (group: migraineurs, controls) x 2 (side: left, right) x 11 (time: 30 second sample increments from baseline, at minutes 3 ½, 4, 4 ½, 7 ½, 8, 8 ½, 11 ½, 12, 12 ½, 14 ½, 19 ½) repeated-measures ANOVA. Time points were selected to correspond with data points in conditions involving painful stimulation. The other five conditions all involved painful stimulation so were analyzed in a 2 (group: migraineurs, controls) x 2 (side: ipsilateral, contralateral to stimulation) x 11 (time: 30 second samples, before {trial 1, 2 & 3}, during {trial 1, 2 & 3} and after {trial 1, 2 & 3} painful stimulation, and 3 and 8 mins after the 3rd trial) repeated-measures ANOVA. Where appropriate, significant interactions were investigated in a series of 2 (group: migraineurs, controls) x 2 (side: ipsilateral, contralateral to stimulation) repeated-measures ANOVA's at each time point. Condition 1 was investigated in 2 (group: migraineurs, controls) x 2 (side: left, right) repeated-measures ANOVA's at each time point. Pulse amplitude was expressed as the percent change from baseline recorded 4 minutes before the first data point. ANOVA results (main effects, interactions) are presented in tables in the following chapters. Means, standard deviations and simple contrasts are presented in supplementary tables in Appendix 6 to11.

Condition comparisons

Symptom ratings and pulse amplitude were compared across conditions using a series of repeated measures ANOVAs. The following contrasts were explored:

- **Response during OKS**

  Conditions: 1 (OKS alone), 4 (ice on temple during OKS) and 6 (hand in ice-water during OKS). Mean ratings across the full period of OKS were calculated. As

preliminary analyses indicated that pulse amplitude increased following painful stimulation with ice (temple, hand), mean pulse amplitude (30 second samples) after ice stimulation was calculated.

- **Response independent of OKS**

Conditions 2 (Ice on temple after OKS), 3 (Ice on temple before OKS) and 5 (Hand in ice-water before OKS). Mean scores were calculated, as listed above.

CHAPTERS FIVE to TWELVE

RESULTS/DISCUSSION PREAMBLE

Results for each of the six testing conditions are presented and discussed individually in Chapters 5 to 10, and later compared in chapters 11 and 12. Specific findings with respect to pain processing in response to cranial pain and non-specific painful stimulation, independently and in relation to OKS are explored in these chapters. Findings are then discussed in more detail in the general discussion at the end of the book (i.e., Chapter 13), in relation to the literature of the existing models of the migraine mechanism, and the overall outcomes of the entire experiment.

CHAPTER 5

RESULTS and DISCUSSION

Condition 1

Optokinetic stimulation (OKS) alone

The purpose of this condition was to investigate whether symptomatic responses evoked during OKS would differ between migraine sufferers and controls. Since migraine sufferers are prone to motion sickness (Golding, 1998; Kuritzky, Ziegler & Hassanein, 1981), it was hypothesized that ratings would be greater in migraine sufferers than in controls during OKS.

Motion sickness is commonly associated with facial pallor and cold sweating (Marcus, Furman and Balaban, 2005) but increases in skin oxygen and flushing, an index of blood flow, have also been observed. In people who do not develop motion sickness skin oxygen decreases (Harm, Beatty and Reschke, 1987). Kolev, Moller, Nilsson and Tibbling (1997) similarly observed increased blood flow in the forehead during motion sickness measured by laser doppler flowmeter. Additionally, sympathetic activation is greater in insusceptible individuals, resulting in cutaneous vasoconstriction throughout motion tests (Harm, 1990).

Blood appears to be diverted away from facial capillaries to deeper blood vessels, as the individual visibly appears pale (Marcus et al., 2005) while blood flow through deeper dermal vessels is heightened (Kolev et al., 1997). This same mechanism may occur in migraine and so explain the characteristic facial pallor observed during attacks (Marcus et al., 2005) while deeper cephalic vessels dilate (Moskowitz, 1993).

Since migraineurs are predisposed to motion sickness, it was hypothesized that extracranial skin blood flow in deeper dermal vessels as measured by

photophlethysmography to OKS would be greater in the migraine group than in controls in the current test.

RESULTS

Symptom ratings

Overall, symptomatic responses were greater in migraine sufferers than controls throughout testing: nausea (mean $\pm$ S.E. = 1.721 $\pm$ .298 *vs* .466 $\pm$ .298; F (1,40) = 8.866, $p < .01$), body temperature (2.110 $\pm$ .303 *vs* .344 $\pm$ .303; F (1,40) = 16.957, $p < .001$), dizziness (1.749 $\pm$ .334 *vs* .686 $\pm$ .334; F (1,40) = 5.048, $p < .05$), drowsiness (1.357 $\pm$ .269 *vs* .361 $\pm$ .269; F (1,40) = 6.840, $p < .05$), and headache (1.167 $\pm$ .225 *vs* .068 $\pm$ .225; F (1,40) = 11.910, $p < .001$). Closer inspection indicated that apart from headache, differences between groups developed early into OKS. Headache, however, was greater in the migraine group the entire time, even prior to OKS (see Figure 5.1.E and Appendix 6.1.5, page 301). Both groups experienced more nausea (main effect for Time: F (10, 31) = 2.599, $p < .05$), dizziness (main effect for Time: F (10, 31) = 2.353, $p < .05$) and elevation in body temperature (main effect for Time: F (10, 31) = 4.460, $p < .01$) during OKS than at baseline. Simple contrast analyses indicated that increases in nausea and body temperature in migraineurs persisted after OKS but dizziness subsided within 5 minutes. In contrast, experience of nausea and dizziness in controls was slight and stabilized quickly mid OKS, and body temperature remained stable throughout.

Unpleasant sensations developed in both groups during OKS (main effect for Time: F (10, 31) = 3.836, $p < .01$). Contrast analyses indicated that in migraineurs unpleasantness was constant, even following OKS. However, controls only reported unpleasantness mid OKS. The extent of unpleasantness overall was greater in migraine sufferers than in controls (2.626 $\pm$ .371 *vs* .714 $\pm$ .371; F (1,40) = 13.291, $p < .01$). The difference between groups was evident from 4 minutes into OKS (see Figure 5.1.E and Appendix 6.1.6, page 302).

Self-motion and visual-illusion developed in both groups during OKS (main effect for Time: Self-motion, F (6, 35) = 3.262, $p < .05$; Visual-illusion, F (6, 35) = 4.131, $p < .01$).

Self-motion was greatest mid OKS for both groups while visual-illusion increased further into OKS. The experience however, was greater in migraine sufferers than in controls (main effect for Group: Self-motion, $F(1, 40) = 5.472$, $p < .05$; Visual-illusion, $F(1, 40) = 6.997$, $p < .05$). Refer to Figure 5.1.G, 5.1.H, Table 5.1 and Appendix 6.1.7, 6.1.8 (pages 303, 304, respectively) .

Sixteen percent of migraine sufferers withdrew from OKS compared with only 5 percent of controls. This difference however, did not reach significant levels (refer to Appendix 13, page 363).

Figure 5.1. A to F demonstrates change in symptom ratings over time. Table 5.1 lists main effects and interactions for each symptom.

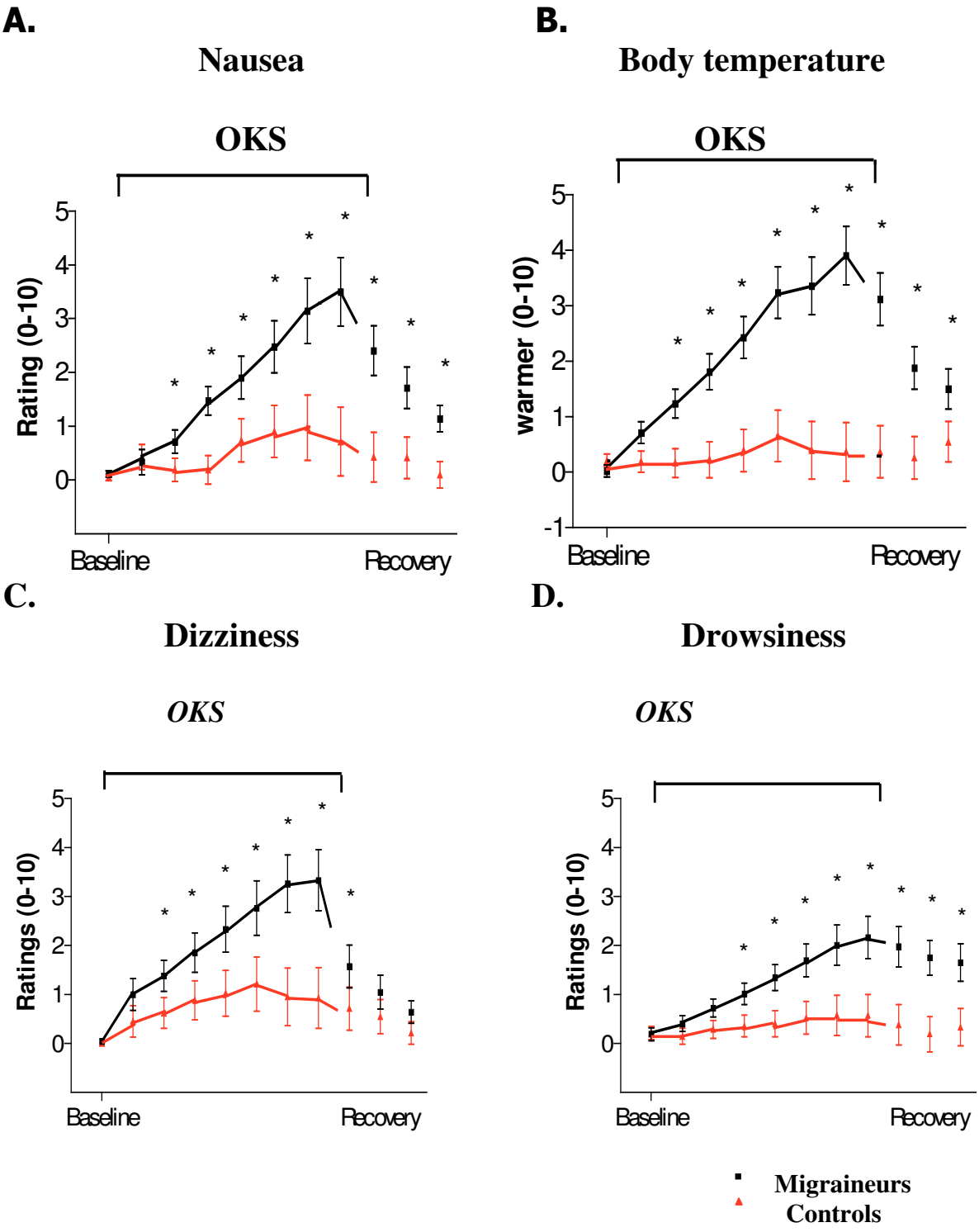


Figure 5.1.A-D. Symptom ratings (± SEM) for migraineurs (n = 21) and controls (n = 21) over 11 time points (every 2 minutes from baseline to minute 20).

OKS = optokinetic stimulation ** statistically significant group difference (* p < .05)*

P.T.O for additional ratings

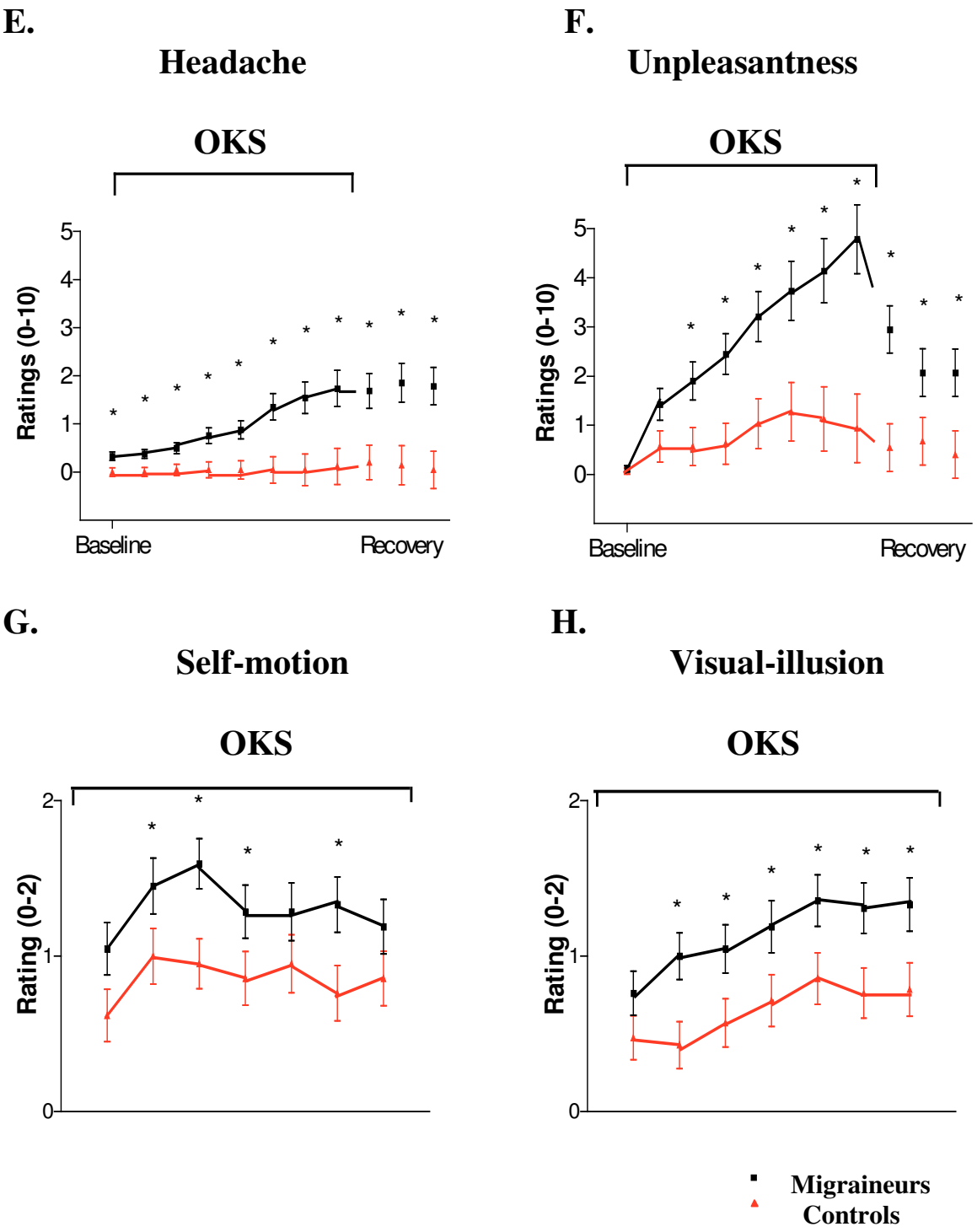


Figure 5.1.E– H. Symptom ratings (± SEM) for migraineurs (n = 21) and controls (n = 21) over 11 time points (every 2 minutes from baseline to minute 20 for Figs E and F) and over 7 time points (every 2 minutes from commencement of OKS for Figs G and H). *OKS = optokinetic stimulation* ** statistically significant group difference (* p < .05)*
Note: Different rating scales for self-motion and visual-illusion (0-2)

Table 5.1. Main effect and interaction F, *p*, and df values from a 2 (group: migraineurs, controls) x 11 (time: every 2 minutes from baseline to minute 20) repeated-measures ANOVA for each rating. Values for Self-motion and Visual-illusion obtained from a 2 (group: migraineurs, controls) x 7 (time: every 2 minutes during OKS) repeated-measures ANOVA.

	F ratios (df)		
	Group	**Time**	**Time x Group**
Nausea	8.866 (1, 40) **	2.599 (10, 31) *	1.569 (10, 31)
Body temperature	16.957 (1, 40) ***	4.460 (10, 31) **	3.016 (10, 31) **
Dizziness	5.048 (1, 40) *	2.353 (10, 31) *	1.378 (10, 31)
Drowsiness	6.840 (1, 40) *	2.129 (10, 31)	1.282 (10, 31)
Headache	11.910 (1, 40) **	1.906 (10, 31)	1.321 (10, 31)
Unpleasantness	13.291 (1, 40) **	3.836 (10, 31) **	2.830 (10, 31) *
Self-motion	5.472 (1, 40) *	3.262 (6, 35) *	.985 (6, 35)
Visual-illusion	6.997 (1, 40) *	4.131 (6, 35) **	.745 (6, 35)

* difference between migraine sufferers and controls statistically significant (* p < .05,** p < .01,*** p < .001)
degrees of freedom differ across the dependent variables because of empty cells

Pulse Amplitude

Facial blood flow increased bilaterally during OKS for both groups (main effect for Time: F (10,31) = 7.001, $p < .001$) and responses between sides were comparable (see Table 5.2). Overall, pulse amplitude increased more in migraine sufferers than in controls throughout the experiment (34% $\pm$ 4% *vs* 9% $\pm$ 4%; F (1,40) = 16.635, $p < .001$). Figure 5.2 and Appendix 6.2.1 (page 305) illustrate these trends.

Pulse amplitude increased in the migraine group throughout the procedure. Vasodilatation in the control group was observed during OKS but returned to baseline levels 5 minutes later (Time x Group interaction: F (10,31) = 2.792, $p < .05$). Appendix Tables 6.2.1 and 6.2.2 (pages 305, 306, respectively) illustrate change over time for each group. As previously described, changes were greater in migraineurs than in controls.

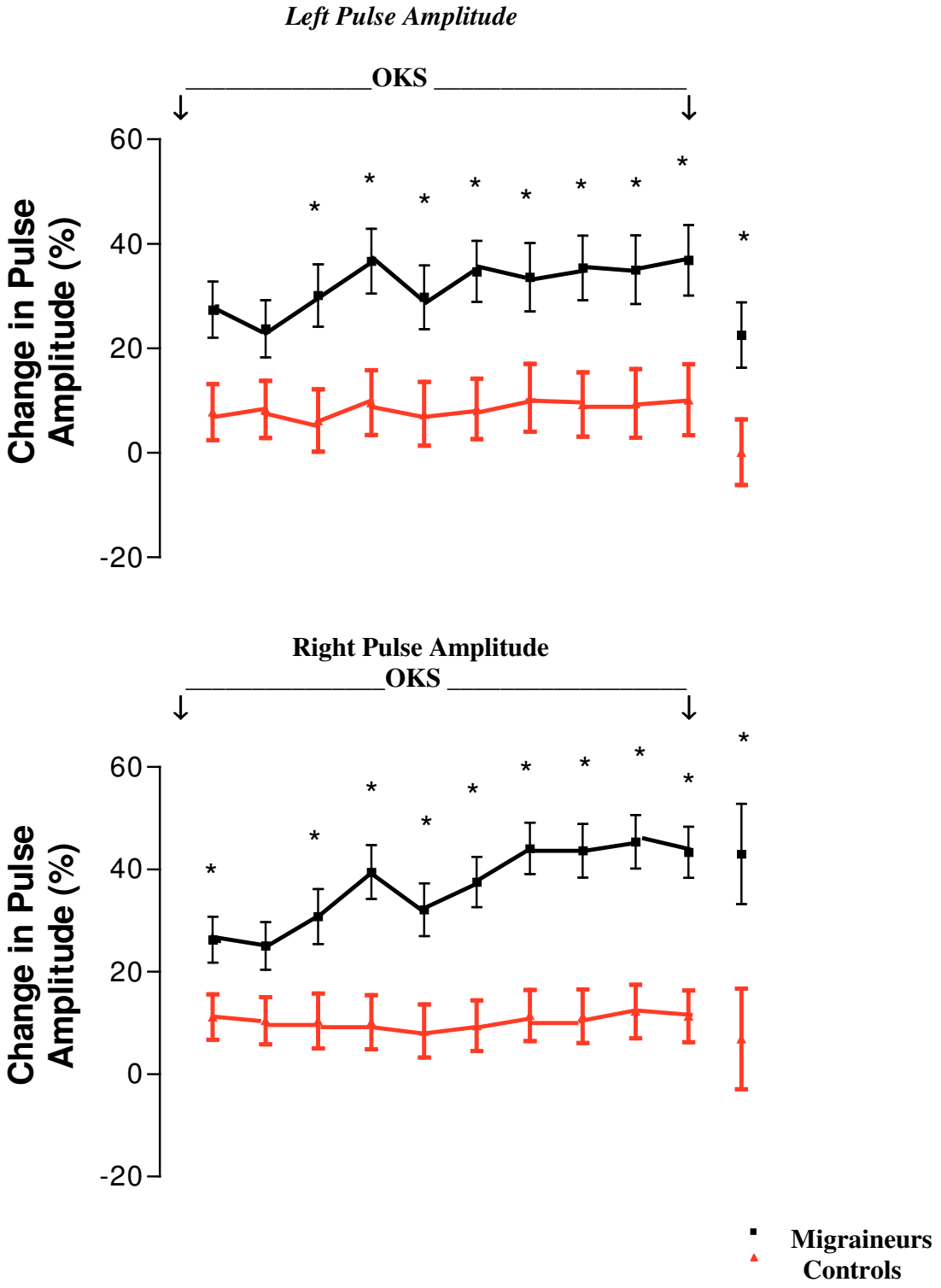


Figure 5.2. Pulse amplitude change (± SEM) for migraineurs (n = 21) and controls (n = 21) over 11 time points (30 second sample increments from baseline, at minutes 3 ½, 4, 4 ½, 7 ½, 8, 8 ½, 11 ½, 12, 12 ½, 14 ½, 19 ½). *OKS = optokinetic stimulation*
** statistically significant group difference (* p < .05)*

Table 5.2. Main effect and interaction F, *p*, and df values from a 2 (group: migraineurs, controls) x 2 (side: left, right) x 11 (time: 30 second sample increments from baseline, at minutes 3 ½, 4, 4 ½, 7 ½, 8, 8 ½, 11 ½, 12, 12 ½, 14 ½, 19 ½) repeated-measures ANOVA for pulse amplitude change.

Main effect	*df*	F	P
Group	1, 40	16.635	.000
Side	1, 40	1.296	.262
Time	10, 31	7.001	.000
Interaction			
Side x Time	10, 31	.455	.906
Side x Group	10, 40	.233	.632
Time x Group	10, 31	2.792	.014
Side x Time x Group	10, 31	.494	.881

DISCUSSION

Effects on symptomatic responses

Summary of major findings

Key findings to emerge from exploring the effects of optokinetic stimulation were:

- Overall, symptomatic ratings were greater in migraine sufferers than in controls. Controls experienced slight nausea, dizziness, self–motion, visual-illusion and associated unpleasantness during OKS. Body temperature did not appear to change, and drowsiness and headache did not develop.

Discussion of effects on symptomatic responses

It was expected that symptomatic ratings would be greater in migraine sufferers than in controls during OKS. In support of the hypotheses, and consistent with the literature, symptoms of motion sickness (nausea, headache, dizziness, drowsiness and perceived increases in body temperature) were greater in migraineurs than in controls throughout the procedure. Visual-illusion, self-motion and, not surprisingly, overall unpleasantness were also greater in migraine sufferers.

As symptoms of motion sickness and migraine are similar, the enhanced symptomatic responses observed in migraine sufferers may reflect activation of neural pathways that produce either motion sickness or migraine. If so, the same neural events may be involved in both conditions. Specifically, brainstem and associated nuclei usually

involved during attacks of migraine (Weiller et al., 1995) might reciprocally initiate headache and other symptoms during OKS.

Effects on pulse amplitude

Summary of major findings

- Increases in pulse amplitude were greater in migraine sufferers than in controls throughout. In controls, vasodilatation was observed during OKS but this response had subsided 5 minutes later.

Discussion of effects on pulse amplitude

As anticipated changes in pulse amplitude were greater in migraine sufferers than in controls during OKS. Increased extracranial blood flow has been observed during motion sickness (Kolev, Moller, Nilsson and Tibbling, 1997) and at the onset of threat (Carrive and Bandler, 1991). It may be that the enhanced vasodilatation observed in migraineurs in the present study represents a stress response to the unpleasant (and familiar in terms of the migraine experience) symptoms of OKS-induced motion sickness. The midbrain PAG is involved in the mediation of defensive behaviour, including modulating fear and anxiety and autonomic and cardiovascular responses (Behbehani, 1995). Therefore, it is tempting to speculate that the enhanced vascular responses observed in migraineurs in this study may indicate disrupted PAG control (hyperexcitable neural responses or weak inhibitory mechanisms).

However, the PAG is part of a circuit involving other areas of the brain in the regulation of fear, anxiety, and autonomic and cardiovascular responses. Specifically, the

hypothalamus, amygdala, cortical, basal ganglia and brainstem nuclei (Venes, 2001; Bray et al., 1999) are also involved in regulation of these reactions. It may be that all, or any, of these areas are faulty in those with a migraine predisposition.

Whatever the mechanism, the continued vasodilatation observed in this group during recovery may demonstrate a neural or vascular hypersensitivity/ "wind-up" (Bray, Cragg, MacKnight and Mills, 1999) that amplifies neurovascular responses.

CHAPTER 6

RESULTS & DISCUSSION

Condition 2

Ice on temple after optokinetic stimulation (OKS)

This condition investigated whether symptomatic responses following painful stimulation of the temple with ice after OKS would differ between migraine sufferers and controls. Since the ice probably stimulated the trigeminal nerve it was hypothesized that headache would develop more readily in the migraine group than controls. Additionally, if transmission of trigeminal impulses impinges on neurons responsible for symptoms other than headache in migraineurs, symptomatic responses other than headache might develop in migraine sufferers more readily than in controls. Furthermore, the superficial temporal artery dilates during some attacks of migraine (Lance and Goadsby, 2002) and forehead blood flow increases readily in migraineurs following painful stimulation of the face and neck (Drummond, 1997). Therefore, it was hypothesized that vascular responses to temple pain would be greater in the migraine group than in controls. As migraine sufferers are prone to motion sickness (Golding, 1998; Kuritzky, Ziegler & Hassanein, 1981) it was anticipated that residual effects from OKS would augment the development of vascular and symptomatic responses.

RESULTS

Symptom ratings

Procedures provoked more nausea (mean ± S.E. = 1.127 ± .254 *vs* .037 ± .270; F (1,45) = 8.649, $p < .01$) and headache (1.810 ± .326 *vs* .333 ± .347; F (1,45) = 9.635, $p < .01$) in migraine sufferers than controls throughout testing (see Figure 6.1.A, 6.1.E and Appendix 7.1.1, 7.1.5, pages 307, 311, respectively). Simple contrast analyses indicated that low–grade nausea (awareness) persisted after OKS in migraineurs and then increased over successive applications of ice. In contrast, nausea was negligible in controls throughout testing. Low-grade headache also persisted after OKS in migraineurs and increased following the initial ice trial. Controls were vaguely aware of headache during the course of the test but it did not develop further. Generally, migraine sufferers were aware of dizziness, even prior to the application of ice, whereas controls reported none (.462 ± .125 *vs* 0 ± 0; F (1,45) = 6.424, $p < .05$). Apart from during the first 2 applications of ice, dizziness was greater in migraine sufferers the whole time (see Figure 6.1.C and Appendix 7.1.3, page 309). Both groups became slightly less drowsy during early applications of ice (main effect for Time: F (9, 37) = 2.206, $p < .05$) but contrast analyses indicated that this effect was significant only in migraine sufferers.

Both groups reported experiencing increased levels of symptom unpleasantness in general, particularly during the application of ice to the temple (main effect for Time: F (9, 37) = 5.180, $p < .001$). Simple contrast analyses indicated that unpleasantness was restricted to when ice was applied in the control group but was more persistent in migraine sufferers. The extent of unpleasantness was greater for migraine sufferers than controls (2.522 ± .343 *vs* .612, ± .366; F (1,45) = 14.479, $p < .001$) throughout the procedure (see Figure 6.1.F and Appendix 7.1.6, page 312).

Pain peaked in intensity and unpleasantness for both groups when ice was applied to the temple (main effect for Time: Pain Intensity, F (8,38) = 21.578, $p < .001$; Pain Unpleasantness, F (8,38) = 15.559, $p < .001$). Ratings were greater in migraine sufferers than controls until just following the final ice application (see Figures 6.1.G, 6.1.H and Appendix 7.1.7, 7.1.8, pages 313, 314, respectively).

Figure 6..1.A to H demonstrate change in symptom ratings over time. Table 6..1 demonstrates main effects and interactions for each symptom.

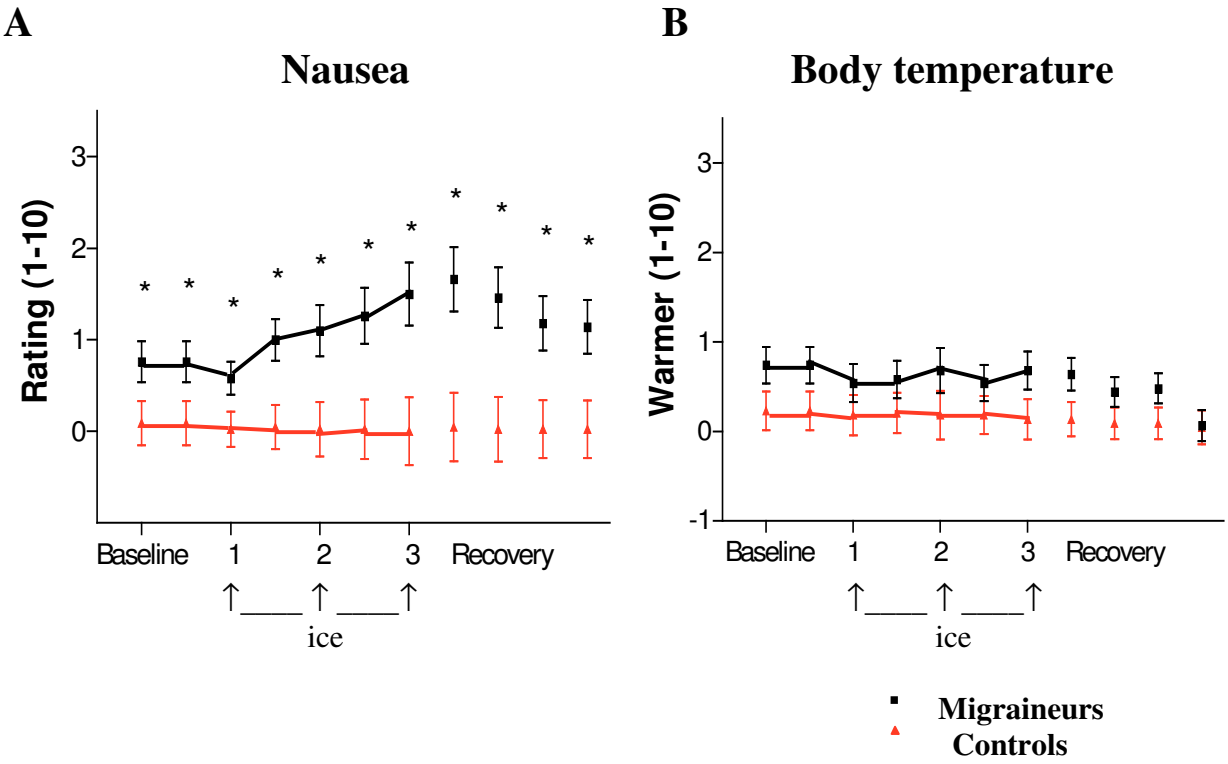


Figure 6.1.A-B. Symptom ratings (± SEM) for migraineurs (n = 25) and controls (n = 22) over 11 time points (every 2 minutes from baseline to minute 20).

** statistically significant group difference (* p < .05)* *P.T.O for additional ratings*

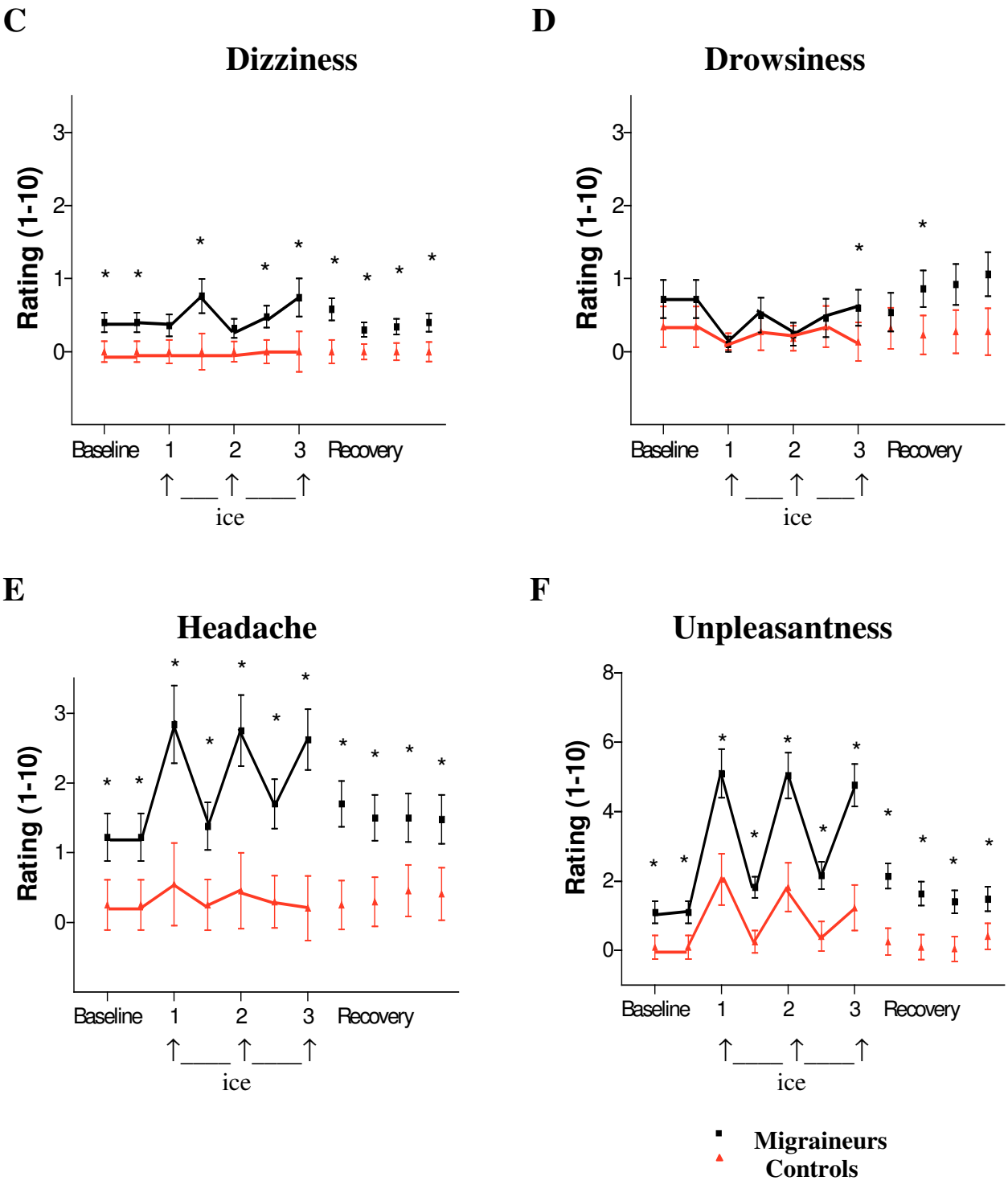


Figure 6.1.C-F. Symptom ratings (± SEM) for migraineurs (n = 25) and controls (n = 22) over 11 time points (every 2 minutes from baseline to minute 20).

** statistically significant group difference (* p < .05)*

Note: Y axis has different rating scales for unpleasantness

P.T.O for additional ratings

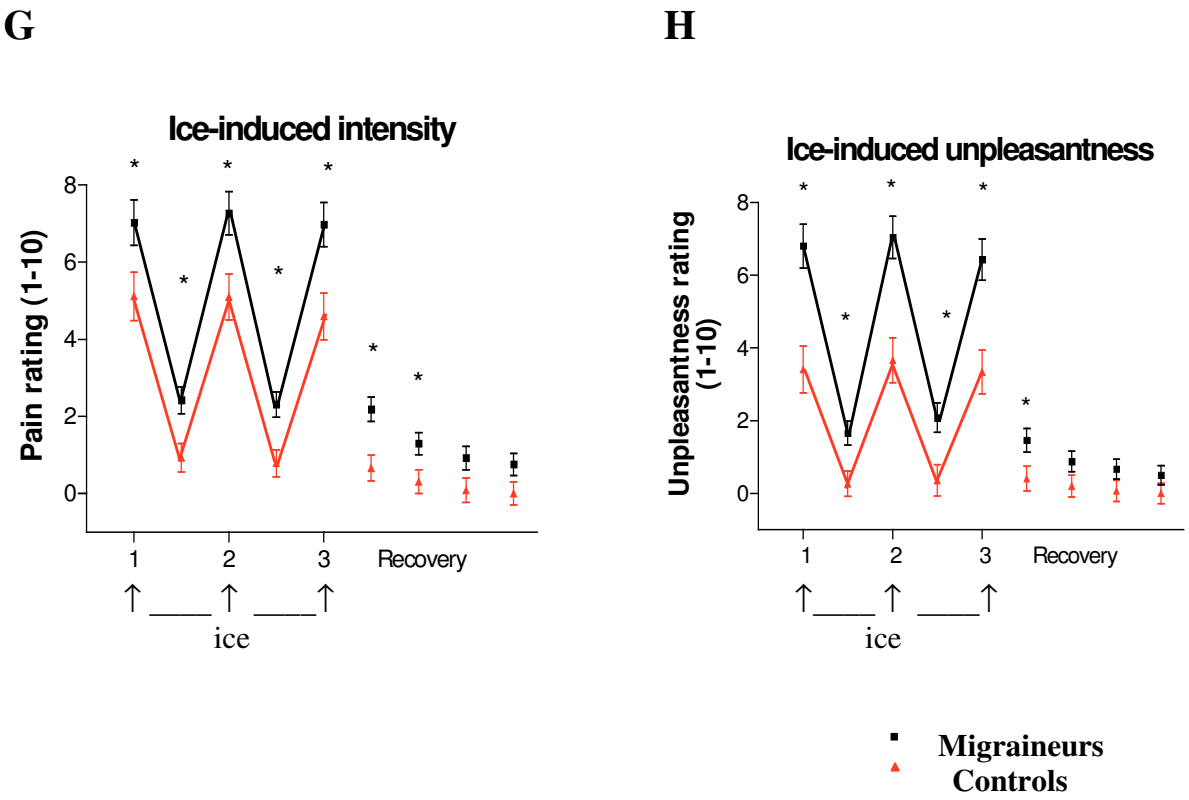


Figure 6.1.G-H.: Symptom ratings (± SEM) for migraineurs (n = 25) and controls (n = 22) over 9 time points (every 2 minutes from ice 1).
** statistically significant group difference (* p < .05)*

Note: Y axis has different rating scales unpleasantness (previous page), ice-induded intensity and ice-induced unpleasantness

Table 6.1. Main effect and interaction F, p, and df values from from a 2 (group: migraineurs, controls) x 11 (time: every 2 minutes from baseline to minute 20) repeated-measures ANOVA for each rating. Ice-induced pain intensity and unpleasantness values obtained from a 2 (group: migraineurs, controls) x 9 (time: every 2 minutes from the first application of ice) repeated-measures ANOVA

	F ratios (df)		
	Group	**Time**	**Time x Group**
Nausea	8.649 (1, 45) **	1.563 (9, 37)	1.911 (9, 37)
Body temperature	2.633 (1, 45)	1.662 (9, 37)	1.220 (9, 37)
Dizziness	6.424 (1, 45) *	1.082 (9, 37)	1.082 (9, 37)
Drowsiness	1.311 (1, 45)	2.206 (9, 37) *	2.197 (9, 37) *
Headache	9.635 (1, 45) **	2.016 (9, 37)	1.766 (9, 37)
Unpleasantness	14.479 (1, 45) ***	5.180 (9, 37) ***	1.357 (9, 37)
Ice-induced intensity	11.398 (1, 45) **	21.578 (8, 38) ***	.800 (8, 38)
Ice-induced unpleasantness	15.745 (1, 45) ***	15.559 (8, 38) ***	1.783 (8, 38)

* difference between migraine sufferers and controls statistically significant (* p < .05,** p < .01,*** p < .001)

degrees of freedom differ across the dependent variables because of empty cells

Pulse Amplitude

Pulse amplitude remained unchanged throughout procedures for both groups and responses between sides were comparable (see Figure 6.2, Tables 6..2, and Appendix 7.2.1 and 7.2.2, pages 315, 316, respectively).

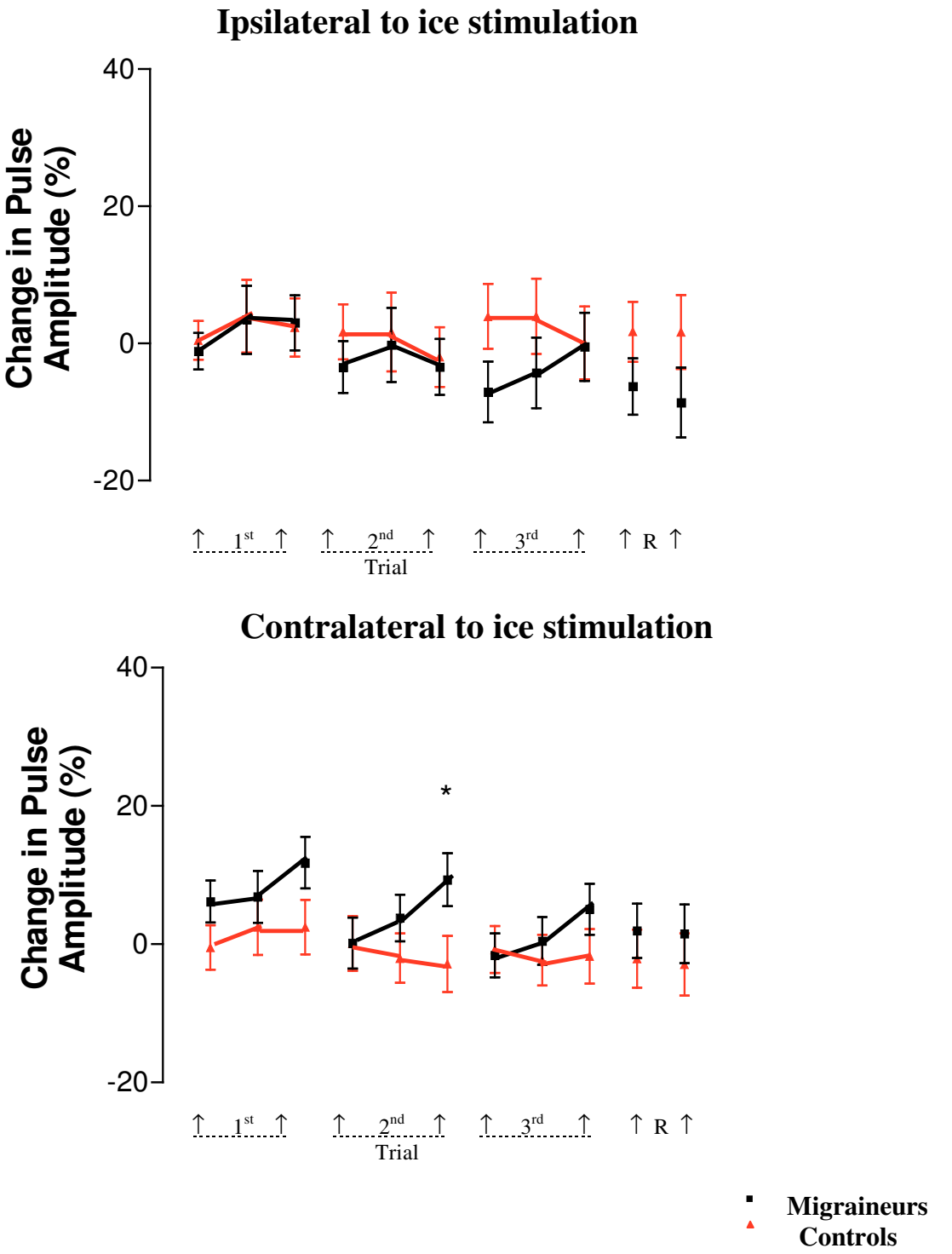


Figure 6.2. Pulse amplitude change (± SEM) for migraineurs (n = 25) and controls (n = 22) over 11 time points (30 second samples: before, during and after ice application {3 trials}, and after 3 and 8 minutes of recovery {R}). The first arrow in each trial represents pulse amplitude before the immersion, and the second arrow represents pulse amplitude after the immersion. ** statistically significant group difference (* $p < .05$)*

Table 6.2. Main effect and interaction F, *p*, and df values from a 2 (group: migraineurs, controls) x 2 (side: ipsilateral, contralateral to stimulation) x 11 (time: 30 second samples, before {trial 1, 2 & 3}, during {trial 1, 2 & 3} and after {trial 1, 2 & 3} ice application to temple, and 3 and 8 mins after the 3rd application) repeated-measures ANOVA for pulse amplitude change.

Main effect	*df*	F	P
Group	1, 45	.007	.936
Side	1, 45	.567	.455
Time	10, 36	1.326	.254
Interaction			
Side x Time	10, 36	1.012	.452
Side x Group	1, 45	3.059	.087
Time x Group	10, 36	1.088	.397
Side x Time x Group	10, 36	.742	.681

DISCUSSION

Effects on symptomatic responses

Summary of major findings

Key findings to emerge from exploring the effects of ice to the temple after OKS were:

- Symptomatic ratings, apart from body temperature and drowsiness, were greater in migraineurs than in controls. A slight awareness of increase in body temperature and drowsiness persisted throughout testing for both groups. As these symptoms were evident even prior to procedures, they were probably carry-over effects from the earlier OKS. Residual nausea, headache and dizziness prior to the ice application were also evident in migraineurs. Headache and nausea subsequently increased from the initial application of ice. Dizziness remained low-grade (an awareness) the entire time. On the other hand, controls remained virtually asymptomatic throughout.
- Overall unpleasantness and pain ratings were greater in migraine sufferers than in controls. In migraine sufferers, unpleasantness to symptomatic changes increased from the initial application of ice and subsided by 6 minutes after the third trial. In controls, overall unpleasantness increased only during the first 2 applications of ice. For both groups, ice-induced intensity and unpleasantness increased during each application of ice to the temple.

Discussion of effects on symptomatic responses

Findings, in part, supported the hypotheses that headache and other symptomatic responses would develop more readily in the migraine group than controls. Apart from

body temperature and drowsiness, symptomatic ratings were greater in migraine sufferers than in controls. Prior to painful stimulation of the temple, migraineurs showed signs of residual effects from the preceding OKS. They commenced testing with a low-grade awareness of nausea, dizziness, drowsiness and a perception of increased body temperature. Additionally, low-grade headache was reported which increased following the initial application of ice. Nausea increased over successive applications of ice and an awareness of increases in body temperature, dizziness and drowsiness persisted throughout. Controls remained practically asymptomatic the entire time.

Application of ice to the temple most likely stimulated branches of the trigeminal nerve. Migraineurs, between attacks of migraine, were more sensitive than controls to painfully cold stimulation of the temple in the presence of residual motion sickness. Not surprisingly, as symptomatic changes were mostly greater in migraine sufferers, overall unpleasantness was enhanced for this group. Activation of the trigeminal sensory system and neurogenic inflammation has been linked to head pain (Moskowitz, 1995) and nausea during migraine attacks (Knight, 2005; Dalhlof and Hargreaves, 1998). The development of these particular symptoms, and the heightened pain reported in the present test by migraineurs, suggests that the trigeminal nerve is also hypersensitive in the interictal period.

However, hypersensitivity of trigeminal afferents between migraine sufferers and controls has not been established. It could be that hypersensitivity may occur at any point anatomically from activation of the somatosensory to the cortex. Furthermore, to conclude "trigeminal hypersensitivity" in migraine sufferers compared to controls based on heightened pain responses may also be problematic. The brain may indeed process pain differently in migraine sufferers, or it may be that this group simply use different criteria in their reported experience of pain. Given that pain is a subjective experience it may have been more appropriate to have compared responses of migraine sufferers with themselves, i.e., pain perception ictally to interictally, rather than to a pain-free control group, as done in this study. However, exposure to the provocative procedures used in this study probably would not have been tolerated during a migraine attack, making data collection impossible, or at best insufficient at that time for meaningful analyses.

Whether symptomatic changes intensified in migraine sufferers in the presence of any residual symptoms following OKS, will be addressed in later sections. In particular, the effects of painfully cold stimulation of the temple independent of OKS will be compared to painfully cold stimulation of the temple after OKS (see chapter 12, page 192-208)

Effects on pulse amplitude

Summary of major findings

- Overall, pulse amplitude remained stable, and reactions between sides were comparable for both groups. Slight vasoconstriction was observed in both groups but did not reach significant levels.

Discussion of effects on pulse amplitude

The lack of extracranial vasodilatation during painful stimulation of the temple in the presence of residual effects of motion sickness is surprising, as it was anticipated that residual effects from OKS would augment the development of vascular responses. The application of ice to the temple was painful and no doubt excited the sympathetic nervous system. This may, in turn, help account for the slight extracranial vasoconstriction observed in both groups. As previously suggested, it may be that the headache observed in migraine sufferers in the present study is symptomatic of the neurogenic inflammatory response. Plasma extravasation and vasodilatation, i.e. neurogenic inflammation, has

been attributed to antidromic activation of afferent C-fibres. In the present case, vasodilatation associated with headache may have occurred in deeper cephalic tissue, e.g. meningeal vasculature, as the trigeminal nerve transmits nociceptive signals from dilated blood vessels of the pia- and dura mater (Frickle, 2001; Frickle, Andres and Von Düring, 2001; Moskowitz, 1993).

As pulse amplitude did not appear to recover in migraine sufferers during the previous procedure (i.e., OKS alone), data was re-analysed using the baseline from the previous condition (see Appendix 12, page 361-362). This analysis indicated that pulse amplitude increased during OKS and remained increased when ice was applied after OKS, particularly in migraine sufferers. Occasional vasoconstriction was evident in controls only. Overall, pulse amplitude was comparable between groups. If some aspect of motion sickness disrupted vasomotor activity at a neural level this should become clearer in light of the vascular response to cold stimulation of the temple: in the absence of motion sickness (see results condition 3, page 127-137) and during OKS induced motion sickness (see results condition 4, page 138-149).

CHAPTER 7

RESULTS and DISCUSSION

Condition 3

Ice on temple before optokinetic stimulation (OKS)

The purpose of this condition was to determine whether symptomatic responses following painful stimulation of the temple with ice would differ between migraine sufferers and controls. As the application of ice could stimulate the trigeminal nerve, it was hypothesized that headache would develop more readily in the migraine group than in controls. Also, if conduction of trigeminal impulses converges centrally on neurons responsible for symptoms other than headache, painful stimulation of the temple might evoke these responses in migraine sufferers more readily than in controls. Enhanced extracranial responses during head pain have been observed (Lance and Goadsby, 2002; Drummond, 1997) so it was hypothesized that vascular responses to temple pain in this test might be greater in the migraine group than in controls.

RESULTS

Symptom ratings

Throughout the procedure changes in symptom ratings were minimal for both groups. Migraine sufferers experienced low-grade headache (head awareness), which built up over the procedure whereas controls were barely aware of headache (mean $\pm$ S.E. = .910 $\pm$ .163 *vs* 028 $\pm$ .170; F (1,46) = 14.033, $p < .001$). While slight headache (head awareness) was observed in migraine sufferers prior to testing, contrast analyses indicated headache increased from the second placement of ice and recovered 6 minutes after the final application. Further contrast analyses indicated that both groups became slightly less drowsy during early applications of ice, but no other symptoms developed. Both groups reported increased levels of unpleasantness to symptoms in general, particularly during application of ice to the temple (main effect for Time: F (9, 38) = 6.599, $p < .001$). Simple contrast analyses indicated that unpleasantness was restricted to when ice was applied in the control group but persisted in migraine sufferers. The extent of unpleasantness overall was greater for migraineurs than controls (1.358 $\pm$ .211 *vs* .370 $\pm$ .220; F (1,46) = 10.487, $p < .01$) particularly during ice applications and following the third trial (see figure 7.1.F and Appendix 8.1.6, page 322).

Understandably, ice-induced pain increased in intensity and unpleasantness for both groups when ice was applied to the temple (main effect for Time: Pain Intensity, F (8,39) = 27.560, $p < .001$; Pain Unpleasantness, F (8,39) = 19.362, $p < .001$). Migraine sufferers generally rated the experience as more intense and unpleasant than controls (see Figure 7.1.G and H and Appendix 8.1.7, 8.2.8, pages 323, 324, respectively).

Figure 7.1.A to H demonstrate change in symptom ratings over time. Table 7.1 demonstrates main effects and interactions for each symptom.

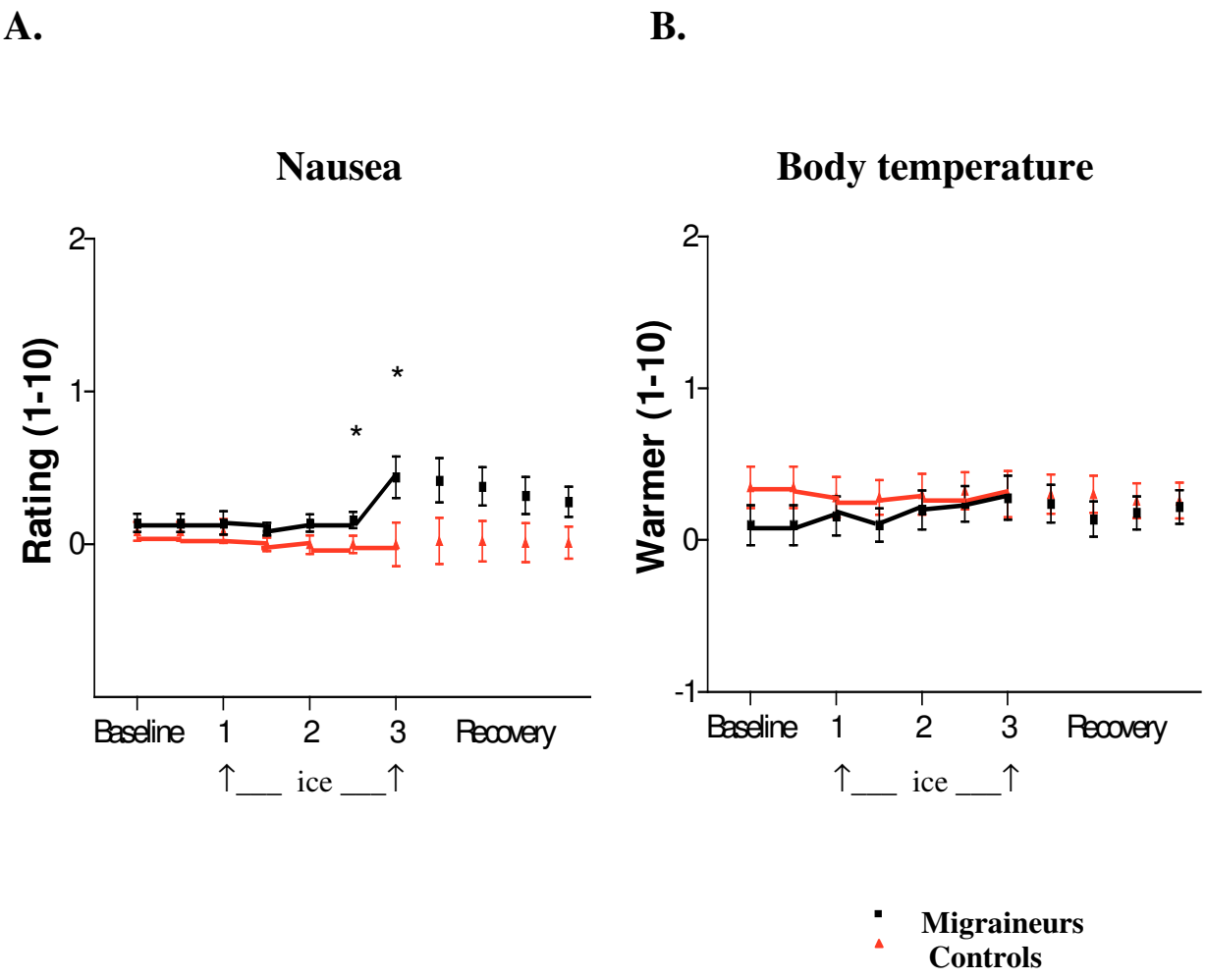


Figure 7.1.A-B. Symptom ratings (± SEM) for migraineurs (n = 25) and controls (n = 23) over 11 time points (every 2 minutes from baseline to minute 20).

** statistically significant group difference (* p < .05)*

P.T.O for additional ratings

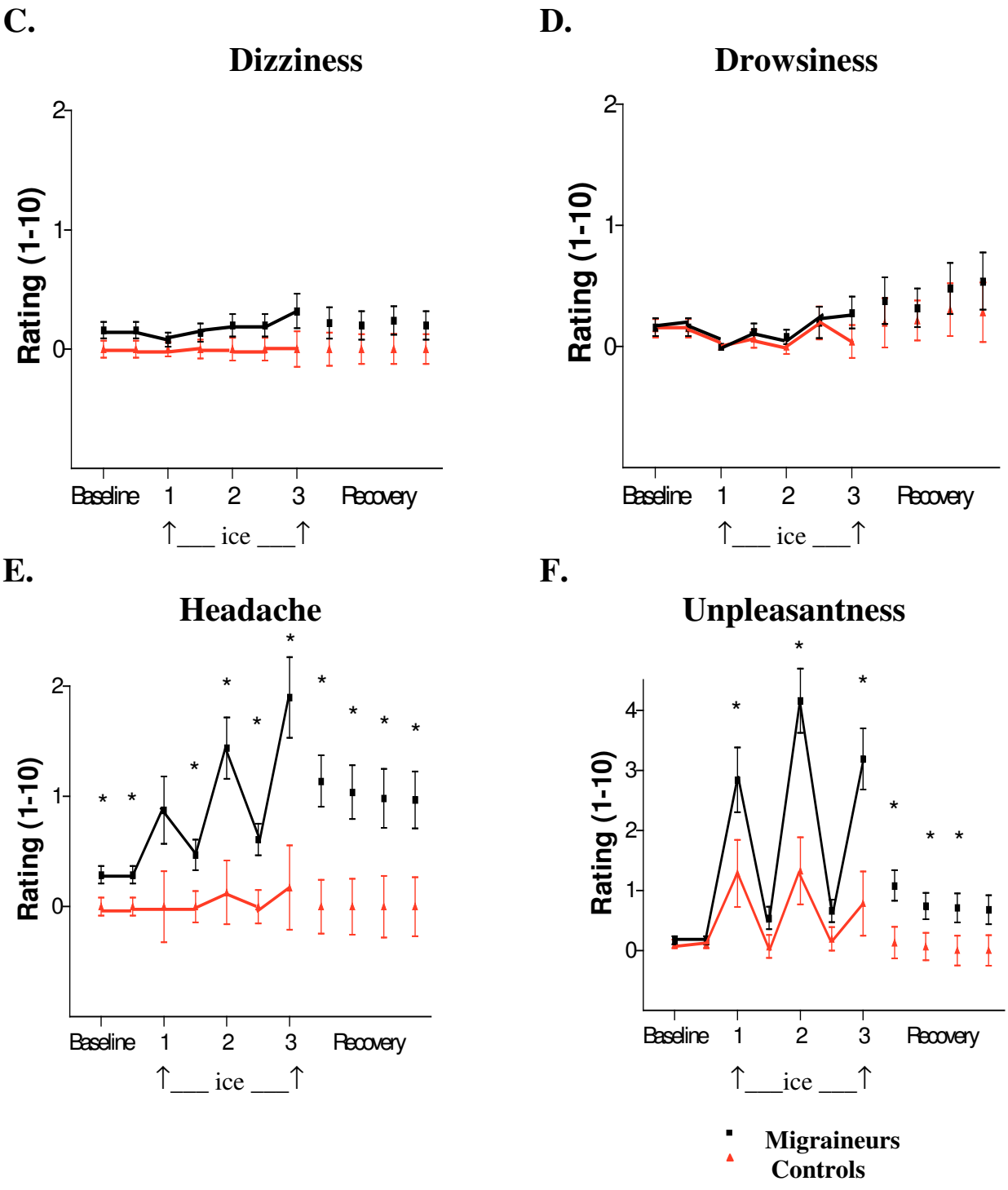


Figure 7.1.C-F. Symptom ratings (± SEM) for migraineurs (n = 25) and controls (n = 23) over 11 time points (every 2 minutes from baseline to minute 20).

** statistically significant group difference (* p < .05)*

Note: Y axis has different rating scales for unpleasantness

P.T.O for additional ratings

G. **H.**

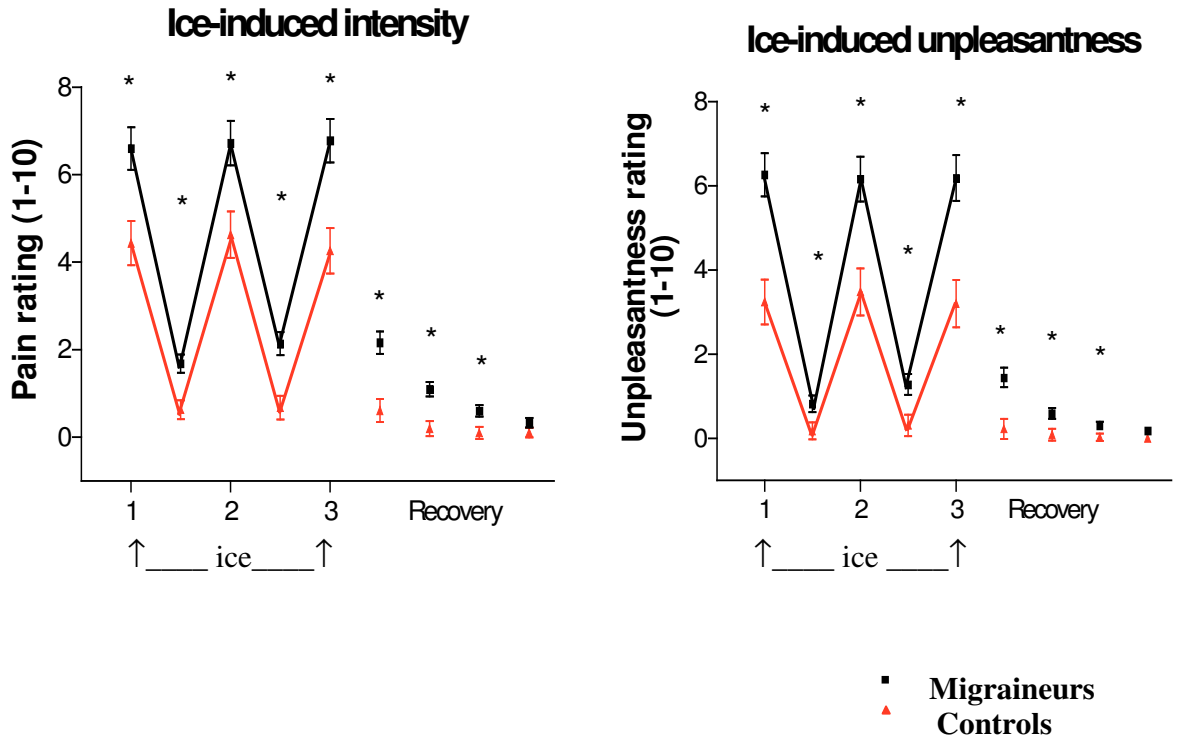


Figure 7.1.G-.H. Symptom ratings (± SEM) for migraineurs (n = 25) and controls (n = 23) over 9 time points (every 2 minutes from ice 1)
** statistically significant group difference (* p < .05)*

Note: Y axis has different rating scales for unpleasantness (previous page) ice-induded intensity and ice-induced unpleasantness

Table 7.1. Main effect and interaction F, *p*, and df values from a 2 (group: migraineurs, controls) x 11 (time: every 2 minutes from baseline to minute 20) repeated-measures ANOVA for each rating. Ice-induced pain intensity and unpleasantness values obtained from a 2 (group: migraineurs, controls) x 9 (time: every 2 minutes from the first application of ice) repeated-measures ANOVA

	F ratios (df)		
	Group	**Time**	**Time x Group**
Nausea	3.964 (1, 46)	1.244 (9, 38)	1.361 (9, 38)
Body temperature	.618 (1, 46)	1.489 (9, 38)	.584 (9, 38)
Dizziness	2.012 (1, 46)	1.034 (6, 41)	1.034 (6, 41)
Drowsiness	.453 (1, 46)	1.732 (9, 38)	.924 (9, 38)
Headache	14.033 (1, 46) ***	1.631 (9, 38)	1.381 (9, 38)
Unpleasantness	10.487 (1, 46) **	6.599 (9, 38) ***	2.839 (9, 38) *
Ice-induced intensity	20.545 (1, 46) ***	27.560 (8, 39) ***	2.745 (8, 39) *
Ice-induced unpleasantness	21.781 (1, 46) ***	19.362 (8, 39) ***	3.364 (8, 39) **

* difference between migraine sufferers and controls statistically significant (* p < .05,** p < .01,*** p < .001)

degrees of freedom differ across the dependent variables because of empty cells

Pulse Amplitude

Pulse amplitude increased bilaterally and progressively in both groups over time (main effect for Time: F (10,37) = 3.403, $p < .01$) but overall increases were greater in migraine sufferers than in controls throughout the condition (25% $\pm$ 4% *vs* 7% $\pm$ 4%; F (1,46) = 11.461, $p < .001$). Figure 7.2, Table 7.2 and Appendix 8.2.1 and 8.2.2 (pages 325, 326, respectively) demonstrate these observations.

Vasodilatation was evident in migraine sufferers throughout testing, even before the initial application of ice to the temple. However, vasodilatation in the control group developed as the procedure progressed. Refer to Appendix 8.2.1 and 8.2.2 (pages 325, 326, respectively).

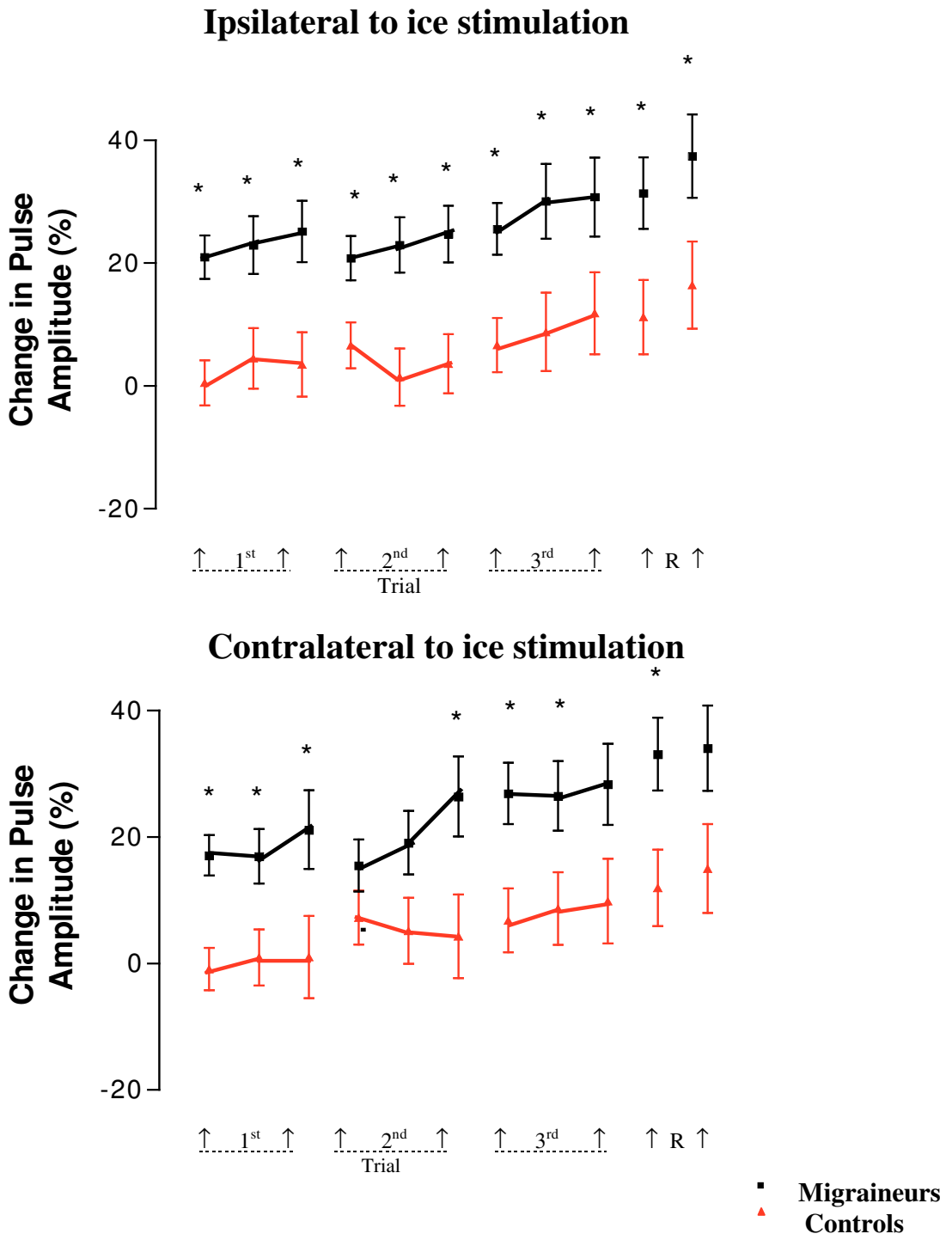


Figure 7.2. Pulse amplitude change (± SEM) for migraineurs (n = 25) and controls (n = 23) over 11 time points (30 second samples: before, during and after ice application {3 trials}, and after 3 and 8 minutes of recovery {R}). The first arrow in each trial represents pulse amplitude before the immersion, and the second arrow represents pulse amplitude after the immersion. * *statistically significant group difference (* $p < .05$)*

Table 7.2. Main effect and interaction F, *p*, and df values from a 2 (group: migraineurs, controls) x 2 (side: ipsilateral, contralateral to stimulation) x 11 (time: 30 second samples, before {trial 1, 2 & 3}, during {trial 1, 2 & 3} and after {trial 1, 2 & 3} ice application to temple, and 3 and 8 mins after the 3rd application) repeated-measures ANOVA for pulse amplitude change.

Main effect	*df*	F	P
Group	1, 46	11.461	.001
Side	1, 46	.295	.590
Time	10, 37	3.403	.003
Interaction			
Side x Time	10, 37	.892	.549
Side x Group	10, 46	.146	.705
Time x Group	10, 37	1.050	.423
Side x Time x Group	10, 37	.542	.849

DISCUSSION

Effects on symptomatic responses

Summary of major findings

Key findings to emerge from exploring the effects of ice to the temple before OKS were:

- Overall, ratings of nausea, body temperature, dizziness and drowsiness remained virtually unchanged and comparable for both groups throughout. However, in a different analysis of these responses (refer to publications related to this study, Drummond and Granston, 2005), it was demonstrated that by the third application of ice nausea increased more so in migraine sufferers than in controls. Headache, overall unpleasantness and ice-induced intensity and unpleasantness, were greater in migraineurs than in controls.

Discussion of effects on symptomatic responses

Results were consistent with the hypothesis that headache would develop more readily in migraine sufferers than in controls. Migraine sufferers were aware of low-grade headache even prior to the procedures, which increased following the second application of ice to the temple. Six minutes after the third ice application, headache gradually subsided to baseline levels of head-awareness. Low-grade nausea (awareness) developed in the migraine group before and during the final application of ice, which at least partly supported the hypothesis that symptoms other than headache might be evoked

in migraine sufferers more readily than in controls. Controls remained asymptomatic throughout.

Thermal nociceptors were excited, apparently more so in migraineurs interictally than in controls to extremely cold sensory provocation. Specifically, ice-induced intensity and upleasantness, headache and not surprisingly, overall unpleasantness were enhanced in the migraine group. Migraine sufferers were more sensitive to painful stimulation of the temple with ice than were controls, and more readily developed headache. It is plausible that headache may have developed following activation of neuronal structures and pathways normally involved in the transmission of head pain (Pietrobon, 2005; Knight, 2005; Silberstein, 2004, 2003; Moskowitz and Macfarlane, 1993). As pointed out, in addition to the development of headache, migraine sufferers experienced nausea by the third application of ice to the temple. Head pain appeared to trigger nausea, suggesting gastrointestinal disturbance in this group, which may similarly occur in a migraine attack.

Effects on pulse amplitude

Summary of major findings

- Pulse amplitude increased bilaterally for both groups over time but more so in migraineurs. In migraine sufferers vasodilatation was evident even before the initial application of ice, but developed in controls as the procedure progressed.

Discussion of effects on pulse amplitude

Increases in pulse amplitude were observed in both groups in response to trigeminal stimulation. However, consistent with hypotheses responses were greater in the migraine group than in controls. The enhanced vascular reactivity observed in migraine sufferers was evident before the application of ice, suggesting a possible defense response in this group in anticipation of the painful stimuli.

Vasodilatation developed in migraineurs even before the initial application of ice, but in controls gradually developed as the procedure progressed. Extracranial blood vessels dilate more readily in migraine sufferers than in controls during exposure to stressful stimulation (Drummond, 1984). Stress is also a commonly sited precipitating and aggravating factor of migraine headache (Spierings, Ranke and Honkoop, 2001; Holm, Lokken and Myers, 1997). It is conceivable that migraineurs in the present study were primed in anticipation of the pending painful stimulus, perhaps because of an association with the all too familiar pain of migraine. Hence, the vasodilator defense response probably accounted for vasodilatation prior to the ice application and also contributed to enhanced reactions when the ice was applied.

CHAPTER 8

RESULTS and DISCUSSION

Condition 4

Ice on temple during optokinetic stimulation (OKS)

This condition investigated whether symptomatic responses following painful stimulation of the temple with ice during OKS would differ between migraine sufferers and controls. As migraineurs are prone to motion sickness (Golding, 1998; Kuritzky, Ziegler & Hassanein, 1981) it was hypothesized that symptomatic ratings would be greater in migraine sufferers than in controls during OKS. Also, as ice on the temple probably stimulated the trigeminal nerve, it was hypothesized that headache would intensify more readily during OKS in the migraine group than in controls. Similarly, if conduction of trigeminal impulses converges on neurons responsible for symptoms other than headache, these symptoms might be enhanced in migraine sufferers during painful stimulation. Also, as facial blood flow increases during motion sickness in susceptible individuals (Harm, 1990; Kolev et al., 1997) and during head pain in migraineurs (Lance and Goadsby, 2002; Drummond, 1997), it was hypothesized that vascular reactions in response to temple pain during OKS would be greater in the migraine group than in controls.

RESULTS

Symptom ratings

Overall, symptomatic responses increased during OKS for both groups (main effect for Time for each response, $p < .05$). Procedures evoked more nausea (mean $\pm$ S.E. = 2.116 $\pm$ .353 vs .473 $\pm$ .319; F (1,38) = 11.910, $p < .001$), dizziness (2.239 $\pm$ .392 vs .578 $\pm$ .354; F (1,38) = 9.892, $p < .01$) and headache (1.968 $\pm$ .351 vs .014 $\pm$ .318; F (1,38) = 17.012, $p < .001$) in migraine sufferers than in controls. Investigation of significant Group by Time Simple Contrast interactions indicated that nausea and dizziness ratings were greater in migraine sufferers than in controls once OKS commenced, before the first application of ice (see Figure 8.1.A, 8.1.C and Appendix 9.1.1, 9.1.3, pages 327, 329, respectively). Headache was greater in migraineurs even before OKS (see Figure 8.1.E and Appendix 9.1.5, page 331). While both groups developed nausea and dizziness during OKS, controls recovered sooner. Headache increased in migraineurs following the first application of ice, but was minimal in controls throughout the procedures (Time x Group interaction, F (10,29) = 3.977, $p < .01$). Body temperature and drowsiness increased during the procedure in migraine sufferers but remained stable in controls (see Appendix 9.1.2, 9.1.4, page 328, 330, respectively).

Unpleasantness overall was greater for migraine sufferers than for controls (3.081 $\pm$ .445 *vs* .886 $\pm$ .403; F (1,38) = 13.361, $p < .001$). Inspection of significant Group by Time Simple Contrast interactions indicated that these ratings were greater in migraine sufferers than in controls throughout the test (see Figure 8.1.F and Appendix 9.1.6, page 332). Otherwise, both groups reported experiencing increased levels of symptom unpleasantness in general, particularly during application of ice to the temple (main effect for Time: F (10,29) = 5.477, $p < .001$). Migraine sufferers experienced unpleasantness throughout testing. Controls however, experienced unpleasantness during the first application of ice and recovered soon after OKS (Time x Group interaction: F (10,29) = 2.498, $p < .05$).

Pain peaked in intensity and unpleasantness for both groups during ice application to the temple (main effect for Time: Pain Intensity, $F(10,29) = 11.179$, $p < .001$; Pain Unpleasantness, $F(9,30) = 8.751$, $p < .001$). Perceptions increased from the initial application of ice in both groups, and while controls recovered after OKS, pain intensity persisted in migraineurs. Investigation of significant Group by Time interactions indicated that ratings were greater in migraine sufferers than in controls throughout the procedures (see Figures 8.1.G, 8.1.H and Appendix 9.1.7, 9.1.8, pages 333, 334, respectively).

Apart from during and after the second application of ice, self-motion was greater in migraine sufferers than in controls (main effect for Group: $F(1, 38) = 8.136$, $p < .01$). Visual-illusion developed more in migraineurs than in controls following the second ice trial (main effect for Group: $F(1, 38) = 5.741$, $p < .05$). Refer to Figure 8.1.I, 8.1.J and Appendix 9.1.9, 9.1.10 (pages 335, 336, respectively).

Twenty-eight percent of migraine sufferers withdrew from OKS and painful stimulation of the temple compared to only four percent of controls ($p<0.05$, see Appendix 13, page 363).

Figure 8.1.A to H demonstrate change in symptom ratings over time. Table 8.1 demonstrates main effects and interactions for each symptom.

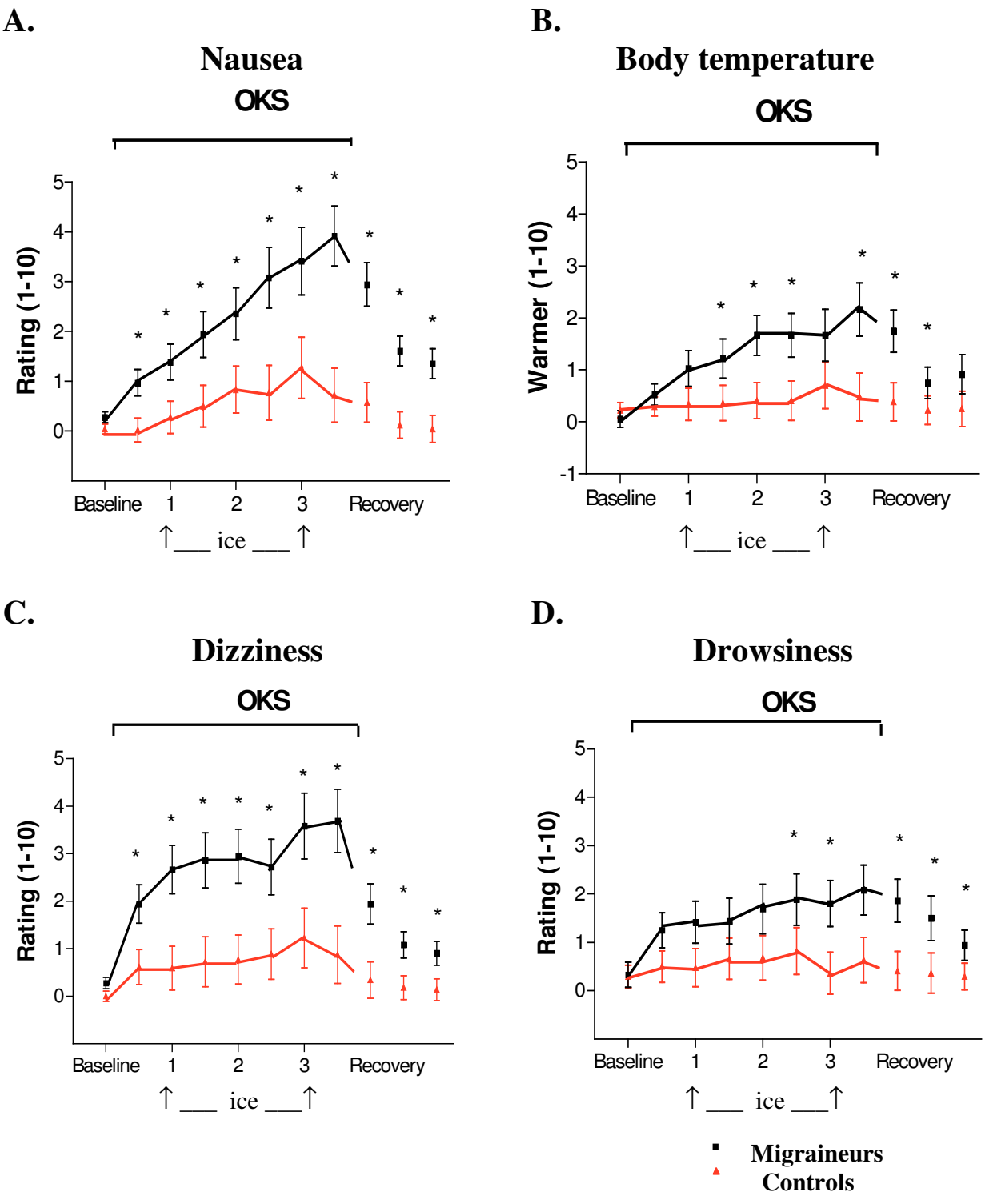


Figure 8.1.A-D. Symptom ratings (± SEM) for migraineurs (n = 18) and controls (n = 22) over 11 time points (every 2 minutes from baseline to minute 20).
OKS = optokinetic stimulation ** statistically significant group difference (* p < .05)*
P.T.O for additional ratings

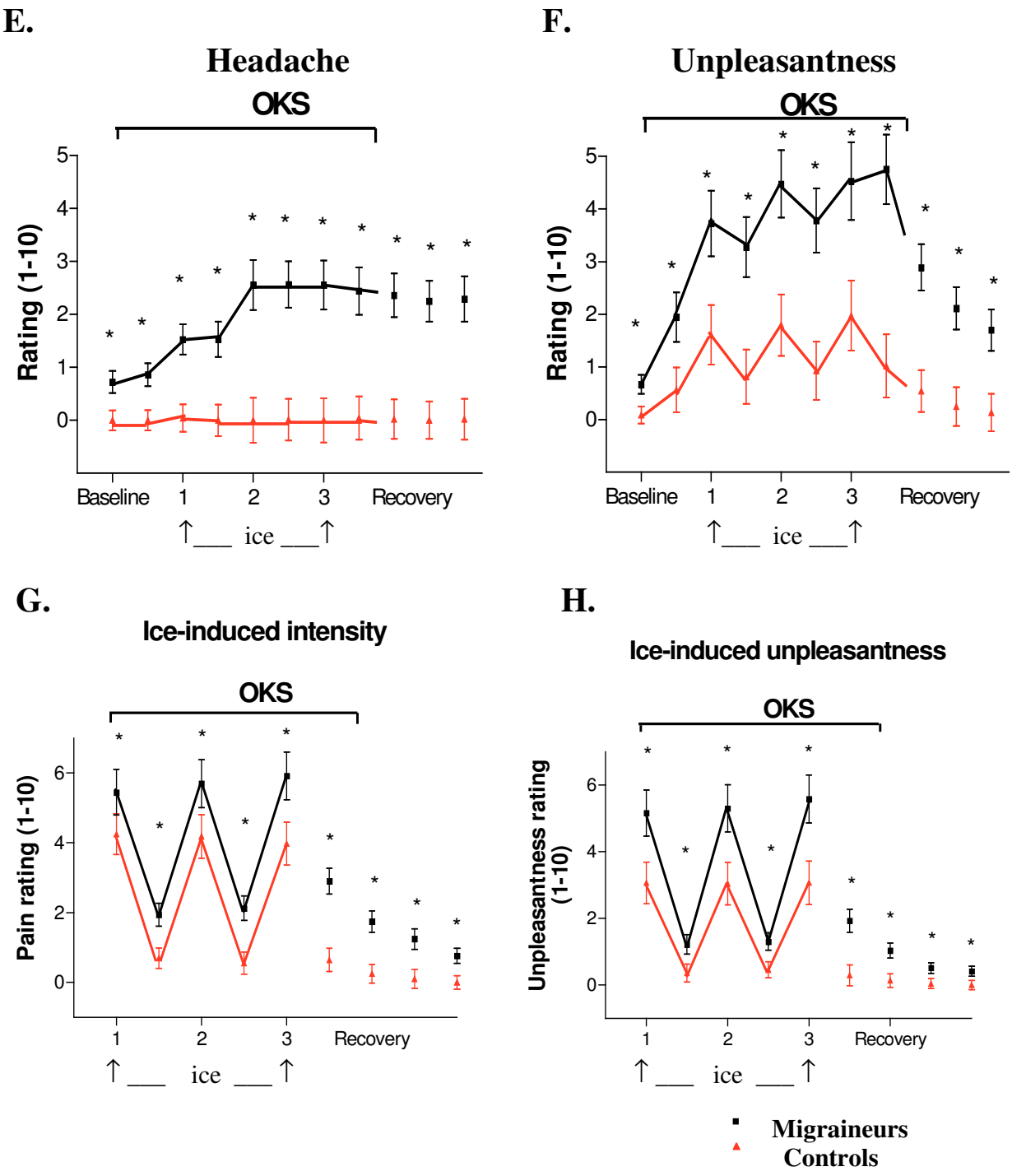


Figure 8.1.E-H. Symptom ratings (± SEM) for migraineurs (n = 18) and controls (n = 22) over 11 time points (every 2 minutes from baseline to minute 20 {E, F}) and over 9 time points (every 2 minutes from ice 1 {G, H}).
OKS = optokinetic stimulation ** statistically significant group difference (* p < .05)*
Note: Y axis has different rating scales for ice-induced intensity and ice-induced unpleasantness. ***P.T.O for additional ratings***

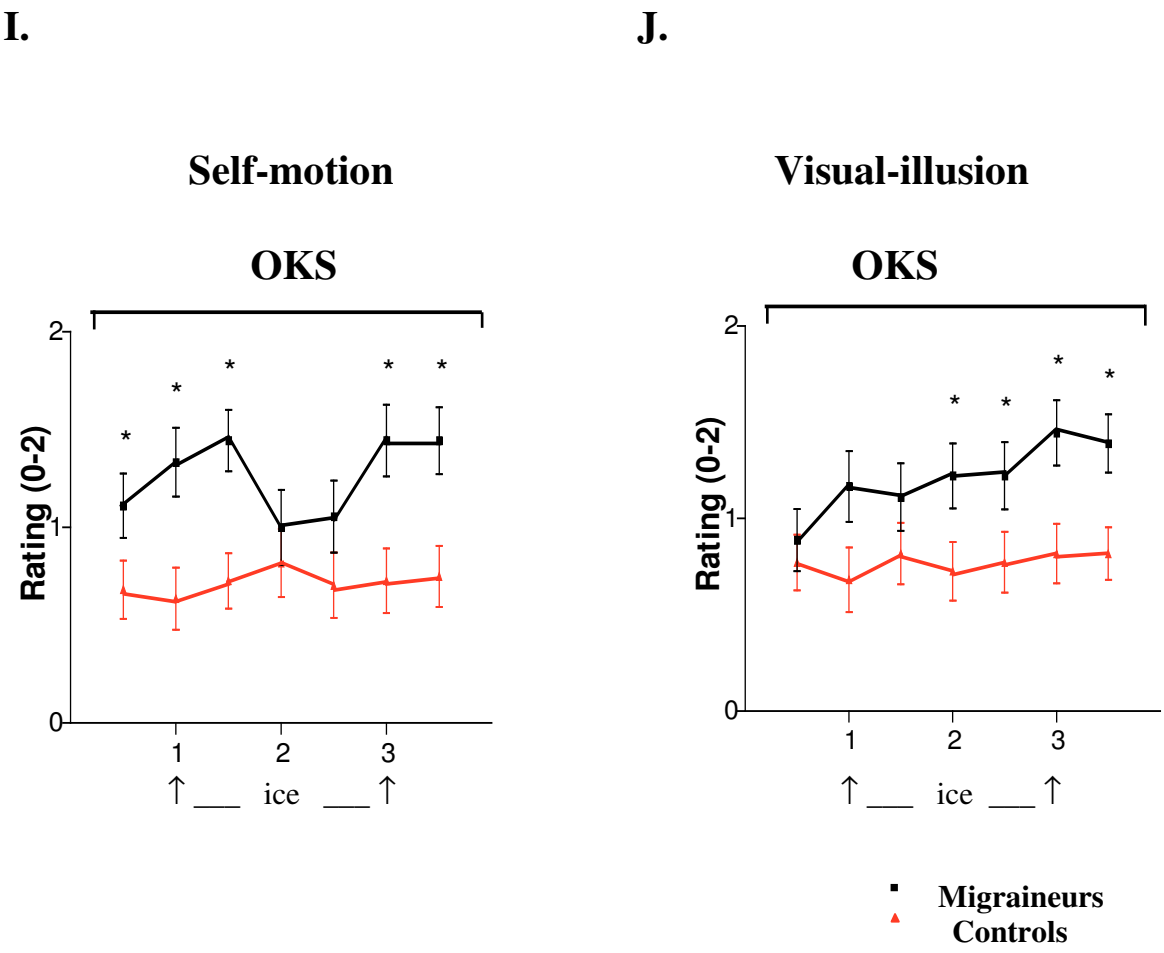


Figure 8.1.I-J. Symptom ratings (± SEM) for migraineurs (n = 18) and controls (n = 22) over 7 time points (every 2 minutes from commencement of OKS).
OKS = optokinetic stimulation * *statistically significant group difference (* $p < .05$)*

Note: Different rating scales for self-motion and visual-illusion (0-2)

Table 8.1. Main effect and interaction F, *p*, and df values from from a 2 (group: migraineurs, controls) x 11 (time: every 2 minutes from baseline to minute 20) repeated-measures ANOVA for each rating. Values for Self-motion and Visual-illusion obtained from a 2 (group: migraineurs, controls) x 7 (time: every 2 minutes during OKS) repeated-measures ANOVA, and ice-induced pain intensity and unpleasantness from a 2 (group: migraineurs, controls) x 9 (time: every 2 minutes from the first application of ice) repeated-measures ANOVA.

	F ratios (df)		
	Group	**Time**	**Time x Group**
Nausea	11.910 (1, 38) ***	3.573 (10, 29) **	1.951 (10, 29)
Body temperature	4.034 (1, 38)	2.369 (10, 29) *	1.481 (10, 29)
Dizziness	9.892 (1, 38) **	2.835 (10, 29) *	1.357 (10, 29)
Drowsiness	3.396 (1, 38)	2.604 (10, 29) *	1.630 (10, 29)
Headache	17.012 (1, 38) ***	4.217 (10, 29) ***	3.977 (10, 29) **
Unpleasantness	13.361 (1, 38) ***	5.477 (10, 29) ***	2.498 (10, 29) *
Ice-induced intensity	10.833 (1, 38) **	11.179 (10, 29) ***	2.897 (10, 29) *
Ice-induced unpleasantness	11.079 (1, 38) **	8.751 (9, 30) ***	3.386 (9, 30) **
Self-motion	8.136 (1, 38) **	1.313 (6, 33)	1.528 (6, 33)
Visual-illusion	5.741 (1, 38) *	1.522 (6, 33)	1.124 (6, 33)

* difference between migraine sufferers and controls statistically significant (* p < .05,** p < .01,*** p < .001)

degrees of freedom differ across the dependent variables because of empty cells

Pulse Amplitude

Pulse amplitude increased bilaterally in both groups during OKS (main effect for Time: F (10,29) = 3.740, $p < .01$). Refer to Figure 8.2 and Table 8.2. Closer inspection indicated that vasodilatation was greater in migraine sufferers than in controls during the second ice trial (see Figure 8.2). Intercept analyses indicated that vasodilatation persisted throughout OKS in both groups and returned to baseline in migraineurs by 5 minutes after OKS but fell below baseline in controls (Time x Group interaction: F (10,29) = 2.878, $p < .05$). Table 8.2 and Appendix 9.2.1 and 9.2.2 (pages 337, 338, respectively) illustrate this observation.

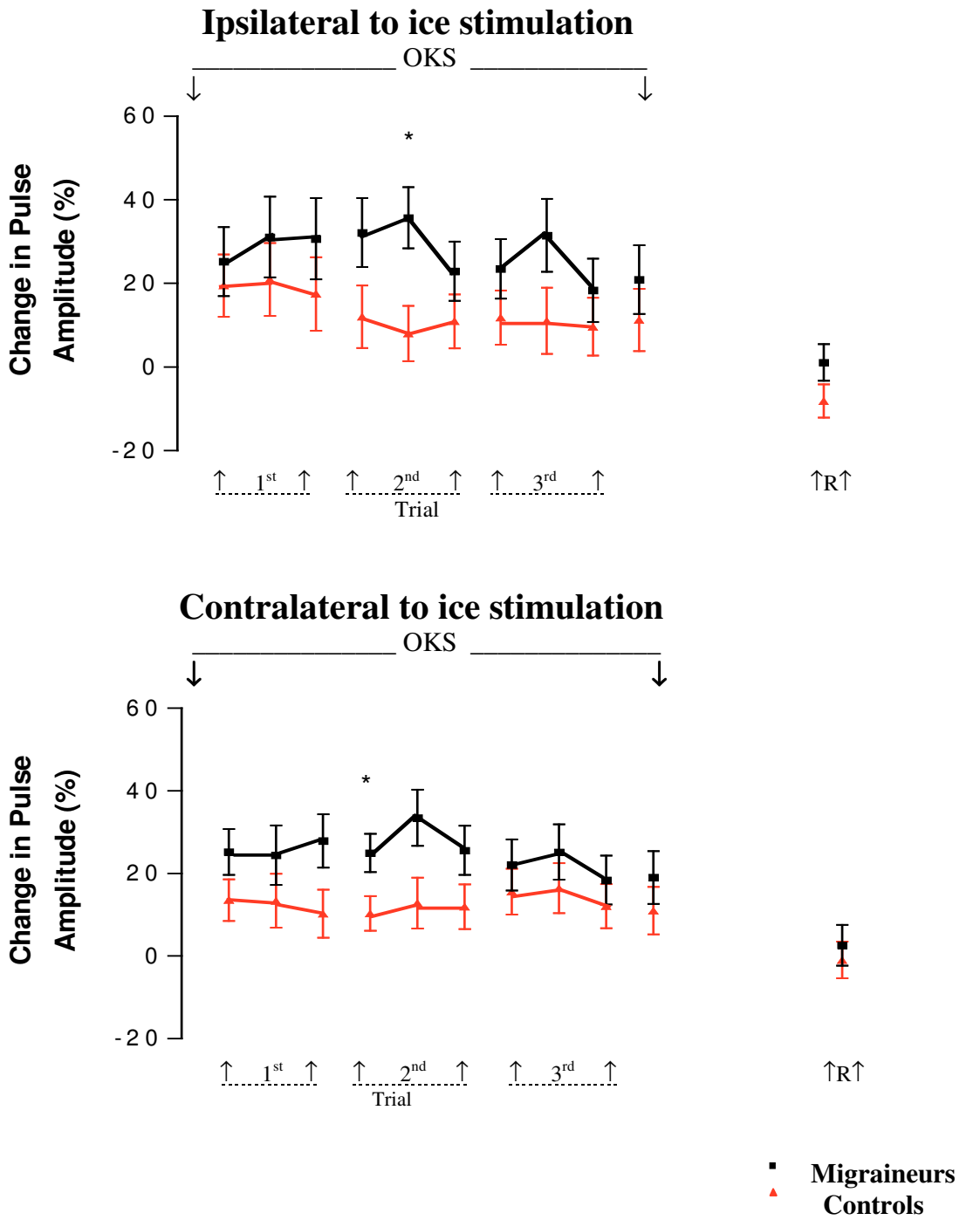


Figure 8.2. Pulse amplitude change (± SEM) for migraineurs (n = 18) and controls (n = 22) over 11 time points (30 second samples: before, during and after ice application to temple {3 trials}, and after 3 and 8 minutes {recovery - R}). The first arrow in each trial represents pulse amplitude before the application, and the second arrow represents pulse amplitude after the application.
OKS = optokinetic stimulation ** statistically significant group difference (* p < .05)*

Table 8.2. Main effect and interaction F, *p*, and df values from a 2 (group: migraineurs, controls) x 2 (side: ipsilateral, contralateral to stimulation) x 11 (time: 30 second samples, before {trial 1, 2 & 3}, during {trial 1, 2 & 3} and after {trial 1, 2 & 3} hand immersion in ice-water, and 3 and 8 mins after the 3rd immersion) repeated-measures ANOVA for pulse amplitude change.

Main effect	*df*	F	P
Group	1, 38	2.969	.093
Side	1, 38	.055	.816
Time	10, 29	3.740	.003
Interaction			
Side x Time	10, 29	.923	.526
Side x Group	1, 38	.073	.789
Time x Group	10, 29	2.878	.013
Side x Time x Group	10, 29	.577	.819

DISCUSSION

Effects on symptomatic responses

Summary of major findings

Key findings to emerge from exploring the effects of ice to the temple during OKS were:

- Overall, ratings of headache, nausea, dizziness, self-motion and visual illusion were greater in migraine sufferers than in controls. Drowsiness and body temperature also increased, more so in migraineurs, but group differences only became evident as the procedure progressed. Apart from slight nausea, dizziness, self-motion and visual illusion, symptomatic ratings barely developed in controls. Migraineurs found the experience generally more unpleasant, and ice-induced pain more intense and unpleasant, than controls.

Discussion of effects on symptomatic responses

As hypothesized, symptomatic ratings were greater in the migraine sufferers than in controls when ice was applied to the temple during OKS. In addition, a greater proportion of migraine sufferers than controls withdrew from OKS, indicating that they were unable to tolerate procedures. Ratings of overall unpleasantness and ice-induced pain were also heightened in migraineurs, probably because symptoms developed more readily in this group. It may also be that migraine sufferers use different criteria in their reported experience of pain and have a lower tolerance threshold in terms of unpleasantness. Ideally, it may have been better to have compared the responses of migraine sufferers with themselves during an attack, than to responses of a normally pain-free group, as done in this study. However, it was methodologically considered impractical to test migraine sufferers during a migraine attack in this study (see comment in Discussion of Results Condition 2, page 124).

OKS most likely triggered visually-induced motion sickness (Takeda, Morita, Horii, Nishiike and Uno, 2001) as symptomatic responses developed in both groups, albeit more so in migraineurs. In addition, trigeminal nociceptors were stimulated by the application of ice to the temple. Migraine sufferers were more sensitive to painful stimulation than controls, and developed headache during the procedure. While vestibular structures are required for the generation of motion sickness (Yates, Miller and Lucot, 1998), trigeminal nuclei are probably involved in the development of symptoms including head pain, during a migraine attack (Moskowitz, 1993). Both of these pathways have been associated with activation of the "vomiting center" (Dahlof and Hargreaves, 1998; Mitchelson, 1992). The enhanced symptomatic responses in migraineurs in this study may be because hypersensitivity persists in these neural pathways in the interictal period. Closely connected and overlapping pathways that typically generate either motion sickness or migraine perhaps interact and augment one another during a migraine attack.

Symptomatic ratings were greater in migraine sufferers than in controls in the presence, or absence (see results condition 1, page 104-114), of painful stimulation of the temple during OKS. Collectively, these findings further suggest trigeminal and brainstem nuclei are hyperexcitable in migraineurs between headaches. Whether symptoms were exacerbated when ice was applied during OKS will be discussed later (see results, comparison of OKS in the presence and absence of painful stimulation of the temple, Chapter 11, pages 175-191).

Effects on pulse amplitude

Summary of major findings

- Pulse amplitude increased bilaterally in both groups during OKS. Vasodilatation subsided in migraineurs by 5 minutes after OKS, but fell below baseline in controls.

Discussion of effects on pulse amplitude

It was hypothesized that vascular reactions in response to temple pain during OKS would be greater in the migraine group than in controls. Contrary to expectations, vascular reactions in response to temple pain during OKS generally did not differ between groups. However, vasodilatation was greater in migraine sufferers than in controls during the second ice trial, indicating vessels were at least more reactive in the migraine group during this period.

Clearly, excessive motion (Kohl, 1985; Eversmann et al, 1978) and painfully cold stimulation, particularly in migraine sufferers (Peroutka, 2004; Hassinger, Semenchuk and O'Brien, 1999), are stressful stimuli. OKS does not involve excessive motion; nevertheless, the disconcerting nature of OKS was possibly a stressful experience for participants in the present study. Facial flushing, an index of blood flow, has been observed during motion sickness (Harm, Beatty and Reschke, 1987), and migraine sufferers are prone to motion sickness (Drummond, 2005; Golding, 2006, 1998; Kuritzky, Ziegler & Hassanein, 1981). Cardiac output increased more so in migraineurs than controls during painfully cold stimulation and cognitive stress (Hassinger et al, 1999). Similarly, extracranial vasodilatation developed more readily in migraine sufferers than in controls during exposure to physical and mental stress (Drummond, 1984). However, in the present test, contrary to these findings, extracranial vascular responses generally did not differ between groups following painfully cold stimulation of the temple during OKS (two stressors). An explanation for these findings is not immediately obvious. OKS in the absence of painful stimulation of the temple, and painful stimulation of the temple in the presence of OKS, are compared respectively with OKS in the presence of painful stimulation of the temple in later sections (see chapter 11, pages 175-191). In light of these findings, physiological mechanisms responsible for the present findings may become more apparent.

CHAPTER 9

RESULTS and DISCUSSION

Condition 5

Hand in ice-water

The purpose of this condition was to act as a comparison with other conditions that explored pain processing in response to cranial pain. In particular, if pain processing is compromised in migraine sufferers, symptomatic ratings to limb pain as well as head pain might be greater in migraine sufferers than in controls. Facial blood flow increases in response to head pain (Lance and Goadsby, 2002; Drummond, 1997), but extracranial vascular responses to limb pain have not previously been investigated. If pain processing is compromised or if defense responses are greater in migraine sufferers, extracranial vascular responses to limb pain might be greater in migraine sufferers than in controls.

RESULTS

Symptom ratings

Symptom ratings remained unchanged during ice-water immersion for both groups (see Appendix 10, pages 339-346). Migraine sufferers experienced a low-grade headache (head awareness) throughout the procedure while controls remained headache-free the entire time (mean $\pm$ S.E. = .237 $\pm$ .078 vs 0 $\pm$ 0; F (1,43) = 4.539, $p < .05$). Simple contrast analyses indicated that headache did not increase in migraine sufferers during the course of the test, and that the small difference between groups was only evident following the first and third immersions (see Figure 9.1.E and Appendix 10.1.5, page 343). In general, unpleasantness ratings were greater in migraine sufferers than in controls (1.741 $\pm$ .262 *vs* .921 $\pm$ .268; F (1,43) = 4.790, $p < .05$). Both groups experienced increased levels of unpleasantness during the procedure, particularly during immersion of the hand in ice-water (main effect for Time, F (9, 35) = 6.247, $p < .001$). Furthermore, ratings of unpleasantness differed between migraine sufferers and controls after the third immersion (Group by Time Simple Contrast interaction, F (1, 43) = 5.532, $p < .05$). Investigation of this interaction indicated that ratings were greater in migraine sufferers than in controls after the third immersion (see Figure 9.1.F and Appendix 10.1.6, page 344).

Ice induced pain, not surprisingly, peaked in intensity and unpleasantness for both groups during immersion of the hand in ice-water (main effect for Time: Pain Intensity; F (8,36) = 62.972, p < .001; Pain Unpleasantness; F (8,36) = 40.688, p < .001). Investigation of significant Group by Time Simple Contrast interactions indicated that ratings were greater in migraine sufferers than in controls during immersions but did not differ between groups during any of the recovery periods following the immersions (see Figures 9.1.G, 9.1.H and Appendix 10.1.7, 10.1.8, pages 345, 346, respectively).

Figure 9.1.A-H illustrates change in symptom ratings over time. Table 9.1 demonstrates main effects and interactions for each symptom.

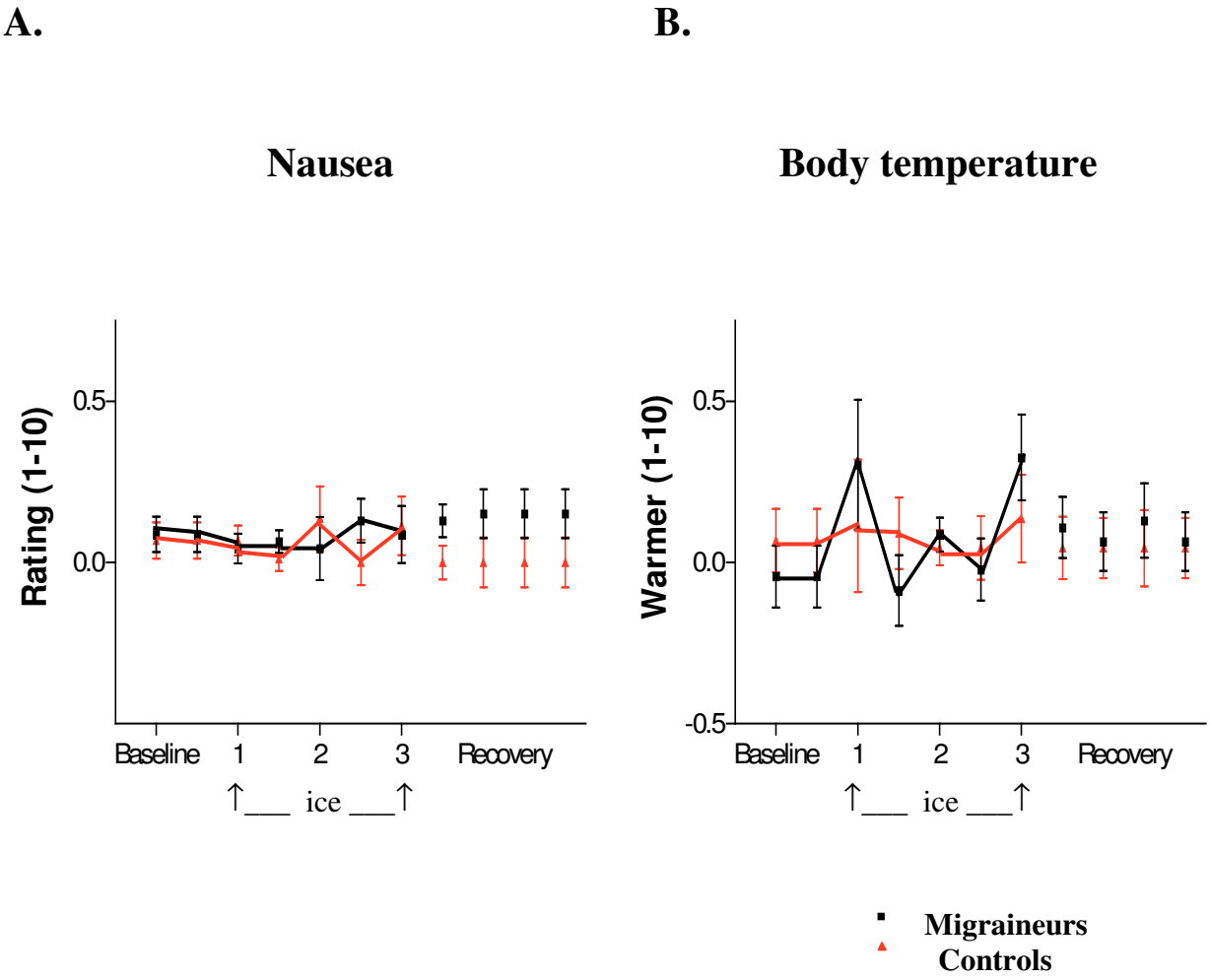


Figure 9.1.A-B. Symptom ratings (± SEM) for migraineurs (n = 23) and controls (n = 22) over 11 time points (every 2 minutes from baseline to minute 20).

P.T.O for additional ratings

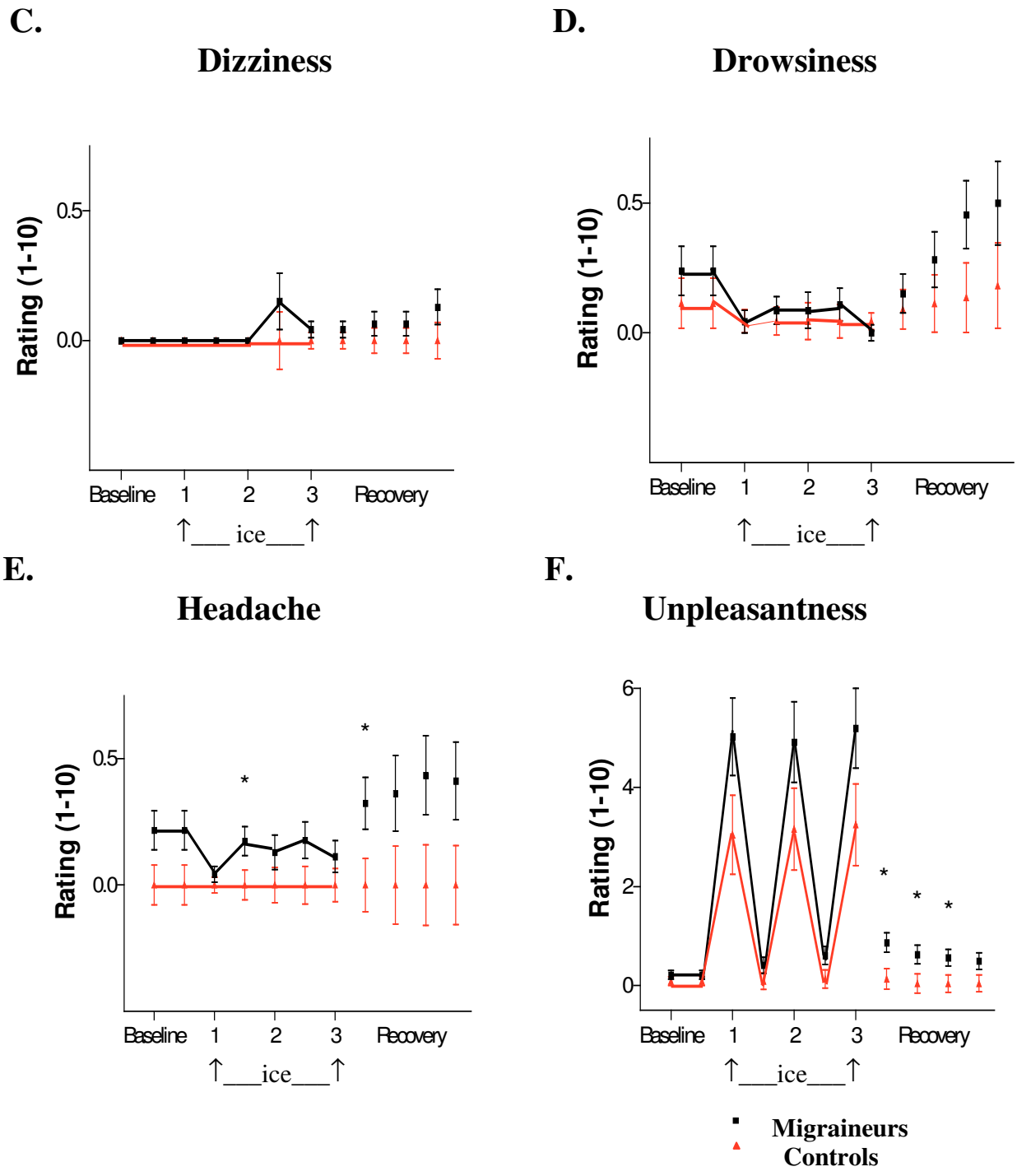


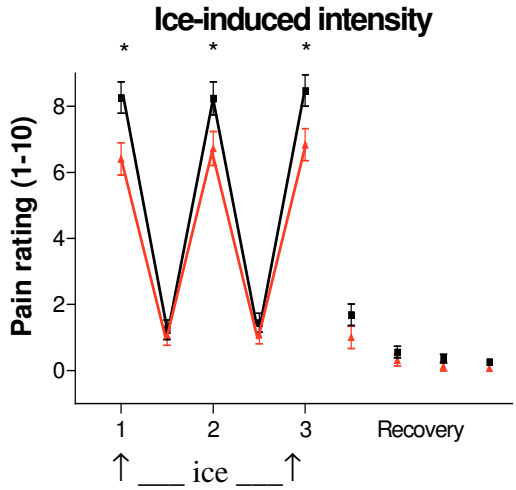
Figure 9.1.C-F. Symptom ratings (± SEM) for migraineurs (n = 23) and controls (n = 22) over 11 time points (every 2 minutes from baseline to minute 20).

** statistically significant group difference (* p < .05)*

Note: Y axis has different rating scales for unpleasantness

P.T.O for additional ratings

G.



H.

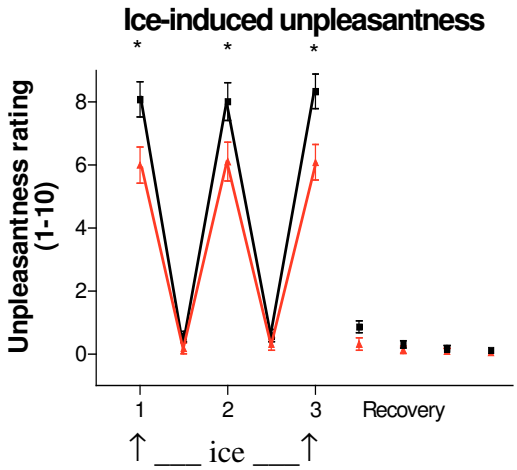


Figure 9.1.G-H. Symptom ratings (± SEM) for migraineurs (n = 23) and controls (n = 22) over 11 time points (every 2 minutes from baseline to minute 20{E, F}) and over 9 time points (every 2 minutes from ice 1{G, H}).
** statistically significant group difference (* p < .05)*

Note: Y axis has different rating scales for unpleasantness (previous page), ice-induced intensity and ice-induced unpleasantness.

Table 9.1. Main effect and interaction F, *p*, and df values from from a 2 (group: migraineurs, controls) x 11 (time: every 2 minutes from baseline to minute 20) repeated-measures ANOVA for each rating. Ice-induced pain intensity and unpleasantness values obtained from a 2 (group: migraineurs, controls) x 9 (time: every 2 minutes from the first application of ice) repeated-measures ANOVA

	F ratios (df)		
	Group	**Time**	**Time x Group**
Nausea	.859 (1, 43)	.955 (7, 37)	1.109 (7, 37)
Body temperature	.014 (1, 43)	.841 (9, 35)	1.093 (9, 35)
Dizziness	2.347 (1, 43)	1.002 (3, 41)	1.002 (3, 41)
Drowsiness	1.445 (1, 43)	1.461 (8, 36)	1.144 (8, 36)
Headache	4.539 (1, 43) *	1.173 (8, 36)	1.173 (8, 36)
Unpleasantness	4.790 (1, 43) *	6.247 (9, 35) ***	1.281 (9, 35)
Ice-induced intensity	5.585 (1, 43) *	62.927 (8, 36) ***	1.279 (8, 36)
Ice-induced unpleasantness	8.551 (1, 43) **	40.688 (8, 36) ***	2.210 (8, 36)

* difference between migraine sufferers and controls statistically significant (* $p < .05$,** $p < .01$,*** $p < .001$)

degrees of freedom differ across the dependent variables because of empty cells

Pulse Amplitude

Overall, increases in pulse amplitude were greater for migraine sufferers than for controls throughout the experiment (26% $\pm$ 4% *vs* 12% $\pm$ 4%; F (1,43) = 5.860, p < .05). A main effect for Side of stimulation (F (1,43) = 7.117, $p < .05$) indicated that increases for both groups were greater ipsilaterally (migraineurs: 29%, $\pm$ 4%; controls: 20%, $\pm$ 4%) than contralaterally (migraineurs: 24% $\pm$ 6%; controls: 4% $\pm$ 6%). Pulse amplitude increased bilaterally in both groups after the hand was withdrawn from ice-water (main effect for Time: F (10,34) = 7.722, $p < .001$). Furthermore, increases persisted during recovery. Figure 9.2, Table 9.2 and Appendix 10.2.1 (page 347) illustrate these trends.

Pulse amplitude had increased in migraine sufferers, but not controls, even before the first cold water immersion. The vasodilator response developed in controls during the first cold water immersion, and persisted in both groups throughout the remainder of the experiment. However, as previously described, changes were greater in migraineurs than controls. During immersions differences were not evident (see Appendix 10.2.1 and 10.2.2, pages 347, 348, respectively).

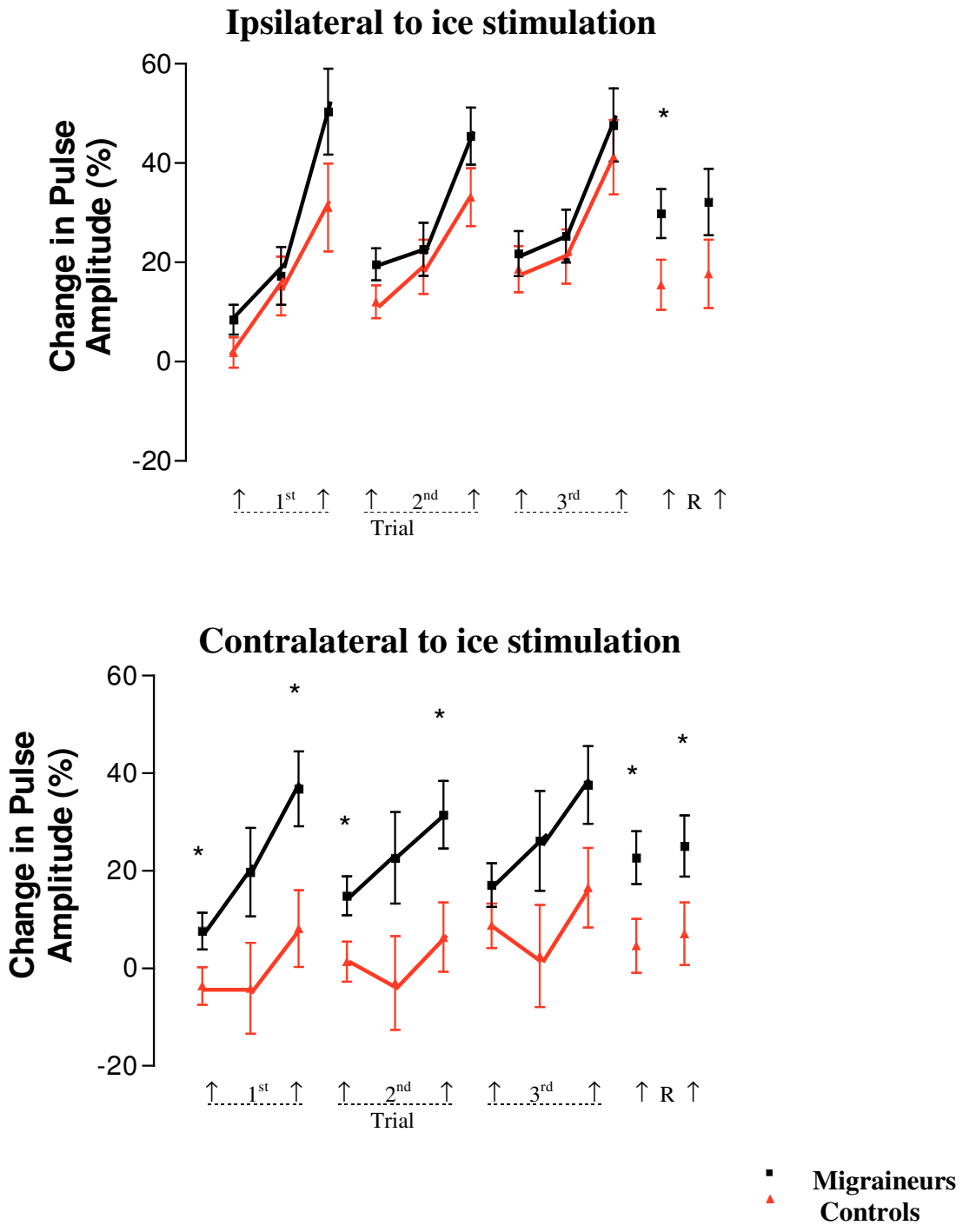


Figure 9.2. Pulse amplitude change (± SEM) for migraineurs (n = 23) and controls (n = 22) over 11 time points (30 second samples: before, during and after hand immersion in ice-water {3 trials}, and after 3 and 8 minutes of recovery {R}). The first arrow in each trial represents pulse amplitude before the immersion, and the second arrow represents pulse amplitude after the immersion.
** statistically significant group difference (* $p < .05$)*

Table 9.2. Main effect and interaction F, *p*, and df values from a 2 (group: migraineurs, controls) x 2 (side: ipsilateral, contralateral to stimulation) x 11 (time: 30 second samples, before {trial 1, 2 & 3}, during {trial 1, 2 & 3} and after {trial 1, 2 & 3} hand immersion in ice-water, and 3 and 8 mins after the 3rd immersion) repeated-measures ANOVA for pulse amplitude change.

Main effect	*df*	F	P
Group	1, 43	5.860	.020
Side	1, 43	7.117	.011
Time	10, 34	7.722	.000
Interaction			
Side x Time	10, 34	2.710	.015
Side x Group	1, 43	1.875	.178
Time x Group	10, 34	.978	.480
Side x Time x Group	10, 34	.668	.745

DISCUSSION

Effects on symptomatic responses

Summary of major findings

Key findings to emerge from exploring the effects of immersing the hand in ice-water were:

- Immersing the hand in ice-water did not induce nausea, headache, dizziness, drowsiness or change in perceived body temperature, either in migraine sufferers or controls, although overall unpleasantness was enhanced when the hand was actually immersed in ice-water. However, ratings specific to ice-induced pain were greater in migraine sufferers.

Discussion of effects on symptomatic responses

The investigation of limb pain was intended to act as a control condition for painful stimulation of the temple and was essentially exploratory; therefore, no specific hypotheses could be generated. However, it was anticipated that if pain processing is compromised in migraine sufferers, symptomatic ratings to limb pain as well as head pain might be greater in migraine sufferers than in controls.

It was found that symptomatic responses during immersion of the hand in ice-water were negligible for both groups. However, participants reported moderate levels of overall unpleasantness. This enhanced response in the absense of symptom development may be because immersion of the hand was perceived as overwhelmingly painful.

Pain attributed directly to the ice-water was greater in migraine sufferers than controls. Pain is both a sensory and affective experience (Venes, 2001). It involves not only the physical perception of a painful stimulus (usually triggered by activation of

peripheral nerves) but also the emotional response to that perception (Silberstein, 2003). It may be that fear of pain and anxiety (defense response) influenced nociceptive intensity in the present study in response to painful stimulation of the limb.

Hyperalgesia (Silberstein, 2003) and cutaneous allodynia (Levy, Jakubowski and Burstein, 2004; Burstein, Cutrer, and Yarnitsky, 2000; Burstein and Jakubowski, 2004; Bustein, Collins and Jakubowski, 2004; Yarnitsky, Goor-Aryeh, Bajwa, Ransil, Cutre, Sottile and Burnstein, 2003) have been observed in migraine sufferers beyond the referred pain area of the head, particularly during a migraine attack. Cutaneous allodynia has also been observed interictally (Ashkenazi, LoPinto and Young, 2005; Kitaj, 2005). Ashkenazi et al. suggested that the cutaneous allodynia observed in their study might be constant as they found it to occur in an individual between attacks. The enhanced reactions to limb pain observed in migraineurs in the interictal period in this study may also be because of persistent hypersensitive nociception, or this group may simply use different criteria in their reported experience of pain.

Effects on pulse amplitude

Summary of major findings

- Increases in temporal pulse amplitude during hand immersion were greater ipsilaterally than contralaterally in both groups but, overall, pulse amplitude increased more in migraineurs than in controls. The vasodilator response was apparent in migraine sufferers even before the first ice-water immersion, but developed in controls during the first immersion. Vasodilatation peaked bilaterally in both groups after the hand was withdrawn from ice-water. The response persisted during recovery.

Discussion of effects on pulse amplitude

If pain processing is compromised in migraine sufferers, or the defense response is greater, vascular responses to limb pain should be greater in migraine sufferers than in controls. In support of these hypotheses, vasodilatation was greater in migraineurs than in controls, even prior to painful stimulation.

Ipsilateral vasodilatation developed in controls during the initial immersion, whereas blood vessels dilated on both sides in migraine sufferers. The overall enhanced bilateral response in migraineurs may, in part, reflect enhanced fear and anxiety (defense response) triggered even in anticipation of the procedure, as migraine sufferers reported more pain (intensity and unpleasantness) during painful stimulation than controls. In addition, atypical autonomic reactivity may also partly account for the augmented vascular responses in migraineurs. The source of the atypical reaction may involve the periaqueductal grey region of the brainstem, which has an integrative function including modulating pain transmission, fear and anxiety, autonomic and cardiovascular responses (Knight and Goadsby, 2001; Behbehani, 1995).

Greater ipsilateral than contralateral extracranial vasodilatation was observed during immersion of the hand in extremely cold water in both groups, which implies that ipsilateral vasodilatation is a normal systemic vasomotor reaction to painfully cold stimulation of the limb.

CHAPTER 10

RESULTS and DISCUSSION

Condition 6

Hand in ice-water during optokinetic stimulation (OKS)

This condition investigated the impact of painful stimulation of the hand during OKS on symptom ratings of motion sickness in migraine sufferers and controls. The intention was to compare outcomes alongside conditions that explored pain processing in response to cranial pain during OKS, as well as OKS alone. As migraine sufferers are prone to motion sickness (Golding, 1998; Kuritzky, Ziegler & Hassanein, 1981) it was hypothesized that symptomatic ratings would be greater in migraine sufferers than in controls during OKS. Also, as vasodilatation has been observed during motion sickness (Harm, 1990; Kolev et al., 1997), it was hypothesized that vascular reactions would be greater in the migraine group than in controls during OKS. Furthermore, if pain processing is compromised in migraineurs, it was anticipated that symptomatic and vascular responses would intensify during limb pain in the migraine group.

RESULTS

Symptom ratings

Procedures provoked more nausea (mean $\pm$ S.E. = 1.543 $\pm$ .293 *vs* .155 $\pm$ .286; $F(1, 37) = 11.505$, $p < .01$), headache (1.474 $\pm$ .324 *vs* .124 $\pm$ .316; $F(1, 37) = 8.902$, $p < .01$)

and dizziness (1.775 $\pm$ .368 *vs* .400 $\pm$ .358; F (1, 37) = 7.172, $p < .05$) in migraineurs than in controls. Overall, migraine sufferers experienced mild nausea while controls felt only marginally nauseated. Apart from baseline and during the second immersion, differences were evident throughout testing (see Figure 10.1.A and Appendix 11.1.1, page 349). Low-grade nausea was evident in both groups prior to immersion of the hand in ice-water, and simple contrast analyses indicated nausea increased in migraine sufferers following the initial ice-water trial. In contrast, nausea in the control group did not change from baseline, apart from during the second ice-water trial (nausea awareness increased). Overall, mild headache developed in migraineurs but was negligible in the control group. Group differences were evident throughout the procedure (see Figure 10.1.E and Appendix 11.1.5, page 353). Slight headache (head awareness) was observed in migraine sufferers at baseline. Furthermore, contrast analyses indicated increases were evident following each hand immersion trial and during the recovery period. Generally, dizziness in migraine sufferers was mild while controls reported awareness. Group differences were apparent in the first half of OKS and after OKS (see Figure 10.1.C and Appendix 11.1.3, page 351). Assessment of individual groups indicated that migraineurs experienced lightheadedness (awareness of dizziness) prior to OKS. Once procedures commenced, mild dizziness developed and participants remained aware of dizziness during recovery. Controls became aware of dizziness after the first ice-water trial but recovered soon after OKS.

Overall, migraineurs were aware of body temperature increases but change was negligible in controls (.702 $\pm$ .157 *vs* .067 $\pm$ .153; F (1,37) = 8.400, $p < .01$). Group differences were evident throughout testing (see Figure 10.1.B and Appendix 11.1.2, page 350). Closer inspection indicated that body temperature in migraine sufferers, apart from during the initial ice-water trial, increased throughout OKS and gradually recovered after OKS.

Prior to testing both groups were slightly aware of unpleasantness. Contrast analyses indicated levels increased during OKS. Increased levels of unpleasantness to symptoms in general were experienced during immersion of the hand in ice-water (main effect for Time: F (10, 28) = 8.325, $p < .001$). In migraine sufferers unpleasantness lingered after OKS whereas controls eventually recovered. The extent of unpleasantness overall was

greater for migraine sufferers than for controls (3.285 $\pm$ .433 *vs* 1.361 $\pm$ .422; F (1,37) = 10.136, $p < .01$) and apart from during the initial immersion, differences were evident throughout testing (see Figure 10.1.F and Appendix 11.1.6, page 354).

Ice-induced pain increased in intensity and unpleasantness for both groups during immersion of the hand in ice-water (main effect: Pain Intensity; F (1, 37) = 16.723, p < .001; Pain Unpleasantness; F (1, 37) = 15.741, p < .001). Investigation of significant Group by Time interactions indicated that ratings were greater in migraine sufferers than in controls during immersions and following the third immersion (see Figures 10.1.G, 10.1.H and Appendix 11.1.7, 11.1.8, pages 355, 356, respectively). Perceptions were elevated throughout procedures in the migraine group though unpleasantness gradually settled. In controls pain intensity was notable from the initial immersion in ice-water until just after OKS but unpleasantness was primarily only reported during immersions.

Self-motion developed in both groups during OKS (main effect for Time: F (6, 32) = 2.623, p < .05). The sensation was greater in migraine sufferers than in controls (main effect for Group: F (1, 37) = 4.778, p < .05), particularly following the third immersion in ice-water (see Figure 10.1.I and Appendix 11.1.9, page 357). Visual-illusion was greater in the migraine group than in controls (main effect for Group: F (1, 37) = 6.541, p < .05) during the first immersion and following the third (see Figure 10.1.J and Appendix 11.1.10, page 358). The experience persisted throughout OKS in both groups but closer inspection of a simple contrast interaction indicated controls reported dramatically less visual-illusion during the first ice immersion (Time x Group interaction: F (6, 32) = 2.460, p < .05). See Appendix 11.1.10, page 358.

Seventeen percent of migraine sufferers withdrew from OKS compared with only 9 percent of controls. This difference however, did not reach significant levels (refer to Appendix 13, page 363).

Figure 10.1.A to H demonstrate change in symptom ratings over time. Table 10.1 demonstrates main effects and interactions for each symptom.

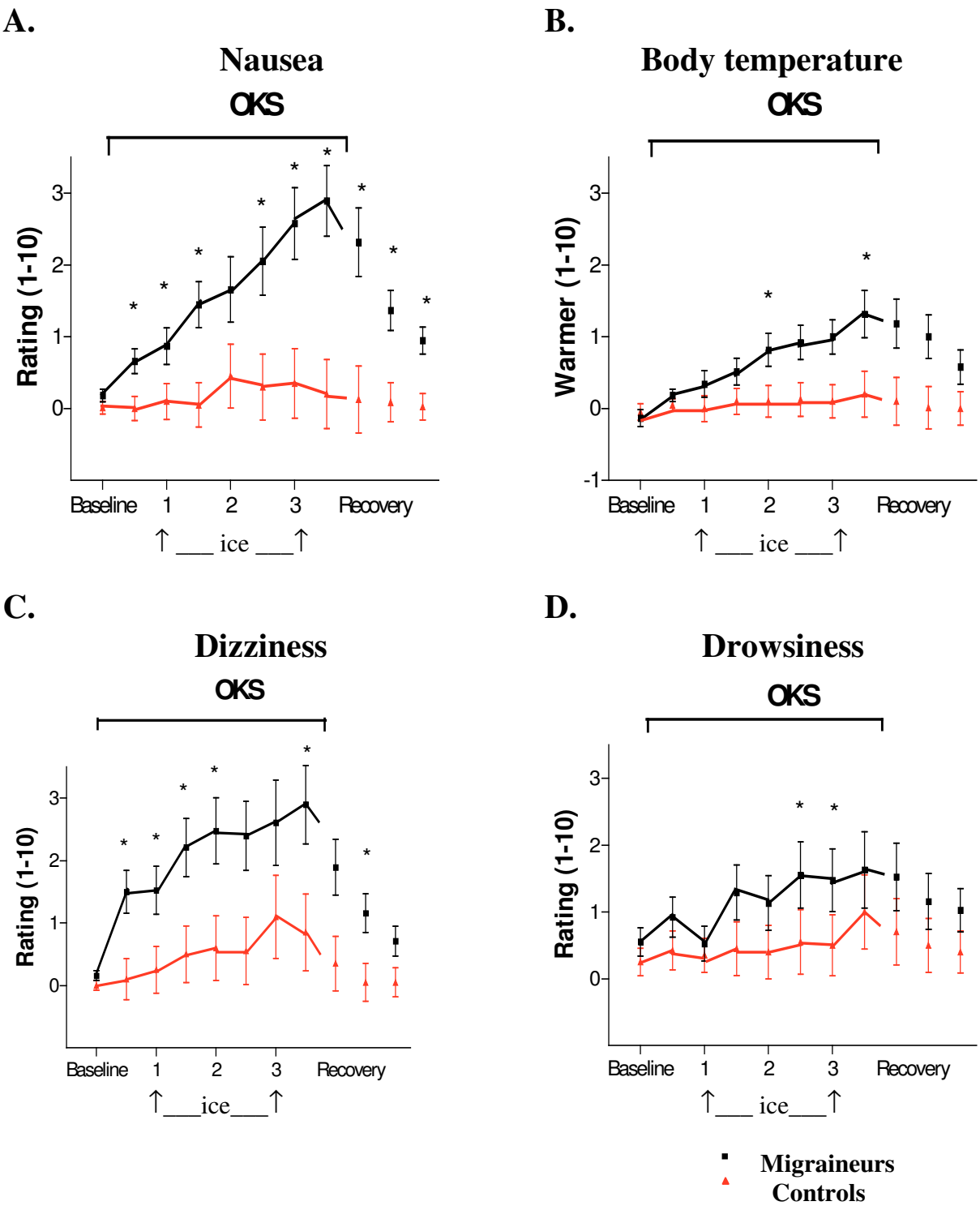


Figure 10.1.A-D. Symptom ratings (± SEM) for migraineurs (n = 19) and controls (n = 20) over 11 time points (every 2 minutes from baseline to minute 20).
OKS = optokinetic stimulation ** statistically significant group difference (* p < .05)*
P.T.O for additional ratings

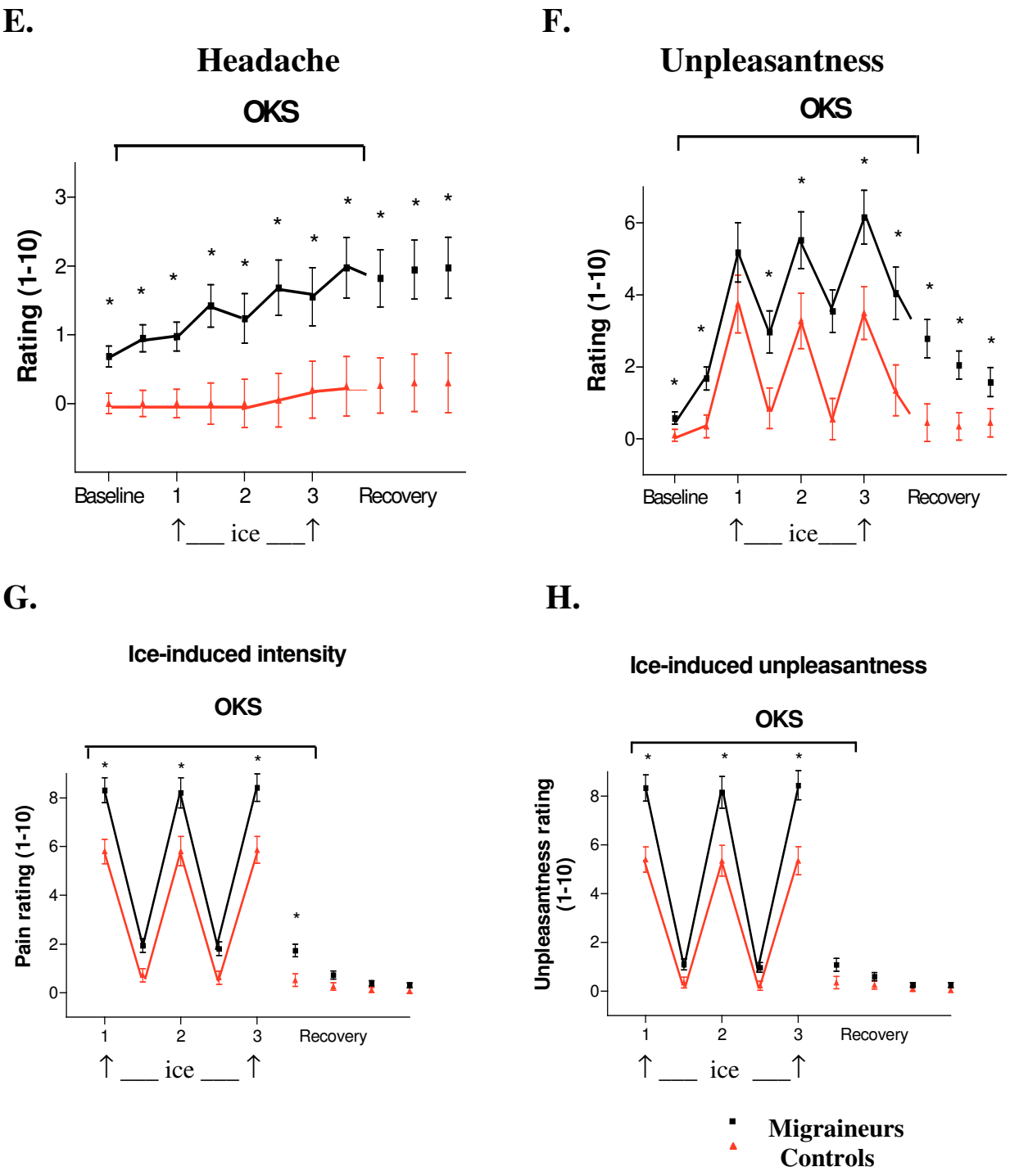


Figure 10.1.E-H.. Symptom ratings (± SEM) for migraineurs (n = 19) and controls (n = 20) over 11 time points (every 2 minutes from baseline to minute 20) {E, F}) and over 9 time points (every 2 minutes from ice 1 {G, H}).

OKS = optokinetic stimulation ** statistically significant group difference (* p < .05)*

Note: Y axis has different rating scales for unpleasantness, ice-induced intensity and ice-induced unpleasantness. *P.T.O for additional ratings*

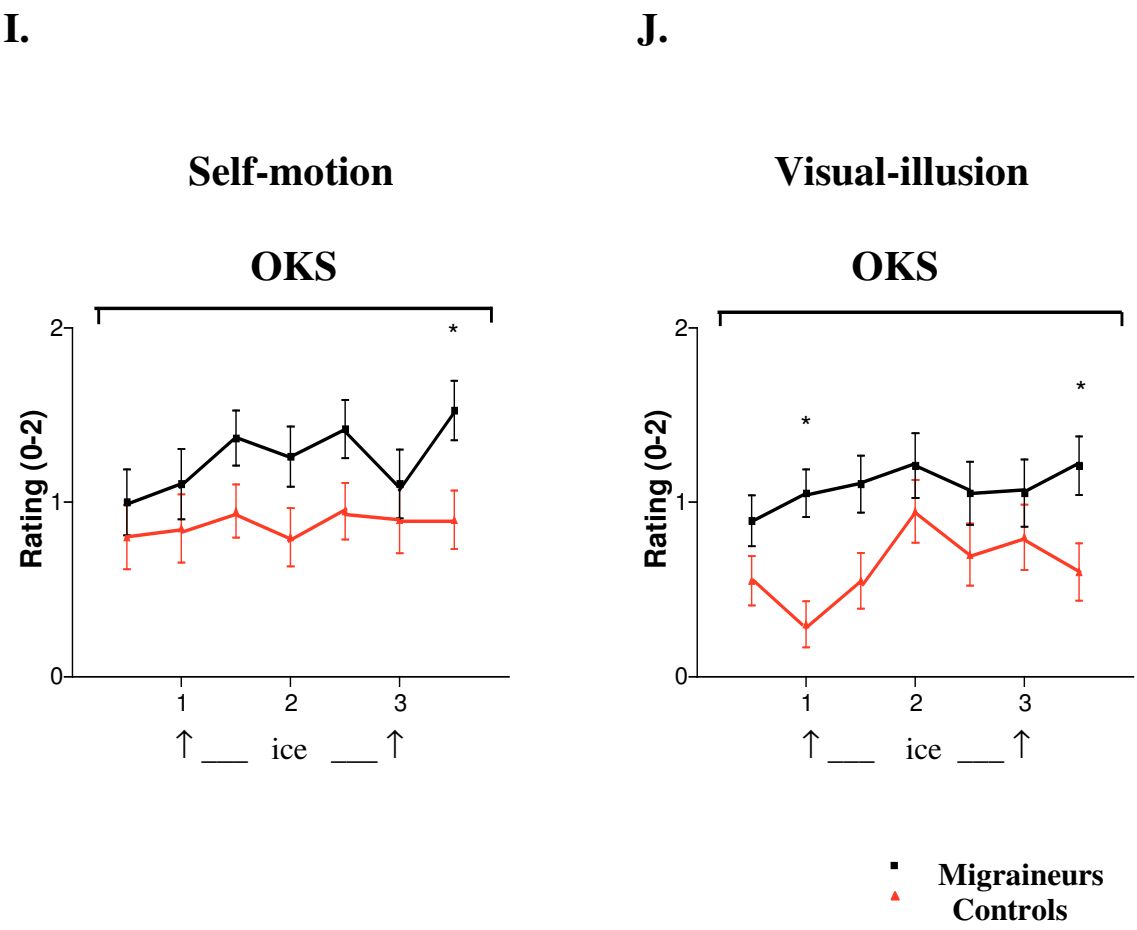


Figure 10.1.I-J. Symptom ratings (± SEM) for migraineurs (n = 19) and controls (n = 20) over 7 time points (every 2 minutes from commencement of OKS).
OKS = optokinetic stimulation * *statistically significant group difference (* $p < .05$)*

Note: Different rating scales for self-motion and visual-illusion (0-2)

Table 10.1. Main effect and interaction F, *p*, and df values from from a 2 (group: migraineurs, controls) x 11 (time: every 2 minutes from baseline to minute 20) repeated-measures ANOVA for each rating. Values for Self-motion and Visual-illusion obtained from a 2 (group: migraineurs, controls) x 7 (time: every 2 minutes during OKS) repeated-measures ANOVA, and ice-induced pain intensity and unpleasantness from a 2 (group: migraineurs, controls) x 9 (time: every 2 minutes from the first application of ice) repeated-measures ANOVA.

F ratios (df)			
	Group	**Time**	**Time x Group**
Nausea	11.505 (1, 37) **	2.007 (10, 28)	2.234 (10, 28)
Body temperature	8.400 (1, 37) **	1.660 (10, 28)	1.494 (10, 28)
Dizziness	7.172 (1, 37) *	1.933 (10, 28)	1.176 (10, 28)
Drowsiness	1.607 (1, 37)	1.545 (10, 28)	1.908 (10, 28)
Headache	8.902 (1, 37) **	1.689 (10, 28)	1.626 (10, 28)
Unpleasantness	10.136 (1, 37) **	8.325 (10, 28) ***	2.230 (10, 28)
Ice-induced intensity	16.723 (1, 37) ***	45.077 (8, 30) ***	2.496 (8, 30) *
Ice-induced unpleasantness	15.741 (1, 37) ***	43.452 (8, 30) ***	3.474 (8, 30) **
Self-motion	4.778 (1, 37) *	2.623 (6, 32) *	1.122 (6, 32)
Visual-illusion	6.541 (1, 37) *	1.330 (6, 32)	2.460 (6, 32) *

* difference between migraine sufferers and controls statistically significant (* $p < .05$,** $p < .01$,*** $p < .001$)
degrees of freedom differ across the dependent variables because of empty cells

Pulse Amplitude

Pulse amplitude was comparable for both groups throughout the procedures. A main effect for Side of stimulation ($F(1, 37) = 14.025$, $p < .001$) indicated that increases for both groups were greater ipsilaterally (migraineurs: 26% $\pm$ 10%; controls: 31% $\pm$ 10%) than contralaterally to painful stimulation (migraineurs: 11% $\pm$ 6%; controls: 14% $\pm$ 6%). Pulse amplitude peaked bilaterally in both groups after the hand was withdrawn from ice-water (main effect for Time: $F(10, 28) = 2.755$, $p < .05$). Pulse volume decreased for both groups and side differences were no longer evident following OKS (Side x Time interaction: $F(10,28) = 2.452$, $p < .05$). Figure 10.2, Table 10.2 and Appendix 11.2.1 and 11.2.2 (pages 359, 360, respectively) illustrate these trends.

Intercept analyses indicated vasodilatation in both groups during OKS before the initial ice-water trial. In the migraine group further vasodilatation followed each ice-water trial but when the hand was immersed pulse amplitude did not differ from preceding levels. Vasodilatation in the control group persisted throughout OKS and both groups recovered soon after OKS (see Appendix 11.2.2, page 360).

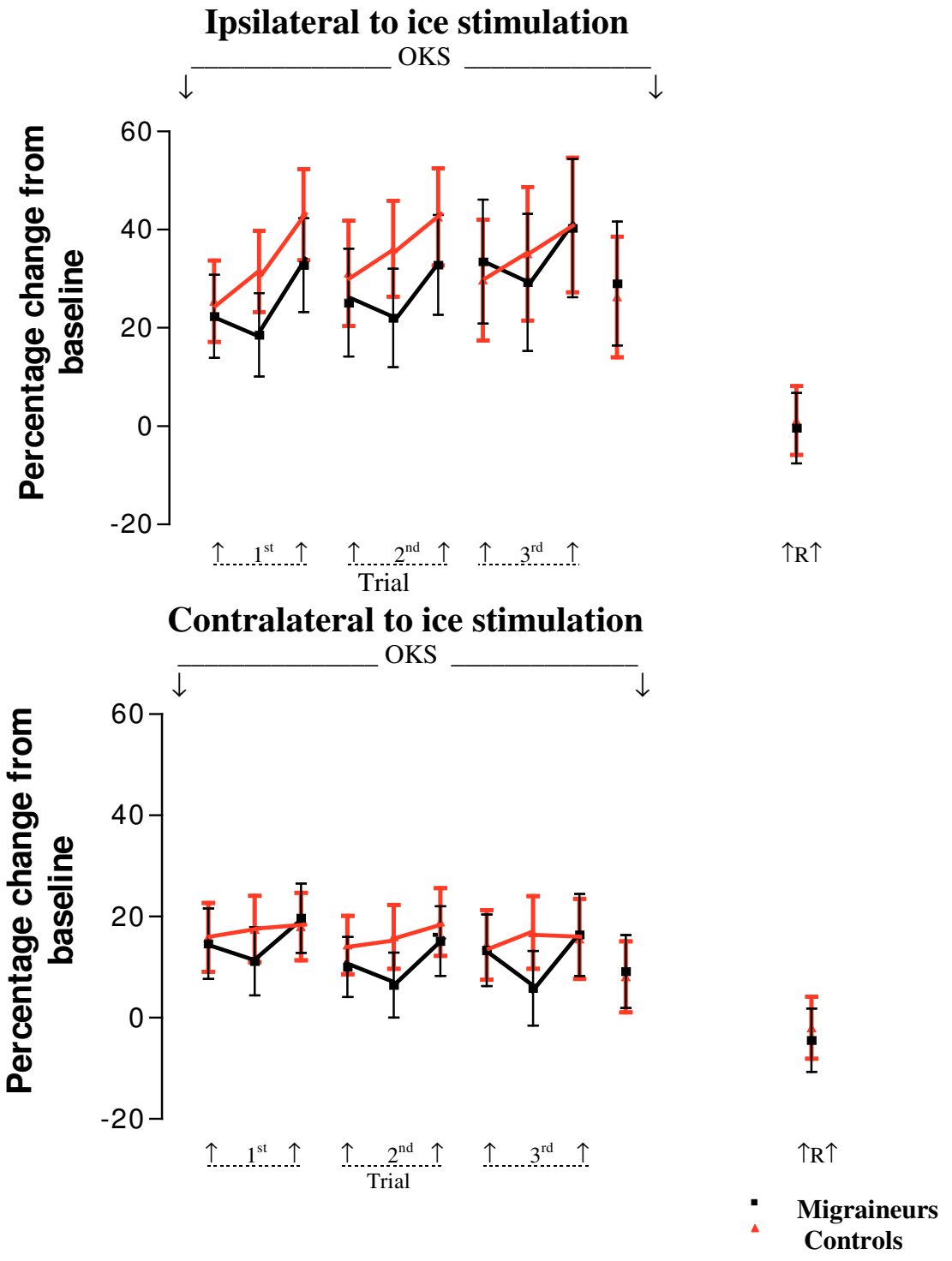


Figure 10.2. Pulse amplitude change (± SEM) for migraineurs (n = 19) and controls (n = 20) over 11 time points (30 second samples: before, during and after hand immersion in ice-water {3 trials}, and after 3 and 8 minutes {recovery - R}). The first arrow in each trial represents pulse amplitude before the immersion, and the second arrow represents pulse amplitude after the immersion. *OKS = optokinetic stimulation*

Table 10.2. Main effect and interaction F, *p*, and df values from a 2 (group: migraineurs, controls) x 2 (side: ipsilateral, contralateral to stimulation) x 11 (time: 30 second samples, before {trial 1, 2 & 3}, during {trial 1, 2 & 3} and after {trial 1, 2 & 3} hand immersion in ice-water during OKS, and 3 and 8 mins after the 3rd immersion) repeated-measures ANOVA for pulse amplitude change.

Main effect	*df*	F	P
Group	1, 37	.165	.687
Side	1, 37	14.025	.001
Time	10, 28	2.755	.017
Interaction			
Side x Time	10, 28	2.452	.030
Side x Group	1, 37	.051	.823
Time x Group	10, 28	.940	.514
Side x Time x Group	10, 28	.576	.820

DISCUSSION

Effects on symptomatic responses

Summary of major findings

Key findings to emerge from exploring the effects of immersion of the hand in ice-water during OKS were:

- In general, ratings of headache, nausea and dizziness were greater in migraine sufferers than in controls. Additionally, increases in body temperature and ratings of self-motion and visual illusion were greater in migraineurs than in controls. Overall, both groups experienced comparable drowsiness. However, before and during the third hand immersion, drowsiness increased in migraineurs. Apart from slight dizziness, visual illusion and self-motion, symptomatic ratings barely developed in controls.
- The procedure was more unpleasant for migraine sufferers than controls. Furthermore, pain ratings were also greater in migraineurs, particularly during immersions.

Discussion of effects on symptomatic responses

The investigation of limb pain during OKS was purely exploratory. In the present study, nausea, headache, dizziness, perceived body temperature increases, visual illusion and self-motion developed more so in migraine sufferers than in controls when the hand was immersed in ice-water during OKS. Furthermore, migraine sufferers reported low-grade headache and drowsiness even prior to the procedures, which may have carried over from the previous procedure involving immersion of the hand in ice-water in the absence of OKS. Throughout the procedures headache increased progressively but drowsiness did not develop further. In contrast, controls remained virtually symptom free

throughout, apart from slight dizziness, visual illusion and self-motion. These findings may simply reflect OKS-induced motion sickness. Whether immersion of the hand in painfully cold water modified symptoms induced by OKS is not clear but the possibility is explored in the next chapter (comparison of conditions involving OKS, Chapter 11, pages 175-191).

OKS probably induced motion sickness, at least in migraine sufferers (Golding, 2006, 1998; Kuritzky, Ziegler & Hassanein, 1981), as symptomatic responses developed during and persisted, largely, after the procedures in this group. Headache, in particular, increased progressively throughout the recovery period. It may be that the gradual worsening of headache in the present study reflected a neural "wind-up" phenomenon (Bray, Cragg, MacKnight and Mills, 1999; Dallel et al, 1999), which was initiated during OKS.

Both groups reported that the procedure was unpleasant. However, this rating was greater in migraine sufferers than in controls. After the procedures migraineurs continued to experience unpleasantness, probably because they remained symptomatic. Conversely, in controls, symptomatic responses, which were minimal, and associated unpleasantness, subsided quickly. Both groups found the ice-water painful. However, pain was greater in migraine sufferers, which may reflect hyperexcitable nociception in this group interictally.

Effects on pulse amplitude

Summary of major findings

- Increases in pulse amplitude were greater ipsilaterally than contralaterally in both groups, and blood flow peaked bilaterally after the hand was withdrawn from ice-water. However, in migraine sufferers, a weak bilateral vasoconstrictor response occurred during immersion of the hand. Vascular responses recovered soon after OKS in both groups.

Discussion of effects on pulse amplitude

It was anticipated that vascular responses would intensify during limb pain in migraine sufferers if pain processing is compromised in this group. Change in pulse amplitude evoked by procedures generally did not differ between groups, suggesting a normal response to immersion of the hand in ice-water. The increased facial blood flow may reflect a stress response triggered in reaction to two consecutive, and tandem, novel stressors - OKS followed by cold stimulation during OKS. As pointed out above, blood flow peaked bilaterally after the hand was withdrawn from ice-water in both groups. In addition, a weak bilateral vasoconstriction occurred during hand immersion in migraineurs, consistent with greater reactivity in the extracranial vasculature of this group than in controls.

Symptomatic responses were enhanced in migraineurs interictally, suggesting that neural pathways were excitable. In particular, the development of headache suggests that the trigeminovascular system was activated in this group. If nociceptive pathways are hypersensitive in migraineurs, it is conceivable that stimulation of the hand may have contributed to the development of headache and, by implication, to activation of the trigeminovascular vasodilatatory reflex.

The asymmetry of the vascular response to painfully cold stimulation of the hand, observed in both groups, implies that ipsilateral vasodilatation is a normal vasomotor reaction to immersion of the hand in ice-water. Curiously, asymmetry preceded the first immersion during OKS. Perhaps the mechanism that induced assymmetry during the previous procedure involving hand immersion before OKS (see Appendix 10.2.1, page 347) persisted, or a conditioned response developed.

CHAPTER 11

RESULTS and DISCUSSION

Comparison of Conditions

1 (OKS alone), 4 (Ice on temple during OKS) and

6 (Hand in ice-water during OKS)

The aim was to explore whether trigeminal nerve activity following stimulation of the temple with ice during OKS would intensify symptomatic and vascular responses in migraineurs compared to controls. To investigate this association OKS alone was compared with ice on the temple during OKS to explore the impact of painful stimulation of the temple during OKS. Ice on the temple during OKS was compared with the hand in ice-water during OKS to investigate the effect of painful cranial stimulation as opposed to elsewhere. The following hypotheses were investigated:

1. As migraineurs are prone to motion sickness (Golding, 1998; Kuritzky, Ziegler & Hassanein, 1981) and show signs of trigeminal nerve sensitivity (Lance, 1993, 2002; Macfarlane, 1993; Moskowitz, 1993; Weiller et al., 1995), it was hypothesized that headache would intensify more readily in migraineurs than in controls when ice was applied to the temple during OKS compared to OKS alone, or combined with hand immersion in ice-water.

2. If trigeminal impulses converge on neurons responsible for symptoms other than headache, these symptoms might be enhanced in migraine sufferers during painful stimulation of the temple.

3. As facial blood flow increases during motion sickness in susceptible individuals (Harm, 1990; Kolev et al, 1997) and during head pain in migraineurs (Lance and Goadsby, 2002; Drummond, 1997), it was hypothesized that vascular reactions in response to temple pain during OKS would be greater, particularly in comparison to OKS alone, in migraine sufferers than in controls.

4. If pain processing is compromised following painful stimulation of the hand during OKS, symptomatic and vascular responses should intensify in the migraine group, particularly in comparison with OKS alone.

RESULTS

Symptom ratings

Ratings during OKS and ice stimulation (temple, hand), and OKS alone (time equivalents), were analyzed in a series of 2 (group: migraineurs, controls) x 3 (condition: OKS alone {condition 1}, ice to temple during OKS {condition 4}, hand in ice-water during OKS {condition 6}) repeated-measures ANOVAs for nausea, body temperature, dizziness, drowsiness, headache, unpleasantness, self-motion and visual-illusion. Simple planned contrasts were used to compare the mean of painful stimulation of the temple during OKS with the mean of OKS alone and immersion of the hand in ice-water during OKS. Ice-induced intensity and ice-induced unpleasantness were analyzed in 2 (group: migraineurs, controls) x 2 (condition: 4 and 6) repeated-measures ANOVAs. Figure 11.1 demonstrates comparative change in symptom ratings across conditions.

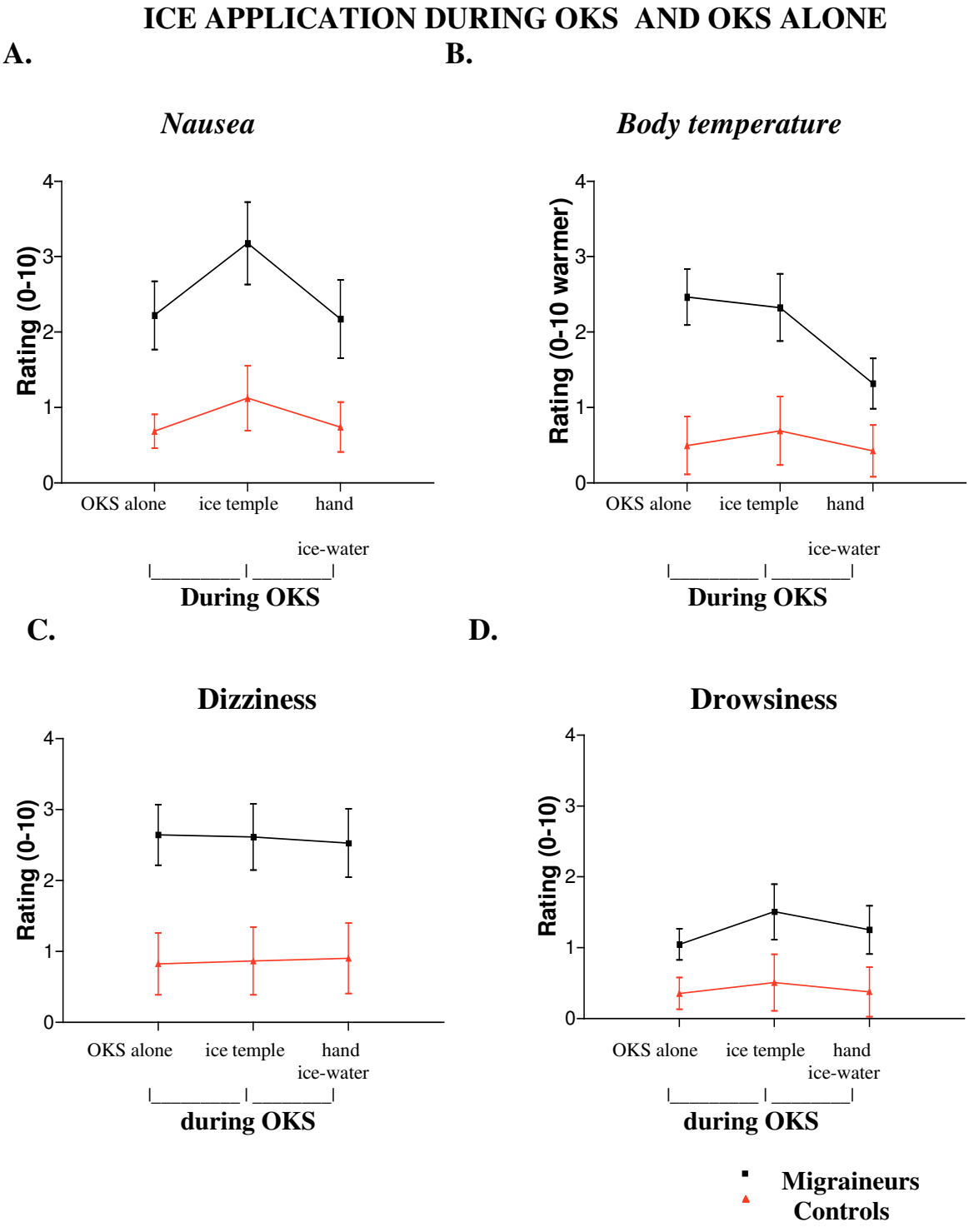


Figure 11.1.A-D. Means ± SEM for migraineurs (n = 23) and controls (n = 22) for OKS alone, ice to the temple during OKS, hand in ice-water during OKS. Mean time during OKS was explored. *OKS = optokinetic stimulation*

P.T.O for additional ratings

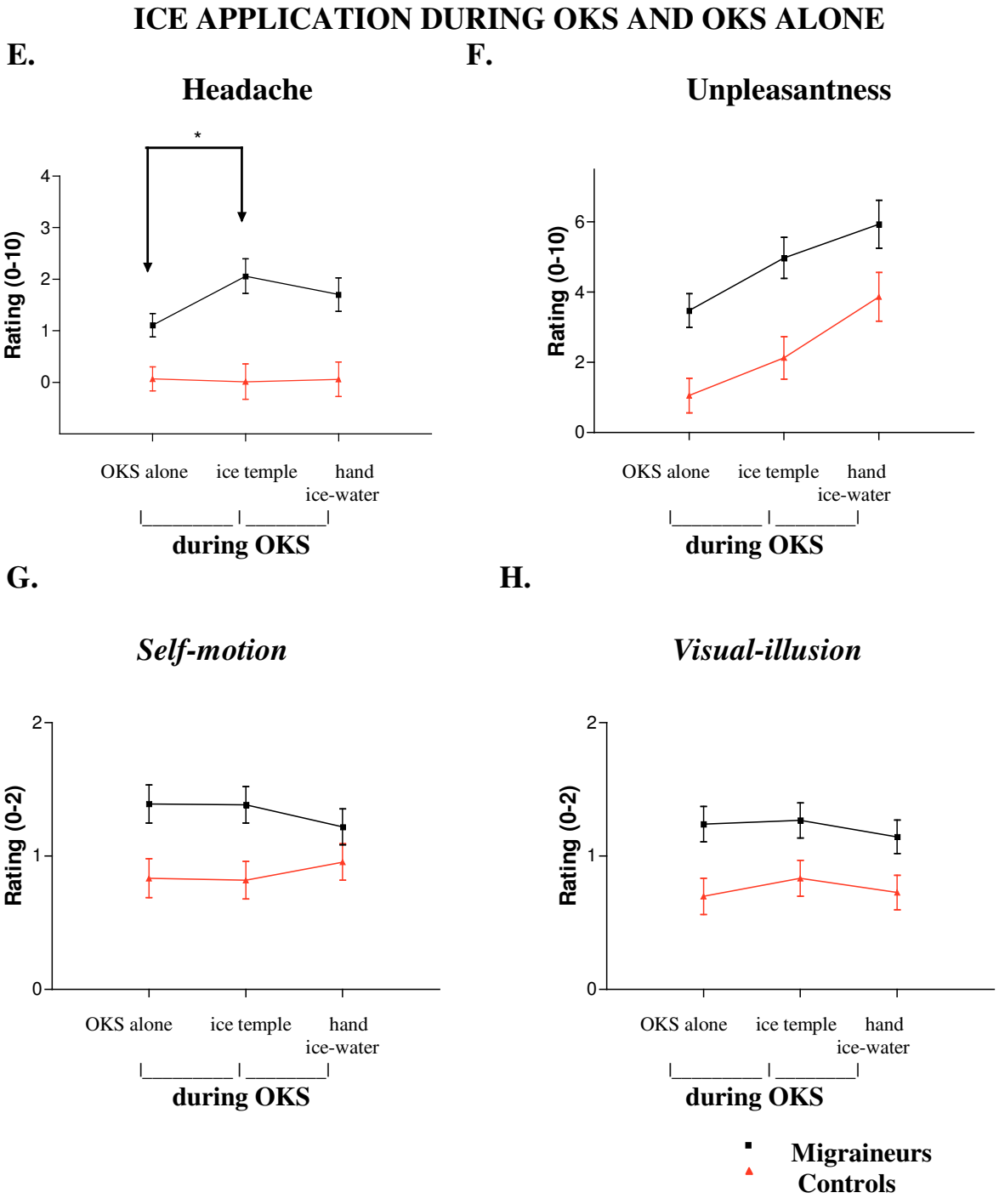


Figure 11.1.E-H.. Means ± SEM for migraineurs (n = 23) and controls (n = 22) for OKS alone, ice to the temple during OKS, hand in ice-water during OKS. Mean time during OKS was explored. *OKS = optokinetic stimulation*

* *statistically significant difference between conditions for migraineurs (P<.05)*

Note: Y-axis has different rating scales for unpleasantness, and self-motion and visual-illusion (0-2) *P.T.O for additional ratings*

ICE APPLICATION DURING OKS

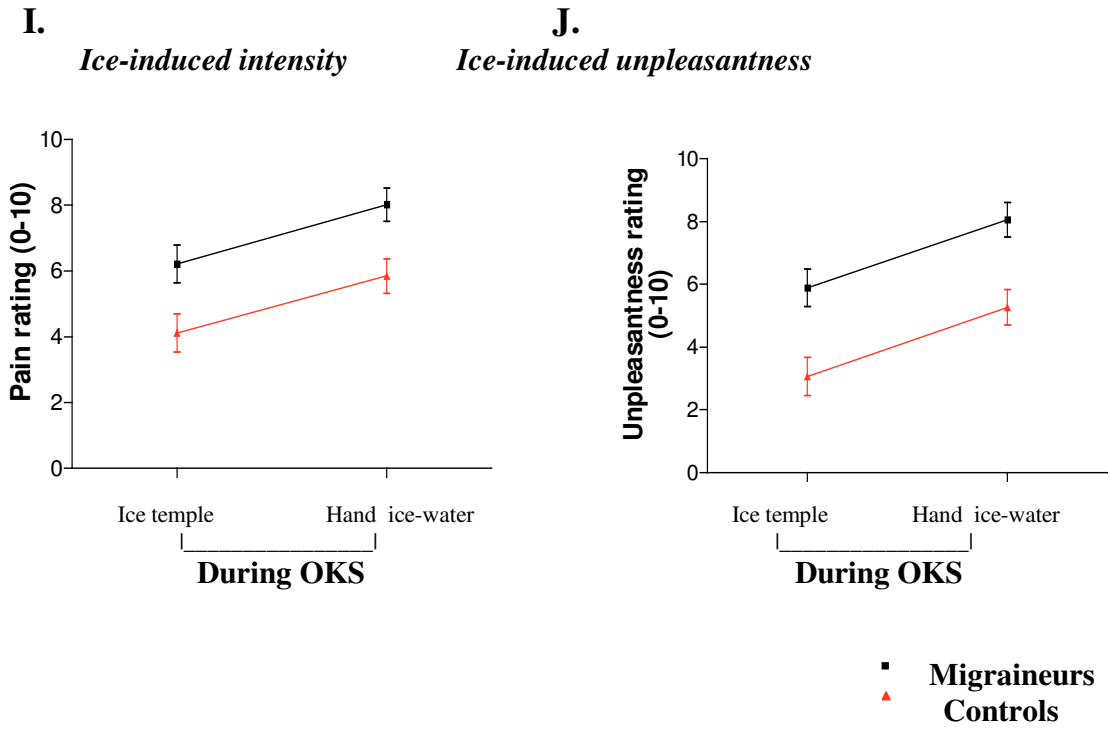


Figure 11.I and J. Means ± SEM for migraineurs (n = 23) and controls (n = 22) for ice to the temple during OKS (mean ice applications), hand in ice-water during OKS (mean ice-water immersions). *OKS = optokinetic stimulation*

Note: Y-axis has different rating scales for ice-induced intensity and unpleasantness

As observed in preliminary analyses, each symptom was greater in migraine sufferers than controls across all three conditions (see table 11.1). Nausea was greater in both groups when ice was applied to the temple during OKS than during OKS alone or when the hand was immersed in ice-water during OKS (main effect for Condition: OKS *vs* OKS ice temple, $F(1, 43) = 7.017$, $p < .05$; OKS ice temple *vs* OKS hand ice-water, $F(1, 43) = 4.936$, $p < .05$). Refer to Figure 11.1.A. While headache developed during each condition in migraineurs, it was greatest when ice was applied to the temple during OKS. Controls, as observed in preliminary analyses, remained headache-free over the three

conditions (Condition x Group contrast interaction: OKS *vs* OKS ice temple, F (1, 43) = 4.891, $p < .05$). Refer to Figure 11.1.E. Ratings of body temperature were greater in both groups when ice was applied to the temple during OKS than when the hand was immersed in ice-water during OKS (main effect for Condition: F (1, 43) = 4.609, $p < .05$). See Figure 11.1.B. Unpleasantness ratings were greater in both groups during OKS with ice stimulation to the temple than during OKS alone (main effect for Condition: OKS *vs* OKS ice temple, F (1, 43) = 14.539, $p < .001$), and during immersion of the hand in ice-water during OKS than ice application to the temple during OKS (main effect for Condition: OKS ice temple *vs* OKS hand ice-water, F (1, 43) = 10.557, $p < .01$). See Figure 11.1.F. Pain was greater in intensity and unpleasantness when the hand was immersed in ice-water than when ice was applied to the temple during OKS (main effect for Condition: Pain Intensity, F (1, 43) = 19.432, $p < .001$; Pain Unpleasantness, F (1, 43) = 26.541, $p < .001$). Figures 11.1.I and 11.1.J illustrate this effect.

Table 11.1. Main effect and interaction F, *p*, and df values from a 2 (group: migraineurs, controls) x 3 (condition: OKS alone {condition 1}, ice to temple during OKS {condition 4}, hand in ice-water during OKS {condition 6}) repeated-measures ANOVA for nausea, body temperature, dizziness, drowsiness, headache, unpleasantness, self-motion and visual-illusion. Mean rating during OKS was explored. *OKS = optokinetic stimulation*

	F ratios (df = 1, 43)		
	Group	**Condition**	**Condition x Group**
Nausea	10.342 **		
OKS *vs* OKS ice temple		7.017 *	.971
OKS ice temple *vs* OKS hand ice-water		4.936 *	.998
Body temperature	10.595 **		
OKS *vs* OKS ice temple		.014	.501
OKS ice temple *vs* OKS hand ice-water		4.609 *	1.567
Dizziness	9.031 **		
OKS *vs* OKS ice temple		.000	.012
OKS ice temple *vs* OKS hand ice-water		.010	.063
Drowsiness	4.382 *		
OKS *vs* OKS ice temple		1.890	.477
OKS ice temple *vs* OKS hand ice-water		1.055	.112
Headache	20.337 ***		
OKS *vs* OKS ice temple		3.914	4.891 *
OKS ice temple *vs* OKS hand ice-water		.464	.773
Unpleasantness	12.311 ***		
OKS *vs* OKS ice temple		14.539 ***	.404
OKS ice temple *vs* OKS hand ice-water		10.557 **	.870
Self-motion	8.845 **		
OKS *vs* OKS ice temple		.010	.001
OKS ice temple *vs* OKS hand ice-water		.026	2.615
Visual-illusion	9.117 **		
OKS *vs* OKS ice temple		.939	.396
OKS ice temple *vs* OKS hand ice-water		1.174	.007

***** statistically significant (* p < .05,** p < .01,*** p < .001)

Table 11.2. Main effect and interaction F, *p*, and df values from a 2 (group: migraineurs, controls) x 2 (condition: ice to temple during OKS, hand in ice-water during OKS) repeated-measures ANOVA for ice-induced intensity and ice-induced unpleasantness. Mean for ice applications were explored. *OKS = optokinetic stimulation*

	F ratios (df = 1, 43)		
	Group	**Condition**	**Condition x Group**
Ice-induced intensity	10.452 **	19.432 ***	.008
Ice-induced unpleasantness	16.244 ***	26.541 ***	.001

***** statistically significant (** p < .01,*** p < .001)

Pulse amplitude

Data was analysed in a 2 (group: migraineurs, controls) x 3 (condition: OKS alone {condition 1}, ice to temple during OKS {condition 4}, hand in ice-water during OKS {condition 6}) x 2 (side: average of left, right {condition 1}; Ipsilateral, contralateral {conditions 4, 6}) repeated-measures ANOVA. Simple planned contrasts were used to compare the mean of painful stimulation of the temple during OKS with the mean of OKS alone and immersion of the hand in ice-water during OKS. Figure 11.2 demonstrates comparative change in pulse amplitude across conditions.

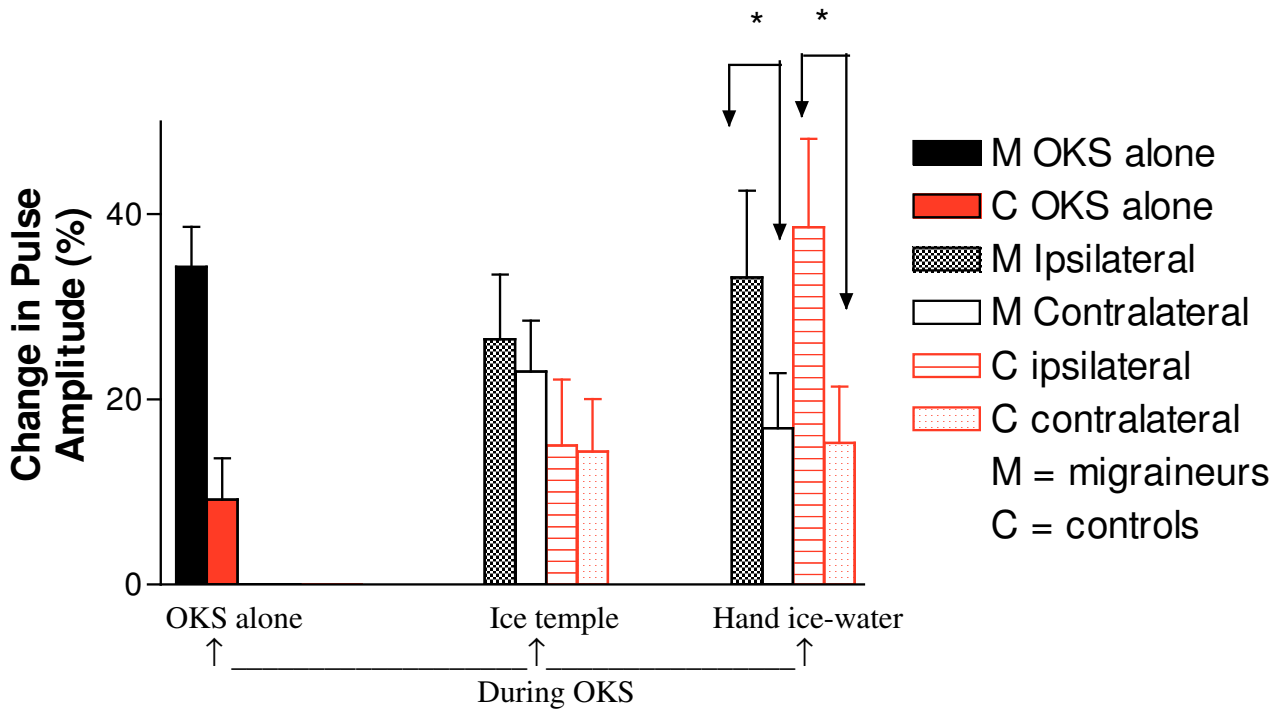


Figure 11.2. Mean ipsilateral and contralateral pulse amplitude change to ice stimulation (temple, hand), and average of left and right sides for OKS alone. Pulse amplitude change (± SEM) for migraineurs (n = 23) and controls (n = 22) 30 seconds after ice stimulation and time equivalents for OKS alone. *OKS = optokinetic stimulation*
* statistically significant within group difference (* $p < .01$)

Vascular responses were comparable across conditions for both groups (Table 11.3). Closer inspection indicated that responses were greater ipsilaterally for both groups after immersion of the hand in ice-water during OKS than after ice was applied to the temple during OKS (main effect for Side: $F(1, 43) = 16.319$, $p < .001$; Condition x Side interaction: OKS ice temple *vs* OKS hand ice-water, $F(1, 43) = 5.862$, $p < .05$). Bilateral responses were comparable for both groups during OKS alone and after ice was applied to the temple during OKS. Table 11.3 and Figure 11.2 illustrate these trends.

Table 11.3. Main effect, interaction and simple contrast F, *p*, and df values from a 2 (group: migraineurs, controls) x 3 (condition: OKS alone {condition 1}, ice to temple during OKS{conditions 4}, hand in ice-water during OKS{conditions 6}) x 2 (side: average left, right {condition 1}; Ipsilateral, contralateral {conditions 4, 6}) repeated-measures ANOVA of mean pulse amplitude 30 seconds after ice stimulation (temple, hand) during OKS and time equivalents for OKS alone. *OKS = optokinetic stimulation*

Main effect	*df= 1, 43*	F	P
Group		3.930	.054
Condition			
OKS *vs* OKS ice temple		.182	.672
OKS ice temple *vs* OKS hand ice-water		1.305	.260
Side		16.319	.000
Interaction			
Condition x Group			
OKS *vs* OKS ice temple		2.645	.111
OKS ice temple *vs* OKS hand ice-water		1.174	.285
Side x Group		.141	.709
Condition x Side			
OKS *vs* OKS ice temple		.209	.650
OKS ice temple *vs* OKS hand ice-water		5.862	.020
Condition x Side x Group			
OKS *vs* OKS ice temple		.099	.754
OKS ice temple *vs* OKS hand ice-water		.453	.504

Table 11.4. Means and standard deviations during OKS alone, ice to the temple during OKS, and hand in ice-water during OKS, of pulse amplitude 30 seconds after ice stimulation (temple, hand) during OKS and time equivalents for OKS alone.

Means ± SD				
	Migraineurs (n = 23)		Controls (n = 22)	
	Average			
OKS alone	34.3 ± 27.8		9.2 ± 8.6	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral
OKS ice temple	26.5 ± 29.9	23.0 ± 33.6	15.0 ± 36.8	14.4 ± 16.0
OKS hand ice-water	33.2 ± 45.8	16.9 ± 35.9	38.6 ± 43.8	15.3 ± 17.8

OKS = optokinetic stimulation

DISCUSSION

Effects on symptomatic responses

Summary of major findings

Ice on temple during OKS vs OKS alone (Condition 4 vs 1, respectively)

- Nausea and unpleasantness were greater when ice was applied to the temple during OKS than during OKS alone for both groups.
- Headache was greater in migraine sufferers when ice was applied to the temple during OKS but controls remained headache-free over both conditions.
- Ratings of dizziness, drowsiness, increases in body temperature, visual illusion and self-motion, were comparable over both conditions for both groups.
-

Ice on temple during OKS vs Hand in ice-water during OKS (Condition 4 vs 6, respectively)

- Headache in migraine sufferers was comparable for both conditions. Controls remained headache-free.
- Nausea and increases in body temperature were greater when ice was applied to the temple than when the hand was immersed in ice-water during OKS for both groups.
- For groups, dizziness, drowsiness, visual illusion and self-motion, were comparable for both conditions.
- Overall unpleasantness, and ice-induced intensity and unpleasantness, were greater when the hand was immersed in ice-water than when ice was applied to the temple during OKS for both groups.

Discussion of effects on symptomatic responses

It was hypothesized that symptomatic ratings would intensify more readily in migraineurs than in controls when ice was applied to the temple during OKS compared to OKS alone, or combined with hand immersion in ice-water. As observed in preliminary analyses, each symptomatic rating was generally greater in migraine sufferers than in controls for all three conditions (see Table 11.1).

Ice on temple during OKS vs OKS alone (Condition 4 vs 1, respectively)

Both groups experienced more nausea when the temple was stimulated with ice during OKS than during OKS alone. Additionally, overall unpleasantness was greater during this condition probably because of the increased nausea. As expected, migraine sufferers experienced increased headache when the temple was painfully stimulated during OKS than during OKS alone. In contrast, controls remained headache-free during both conditions. Remaining ratings were comparable across conditions for both groups.

The cranial sensory anatomy involves convergence of visceral (blood vessels) and somatic (head/facial musculature) nerve fibres on to the same central interneurons. Central projections include the trigeminal nucleus caudalis (TNC), which mediates pain responses, and the nucleus tractus solitarius (NTS) which mediates autonomic responses, e.g., vomiting (see Macfarlane for a review of the literature, 1993). A functional connection is believed to exist between the TNC and the NTS. It is conceivable that trigeminal nerve stimulation during the application of ice to the temple provoked headache in migraine sufferers. Nausea increased in both groups but more so in migraineurs. Remaining symptomatic ratings were not altered following temple pain during OKS, which suggests a specific association between nausea and head pain. The increased nausea coupled with increased headache observed in migraine sufferers when the temple was painfully stimulated during OKS implies a mutual interaction between the

TNC and NTS. If so, it may be that these cardinal symptoms compound one another during a migraine attack.

Ice on temple during OKS vs hand in ice-water during OKS (Condition 4 vs 6, respectively)

Headache did not depend on whether the temple or hand was painfully stimulated during OKS. Neuronal events mediating the headache phase of migraine are believed to involve the trigeminovascular system and its central projections (Welch, 2003). In the present study it may be that this circuitry was somehow activated in migraineurs during OKS in the absence of painful stimulation, and painful stimulation facilitated this response (Ashkenazi et al., 2005). In contrast, controls remained headache-free in all three conditions.

Both groups experienced more nausea and increases in body temperature during OKS when ice was applied to the temple than when the hand was immersed in ice-water. However, despite the enhanced responses, overall unpleasantness, and ice-induced intensity and unpleasantness, were greater when the hand, not the temple, was stimulated during OKS. Migraine sufferers were more sensitive than controls to painfully cold stimulation. However, both groups found the ice-water painful and immersion of the hand appeared to modify the effects of OKS. As pointed out, nausea and increases in body temperature were greater when ice was applied to the temple than when the hand was immersed in ice-water during OKS. Nevertheless, responses were greater in migraine sufferers than in controls for both conditions.

Nociceptive stimulation of the hand possibly triggered DNIC (Bouhassira, Chollet, Coffin, Lemann, Le Bars, Willer and Jian 1994; Dallel et al., 1999) in migraine sufferers, thereby inhibiting the less intense symptoms of motion sickness, in this case nausea and body temperature. Nausea and perceived changes in body temperature are not nociceptive sensations. However, nausea is a noxious sensation so may be nociceptive linked. It is believed that the analgesia, which follows exposure to a stressor, is mediated by opioid or non-opioid systems and the activation of descending pain inhibitory pathways (Malan, 2005). Alternatively, the intense pain during hand

immersion may have simply distracted participants' attention away from other less intense sensations, such as nausea and body temperature. Whatever the mechanism, it is certainly conceivable that the extremely cold stimulus overpowered the usual sensation of warmth reported during motion sickness (Harm, 1990). Remaining symptomatic ratings including headache, dizziness, drowsiness, visual illusion and self-motion were comparable, irrespective of whether the temple or hand was painfully stimulated during OKS, for both groups.

Effects on pulse amplitude

Summary of major findings

Ice on temple during OKS vs OKS alone (Condition 4 vs 1, respectively)

- Vascular changes were comparable over both conditions for both groups.

Ice on temple during OKS vs Hand in ice-water during OKS (Condition 4 vs 6, respectively)

- Overall vascular responses were comparable in both groups. Furthermore, the ipsilateral response was greater than the contralateral response when the hand was immersed in ice-water during OKS.

Discussion of effects on pulse amplitude

Ice on temple during OKS vs. OKS alone (Condition 4 vs. 1, respectively)

It was anticipated that facial blood flow would be greater in migraine sufferers than in controls when the temple was stimulated during OKS than during OKS alone. Contrary to expectations, vascular responses were comparable across conditions for both groups. Preliminary findings demonstrated that pulse amplitude increased more so in migraine sufferers than in controls during OKS alone. However, vascular reactivity to painful stimulation of the temple during OKS did not differ between groups. It appears that the additional component of painfully cold stimulation during OKS augmented extracranial vasodilatation in controls to resemble that observed in migraine sufferers. Extracranial vasodilatation may form part of a defense response to noxious or threatening stimuli (Carrive and Bandler, 1991; Kolev et al., 1997; Bandler and Shipley, 1994). The midbrain periaqueductal gray (PAG) is involved in the mediation of defensive behaviour including modulating fear and anxiety and autonomic and cardiovascular responses (Behbehani, 1995), so may have been activated in both groups when pain was combined with OKS. The enhanced response in migraineurs during OKS alone may indicate disrupted PAG control – hyperexcitable neural responses or weak inhibitory mechanisms in this group. Vascular changes across conditions, regardless of whether the temple was painfully stimulated during OKS, were equivalent for both groups. Nevertheless, headache was greater in migraine sufferers than controls, suggesting that a mechanism other than extracranial vasodilatation was responsible for headache.

Ice on temple during OKS vs hand in ice-water during OKS (Condition 4 vs 6, respectively)

Overall, vascular responses were comparable in both groups, though the ipsilateral response was greater than the contralateral response when the hand was immersed in ice-water during OKS. As discussed previously (chapters 9, 10), this asymmetrical reaction to painfully cold stimulation of the limb in both groups suggests that ipsilateral vasodilatation is a normal response.

Extracranial blood vessels usually dilate more readily in migraine sufferers than in controls during exposure to stressful stimuli (Drummond, 1984) and cardiac output increases more so in migraineurs in response to cold- and cognitive-stress (Hassinger, Semenchuk and Obrien, 1999). In view of this it was expected that vasodilatation would be greater in migraineurs than in controls in the present study during stressful procedures (temple pain during OKS, hand pain during OKS), yet it developed equally in both groups. It seems that the added stress of painfully cold stimulation during OKS boosted vascular responses in controls to resemble those of migraine sufferers. Therefore, for both groups the vasodilator stress response was activated comparably across both conditions.

CHAPTER 12

RESULTS and DISCUSSION

Comparison of Conditions

2 (ice on temple after OKS), 3 (Ice on temple) and 5 (Hand in ice-water)

The intention was to determine whether painful stimulation of the temple would promote symptoms of discomfort and intensify vascular responses in migraine sufferers compared to controls. Ice was applied to the temple after OKS and independent of OKS to explore the impact of painful stimulation in the presence of residual effects from OKS. Ice to the temple (independent of OKS) was compared with immersing the hand in ice-water (independent of OKS) to gauge the effect of painful stimulation to the head as opposed to elsewhere (the control condition).

Bearing in mind the migraine sufferer's susceptibility to motion sickness (Golding, 1998; Kuritzky, Ziegler & Hassanein, 1981), sensitive trigeminal system (Lance, 1993, 2002; Macfarlane, 1993; Moskowitz, 1993; Weiller et al., 1995), and vasodilatation during motion sickness (Harm, 1990; Kolev et al., 1997) and head pain (Lance and Goadsby, 2002; Drummond, 1997); the following hypotheses were investigated:

1. Headache would develop more readily in migraineurs than in controls when ice was applied to the temple, particularly after OKS (in the presence of residual motion sickness) compared to immersion of the hand in ice-water, independent of OKS.

2. If trigeminal impulses converge on neurons responsible for symptoms other than headache in migraineurs, these symptoms would develop more readily in migraine sufferers than in controls during painful stimulation of the temple than the hand. Additionally, symptomatic responses might intensify in the presence of any residual symptoms following OKS to a greater extent in migraine sufferers than in controls.

3. Facial blood flow would be greater in migraine sufferers than in controls when ice was applied to the temple, particularly during stimulation of the temple after OKS (in the presence of residual motion sickness).

RESULTS

Symptom ratings

Ratings were analyzed in a series of 2 (group: migraineurs, controls) x 3 (condition: ice to temple before and after OKS, hand in ice-water) repeated-measures ANOVAs. Simple planned contrasts were used to compare the mean of painful stimulation of the temple with painful stimulation of the temple after OKS, and immersion of the hand in ice-water. Figure 12.1 demonstrates comparative change in symptom ratings across conditions.

ICE APPLICATION AFTER AND INDEPENDENT OF OKS

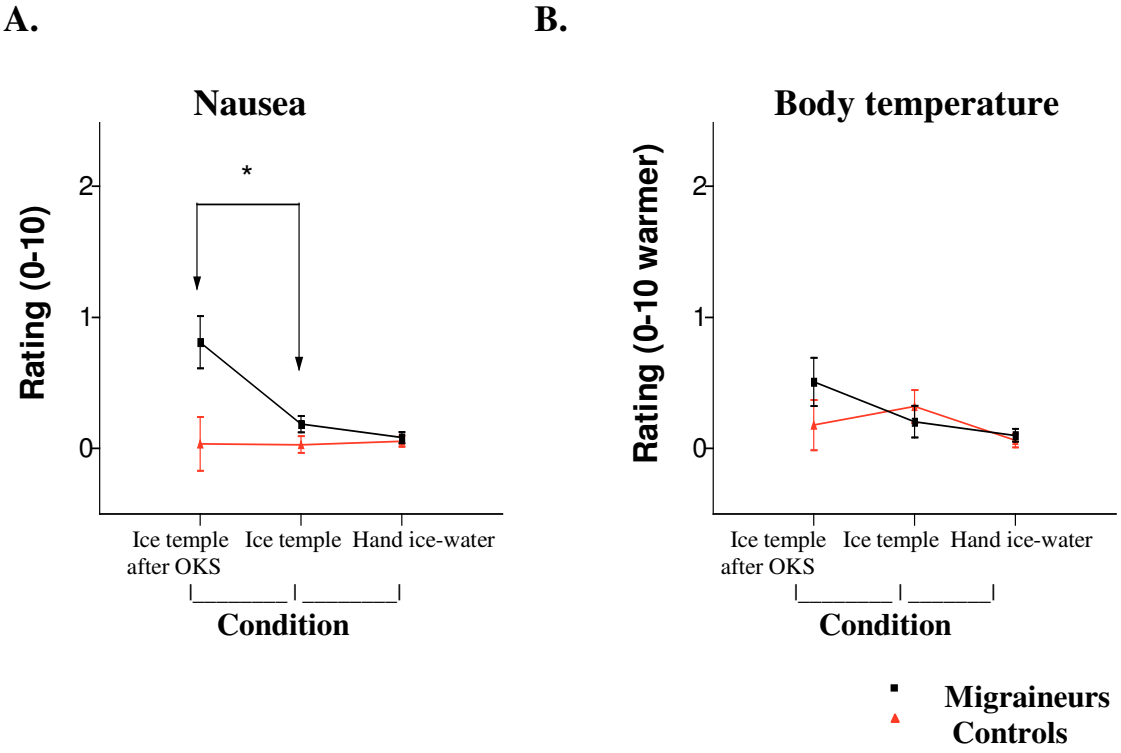


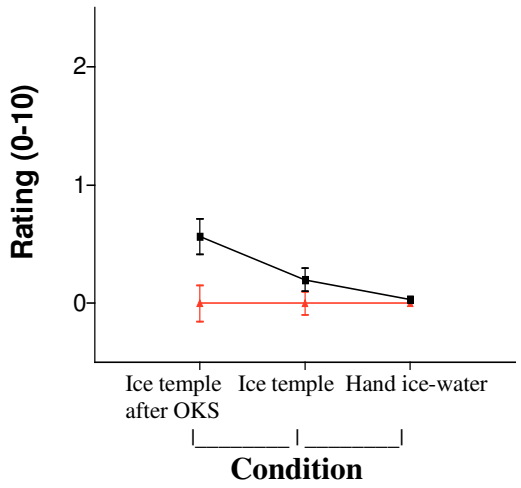
Figure 12.1.A-B Means ± SEM for migraineurs (n = 23) and controls (n = 22) for ice to the temple after OKS, ice to the temple and hand in ice-water. Mean rating from minutes 2-14 was explored. *OKS = optokinetic stimulation*

** statistically significant difference between conditions for migraineurs (*P<.05)*

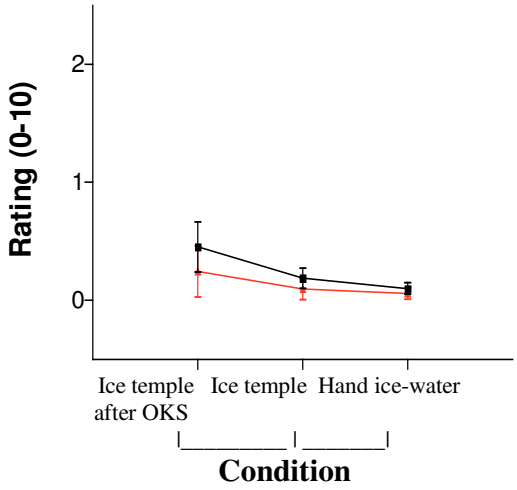
P.T.O for additional ratings

ICE APPLICATION AFTER AND INDEPENDENT OF OKS

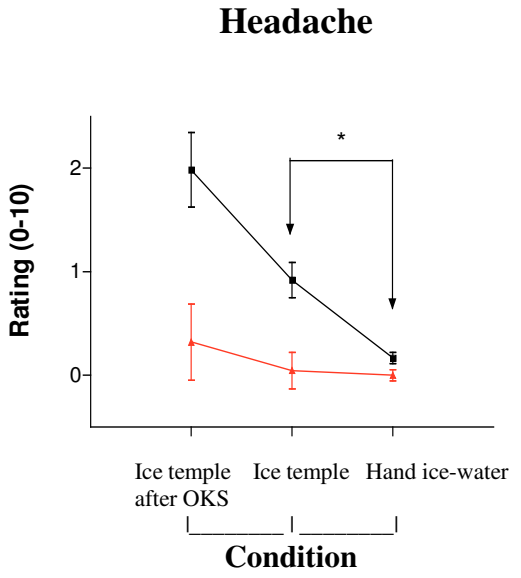
C.



D.



E.



F.

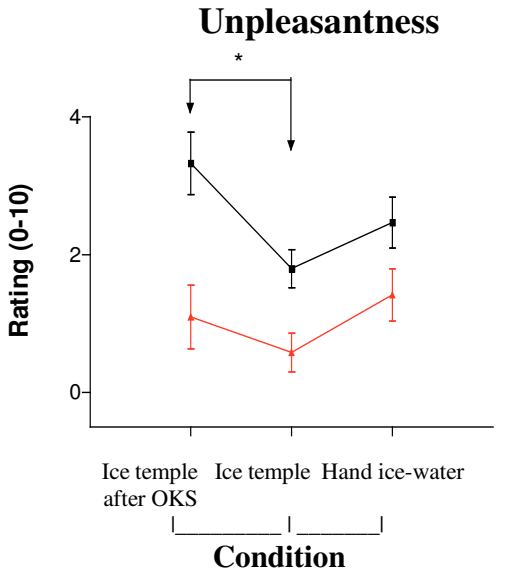


Figure 12.1C-F. Means ± SEM for migraineurs (n = 23) and controls (n = 22) for ice to the temple after OKS, ice to the temple and hand in ice-water. Mean rating from minutes 2-14 was explored. *OKS = optokinetic stimulation*

* *statistically significant difference between conditions for migraineurs (*P<.05)*

Note: Y-axis has different rating scales for unpleasantness

P.T.O for additional ratings

ICE APPLICATION AFTER AND INDEPENDENT OF OKS

G. **H.**

Ice-induced intensity ***Ice-induced unpleasantness***

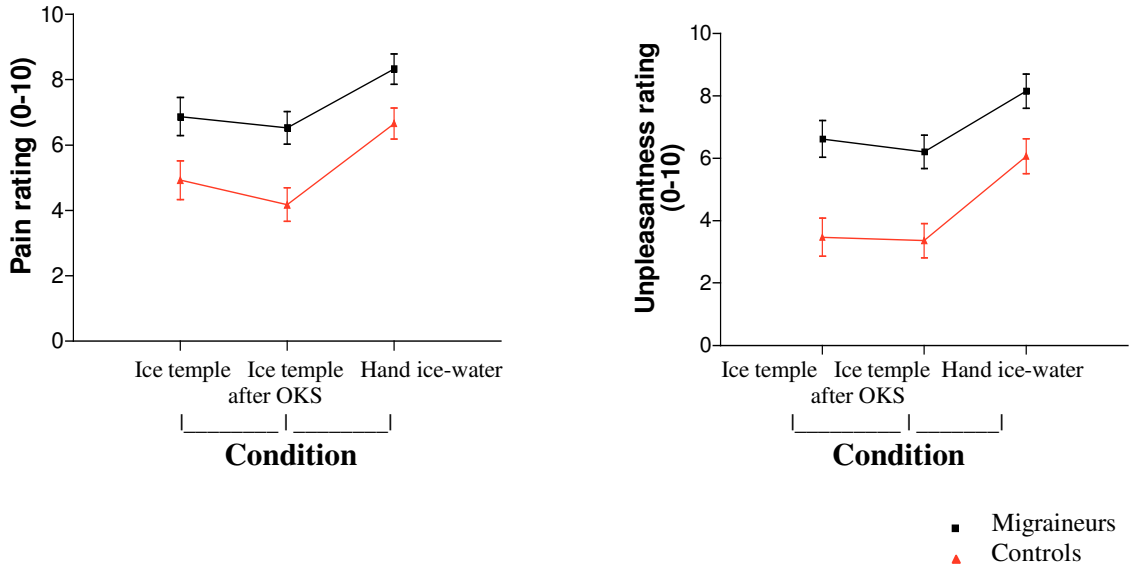


Figure 12.1.G-H. Means ± SEM for migraineurs (n = 23) and controls (n = 22) for ice to the temple after OKS, ice to the temple and hand in ice-water. Mean rating from minutes 2-14 was explored. *OKS = optokinetic stimulation*

Note: Y-axis has different rating scales for unpleasantness (previous page), and ice-induced intensity and ice-induced unpleasantness.

Ice on temple before *vs* after OKS (Condition 3 vs 2, respectively):

The pattern of findings indicates that nausea and headache were greater when ice was applied to the temple after OKS than during ice to the temple independent of OKS (main effect for Condition, ice to temple after OKS *vs* ice temple: Nausea, F (1, 43) = 6.529, $p < .05$; Headache, F (1, 43) = 7.457, $p < .01$). Closer inspection indicated that this only applied to migraineurs, particularly for nausea (Condition x Group contrast interaction, ice to temple after OKS *vs* ice temple, Nausea: F (1, 43) = 6.263, $p < .05$).

Unpleasantness ratings were greater when the temple was stimulated with ice after OKS than independent of OKS (main effect for Condition, ice to temple after OKS *vs* ice temple, Unpleasantness: F (1, 43) = 17.476, $p < .001$), particularly for migraineurs (Condition x Group contrast interaction, ice to temple after OKS *vs* ice to temple, Unpleasantness: F (1, 43) = 4.322, $p < .05$). See Figure 12.1.F.

Temple pain *vs* limb pain (Condition 3 vs 5, respectively) :

Nausea was minimal during both conditions in migraine sufferers, and when the hand was immersed in ice-water headache was negligible in comparison to when the temple was stimulated with ice. In controls ratings of nausea and headache were minimal in all three conditions (main effect for Condition, ice to temple *vs* hand in ice-water, Headache: F (1, 43) = 11.176, $p < .01$; Condition x Group contrast interaction, F (1, 43) = 8.722, $p < .01$). Refer to Figures 12.1.A and 12.1.E. Ratings of body temperature were lower in both groups when the hand was immersed in ice-water than when ice was applied to the temple (main effect for Condition, ice to temple *vs* hand ice-water, Body temperature: F (1, 43) = 4.553, $p < .05$). See Figure 12.1.B. When the hand was immersed in ice-water ratings of overall unpleasantness, and ice-induced intensity and unpleasantness, were greater than when ice was applied to the temple independent of OKS (main effect for Condition, ice temple *vs* hand ice-water: Unpleasantness, F (1, 43) = 8.650, $p < .01$; Pain Intensity, F (1, 43) = 35.513, $p < .001$; Pain Unpleasantness, F (1, 43) = 29.557, $p < .001$), and as observed in preliminary analyes, were greater in migraine sufferers than in controls. Figures 12.1.F, 12.1.G and 12.1.H illustrate this effect.

Table 12.1. Main effect and interaction F, *p*, and df values from a 2 (group: migraineurs, controls) x 3 (condition: ice to temple after OKS, ice to temple, hand in ice-water) repeated-measures ANOVA for nausea, body temperature, dizziness, drowsiness, headache and unpleasantness. Mean rating from minutes 2-14 for migraineurs (n = 23) and controls (n = 22) was explored. *OKS = optokinetic stimulation*

	F ratios (df = 1, 43)		
	Group	**Condition**	**Condition x Group**
Nausea	6.659 *		
Ice temple after OKS *vs* Ice temple		6.529 *	6.263 *
Ice temple *vs* Hand ice-water		.787	2.374
Body temperature	.379		
Ice temple after OKS *vs* Ice temple		.446	3.417
Ice temple *vs* Hand ice-water		4.553 *	.858
Dizziness	6.527 *		
Ice temple after OKS *vs* Ice temple		3.870	3.870
Ice temple *vs* Hand ice-water		1.567	1.567
Drowsiness	.727		
Ice temple after OKS *vs* Ice temple		2.047	.157
Ice temple *vs* Hand ice-water		.837	.146
Headache	15.641 ***		
Ice temple after OKS *vs* Ice temple		7.457 **	2.584
Ice temple *vs* Hand ice-water		11.176 **	8.772 **
Unpleasantness	12.785 ***		
Ice temple after OKS *vs* Ice temple		17.476 ***	4.322 *
Ice temple *vs* Hand ice-water		8.650 **	.107

***** statistically significant (* p < .05,** p < .01,*** p < .001)

Table 12.2. Main effect and interaction F, *p*, and df values from a 2 (group: migraineurs, controls) x 3 (condition: ice to temple after OKS, ice to temple, hand in ice-water) repeated-measures ANOVA for ice-induced intensity and ice-induced unpleasantness. Mean rating for ice applications for migraineurs (n = 23) and controls (n = 22) were explored. *OKS = optokinetic stimulation*

	F ratios (df = 1, 43)		
	Group	**Condition**	**Condition x Group**
Ice-induced intensity	10.283 **		
Ice temple after OKS *vs* Ice temple		3.419	.473
Ice temple *vs* Hand ice-water		35.515 ***	.899
Ice-induced unpleasantness	16.285 ***		
Ice temple after OKS *vs* Ice temple		.792	.274
Ice temple *vs* Hand ice-water		29.557 ***	.796

***** statistically significant (** p < .01,*** p < .001)

Pulse amplitude

Responses were analysed in a 2 (group: migraineurs, controls) x 3 (condition: ice to the temple before and after OKS, hand in ice-water) x 2 (side: Ipsilateral, contralateral) repeated-measures ANOVA. Simple planned contrasts were used to compare the mean of painful stimulation of the temple with painful stimulation of the temple after OKS, and immersion of the hand in ice-water. Figure 12.2 demonstrates comparative change in pulse amplitude across conditions.

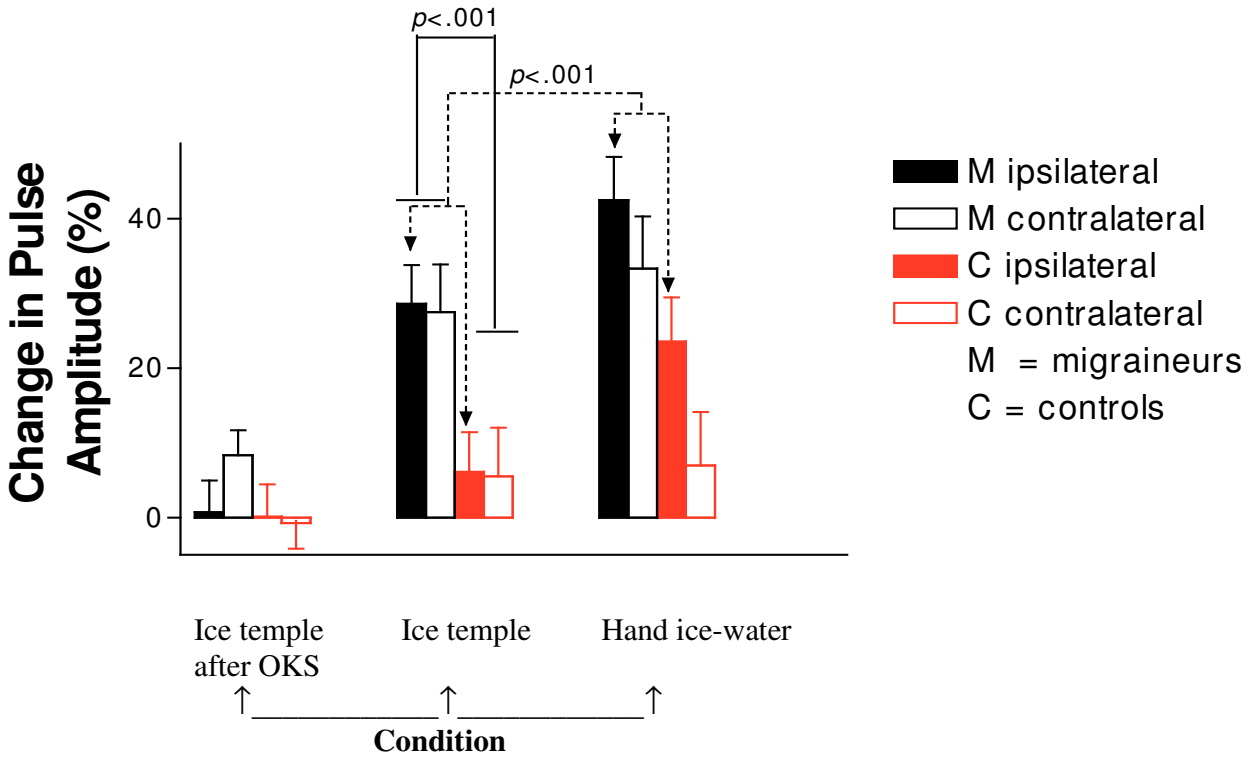


Figure 12.2. Mean ipsilateral and contralateral pulse amplitude change (± SEM) to ice stimulation (temple, hand) for migraineurs (n = 23) and controls (n = 22) 30 seconds after ice stimulation. *OKS = optokinetic stimulation*
Between group difference: ⊥
Between condition side difference for both groups: **...:...** (ipsilateral)

Vascular responses were greater when the temple was stimulated with ice independent of OKS, than during stimulation after OKS (main effect for Condition, ice to temple after OKS *vs* ice temple: F (1, 43) = 12.192, $p < .001$). However, as observed in preliminary analyses, this effect was greater in migraine sufferers than in controls (Condition x Group interaction, ice temple after OKS *vs* ice to temple: F (1, 43) = 4.213, $p < .05$). Vascular responses were greater still when the hand was immersed in ice-water compared to when the temple was stimulated with ice independent of OKS (main effect for Condition, ice to temple *vs* hand ice-water: F (1, 43) = 5.079, $p < .05$). Closer inspection indicated that responses were greater ipsilaterally after immersion of the hand in ice-water than when ice was applied to the temple independent of OKS (Condition x Side interaction, ice temple *vs* hand ice-water: F (1, 43) = 5.595, $p < .05$). Tables 12.3 and 12.4, and Figure 12.2 illustrate these trends.

Table 12.3. Main effect, interaction and simple contrast F, *p*, and df values from a 2 (group: migraineurs, controls) x 3 (condition: ice to temple after OKS, ice to temple, hand in ice-water) x 2 (side: Ipsilateral, contralateral) repeated-measures ANOVA, of mean pulse amplitude 30 seconds after ice stimulation (temple, hand).
OKS = optokinetic stimulation

Main effect	*df = 1, 43*	F	P
Group		11.405	.002
Condition			
Ice temple after OKS *vs* Ice temple		12.192	.001
Ice temple *vs* Hand ice-water		5.079	.029
Side		3.862	.056
Interaction			
Condition x Group			
Ice temple after OKS *vs* Ice temple		4.213	.046
Ice temple *vs* Hand ice-water		.002	.964
Side x Group		2.137	.151
Condition x Side			
Ice temple after OKS *vs* Ice temple		.948	.336
Ice temple *vs* Hand ice-water		5.595	.023
Condition x Side x Group			
Ice temple after OKS *vs* Ice temple		1.057	.310
Ice temple *vs* Hand ice-water		.604	.441

Table 12.4. Means and standard deviations during OKS alone, ice to the temple during OKS, and hand in ice-water during OKS, of pulse amplitude 30 seconds after ice stimulation (temple, hand). *OKS = optokinetic stimulation*

Means ± SD				
	Migraineurs (n = 23)		Controls (n = 22)	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral
Ice temple after OKS	0.7 ± 25.1	8.3 ± 21.4	0.1 ± 13.5	-0.7 ± 7.1
Ice temple	28.6 ± 31.9	27.5 ± 39.5	6.1 ± 14.1	5.5 ± 16.5
Hand ice-water	42.4 ± 32.9	33.3 ± 43.4	23.5 ± 21.1	7.0 ± 18.2

DISCUSSION:

Effects on symptomatic responses

Summary of major findings

Ice on temple before vs after OKS (Condition 3 vs 2, respectively):

- Headache and nausea (particularly in migraine sufferers), was rated higher when ice was applied to the temple after OKS than when ice was applied independent of OKS. However, in controls all symptomatic ratings were negligible regardless of condition. During painful stimulation before OKS, symptoms barely developed in migraine sufferers apart from mild headache and low-grade nausea.

- Unpleasantness in response to the development of symptoms was greater when ice was applied to the temple after OKS than before OKS, particularly for migraine sufferers. In addition, ratings of unpleasantness were greater in migraineurs than in controls regardless of the procedure.
- Ice-induced pain ratings were comparable across conditions. However, ratings were greater in migraineurs than in controls throughout both procedures.

Temple pain *vs* limb pain (Condition 3 vs 5, respectively) :

- Headache was greater in migraine sufferers when the temple was stimulated with ice than when the hand was immersed in ice-water. Controls remained headache-free.
- Ratings of nausea, dizziness and drowsiness were minimal regardless of condition for both groups.
- Perceived increases in body temperature were lower in both groups when the hand was immersed in ice-water than when ice was applied to the temple.
- Overall unpleasantness, and ice-induced intensity and unpleasantness, were greater during painful stimulation of the limb than during painful stimulation of the temple. However, ratings were greater in migraine sufferers than in controls, for both procedures.

Discussion of effects on symptomatic responses

Ice on temple before vs after OKS (Condition 3 vs 2, respectively):

For both groups, headache, and nausea (particularly in migraine sufferers), were rated higher during painful stimulation of the temple after than before OKS. Closer inspection indicated that in controls, regardless of condition, overall symptomatic

responses were negligible. It appeared that some aspect of OKS intensified head pain and nausea in migraineurs. Therefore, these cardinal responses developed more readily in migraineurs than in controls during painful stimulation in the presence of residual motion sickness.

OKS can excite vestibular structures and, in turn, the vomiting centre (Drummond, 2005, 2002; Mitchelson, 1992). The vomiting centre in the NTS is also activated during migraine headache. As migraine headache is associated with activation of the trigeminal nerve it may be that the TNC communicates with the NTS during the migraine crisis (Knight, 2005). Indeed, it appears that during migraine and motion sickness these centres have a functional connection. Since nausea and headache developed in the present study in migraineurs more so during painful stimulation of the temple after rather than before OKS, it is feasible that OKS may have excited vestibular pathways, and that painful stimulation of the temple after OKS may have excited trigeminal pathways. Nausea, in particular, was greater when the trigeminal nerve was stimulated after OKS than before OKS. During OKS, signals from the vestibular system may have converged on the NTS. Subsequent signals from the TNC following painful stimulation of the temple after OKS may have simultaneously converged on NTS nuclei, thus heightening sensitivity in the "vomiting center" in migraine sufferers.

It is also possible that trigeminal stimulation boosted vestibular activity directly, as Marano, Marcelli, Di Stasio, Bonuso, Vacca, Manganelli, Marciano and Perretti (2005) observed that painful trigeminal stimulation increased spontaneous nystagmus in migraineurs. Provocation of spontaneous nystagmus is probably a reasonable marker of vestibular involvement as it has been demonstrated that spontaneous nystagmus has vestibular origins (Cutrer and Baloh, 1992; Kuritzsky, Toglia and Thomas, 1981; Savundra, Carroll, Davies and Luxon, 1997). Migraine certainly is more common in those who experience dizziness (Neuhaser, Leopold, von Brevern, Arnold and Lempert, 2001), which may further suggest that trigeminal and vestibular pathways are functionally linked. In the present study migraineurs experienced slightly more dizziness after than before OKS. Therefore, it may be that painful trigeminal signals boosted vestibular activity and, in turn, the emetic circuit. Alternatively, the enhanced dizziness may merely reflect residual effects of motion sickness.

Nausea increased gradually from the commencement of the procedure when ice was applied to the temple after OKS (see Figure 6.1.A, page 117), whereas nausea did not develop until the final painful application during ice to the temple in the absence of OKS (see Figure 7.1.A, page 129). Residual activity in emetic, trigeminal or vestibular circuits may have enhanced the nauseating effect of head pain after OKS. OKS clearly seemed to influence the development of headache, nausea and dizziness in migraine sufferers, as these symptoms did not develop as readily during the application of ice to the temple in the absence of OKS.

Ratings of drowsiness and perceived increases in body temperature were also greater when the temple was painfully stimulated after OKS than before OKS, in migraine sufferers, probably due to the residual effects of OKS. However, differences between conditions did not reach significant levels.

For both groups, and particularly for migraineurs, the development of symptoms following the application of ice to the temple after OKS was perceived as more unpleasant than before OKS. This, no doubt, was because symptoms developed more readily during painful stimulation after OKS.

Ice-induced pain ratings were comparable for each condition in both groups. Apart from mild headache, reported in migraine sufferers during painful stimulation of the temple after OKS, symptoms were generally minimal in both conditions for both groups. Therefore, participants were probably equally focused on the painfully cold stimulus whether applied before or after OKS. Migraine sufferers, however, reported that the application of ice to the temple was more painful than controls, suggesting hyperexcitable nociception in this group.

Temple pain *vs* limb pain (Condition 3 vs 5, respectively):

In migraine sufferers headache was more intense when the temple was stimulated with ice than when the hand was immersed in ice-water. Headache did not develop at all when the hand was immersed in ice water. It appeared that temple pain initiated headache in migraineurs, suggesting that trigeminal nerve impulses generated the

enhanced nociception. In contrast, controls remained headache-free throughout all three procedures.

Ratings of nausea, dizziness, drowsiness and perceived increases in body temperature were generally minimal regardless of condition for both groups. Furthermore, perceived increases in body temperature were lower in both groups when the hand was immersed in ice-water than when ice was applied to the temple. Noxious stimulation of the limb was certainly more painful than noxious stimulation of the temple, for both groups. Immersion of the hand in ice-water was probably more extreme than applying an ice block to the temple as it involved exposure of a greater surface area of skin.

Interestingly, for both groups overall unpleasantness in response to the development of symptoms was greater during painful stimulation of the hand than during painful stimulation of the temple, even though body temperature, and nausea and headache, in migraineurs, were generally greater during temple pain. Perhaps because limb pain was overwhelmingly more painful than head pain, it was perceived as the more unpleasant condition overall.

Effects on pulse amplitude

Summary of major findings

Ice on temple before vs after OKS (Condition 3 vs 2, respectively):

- Vascular responses were greater when the temple was stimulated with ice independent of OKS than after OKS, in both groups. This effect was greater in migraine sufferers than in controls.

Temple pain *vs* limb pain (Condition 3 vs 5, respectively):

- Pulse amplitude was generally greater when the hand was immersed in ice-water than when ice was applied to the temple in both groups. Responses were greater ipsilaterally after immersion of the hand in ice-water than when ice was applied to the temple independent of OKS.

Discussion of effects on pulse amplitude

Ice on temple before vs after OKS (Condition 3 vs 2, respectively):

Vascular responses were greater when the temple was stimulated with ice independent of OKS than after OKS, in both groups. However, it was expected that facial blood flow would be greater in migraine sufferers than in controls when ice was applied to the temple after (in the presence of residual motion sickness) than before OKS.

Preliminary analyses (see chapter 6, page 126) indicated that extracranial vasodilatation persisted after OKS in migraine sufferers, hence data was re analysed using the baseline before OKS (see Appendix 12, pages 361-362). When analysed with a different baseline it appeared that pulse amplitude increased during OKS and remained so when ice was applied to the temple after OKS, particularly in migraine sufferers. In addition, vascular responses were found to be comparable in each condition, for both groups. This effect was greater in migraine sufferers than in controls.

Temple pain *vs* limb pain(Condition 3 vs 5, respectively):

Overall, extracranial vascular increases were greater during limb pain than head pain, for both groups, suggesting that vascular reactivity was not entirely mediated by trigeminal nerve activity.

Facial blood flow increased more readily in migraine sufferers than in controls during temple pain. During limb pain, overall increases in pulse amplitude were greater ipsilateral than contralateral to stimulation, and were greater in migraine sufferers than controls contralaterally. The defense response was assumed to at least partly account for the enhanced vascular response observed in migraineurs during temple pain. Atypical autonomic reactivity may have also influenced facial blood flow during limb pain and will be discussed next.

Drummond (1999) found that anger and embarrassment provoked increases in facial blood flow but decreases in the hand. He suggested that this might represent a defense response mediated in the periaqueductal gray matter in areas that link pain and emotional processing centres in the cerebral cortex and the brain stem (Bandler and Shipley, 1994).

The asymmetry of the response appeared to be a normal reaction to hand immersion in both groups, implying that mechanisms other than a general widespread sympathetic response (Strandring, 2005) to painful stimulation was responsible. In contrast, side differences were not apparent during painful stimulation of the temple.

CHAPTER 13

GENERAL DISCUSSION

In this chapter key findings are summarized and then discussed in light of the relevant literature/models of the migraine mechanism, for symptomatic and vascular responses, respectively. Following this, general methodological issues associated with the project are addressed, followed by directions for further research, and conclusions.

13.1. SYMPTOMATIC RESPONSES

Discussion of findings

In this major section, aspects of OKS, trigeminal stimulation, and hyperexcitability in trigeminal and brain stem nuclei in migraine sufferers are discussed. In light of this review, the relationship between head pain and nausea, two cardinal symptoms of migraine, is examined in depth. Observations during limb pain and psychophysical factors in relation to pain are then discussed.

Symptoms generally develop more readily in migraine sufferers than in controls during OKS

Symptomatic responses generally developed more readily in migraineurs than in controls, particularly during the three procedures involving OKS and during temple pain after OKS in the presence of residual motion sickness.

This section focuses on aspects of motion sickness. First, the neurophysiology of nausea, and nociceptive and non-nociceptive pathways that may converge on emetic circuits, is introduced. The focus is then directed to OKS-induced motion sickness and its impact on pain processing. Nausea is explored next in relation to both maladies - migraine and motion sickness. Following this, motion sickness in migraine sufferers, with respect to interconnected neural pathways, particularly vestibular and emetic, are considered. Whether symptoms of motion sickness are a defense response is also discussed. This section concludes with a summary of key points related to OKS-induced symptoms.

Mechanism of nausea

Although many different maladies cause nausea and vomiting (motion sickness, migraine, morning sickness, toxin ingestion) the same central circuitry (the 'vomiting center') in the brainstem is thought to coordinate emesis (Dahlof and Hargreaves, 1998; Mitchelson, 1992). Vomiting is frequently, but not always, heralded by nausea. Furthermore, nausea - an unpleasant wave-like sensation in the throat, epigastrium or abdomen - does not always culminate in vomiting (Venes, 2001). Nausea, a cardinal symptom of migraine, was of particular interest in the present study. Plausibly, an association exists between the sensation of nausea and activation of the 'vomiting centre', which comprises part of the nucleus tractus solitarius (NTS) and the dorsal motor nucleus of the vagus (Dahlof and Hargreaves, 1998; Mitchelson, 1992).

Three different afferent pathways converge on the 'vomiting centre': the chemoreceptor trigger zone (CTZ), gastrointestinal visceral afferents, and the labyrinth (Noriaki et al., 1993). Visceral (via: vagal and sympathetic nerves) and labyrinth (via

vestibular(via vestibular nuclei) input has direct synaptic contact with the "vomiting centre" but the CTZ, located in the area postrema at the floor of the fourth ventricle on the upper surface of the medulla, detects emetic signals via circulating chemical stimuli in plasma and cerebral spinal fluid (Borison, 1989; Leslie, 1986; Yates, Grėlot, Kermon, Balaban, Jakuš and Miller, 1994).

Perhaps the so-called "vomiting center" also receives indirect input via the cerebellum as cerebellovestibular connections project to superior, medial and inferior vestibular nuclei (Standring, 2004). Vestibular inputs to the nucleus tractus solitarius were demonstrated to come directly from medial and inferior vestibular nuclei in the cat (Yates et al., 1994) and rabbit (Balaban and Beryozkin, 1994).

The vagal nucleus, also known as the dorsal motor nucleus of the vagus, is a general efferent nucleus and the largest parasympathetic nucleus in the brain stem. Approximately 80% of its neurones give rise to the preganglionic pararsympathetic fibres of the vagus nerve. Also, sparse vagal afferents that supply the gastrointestinal system project directly to the NTS (Helke, 2001). The muscular contractions associated with vomiting are coordinated by efferent motor fibres in the vagus.

Multiple neural pathways including nociceptive may converge on the NTS

Multiple pathways may mediate nociceptive inputs to the NTS, which perhaps explains why symptoms such as headache developed during OKS in this study, particularly in migraine sufferers. In a review of the literature, Boscan, Kasparov and Paton (2002) illustrate the potential for integration of visceral and somatic afferents within the NTS. They site evidence that cardio-respiratory afferent regions in the NTS receive direct projections from the spinal cord and express c-fo*s* immuno-reactivity in response to noxious stimulation of the limb, cornea and stomach. The immediate response gene c-fo*s* plays a role in the alteration of cellular responses to pain signals (Moskowitz, 1993). Boscan et al. (2002) studied the interaction between nociceptive and baroreceptive activity in the NTS in rats involving mechanical stimulation of the paw,

electrical stimulation of the brachial nerve, and paced microinjections of $GABA_A$ antagonist - bicuculline methiodide, substance P, and the NK_1 receptor antagonist –CP-99,994 into the NTS. They concluded that somatic nociceptive afferents activate NK_1 receptors, which in turn enhance the release of GABA in the NTS. This activation inhibits the baroreceptor cardiac reflex. These researchers claim this inhibition may facilitate and maintain the tachycardia and pressor response that is associated with pain. Based on their electrophysiological findings they suggest that multiple pathways may mediate nociceptive inputs to the NTS. Consistent with the literature they point out that nociceptive information may be relayed directly via the dorsal horn, or indirectly via lamina 1 neurons and the lateral cervical nucleus in the spinal cord, to the NTS. Additionally, other brainstem and midbrain regions may forward nociceptive information to the NTS, e.g. the rostal ventrolateral medulla, parabrachial complex and periaqueductal grey matter. Spinal, brainstem and midbrain structures *per se* were not directly investigated in the present study, but as symptoms including headache and nausea developed, particularly in migraine sufferers exposed to OKS, it is plausible that a number of these pathways were activated.

Consistent with the notion that multiple pathways impact on the NTS, in a series of studies involving stimulation of vagal and sympathetic abdominal and cardiac visceral afferents, Longhurst, Tjen-A-Looi and Fu (2001) observed an interaction of sympathetic and vagal parasympathetic afferents in the NTS. In particular, myocardial ischemia is a condition where both vagal and sympathetic cardiac afferent reflexes are activated. Nausea, vomiting, inhibitory responses (e.g., bradycardia, hypotension) and excitatory responses (e.g., tachycardia, hypertension) have all been observed during this state. It is thought that nausea (and vomiting), and inhibitory cardiovascular responses are mainly facilitated by vagal efferents while excitatory cardiovascular responses are a function of sympathetic efferents. During the vomiting process outputs initiated by the medulla include: sweating and increased heart rate, a SNS response; increased salivation, a PNS response; and motor responses involving abdominal muscles. This collective activity may demonstrate central integration of opposing reflexes (vagal/PNS and SNS) in the NTS as Longhurst et al. (2001) suggest. Some pathways from the viscera and pharynx (gagging: glossopharyngeal, trigeminal afferents) are thought to bypass the CTZ and

input directly into the NTS. Perhaps the central integration of opposing reflexes, believed to occur during emesis, to some extent underlie nausea, which commonly precedes vomiting. Sensory and emotional (pain, sight, smell, anticipation) inputs to the 'vomiting centre' are mediated via higher brain centres but motion sickness is thought to have input through the cerebellum/vestibular apparatus (Dahlof and Hargreaves, 1998; Mitchelson, 1992). A number of these pathways could conceivably be activated in a migraine attack.

OKS-induced motion sickness and impact on nociception

OKS most likely triggered visually-induced motion sickness (Takeda, Morita, Horii, Nishiike and Uno, 2001) as symptomatic responses developed in both groups, albeit more so in migraineurs. Migraine sufferers were more sensitive to painful stimulation than controls, and developed headache during the procedure. Drummond (2002) found that migraine sufferers were more sensitive than controls in terms of nausea and headache, after OKS, and scalp tenderness increased in the most nauseated subjects. Scalp tenderness was assessed using an algometer to each side of the forehead. Drummond proposed that the disturbance responsible for nausea also sensitized primary or secondary trigeminal nociceptors or released inhibitory controls on their discharge.

Nausea in migraine and motion sickness

Nausea and vomiting in migraine (Dahlof and Hargreaves, 1998) and in motion sickness (Takeda et al., 2001; Cass et al., 1997) is presumed to start within the central nervous system. In further support of central generation of nausea in motion sickness, Levine, Chillas, Stern and Knox (2000) found that while gastric tachyarrythmia resolved following administration of serotonin (5-HT) receptor-antagonist antiemetics during OKS, nausea (and other symptoms of motion sickness) still developed. These researchers concluded that nausea (associated with motion sickness) was not purely dependent on the

presence of tachyarrhythmia/stomach-discomfort. They suggested that activity in multiple pathways contributes to the sensation of nausea. Peripheral pathways, however, mediate the actual vomiting process (Lang, 1999; McMillin, Richards, Mein and Nelson, 1999).

Motion sickness in migraine sufferers

Enhanced symptomatic responses in migraine sufferers observed during OKS in the present study may reflect activation of neural pathways that mediate symptoms of motion sickness and migraine. Signals from the vestibular system are required for triggering motion sickness (Yates, Miller and Lucot, 1998). Visually-induced motion sickness from OKS does not involve direct vestibular stimulation but, instead, involves converging sensory inputs (vestibular, visual, somatosensory) that are at variance with sensory integration from the 'neural store' (memory, past experience) (Takedo et al., 2001). This neural mismatch results in motion sickness. As symptoms of motion sickness and migraine are similar, the same neural events may be involved in both conditions. Specifically, brainstem nuclei usually involved during attacks of migraine (Weiller et al., 1995) might reciprocally initiate headache and other symptoms during OKS.

Convergent neural pathways

Anatomical pathways involved in the generation of symptoms (e.g., nausea/vomiting, dizziness) of motion sickness and migraine, may be shared. Activation of "the vomiting centre" nuclei could conceivably lead to nausea/vomiting, which in turn because of neural interconnections, may activate vestibular nuclei and so initiate the sensation of dizziness. As previously pointed out, the vestibular apparatus is also involved in motion sickness. In this case, impulses from the vestibular apparatus travel to the vestibular nucleus, then through the cerebellum to the 'vomiting centre' (Mitchelson, 1992).

Takedo et al. (2001) propose that a hypersensitive 'emetic center' (low threshold for the emetic response) underlies susceptibility to motion sickness. As the same central

mechanisms orchestrate emesis, regardless of the triggering condition, and migraine sufferers are prone to motion sickness, 'vomiting centre' hypersensitivity could also explain the recruitment of nausea in a migraine attack.

Dizziness/vertigo in migraine

The experience of dizziness or vertigo is frequently reported during attacks of migraine as well as in the headache free interval (Marano, Marcelli, Di Stasio, Bonuso, Vacca, Manganelli, Marciano and Perretti, 2005; Baloh, 1997; Cutrer and Baloh, 1992), and nausea is often coupled with dizziness/vertigo during an attack (Baloh, Foster, Yue and Nelson, 1996; Harris, 1999). This may reflect an interaction between the trigeminal and vestibular systems. Consistent with this interaction, Marano et al. (2005) found that spontaneous nystagmus developed more readily in migraineurs than in controls following unilateral electrical stimulation of the supraorbital region of the forehead. Lesions associated with vestibular structures commonly produce rhythmic eye movements or nystagmus (Venes, 2001). The findings of Marano et al. (2005) may indicate dysfunction of the vestibular system in migraineurs and a functional connection between the vestibular and trigeminal systems. In the case of motion sickness, impulses are relayed from vestibular nuclei to the cerebellum, and then to the "vomiting center" (Mitchelson, 1992). Motion sickness symptoms develop readily in most migraine sufferers but motion sickness is not comorbid with common peripheral vestibular disorders, such as Meniere's disease, benign paroxysmal positional vertigo or vestibular neuritis (Marcus, Furman annd Balaban, 2005). The reciprocal relationship between motion sickness and migraine lends further support to the notion that anatomical pathways involved in their generation may be shared.

Symptoms of motion sickness as a possible defense response

In the case of motion sickness, Triesman (1977) suggests that symptoms represent a defense response, similar to the protective reflex of vomiting that follows gastric

irritation in response to ingestion of a toxin. The sensory conflict generated in motion sickness may trigger nausea, but in the instance of motion sickness this is due to a false perception that a neurotoxin is involved.

Interestingly, Rohleder, Otto, Wolf, Klose, Kirschbaum, Enck and Klosterhalfen (2006) demonstrated gender specific patterns during nauseogenic body rotation in the production of pro-inflammatory cytokine production and the sensitivity of stimulated cytokine production to glucocorticoid suppression. In healthy males, stress responses during body rotation stimulated pro-inflammatory cytokine production, and the sensitivity of stimulated cytokine production was linked to glucocorticoid suppression. In females, however, glucocorticoid sensitivity increased and changes in inflammatory responses were minimal. In the present study, perhaps the threat to homeostasis during motion sickness triggered neurogenic inflammation to defend the brain of the susceptible individual, in addition to nausea/emesis.

Inflammation is an immunological defense against injury, infection or allergy (Bray et al., 1999; Davis, 2001; Kemper, Meijler, Korf and Ter Horst, 2001). When tissue is traumatised or threatened the immune system is activated and a local inflammatory response begins as the first line of defense. Numerous proteins including cytokines are released that signal a cascade of chemical events to regulate inflammation and immune responses. Cytokines are able to alter cells that produce them (autoendocrine effect), change neighbouring cells (paracrine effect), or affect cells systemically (endocrine effect). Systemic inflammatory responses occur when foreign proteins are detected in the blood stream and immune responses or cytotoxic T-cells are activated.

In their review of the literature, Kemper et al. (2001) reported that changes of serum levels of complement and immunoglobulins, histamine, cytokines and immune cells were sometimes observed in migraine sufferers, suggesting that immune function in migraineurs might be altered. However, Kemper et al. point out that these findings were not replicated in the majority of studies. Hence, in light of the available evidence, it was concluded that there is no definitive evidence of an immune dysfunction in migraineurs.

However, it is well recognized that a local neurogenic inflammatory response of the meningeal vasculature is specifically associated with migraine pathogenesis (Moskowitz, 1993). As migraine sufferers developed headache during OKS in the present study, it is

tempting to speculate that an immunological inflammatory defense reaction occurred in deeper structures of the brain, initiated in response to stressful procedures. On the other hand, it appears that meningeal neurogenic inflammation may simply be a process that occurs in the period before the headache phase of a migraine attack rather than being a force for the headache, as the anti-migraine drug Bosentan blocks plasma protein extravasation but has no vasoconstrictive effects, and does not alleviate head pain during the headache phase of the attack (May, Gijsman, Wallnofer, Jones, Diener and Ferrari, 1996).

In the present study, the stress of OKS-induced motion sickness may well have provoked activity in the hypothalamic-pituitary-adrenal axis and the autonomic nervous system (Kajantie and Phillips, 2006). In Rohleder's study (2006) increases in endocrine responses (adrenocorticotrophic hormone, cortisol and antidiuretic hormone) were observed in both sexes during rotation-induced motion sickness. All endocrine responses habituated over time except for the cortisol response in males. Gender specific patterns in the production of stress hormones are also seen in response to various other stressors including physical, mental and psychosocial tasks (Kajantie and Phillips, 2006).

Furthermore, perhaps the stress/defense response to the disconcerting state of motion sickness (Drummer, Stromeyer, Reipl, König, Strollo, Lang, Maass, Rocker and Gerzer, 1990; Otto, Riepl, Otto, Klose, Enck and Klosterhalfen, 2005; Reichardt, Üngörgil, Reipl, Schedlowski, Lehnert and Enck, 1997; Rohleder, Otto, Wolf, Klose, Kirschbaum, Enck and Klosterhalfen, 2006) added to or facilitated vascular and symptomatic responses during OKS.

Key points: OKS-induced symptoms

Migraine sufferers were more sensitive to OKS-induced motion sickness than controls. The similarity of symptoms during motion sickness and migraine imply that neural pathways in their manifestation are shared. It is also plausible that the stress-response augmented symptomatic responses during OKS.

Trigeminal stimulation increases nausea and headache more readily in migraine sufferers than in controls

In the present study, headache and nausea increased progressively in migraine sufferers but not in controls following painful stimulation of the temple. Among other possibilities, this may indicate dysfunction of the trigeminal brainstem nuclear complex in migraine.

This section discusses the trigeminal nerve in relation to head pain and nausea. The structure and function of the trigeminal nerve is described. Activation of the trigeminal sensory system during migraine is discussed next with respect to head pain and nausea during an attack. The neurophysiology of nociception in general is described, followed by a more specific discussion related to the mechanism of head pain during a migraine attack. The neurogenic inflammatory response and hyperexcitable nociception in migraine sufferers are considered. This section concludes with a summary of key points related to the role of the trigeminal nerve in the development of symptoms in migraine sufferers.

Anatomy of the trigeminal nerve

Application of ice to the temple most likely stimulated the ophthalmic branch of the trigeminal nerve and possibly the maxillary and mandibular nerves as all three divisions converge in the temple. The trigeminal nerve is the largest of the cranial nerves. It transmits sensory information from most of the scalp, face, oral and nasal cavities and relays motor signals to the muscles of mastication. Three branches of the trigeminal nerve converge to form the trigeminal or gasserian ganglion: the mandibular (sensory and motor), ophthalmic and maxillary (sensory). The main sensory root of the trigeminal nerve is situated within the pons (Silberstein, 2003; Waxman, 2003; Woolfall and Coulthard, 2001). The ophthalmic branch of the trigeminal nerve carries sensory information from the nose, paranasal sinuses and upper face. Deeper brain structures including the large cerebral vessels, venous sinuses and dura mater, are supplied by

afferent sensory fibres which project through the ophthalmic division. Theses fibres then converge in the brainstem with primary afferents from the ophthalmic and occipital structures onto second order neurons in the caudal trigeminal nucleus (TNC) (Knight, 2005).

The TNC receives input from the trigeminal nerve and contains neurons that discharge when the meninges are stimulated (Moskowitz, 1993). Pain and temperature fibres in the trigeminal nerve enter the brain stem and descend within the spinal tract. Pathways then pass to the thalamus. Subnuclei for proprioception project to the mesencephalon, and reflex connections pass to the cerebellum and motor nuclei of cranial nerves V, VII and IX (Waxman, 2003). Trigeminal nerve afferents convey pain, thermal and tactile information from the face, cerebral vessels and dura mater, to higher brain centres. Also, pressure and kinesthetic sensations from teeth, gums and the temporomandibular joint are conveyed to higher brain centers (Carpenter, 1985).

Trigeminal nerve stimulation in relation to migraine headache

Knight (2005), in a review of the literature, points out that trigeminal brainstem structures form an intricate and complex system of converging projections, a "nociceptive loop". Imaging studies also confirm that neural activity/brainstem structures (medulla, pons, midbrain) play a role in the generation of migraine headache (Borsook, Burstein, Moulton and Becerra, 2006; Weiller, May, Limmroth, Juptner, Kaube, Schayck and Diener, 1995). Clearly, activation of the trigeminal sensory system is linked to head pain and nausea during attacks (Knight, 2005; Dalhlof and Hargreaves, 1998).

The trigeminal nerve innervates the meninges and may contribute to the development of a migraine attack (Bolay, Rueter, Dunn, Huang, Boas and Moskowitz, 2002). While the brain itself is generally insensate (Strandring, 2005), headache pain is generated from trigeminovascular input presumably from the meningeal and extracranial blood vessels (Silberstein, 2003; Moskowitz, 1993). Trigeminovascular activation may also trigger

nausea and vomiting because of potential functional connections between the trigeminovascular system and the Nucleus Tractus Solitarius (Knight, 2005).

Direct stimulation of the trigeminal nerve is a useful and convenient diagnostic and research tool that has helped clarify the neurophysiology of the trigeminal nerve and closely associated brain structures (e.g., Grosser, Oelkers, Hummel, Gesslinger, Brune, Kobal and Lotsch, 2000; Honey, Bland-Ward, Connor, Feniuk and Humphrey, 2002; Valls-Solé, 2005). In the present study trigeminal nociception was stimulated thermally with the application of ice to the temple.

Effects of trigeminal stimulation on nausea

It is conceivable that trigeminal nerve stimulation during the application of ice to the temple provoked headache in migraine sufferers in the present study. As previously pointed out, the cranial sensory anatomy involves convergence of visceral (blood vessels) and somatic (head/facial musculature) nerve fibres on to the same central interneurons. Central projections include the trigeminal nucleus caudalis (TNC), which mediates pain responses, and the nucleus tractus solitarius (NTS) which mediates autonomic responses, e.g., vomiting (see Macfarlane for a review of the literature, 1993). A functional connection is believed to exist between the TNC and the NTS.

Knight (2005) suggested that trigeminovascular activation triggers the emetic response as these symptoms are alleviated by antimigraine medication targeting the 5-$HT_{1B/1D}$ receptors in the NTS. In support of this, remarkable levels of 5-HT_{1D} and 5-HT_{1F} binding-site areas were found in the TNC and NTS during analyses of brain tissue (Pascual, del Arco, Romon, del Olmo, Castro and Pazos, 1996). An action of triptans on these brain nuclei may contribute to the anti-emetic and analgesic therapeutic effects of this group of drugs. It is also likely that the NTS modulates trigeminal nociception in the TNC since visceral nociception requires an intact NTS (Wietelak, Roemer and Maier, 1997).

In the present study nausea increased in both groups when ice was applied to the temple, but more so in migraineurs. The other symptomatic ratings generally did not

change following temple pain during OKS, which suggests a specific association between nausea and head pain. The increased nausea, coupled with increased headache observed in migraine sufferers when the temple was painfully stimulated after and during OKS, implies a mutual interaction between the TNC and NTS. If so, it may be that the cardinal symptoms of nausea and headache compound one another during a migraine attack.

Neurophysiology of nociception

Pain occurs when stimulation is intense enough to threaten or to cause tissue injury (Bray et al., 1999). Free nerve endings in peripheral and cranial nerves are believed to be the specific nociceptors for pain and also serve as thermo- and mechanoreceptors (Slaughter, 2002). Painful mechanical, chemical or thermal stimulation can activate nociceptors. Nociceptive pain fibres consist of rapid firing thinly myelinated A-delta fibres and slower conducting unmyelinated C fibres (including polymodal C fibres) (Waxman, 2003). A-delta fibres are sensitive to high intensity mechanical or cold thermal stimuli while C fibres signal high intensity mechanical, thermal (cold and hot) and noxious chemical stimuli (Bray, Cragg, MacKnight and Mills, 1999; FitzGerald and Folan-Curran, 2002). Nociceptive axons arise from, and transmit, information to the dorsal root ganglia of the spinal cord and the trigeminal ganglia (Barker and Barasi, 2001; Waxman, 2003). The brain stem spinal trigeminal nucleus and the dorsal horn of the spinal cord are the initial sites of synapse in the central nervous system (Silberstein, 2003).

Mechanical and thermal stimuli to the skin evoke specific painful sensations (Ochoa and Yarnitsky, 1994). Mechanical stimuli usually activate myelinated A-delta fibres and unmyelinated C polymodal nociceptors and induce a sharp or dull pain without any thermal quality. During high noxious temperatures unmyelinated C polymodal nociceptors mediate the characteristic burning pain sensation (Ochoa and Torebjörk, 1989). Low temperature stimuli activate small myelinated fibres and cold specific channels at the primary afferent level (Adriaensen, Handwerker and van Hees, 1983).

Noxious low temperature stimuli co-activate unmyelinated C polymodal nociceptors, which is thought to evoke the typical painful cold sensation rather than burning pain (LaMotte and Thalhammer, 1982). Interestingly, when myelinated fibres are blocked leaving only the C fibres to transmit the afferent message, low temperature stimuli no longer induce the cold pain sensation. Instead, an unexpected sensation of burning is perceived (Yarnitsky and Ochoa, 1990). To explain this paradox, Ochoa and Yarnitsky (1994) suggest that the cold pain afferent message involves participation of both myelinated A-delta fibres and unmyelinated C fibres to override the perceived burning quality observed during blockade of myelinated fibres. The quality of pain was not formally measured in the present study but anecdotally both groups reported a dull aching cold pain consistent with the concept of Ochoa and Yarnitsky, of dual activation of A and C fibres in the sensation of cold pain. The experience of pain was more intense and unpleasant in migraine sufferers, consistent with hypersensitive nociception in this group.

Neurophysiology of migraine

In a review of the literature, Burstein (2001) outlined several theories that may explain the initiation of pain in a migraine attack. Activation of peripheral sensory fibers that innervate intracranial blood vessels and the dura has been proposed. It has also been proposed that pain activates descending pathways that facilitate processing of pain signals by spinal cord neurons. Alternatively, suppression of descending pathways that inhibit such processing of pain signals in the spinal cord has been implicated in the initiation of migraine pain.

The periaqueductal gray (PAG), the locus coeruleus (LC) and the raphe nuclei (RN) are probably major components of descending modulatory brainstem pain pathways. Weiller, May, Limmroth, Juptner, Kaube, Schayck, Coenen and Diener (1995) found rCBF values in the distribution of the PAG, LC and RN were higher during migraine, even after pain-relieving treatment, than during the headache-free interval.

Earlier studies demonstrated that headache resulted from stimulation of the PAG (Hass, Kent and Friedman, 1993; Raskin, Hosobuchi and Lamb, 1987) and to a lesser degree the thalamus (Raskin, et al., 1987). Raskin et al. studied 175 pain patients implanted with stimulating electrodes in the PAG and/or thalamus for pain relief from 1977 to 1982. Headache was observed in 13, previously headache-free, individuals immediately, or soon after they underwent implantation, particularly in the PAG, and to a lesser extent (2 patients) in the thalamus. Some patients experienced migrainous headache (pounding headache with nausea and visual disturbance). The remaining 160 individuals in Raskin's study experienced pain relief for their original pain problem and did not develop headache. Elsewhere, a solitary lesion of multiple sclerosis in the PAG region led to severe headache (the worst of her life) in a patient with a virtually unremarkable medical history (Hass et al., 1993).

Consistent with Weiller's (1995) imaging studies which isolated the PAG as a major component of modulating pain pathways, these earlier studies (Hass et al., 1993; Raskin et al., 1987) indicated that disruption to the PAG, a specific region of the midbrain, generated headache in otherwise headache-free individuals.

Despite the appealing logic that the PAG may somehow be linked to the generation of headache, more rigorous research is required, involving larger sample sizes than provided by those early studies of Hass et al. and Raskin et al. Neuroimaging (Weiller et al., 1995) indeed implicates the involvement of brainstem structures during attacks of migraine. The challenge is to establish whether activation of this area was a cause or consequence of the headache. It may be that brainstem activation during attacks is due to neuronal discharge when the meninges are stimulated (Moskowitz, 1993) rather than from activation of trigeminal afferents. In any case, the brainstem appears to be part of a neural circuit; the abnormality in those with migraine may feasibly extend beyond the brainstem.

Neurogenic inflammation

During a migraine attack an inflammatory process (neurogenic inflammation) may occur at the site of trigeminal nerve terminals. Neurotransmitters within nociceptive pain fibres, glutamate and the neuropeptides substance P, calcitonin gene-related peptide (CGRP), and neurokinin A, are released from trigeminal nerve sensory terminals. These neuropeptides may activate mast cells, endothelial cells, and platelets. In turn, other extracellular chemical mediators (e.g., amines, metabolites) are released. This chemical cascade of activated cells and injured tissue leads to hyperalgesia and pain, and stimulation of an early immediate response gene c-*fos* in the trigeminal nucleus caudalis of the brain stem (Moskowitz, 1993; Silberstein, 2003). The central convergence of the ophthalmic branch of the trigeminal nerve and branches of C2 nerve roots in the brain stem possibly explains why head pain is typically located over the frontal and temporal regions of the head, and referred pain is experienced in parietal, occipital and upper cervical areas (Angus-Leppan, Lambert and Michalicek, 1997; Goadsby, Lipton and Ferrari, 2002).

In the present study, migraine sufferers were more sensitive to painful stimulation of the temple with ice than were controls, and more readily developed headache. As the trigeminal sensory system and neurogenic inflammation has been linked to head pain (Moskowitz, 1995), perhaps this inflammatory response played some part in eliciting the headache and hyperalgesia observed in migraine sufferers in the present study. In any case, painful stimulation of the temple may have led to activation of afferent fibres of the trigeminal ganglion. Subsequently, second-order neurons in the trigeminal nucleus caudalis (TNC), and regions involved in the processing and perception of pain (thalamus, PAG and cortex), may have been activated. Findings may also indicate that descending pathways that facilitate pain are dysfunctional in migraineurs, and may provoke trigeminal neuronal hyperexcitability (Pietrobon and Striessnig, 2003), or pathways that suppress pain may fail (Burstein, 2001).

Hyperexcitable nociception in migraine sufferers

Hyperalgesia has been observed during migraine headache (Burstein, Cutrer, and Yarnitsky, 2000; Burstein, Collins and Jakubowski, 2004; Burstein and Jakubowski, 2004; Levy, Jakubowski and Burstein, 2004; Yarnitsky, Goor-Aryeh, Bajwa, Ransil, Cutre, Sottile and Burnstein, 2003) and interictally (Kitaj and Klink, 2005). Consistent with the notion of constant nociceptive sensitivity, Caputi and Firetto (1997) suggested that mechanical hyperalgesia, seen in the interictal period, of the emergence points of the supraorbital and greater occipital nerves in migraine sufferers, is a sign that extracranial perivascular nociception is constantly sensitive with consequent central hypersensitivity. They found that the frequency and intensity of headache attacks in migraine sufferers was alleviated following analgesic blockade of these epicranial nerves, particularly in individuals sensitive to pressure at these points. They considered that this constantly sensitized state might be the basis of the trigger for the migraine crisis. Mechanical hyperalgesia in remote areas of the skin has also been relieved following the control of similarly focused nociceptor discharge (Penfield, 1932). Caputi and Firetto (1997) proposed that the analgesic nerve block reduced peripheral sympathetic activity (perivascular) and that this response represented a normalization of the excitability threshold to endogenous and/or exogenous migraine triggers. Consistent with this premise, Goadsby (2001) suggests that the source of pain in migraine is probably more to do with the "abnormal perception of the normal" than the activation of nocieptive pathways in the usual way that pain is generated, e.g., photophobia is normal light exaggerated, phonophobia is normal sound amplified.

In the present study symptomatic responses were enhanced in migraineurs interictally, suggesting that neural pathways were excitable.

Key points: role of the trigeminal nerve in the development of symptoms in migraine sufferers

This study demonstrated that migraine sufferers were particularly sensitive to ice-induced stimulation. Headache and nausea developed in migraineurs during this procedure but not in controls. The findings suggest that nociceptive pathways were more reactive in migraine sufferers, while the concurrent development of nausea implies a specific link with head pain.

Hyperexcitablity in trigeminal and other brain stem nuclei in migraine sufferers interictally

In the present study, symptomatic responses including head pain, nausea and dizziness were enhanced in migraine sufferers in the headache-free interval, during OKS and temple pain. It appeared that particularly in migraine sufferers, temple pain activated trigeminal nuclei (leading to head pain) and OKS activated vestibular nuclei (leading to dizziness) and, in turn, the "vomiting center" (leading to nausea). Symptomatic ratings were also greater in migraine sufferers than in controls in the absence of painful stimulation of the temple during OKS (OKS alone). Collectively, these findings suggest that trigeminal and other brainstem nuclei are hyperexcitable in migraineurs between headaches.

For both groups, symptomatic responses tended to be greater during OKS and painful stimulation of the temple, than painful stimulation of the limb during OKS or OKS alone. Also, responses tended to be greater when the temple was painfully

stimulated after OKS than before OKS, which probably reflected residual motion sickness from the preceding OKS.

The development of symptoms during trigeminal nerve stimulation in the presence of OKS, and in the presence of residual motion sickness, are discussed next. Sensory hyperacuity in migraine sufferers, and possible mechanisms accounting for hypersensitivity, such as neural wind-up and hypersensitive thermoregulation are also considered. Finally, this section of the discussion concludes with an overview of key points relevant to brain stem hyperexcitability in migraine sufferers.

Symptoms developed more readily in migraine sufferers than in controls when the trigeminal nerve was painfully stimulated during OKS

As hypothesized, symptomatic ratings generally were greater in migraine sufferers than in controls when the temple was painfully stimulated during OKS. Headache, particularly, was greater in migraine sufferers when ice was applied to the temple during OKS than during OKS alone. Neuronal events mediating the headache phase of migraine are believed to involve the trigeminovascular system and its central projections (Welch, 2003). In the present study it may be that this circuitry was somehow activated in migraineurs during OKS in the absence of painful stimulation, and painful stimulation facilitated this response (Ashkenazi et al., 2005).

Headache developed comparably during OKS + painful stimulation in migraineurs, regardless of the source of pain (temple or hand), suggesting that pain processing may be generally compromised in this group. Saito et al. (2006) investigated limb pain in childhood in a family of migraine sufferers and observed that limb pain was often provoked by cold conditions. During limb pain levels of the neuropeptides calcitonin gene-related peptide (CGRP) and substance P (SP) were elevated. They suggested that an abnormal release of these transmitters in vascular walls in the extremities might be crucial in the pathophysiology of limb pain, similar to the case of the trigeminovascular explanation for migraine. These findings imply that pain perception may be generally compromised in migraine sufferers. Neuropeptide release in response to cold

stimulation was not measured in the current study. Nevertheless, the enhanced limb pain observed in migraine sufferers may reflect hyperexcitable nociception in the interictal period.

Ratings of overall unpleasantness were also heightened in migraineurs, probably because symptoms developed more readily in this group.

Symptoms develop more readily in migraine sufferers than in controls during trigeminal stimulation in the presence of residual motion sickness

As discussed, activation of the trigeminal sensory system has been linked to head pain and nausea during attacks of migraine (Dalhlof and Hargreaves, 1998; Knight, 2005). In the present study, headache and nausea increased progressively in migraine sufferers following painful stimulation of the temple in the presence of residual motion sickness, but not in controls. This may indicate dysfunction of control of nociception in the trigeminal brainstem nuclear complex in migraine.

Clearly, migraineurs, between attacks of migraine, were more sensitive than controls to painfully cold stimulation of the temple in the presence of residual motion sickness. Not surprisingly, as symptomatic changes generally were greater in migraine sufferers, overall unpleasantness was enhanced for this group. Activation of the trigeminal sensory system and neurogenic inflammation has been linked to head pain (Moskowitz, 1995) and nausea during migraine attacks (Dalhlof and Hargreaves, 1998; Knight, 2005). The development of these particular symptoms, and the heightened pain reported in the present test by migraineurs, suggest that the trigeminal system remains hyperexcitable in the interictal period.

Drummond (2002) similarly found that nausea increased and headache persisted after OKS more so in migraine sufferers, interictally, than in controls. Furthermore, pain in the fingertips, assessed using a pressure algometer, increased more in migraineurs after OKS. However, contrary to the present study, scalp tenderness, also assessed using an algometer, but applied to the forehead, was comparable between groups after OKS. In an earlier study, Drummond (1987) found that scalp tissue was tender in migraine and

tension headache patients during headache and this persisted for several days after headache had subsided. During the headache-free interval scalp sensitivity did not differ from controls. Drummond proposed that a disruption in central pain processing in the trigeminal system might account for scalp tenderness during headache. Hyperalgesia in the fingertips of migraine sufferers in the presence of residual motion sickness may indicate a spread of sensitization from trigeminal nuclei (Drummond, 2002), in the same way that sensitization spreads during a migraine attack (Burstein, 2000). Drummond's earlier findings, similar to findings in the present study, suggest that a dysfunction of processing nociception in the trigeminal brainstem nuclear complex may contribute to the migraine predisposition.

Headache and nausea generally were greater when the temple was painfully stimulated after OKS than before OKS, particularly in migraine sufferers, most likely due to residual motion sickness from the preceding OKS.

Sensory hyperacuity in migraine

Drummond (1986) found that light- induced glare and pain ratings were greater in migraineurs and tension headache sufferers during the headache-free interval than in controls. In addition, photophobia increased in migraine sufferers during painful stimulation of the forehead with ice (Drummond and Woodhouse, 1993) and mechanical stimulation of the nose and neck (Drummond, 1997). Interestingly, he found in an earlier study (Drummond, 1987) that tenderness in the forehead and temples in response to algometer pressure was greatest in migraine and tension headache sufferers who reported most light-induced pain. He suggested that hyperexcitability of trigeminal pain pathways persists subclinically in migraine sufferers between episodes of headache. Trigeminal nerve discharge probably contributes to photophobia in migraine; and during headache, visual and trigeminal input could interact to exacerbate pain (Drummond, 1986, 1997). Similarly, Main, Dowson and Gross (1997) found that migraineurs were more sensitive to light and also sound in the headache-free interval than were controls. They proposed that a central-processing mechanism might make migraineurs more sensitive to light, sound and possibly other sensory stimuli.

In the present study trigeminal thermal nociceptors appeared to be more sensitive in migraineurs interictally than in controls to extremely cold sensory provocation. Specifically, ice-induced intensity and upleasantness, headache and overall unpleasantness were enhanced in the migraine group. However, enhanced responses in migraine sufferers may also reflect a difference in reporting style. This possibility is discussed later in this chapter ("psychophysical report of pain", pages 338-339).

Neural wind-up

In migraineurs symptomatic responses developed during and persisted, largely, after the procedures. Headache, in particular, increased progressively throughout the recovery period. The gradual amplification of headache in the present study may reflect a neural "wind-up" phenomenon (Bray, Cragg, MacKnight and Mills, 1999; Dallel et al., 1999), which was initiated during OKS.

Dallel, Duale, Luccarini and Molat (1999) demonstrated a progressive "wind-up" response of spinal trigeminal nucleus oralis convergent neurons during repetitive supramaximal percutaneous electrical stimulation. Elsewhere (Katsarava et al., 2004) central antinociceptive mechanisms were investigated using the "nociceptive" blink reflex (nBR) following administration of acetylsalicylic acid and zolmitriptan in migraineurs and healthy controls. Katsarava found nBR responses were not blocked in controls, or migraineurs interictally. However, responses were suppressed in migraine sufferers during an attack, suggesting that antinociceptive effects of migraine-specific drugs on trigeminal pain processing are different during and outside of headache.

Hypersensitive thermoregulation in migraine sufferers

Facial pallor (decreased blood flow) and cold sweating is typically associated with motion sickness and migraine (Marcus et al., 2005). In this study, perceived increases in body temperature, coupled with enhanced vasodilatation, were greater in migraine

sufferers than controls, particularly during OKS alone. On the other hand, although vasodilatation was observed in controls, body temperature remained at a comfortable level throughout testing. Kolev et al. (1997) suggest that feelings of warmth (accompanying vasodilatation) reported during motion sickness, may reflect passage of blood through arterio-venous anastomoses (part of the infrastructure of microcirculatory blood flow), which play a role in thermoregulation. This association (microcirculation/thermoregulation) may explain the perception of elevated body temperature observed in migraine sufferers. It may be that migraineurs are hypersensitive to changes in blood flow, particularly through cranial vessels.

Key points: hyperexcitability in trigeminal brain stem nuclei in migraine sufferers

Symptomatic responses generally were enhanced in migraine sufferers interictally during temple pain in the presence of OKS, and during temple pain in the presence of residual motion sickness. Perhaps atypical responses in this group are an indication that sensory processing in the trigeminal brain stem nuclear complex is compromised in migraineurs.

Interaction between head pain and nausea

Symptoms associated with migraine headache, other than head pain, include nausea, photophobia, phonophobia, osmophobia, fatigue and numerous disturbances in autonomic, mental, sensory and motor functions (Burstein, 2001). In the present study, in addition to the development of headache, migraine sufferers experienced nausea in response to painful stimulation of the temple.

Specifically, migraine sufferers developed nausea in the presence of head pain, suggesting a susceptibility to gastrointestinal sensations in this group. However, controls remained asymptomatic. Abdominal migraine is associated with nausea and vomiting and typically occurs in infancy, childhood, and adolescence (IHS classification, 2004), then apparently evolves into more typical migraine during puberty and early adulthood (Blau and MacGregor, 1995; d'Onofrio, Cologno, Buzzi, Petretta, Caltagirone, Casucci and Bussone, 2006). Recently, d'Onofrio et al. (2006) described a rare case of an adult woman who fulfilled the diagnostic criteria for late onset abdominal migraine. Abdominal pain attacks began in her adolescence and persisted until age 21. Thereafter she experienced migraine head pain accompanied by nausea, photophobia and phonophobia. However, the transition of childhood abdominal migraine to adult migraine and abdominal migraine as a feature of adult migraine has been challenged. Blau and MacGregor (1995) claim that in the majority of migraine sufferers there is an absence of abdominal discomfort during a migraine attack, which led them to conclude that abdominal pain is not a feature in adult migraineurs. Despite these contrary views, the link between gastrointestinal disturbance and head pain in migraine is certainly well documented (Blau, 1993; Botney, 1981; Olesen, 1978; Rasmussen, Jensen and Olesen, 1991).

An association between head pain and nausea was observed in children with a history of migraine (Jan, Camfield, Gordon and Camfield, 1997). After mild head injury these children were more likely to vomit than children without a history of migraine. The experience of visceral pain has also been associated with nausea. There is a higher incidence of postoperative nausea and vomiting following intra-abdominal operations (Andrew, 1992; Mitchelson, 1992) and during radiation therapy if the abdomen is irradiated (Gerstner, 1960). This is possibly because afferent pathways to the vomiting centre are activated following the handling of viscera during operative procedures, or because of tissue damage to viscera following radiation therapy (Mitchelson, 1992). Additionally, head irradiation may raise intracranial pressure from local oedema and inflammation (tissue damage), which then appears to stimulate nausea and vomiting. The administration of glycerol following head irradiation reduced intracranial oedema and controlled the emetic response (Tourtellotte, Reinglass and Newkirk, 1972). Specifically,

the pathway involved in visceral nociceptor-induced nausea and vomiting may include activation of visceral afferents, which subsequently activate the nucleus tractus solitarious (NTS) (Barber and Yuan, 1989) and reticular formation (Blair, 1985) of the brain stem. Neural information from these areas is relayed to the cerebral cortex for conscious perception.

It is believed that nausea and vomiting develop in migraine headache because of close reciprocal functional interconnections between the trigeminovascular system and the NTS (Knight, 2005). In the present study, migraine sufferers initially developed headache following painful stimulation of the temple before OKS. Nausea gradually developed as the procedure progressed. It is conceivable that painful stimulation in the interictal period may have triggered nausea via trigeminovascular activation, as could occur in a migraine attack. Since 5-HT specific antimigraine compounds alleviate nausea and headache, this may indicate an action via the 5-$HT_{1B/1D}$ receptors in the NTS (Hoskin, Lambert and Donaldson, 2004).

Observations during limb pain:

This section initially explores enhanced symptomatic responses in migraine sufferers during limb pain + OKS. The discussion then focuses on heightened pain perception reported by this group compared to controls in relation to aspects of nociception and central pain modulation involved in the experience of pain.

Symptoms generally developed more readily in migraine sufferers than in controls when the hand was painfully stimulated during OKS

Nausea, headache, dizziness, perceived body temperature increases, visual illusion and self-motion developed more so in migraine sufferers than in controls when the hand was immersed in ice-water during OKS. Migraine sufferers reported low-grade headache and drowsiness even prior to the procedures. Throughout the procedures headache increased progressively but drowsiness did not develop further. In contrast, controls remained virtually symptom free throughout, apart from slight dizziness, visual illusion and self-motion. It appears that OKS induced motion sickness, at least in migraine sufferers.

Pain perception was greater in migraine sufferers than in controls

For both groups symptomatic responses barely developed throughout testing when the hand was immersed in ice-water. However, participants reported moderate overall unpleasantness, particularly during actual immersions. Pain attributed directly to the ice-water, however, was greater in migraine sufferers than controls.

When immersion of the hand was combined with OKS, similarly, both groups reported the experience was unpleasant. However, this was greater in migraine sufferers than in controls. After the procedures migraineurs continued to experience unpleasantness, probably because they remained symptomatic. Conversely, in controls, symptomatic responses, which were minimal, and associated unpleasantness, subsided quickly. Both groups found the ice-water painful. However, pain was greater in migraine sufferers, which may reflect hyperexcitable nociception in this group interictally.

Consistent with this possiblity, cutaneous allodynia has been observed distant from the referred pain area of the head during migraine headache (Burstein, Collins and Jakubowski, 2004; Burstein, Cutrer, and Yarnitsky, 2000; Burstein and Jakubowski,

2004; Levy, Jakubowski and Burstein, 2004; Yarnitsky, Goor-Aryeh, Bajwa, Ransil, Cutre, Sottile and Burstein, 2003) and interictally (Kitaj and Klink 2005).

Nociception

It is possible that neural mechanisms that generate pain perception are hypersensitive in migraine sufferers (Woolf, 2003) even if, as Rachman and Eyrl (1989) propose, migraine sufferers magnify the real extent of pain qualities on recall. Hyperalgesia (Silberstein, 2003) and cutaneous allodynia (Burstein et al., 2004; Burstein et al., 2000; Burstein and Jakubowski, 2004; Levy et al., 2004; Yarnitsky et al., 2003) have been observed in migraine sufferers beyond the referred pain area of the head, particularly during a migraine attack. The Burstein group rationalize that during a migraine attack the intense volley of sensory impulses on second-order sensory neurons in the brainstem causes them to become sensitized and to facilitate pain transmission from the periphery to the central nervous system. Cutaneous allodynia has also been observed interictally (Kitaj and Klink, 2005) and, recently, dynamic (brush) and static (pressure) mechanical stimulation of the posterior neck and inner forearm evoked cutaneous allodynia and referred pain to the usual side of migraine headache was detected in a woman between attacks of migraine (Ashkenazi, LoPinto and Young, 2005). Ashkenazi et al. suggested that the cutaneous allodynia in this individual might be constant as they found it to occur between attacks. Hence, it is conceivable that the enhanced reactions to limb pain in migraineurs observed in the interictal period in this study may also be because of persistent hypersensitive nociception.

Central pain modulation

Migraine sufferers were more sensitive than controls to painfully cold stimulation. It is likely that cold stimulation stimulated A-delta and unmyelinated C fibres (Bray et al.,

1999; FitzGerald and Folan-Curran, 2002). Melzack and Wall (1965) originally proposed that pain (A-delta, C fibres) and pressure (A-beta) fibres interact to either inhibit or excite neurons in the anterolateral system, leading to the suppression or production of pain. However, evidence for this theory has been disputed, even by Melzack himself (see Schneider and Tardis, 1986 for a review of the literature). Nevertheless, Schneider and Tardis point out that one of the main premises of the Melzack-Wall theory, the capability of the nervous system to either augment or inhibit the perception of pain, has been demonstrated with therapeutic techniques – e.g., distracting music in a dentist's chair lessens the pain intensity of the dentist's drill, or pain relief via acupuncture needles. Melzack and Wall (1965) explain that this kind of stimulation activates areas of the brain including those involved in audition, emotion and memory. The reticular formation receives this information which then triggers impulses that travel down the spinal cord to the substantia gelatinosa. Neuronal activity in the anterolateral system is then suppressed, thereby closing a spinal "gate", shutting off the perception of pain. Barker and Barasi (2001) point out that while Melzack and Walls' "gate theory" demonstrates how segmental counter irritation with non-painful stimuli "gates out" painful stimuli, supraspinal input can also "gate out" noxious stimuli.

More recent research has further demonstrated that there is a central descending pain suppression circuit which explains the action of analgesic agents, e.g., drugs, acupuncture, and placebos (Schneider and Tardis, 1986). Also, Diffuse Noxious Inhibitory Controls (DNIC) have been demonstrated to alter the expression of pain (Dallel et al., 1999). These are potent and enduring inhibitory controls that modulate the activity of convergent neurons. They can be triggered via conditioning nociceptive stimuli applied distant from the vicinity of the excited neuron. DNIC are mediated by a supraspinal loop (Morton, Maisch and Zimmerman, 1987) and play a role in pain modulation in humans and animals (Villaneuva and Le Bars, 1995). Chemical mediators involved in DNIC are opioid peptides and serotonin (Chitour, Dickenson and LeBars, 1982; Le Bars, Chitour, Kraus, Dickenson and Besson, 1981).

Dallel et al. (1999) found that activity of the spinal trigeminal nucleus oralis convergent neurons can be suppressed by noxious heat stimulation of the tail in rats, and that enduring post-stimulus effects follow this. These neurons have similar

characteristics to those of the spinal trigeminal nucleus caudalis and the spinal dorsal horn. The convergent neurons of these structures are indirectly activated by cutaneous C fibre discharge. Interestingly, Bouhassira, Chollet, Coffin, Lemann, Le Bars, Willer and Jian (1994) found that painful visceral stimuli involving distention of the stomach via an inflated balloon, inhibited the spinal nociceptive RIII reflex, a somatic nociceptive flexion reflex obtained via painful stimulation of the sural nerve. Bouhassira et al. suggest that painful visceral stimulation activated DNIC in the same way that nociceptive somatic stimulation activates DNIC.

Alternatively, the "gate theory" (Melzack and Wall, 1965; Venes, 2001), a system analogous to DNIC, suggests that pain is hindered from reaching higher levels of the central nervous system by the stimulation of larger sensory nerves (Venes, 2001; Waxman, 2003). For instance, as spinal nerves are composed of a higher proportion of unmyelinated C fibres than the trigeminal nerve (Young, 1977), C-fibre input would probably dominate in spinal nerves. The neural pathway for pain suppression comprises the periaqueductal gray, nucleus raphe magnus, dorsolateral column, spinal cord and the anterolateral system. The intense pain provoked by painful stimulation of the hand in this study, may well have excited a greater ratio of C-fibres than did the trigeminal nerve during painful stimulation. This bias perhaps inhibited more minor symptoms of motion sickness such as perceived increases in body temperature. This notion may be worthwhile exploring further, and is discussed later in this chapter (Further research, page 265).

Key points: effects of painful stimulation of the limb in the development of symptoms in migraine sufferers

Migraine sufferers more readily developed symptoms during limb pain + OKS, than controls. The enhanced pain perception reported by this group during limb pain, irrespective of OKS, suggested that nociception may generally be compromised in migraine sufferers.

Psychophysical report of pain

Whether heightened ratings of discomfort were an accurate account of the sensory experience of migraine sufferers or an effect of response bias is uncertain. However, Rachman and Eyrl (1989) found that chronic headache sufferers tend to magnify the real extent of pain as they recalled episodes as more painful than they had reported at the time of the pain. Other researchers (Ferguson and Ahles, 1997) found that pain-patients, including chronic headache sufferers who reported high levels of "private body consciousness", e.g., "I can feel my heart beating", "I know immediately when my mouth gets dry", reported more imagined pain than those reporting low levels of "private body consciousness". Asmundson, Norton and Veloso (1999) similarly found that patients with recurring headache who were high in "anxiety sensitivity" reported greater levels of distress in response to pain. Ferguson and Ahles (1997) suggested that "private body consciousness" and "anxiety sensitivity" might be similar constructs. Individuals reporting high levels of these characteristics may, in turn, have heightened sensitivity to noxious stimulation and so report higher levels of pain.

Fear of pain in patients with recurrent headaches has also been found to play a role in psychological distress and disruption of lifestyle activities (Hursey and Jacks, 1992). It may be that migraine sufferers tend to over report discomfort due to fear of developing symptoms associated with a migraine attack. Fear or anxiety regarding the onset of pain and other symptoms may have influenced migraine sufferers' self-report in the present study. Therefore, fear of pain needs to be considered when interpreting differences between groups. On the other hand, Ferguson and Ahles (1997) found that controls did not differ from pain patients on "private body consciousness", suggesting that "private body consciousness" is a dispositional variable and not necessarily a condition that develops after chronic pain onset. Perhaps then, the enhanced symptomatic ratings seen in migraine sufferers in the present study may reflect a real sensory experience.

Pain is both a sensory and affective experience (Venes, 2001). It involves not only the physical perception of a painful stimulus (usually triggered by activation of peripheral nerves) but also the emotional response to that perception (Silberstein, 2003). Hursey and Jacks (1992) investigated the influence of fear of pain on nociceptive intensity of the

pain stimulus. They found that chronic tension headache sufferers displayed greater fear of (imagined) severe and medical pain and lower fear of minor pain; and that fear of pain was related to impact on life (disruption of activities) rather than to frequency, duration and/or severity of headache. Non-headache controls made less sharp distinctions between types of potentially painful situations. Rachman and Eyrl (1989) studied individuals suffering recurrent painful episodes (headache or menstrual) and cautioned there is a tendency for sufferers to recall episodes as more painful than they had reported at the time of the pain. They suggested that this may serve a protective function. In regard to Hursey and Jacks' study, the magnification of the real extent of pain needs to be considered in interpreting differences between groups.

On the other hand, Bishop, Jeffrey, Borowiak and Wilson (2001) compared migraine sufferers with tension headache sufferers and headache-free controls by correlating anxiety/fear of pain with pain thresholds and tolerance levels to a cold pressor task. They found, somewhat contrary to Hursey and Jacks' (1992) findings, no differences between groups on pain related anxiety (escape and avoidance, fearful appraisals of pain, and physiological anxiety symptoms associated with pain). Despite these contradictory reports, it may be that in the present study the enhanced reaction to ice-water pain in migraineurs was because the stimulus was severe enough to instill fear of the pain (as predicted by Hursey and Jacks) that was greater than, or boosted the actual intensity of the painful stimulus (as proposed by Rachman and Eyrl, 1989). Participants in this study, unlike the tension headache sufferers in Hursey and Jacks' study, may be a more sensitive group due to their migraine experience, so fear may also be related to frequency, duration and severity of headache as well as to the disruptive impact of headaches on normal activities.

13.2. PULSE AMPLITUDE

Discussion of findings

Vascular responses may have been mediated by the following mechanisms:

1. Defense response
2. Frontotemporal vascular response to ice applied to the temple
3. Faulty pain processing in migraine sufferers may have affected pulse amplitude generally

These mechanisms are discussed next.

Defense response

Facial pallor is usually associated with motion sickness (Marcus et al., 2005), suggesting decreased blood flow. However, blood flow in deeper dermal vessels increased during procedures in the present study including OKS induced motion sickness. Pulse amplitude increased for both groups during OKS alone but more so in migraineurs than in controls. Kolev, Moller, Nilsson and Tibbling (1997) also observed an increase in blood flow in the forehead during motion sickness, measured by laser doppler flowmetry. Elsewhere, motion sickness provocation led to increases in skin oxygen and flushing, an index of blood flow, in susceptible individuals (Harm, Beatty and Reschke's study cited in Harm, 1990). However, decreases in flow were observed in the fingertips (Cheung and Hofer, 2001; Cowing et al., 1986; Kolev et al., 1997). Kolev and colleagues suggested that different densities of sympathetic innervation and skin vasculature in the fingertip and forehead may account for this variation. Carrive and

Bandler (1991) observed that blood flow redistributed between head and limbs at the onset of defensive reactions in cats provoked by injection of an excitatory amino acid into the lateral periaqueductal gray (PAG). Extracranial vasodilatation was evoked at the onset of threat displays (presumably to assist muscle tone in the face) but increases were not observed in the hindlimbs until flight behaviour developed (to assist muscle tone in the limbs/body).

A similar vascular defense response may occur in humans when exposed to noxious and stressful motion sickness provocation procedures: i.e., confrontation with the 'threat' component of the defense response. The blood flow variations between forehead and finger during rotation, observed by Kolev et al. (1997) may reflect this 'threat' response. This reaction may also account for the extracranial vasodilatation observed in the present study. In Kolev and colleagues' study, pulse volume returned to baseline levels following rotation (as did other autonomic responses: heart/respiration rate). In the present study pulse volume did not recover in migraine sufferers after termination of OKS, particularly during OKS alone. However, procedural differences between the present study and Kolev's study make a direct comparison of findings difficult. In Kolev's study participants were exposed to eccentric vertical axis rotation and blood flow was measured by laser Doppler flowmetry. In contrast, in the present study participants were exposured to OKS, and pulse amplitude was assessed via photoelectric plethysmography.

The midbrain PAG is involved in the mediation of defensive behaviour, including modulating fear and anxiety and autonomic and cardiovascular responses (Behbehani, 1995). Therefore, the enhanced vascular responses observed in migraineurs in the present study during OKS in the absence of painful stimulation (OKS alone) and during painful stimulation before OKS, regardless of the source of pain, may indicate disrupted PAG control (hyperexcitable neural responses or weak inhibitory mechanisms).

To follow, the discussion explores the potentially stressful effects of procedures used in the present study. Specifically, the defense response is discussed in relation to the trigeminovascular reflex, and vascular responses during OKS and stressful procedures generally.

Trigeminovascular response as a possible defense response

Just as nausea and vomiting is believed to be an instinctive defense response to a possible toxin (Endo et al., 2000; Mitchelson, 1992), the trigeminovascular response (with associated neurogenic inflammation) has been suggested as a defense mechanism (Lewis, 1937; Moskowitz, 1991). Disturbances in the brain or its blood supply (metabolic changes or circulating factors) may be responsible for triggering neurogenic inflammation (Buzzi, Bonamini and Moskowitz, 1995). Neurogenic inflammation involves a surge of vasoactive neurotransmitters (substance P, neurokinin A, calcitonin gene-related peptide) causing vasodilatation and tissue edema, extra- and intracranially, which leads to vasodilatation, the development of hyperalgesia and possibly the prolonged pain associated with a migraine attack (Moskowitz, 1993). In this regard, Buzzi and others (1995) suggest that headache may be considered a consequence of threatened injury to the brain. It is also possible that symptoms typical of a migraine attack develop because of anatomical connections between the trigeminal system and autonomic structures in the brainstem.

Defense response during OKS

In the present study the enhanced vasodilatation observed in migraineurs during OKS alone may, indeed, serve a protective function in response to the unpleasant (and familiar in terms of the migraine experience) symptoms of motion sickness. Whatever the mechanism, the continued vasodilatation observed in migraineurs during recovery

may demonstrate a neural or vascular hypersensitivity/ "wind-up" (Bray, Cragg, MacKnight and Mills, 1999) that amplifies neurovascular responses.

Contrary to expectations, vascular reactions in response to painful stimulation during OKS did not differ between groups, irrespective of the source of pain. Vasodilatation developed bilaterally in both groups during OKS. It seems that the added stress of painfully cold stimulation during OKS boosted vascular responses in controls to come in line with migraine sufferers. Apparently the vasodilator stress response was activated comparably across both conditions (temple pain during OKS, hand pain during OKS), for both groups. When the temple was painfully stimulated during OKS, responses subsided in migraineurs by 5 minutes after OKS but fell below baseline in controls. When the hand was immersed in ice-water during OKS, responses recovered soon after OKS, in both groups.

Motion sickness has been found to influence the facial microcirculation (Harm, 1990; Kolev, Möller, Nilsson and Tibbling, 1997). Interestingly, in Kolev's study involving eccentric vertical axis rotation, the vasodilator effect immediately peaked at the commencement of rotation (during vestibular stimulation), even before the onset of motion sickness. The authors suggest that this may have been a stress response induced from excessive motion. Kohl (1985) points out that the stress of excess motion induces changes in circulatory hormones, including plasma levels of cortisol, ACTH, growth hormone, prolactin, vasopressin, norepinephrine and epinephrine (Eversmann, Gottsman, Ulbrecht and von Werder, 1978; Kohl, 1985).

One of the antidiuretic hormones, plasma argenine vasopressin (pAVP) is sometimes used to explore the effects of physical and psychological stress. pAVP levels have been found to increase during physical stress (Nettles et al., 2000), including after motion sickness induced-rotary stimulation (Xia, Zheng-Lin, Gho-Hua and Ji-Wei, 2005). Increased levels in antidiuretic hormone have also been observed following rotation around a vertical axis in both nauseated and unaffected subjects (Otto et al., 2005). Conversely, AVP inhibition has been observed following psychological stress (Nettles et al., 2000). It has been suggested that AVP inhibition following psychological stress may serve a protective function in anticipation of the need for AVP with physical stress (Becker, Grecksch, Bernstein, Hollt and Bogerts, 1999). Clearly,

physical and emotional aspects of the stress response, and how they may impact on one another, are intricate.

OKS involves physical (e.g., perceptual changes and the development of symptoms of motion sickness) and psychological (e.g., emotional reactions to physical changes) components of the stress response. Kohl (1985) reported that epinephrine and norepiniephrine levels were elevated during motion sickness and that non susceptible subjects displayed a more pronounced increase. In the present study the vasodilator stress response was activated comparably during OKS in the presence of painful stimulation, for both groups. Symptoms of motion sickness developed in migraine sufferers yet barely developed in controls. Thus, these findings also suggest that motion sickness provoking conditions might be considered stressful regardless of whether symptoms of motion sickness develop.

Specific brain structures appear to play an important role in the stress response including the hippocampal complex in the limbic system. Nettles et al. (2000) explored the plasma argenine vasopressin, hypothalamic-pituitary-adrenal-axis response to psychologically stressful stimuli using novel acoustic stress. In one study responses to novel acoustic stress were assessed in rats with bilateral excitotoxic lesions of the ventral subiculum and the ventral hippocampus. In another study responses were observed in relation to small lesions in the ventral hippocampal formation, which included projections to the neuroendocrine hypothalamus and other fields. These lesions blocked inhibitory AVP responses to psychologically stressful stimuli compared to healthy control rats, implying that hippocampal areas of the limbic system also play a role in the argenine vasopressin, hypothalamic-pituitary-adrenal-axis response to stressful stimuli. It is accepted that the limbic system plays an integral role in processing sensory information from the association cortices necessary for perception and movement, and also in mediating emotional responsiveness to a stimulus (Barker and Barasi, 2001). Indeed, this neural area was most likely activated during OKS in the present study. Perhaps, the various neural pathways involved in the defense response, in some combined way, contributed to the changes in facial blood flow, observed during stressful procedures in this study.

Furthermore, it is well accepted that the periaqueductal grey (PAG) is involved in the stress response and autonomic regulation (Behbehani, 1995). Bandler and Carrive (1988) administered microinjections of D.L. homocysteic acid (DLH) in the pretentorial PAG, a specific site they observed evoked a "threat display" (hisses, howls, retraction of the corners of the mouth and ears) in the freely moving cat. In a follow-up study Carrive and Bandler (1991) administered DLH into a restricted portion of the lateral pretentorial PAG in unanesthetized and paralyzed decerebrate cats and observed extracranial vasodilatation. The vasodilatation observed in the present study may have been influenced, at least in part, by the release of stress-related hormones (Eversmann, Gottsman, Ulbrecht and Werder, 1978; Kohl, 1985) triggered during the disconcerting and unpleasant OKS experience. This may reflect a defense response involving the PAG, similar to that observed by Carrive and Bandler (1991).

Stressful procedures and the defense response

Extracranial blood vessels dilate more readily in migraine sufferers than in controls during exposure to stressful stimulation (Drummond, 1984). Consistent with the notion of a general vascular dysfunction in migraineurs, Hassinger, Semenchuk and Obrien (1999) found that cardiac output increased more in migraine sufferers than in controls in response to pain-stress (cold pressor task) and cognitive-stress (arithmetic task). In the present study vasodilatation was evident in migraine sufferers even before the stressfully cold stimulus (an ice block on the temple or immersion of the hand in cold water) was applied before OKS, thereby suggesting that anticipatory anxiety provoked a defense response in this group.

Anticipation of pain and fear-avoidance has been documented in chronic back pain sufferers (Pfingsten, Leibing,Harter, Kroner-Herwig, Hempel, Kronshage and Hildebrandt, 2001), as well as in chronic headache sufferers, including those with migraine (Asmundson, Norton and Veloso, 1999; Hursey and Jacks, 1992). Stress is also a commonly sited precipitating and aggravating factor of migraine headache (Holm, Lokken and Myers, 1997; Spierings, Ranke and Honkoop, 2001). It is conceivable that

migraineurs in the present study were primed in anticipation of the pending painful stimulus, perhaps raising an association with the all too familiar pain of migraine. Hence, the vasodilator defense response probably accounted for vascular increases prior to procedures and also contributed to enhanced reactions during painful and unpleasant procedures. Conversely, in controls vasodilatation became evident from the commencement of painful procedures. The defense response perhaps influenced vascular reactions in both groups. However, the early increase in facial blood flow observed in migraine sufferers implies hyperexcitable vascular responses in this group.

Key points relevant to the defense response and pulse amplitude change

Vasodilatation was observed in both groups throughout procedures in the present study. Findings suggest, at least in part, that the defense response contributed to vascular changes.

Frontotemporal vascular response to ice applied to the temple

This section of the discussion considers trigeminovascular mechanisms, which may be responsible for changes in facial blood flow observed during painful stimulation of the temple in this study. The link between vascular changes and headache is discussed. Extracranial blood flow fluctuations normally observed in the skin are described next with respect to stressful procedures (cold stimulation and OKS) used in the present study. Sympathetic nerve activity and findings that facial blood flow is particularly reactive in migraine sufferers is explored. Whether or not motion sickness somehow disrupted vasomotor activity in migraine sufferers in the present study is also considered. Finally,

the observation that head pain does not seem to be associated with extracranial vasodilatation is made.

Trigeminovascular response in migraine sufferers

For both groups extracranial pulse amplitude increased bilaterally when ice was applied to the temple independent of OKS, but more so in migraine sufferers. Vasodilatation was evident in migraineurs even before the initial application of ice, but gradually developed in controls as the procedure progressed.

Vasodilatation of cranial vessels (extra- and intracranial) has been observed during migraine headache (Baloh, 1997; Lance, 1993; Lance and Goadsby, 2002) and has long been regarded as important in the pathophysiology of migraine symptoms (Wolff, 1972; Botney, 1981; Moskowitz, 1993). It is generally agreed that migraine is the result of brain-related changes or dysfunction within the sensory centres of the brain (Knight, 2005; Larkin, 1997). Borsook, Burstein, Moulton and Becerra (2006) describe migraine as a neurovascular disorder involving dysfunction of the trigeminovascular system. Cerebral blood vessels innervated by sensory fibres of the trigeminal nerve may dilate in response to activation of brainstem centres that regulate vascular tone and pain sensations (Buzzi and Moskowitz, 2005). The trigeminovascular system is believed to provoke a neurogenic inflammatory reaction that causes pain (Larkin, 1997; Moskowitz, 1993). Larkin (1997) and MacFarlane (1993) point out that although blood vessels become involved, the pain actually results in the release of pain-related chemicals (e.g., substance P, calcitonin gene-related peptide, and neurokinin A) via trigeminal neurons into areas surrounding the blood vessels. In the present study vasodilatation was observed in migraineurs and controls in response to trigeminal stimulation. The enhanced vascular reactivity observed in migraine sufferers suggests hyperexcitable trigeminal vascular reflexes in this group between headaches.

Link between vascular changes and headache

Headache developed more readily in migraine sufferers than in controls during all testing sessions, apart from during limb immersion in the absense of OKS. In contrast, controls remained headache-free throughout all procedures. As previously suggested, the headache observed in migraine sufferers in the present study may be due to a neurogenic inflammatory response and the release of neuropeptides, including CGRP. Plasma extravasation and vasodilatation, i.e., neurogenic inflammation, has been attributed to antidromic discharge of afferent C-fibres. In the present case, vasodilatation may have occurred in deeper cephalic tissue, e.g. meningeal vasculature, as the trigeminal nerve transmits nociceptive signals from dilated blood vessels of the pia- and dura mater (Frickle, 2001; Frickle, Andres and Von Düring, 2001; Moskowitz, 1993).

Mechanisms regulating central sensitization are thought to underlie migraine susceptiblity (Edvinsson and Uddman, 2005). Changes in environmental, physiological or psychological states are believed to trigger migraine headache in susceptible individuals. Edvinsson and Uddman outline theories that explain how a migraine attack is initiated. It may be that peripheral sensory fibres innervating the dura and cranial blood vessels are activated. Alternatively, descending pathways that process pain signals may be activated, or descending pathways that inhibit pain-processing signals in the trigeminal nuclei and spinal cord are suppressed. Buzzi, Bonamini and Moskowitz (1995) suggest that any stimulus which activates trigeminal sensory fibres activates the trigeminovascular system and leads to extra/intracranial changes in the cephalic circulation. In turn, headache and various autonomic responses occur, most likely because of close anatomical connections between the trigeminovascular system and autonomic structures in the brainstem. A local inflammatory response probably occurred following painful stimulation in the present study. However, as migraine sufferers developed headache, it appeared that trigemino sensory fibres may have activated brainstem nuclei responsible for head pain.

Edvinsson and Uddman (2005) explain that the trigeminovascular vasodilatory reflex, in part, is generated via CGRP and VIP, probably to offset cerebrovascular constriction. Walters, Gillespie and Moskowitz (1986) suggest that the trigemino-

parasympathetic vasodilator reflex in intracranial vessels may serve to defend the blood supply to the brain during inflammatory responses, or may assist in thermoregulation. Painful stimulation of the eye has evoked the trigemino-parasympathic reflex leading to extracranial vasodilatation in migraine sufferers and normal controls (Avnon, Nitzan, Sprecher, Rogowski and Yarnistsky, 2003, 2004; Drummond, 1992, 1993; Drummond and Lance, 1992).

In the present study, exposure to stressful procedures may have induced a vasodilatory stress-induced response in both groups. Migraine sufferers, however, developed headache, suggesting that the trigeminovascular system was activated, perhaps due to hyperexcitable trigeminovascular reflexes in this group.

Extracranial blood flow fluctuations

Painfully cold stimuli activate pain and temperature receptors that pass through the spinothalamic tracts to the reticular formation; consequently the descending sympathetic nervous system (SNS) is activated (Peroutka, 2004). The vasculature of the skin is under sympathetic control (Harm, 1990) and vasoconstriction is attributed to sympathetic nerve activity (Honey, Bland-Ward, Connor, Feniuk and Humphrey, 2002). The initial defense response and related blood flow increases (Carrive and Bandler, 1991) observed in the present test when the temple and hand were painfully stimulated during OKS generally appeared to subside soon after the procedures, for both groups. The disappearance of a vasodilatation response in both groups in the recovery period, and the extracranial vasoconstriction observed in controls, particularly, after the temple was painfully stimulated during OKS, may have been due to sustained activation of the SNS.

In the present study blood flow peaked bilaterally after the hand was withdrawn from ice-water in both groups. In addition, a weak bilateral vasoconstriction occurred during hand immersion in migraineurs.

Furthermore, Kolev et al. (1997) reported that blood flow in deeper dermal vessels fluctuated as motion sickness developed, i.e., peaked at vestibular stimulation, subsided, then gradually increased during epigastric awareness, epigastric discomfort and nausea,

and peaked again at retching. Kolev et al. suggested that an autonomic response resembling an unspecific stress reaction to unfamiliar sensory cues probably triggered orienting (Siniatchkin, Gerber, Kropp, Voznesenskaya and Vein, 2000; Sokolov, 1963) or startle reflexes (Sokolov, 1963). The increased facial blood flow observed in the present study at the onset of OKS may also reflect a stress response triggered in reaction to unusual sensory cues. However, vasodilatation did not peak at the onset of OKS as occurred in Kolev's study, regardless of whether or not cold stimulation was applied shortly following the commencement of OKS. Given the disparate findings between these studies, the mechanism responsible for the vasodilatatory peak at the onset of vestibular stimulation observed in Kolev's study is not clear.

Extracranial vasculature more reactive in migraine sufferers

Extracranial blood flow was generally more reactive in migraine sufferers than in controls to a range of stimuli in the present study. Specifically, vasodilatation was greater in migraine sufferers than in controls during OKS alone and during painful stimulation in the absence of OKS. However, during painful stimulation in the presence of OKS, vasodilatation was comparable for both groups. For both groups pulse amplitude remained unchanged when ice was applied to the temple after OKS. Curiously, slight vasoconstriction was observed but did not reach significant levels. During limb pain, blood flow peaked bilaterally after the hand was withdrawn from ice-water, for both groups, and a weak bilateral vasoconstriction occurred for migraine sufferers when the hand was immersed.

The vasculature of the skin is under sympathetic control. In the face, pallor is the result of vasoconstriction, and vasodilatation produces flushing. Increased sympathetic activity causes vasoconstriction, and sympathetic withdrawal or inhibition leads to vasodilatation (Harm, 1990). At high body temperatures, active sympathetic vasodilatation also augments facial flushing (Drummond and Finch, 1989).

Honey, Bland-Ward, Connor, Feniuk and Humphrey (2002) considered the role of neurochemical messengers linked to sympathetic nerve activity, which may have accounted for fluctuation in vasculature observed in their study. A transient vasoconstriction was observed in dural blood vessels following electrical stimulation of perivascular trigeminal nerves in anaesthetized rats (Honey et al., 2002). This vasoconstriction was similarly attributed to sympathetic nerve activity: the release of catecholamine neurotransmitters from sympathetic nerve stimulation. Vasodilatation followed vasoconstriction and was attributed to CGRP release from activated afferent A-delta fibres in the dura mater. The vasodilator response was not observed when Substance P was applied. Williamson, Hargreaves, Hill and Shepheard (1997) found the CGRP antagonist, human αCGRP inhibited the vasodilator response, further suggestive that CGRP mediates vasodilatation.

A peripheral cold stimulus activates pain and temperature receptors that pass through the spinothalmic tracts to the reticular formation, and activates the descending sympathetic nervous system (Peroutka, 2004). In the present study there was a lack of extracranial vasodilatation during painful stimulation of the temple in the presence of residual effects of motion sickness. The reason why the response was absent is uncertain, because the application of ice to the temple was painful and no doubt excited the sympathetic nervous system. As pointed out in an earlier chapter (chapter 12, page 239), pulse amplitude did not appear to recover in migraine sufferers during the previous procedure (i.e., OKS alone), hence data was re analysed using the baseline from the previous condition (see Appendix 12, page 362). When analysed with a different baseline it appeared that pulse amplitude increased during OKS and remained so when ice was applied to the temple after OKS, particularly in migraine sufferers. Whether or not some aspect of motion sickness disrupted vasomotor activity at a neural level in migraine sufferers is discussed next.

Headache does not appear to be related to extracranial vasodilatation

Headache developed more readily during temple pain after than before OKS in migraine sufferers but was not obviously related to extracranial blood flow changes. Clearly, headache intensified when the temple was painfully stimulated during or after OKS but vascular responses did not intensify, as might be presumed would occur if headache is indeed caused by swollen cranial blood vessels in migraine sufferers (Larkin, 1997).

Indeed, Drummond and Lance (1983) found that headache is not necessarily related to extracranial vasodilatation. Drummond and Lance compared the pulse amplitude of extracranial blood vessels with the intensity of pain during unilateral migraine headache. Pulse amplitude of the superficial temporal artery and its main frontotemporal branch were recorded with pulse transducers. They found that pain appeared to be of extracranial vascular origin in approximately one-third of patients, was of intracranial origin in one-third, and had no obvious vascular component in the remaining one-third. It appeared that extracranial vessels contributed to the pain of migraine headache in only a minority of cases.

While blood vessels are clearly involved in head pain, they appear to play a secondary role. Hence they are probably part of a more complex process that originates not in vessels, but in the brain (Larkin, 1997). As Macfarlane (1993) proposes, vasodilatation may therefore be more an epiphenomenon to sensory nerve activation, rather than the cause of it, or the subsequently observed sustained headache during an attack.

Key points: trigeminovascular reflex and pulse amplitude change

Extracranial vasculature was indeed more reactive in migraine sufferers than in controls in the present study. The development of headache in migraineurs suggested that trigeminovascular reflexes may be hyperexcitable in this group. However, head pain did not appear to be related to vascular responses as, while headache intensified, vascular responses did not.

Faulty pain processing in migraine sufferers may have affected pulse amplitude generally

The possibility that autonomic responses in migraine sufferers may be compromised, in turn, effecting vascular reactivity in this group, is discussed. Mechanisms thought to regulate cutaneous blood flow are also considered. Finally, the asymmetrical vascular response observed during limb pain is discussed.

Possible sympathetic and parasympathetic dysfunction in migraine

Possible autonomic dysfunction in migraine

Autonomic activation such as lacrimation, conjunctival injection and nasal congestion commonly observed during cluster headache, has also been observed during severe unilateral migraine headache (Frese, Evers and May, 2003). Interestingly, Frese and colleagues found that experimental head pain (subcutaneous injection of capsaicin to the forehead) also evoked autonomic symptoms in healthy controls, suggesting a normal response to trigeminal pain. This response was specific to painful stimulation of the ophthalmic branch of the trigeminal nerve. Perhaps then, autonomic signs are not an exclusive feature of some primary headache syndromes but appear secondary to painful stimulation of the opthalamic branch of the trigeminal nerve (Frese et al., 2003).

Human studies have suggested sympathetic- and parasympathetic hypofunction in migraine (Pogacnik, Sega, Pecnik, and Klauta, 1993; Havanka-Kanniaininen, Tolonen and Mylyla, 1988). Peroutka (2004) proposed chronic sympathetic dysfunction in migraine sufferers (an imbalance of sympathetic co-transmitters). Specifically, he proposed that a migraine attack involves depletion of norepinephrine (leading to vasodilatation) and increases in dopamine (related to nausea, vomiting and yawning), prostaglandins (related to increases in pain sensitivity) and adenosine (associated with sedation). Consistent with the notion of atypical sympathetic involvement in

migraineurs, increases in plasma norepinephrine levels during the cold pressor test were found to be significantly less in migraineurs than in controls (Takeshima, Takao, Urakami, Nishikawa and Takahashi, 1989).

Failure of descending pain control mechanisms involving vascular and autonomic control (Hass, Kent and Friedman, 1993; Weiller, May, Limmroth, Jŭptner, Kaube, Schayck, Coenen and Diener, 1995), and connections between pain control- and parasympathetic nuclei in the brainstem, might also contribute to migraine (Lance, Lambert, Goadsby and Duckworth, 1983; Matharu and Goadsby, 2002). Cranial parasympathetic outflow and dysfunctional pain modulation within the brainstem have been posited to intensify head pain and be responsible for extracranial vasodilator and other autonomic disturbances during attacks (Avnon, Nitzan, Sprecher, Rogowski and Yarnitsky, 2003; Drummond, 1997). Avnon et al. (2003) observed forehead vasodilatation in response to instillation of soapy water into the eye in migraineurs between attacks, which appears to be a normal response. Also, increased cranial blood levels of vasoactive intestinal polypeptide (a parasympathetic neurotransmitter) has been observed in migraine attacks associated with lacrimation and rhinorrhoea, a further indicator of parasympathetic involvement in the disorder (Goadsby, Edvinsson and Ekman, 1990).

The present findings suggest that limb pain evoked an autonomic (defense response) extracranial vasodilatation, more so in migraineurs. Furthermore, vasodilatation was greater ipsilaterally than contralaterally to painful limb stimulation in this study. Asymmetry was also observed by Drummond and Lance (1984) during migrainous attacks as heat loss was greater for unilateral headaches (on the affected side) during throbbing headache. However, the enhanced ipsilateral response seen in both groups in this study (also observed by Drummond, 2006) implies a normal systemic vasomotor reaction to immersion of the hand in ice-water. The overall enhanced response seen in migraineurs suggests a possible dysfunction originating in the midbrain or brainstem. Specifically, as the periaqueductal grey region of the brainstem has an integrative function including modulating pain transmission, fear and anxiety, autonomic and cardiovascular responses (Behbehani, 1995; Knight and Goadsby, 2001), it is tempting to speculate that this is the source of the atypical reaction observed in migraineurs.

Consistent with a hyperexcitable defense response or greater fear in migraine sufferers, the contralateral response was greater in migraineurs than controls when the hand was painfully stimulated in the absence of OKS. The ipsilateral response was similar in both groups during this procedure.

Mechanisms regulating cutaneous blood flow

In the present study, given the vasoconstrictor response during hand immersion + OKS in migraineurs, it appears that the extracranial vasculature is more reactive to stimuli in this group than in controls. It may be that low blood flow was mediated via a sympathetic noradrenergic vasoconstrictor response (for a review of the literature see Kolev et al., 1997) possibly triggered from the shock of the painfully cold immersion or it could be a specific constrictor response to cold hand immersion.

Asymmetric vascular response during limb pain

During limb pain ipsilateral responses were greater than contralateral responses, for both groups. However, application of ice to the temple did not provoke a unilateral response.

Sympathetic reactions are generally assumed to be widespread mass responses to a wide variety of stimuli (e.g., response to fear) involving simultaneous discrete activation of systems within the organism (cutaneous vasoconstriction; vasodilatation to heart, muscles and brain; sphincter contraction; peristalsis depression) (Standring, 2005). However, recent research (Drummond, 2006) challenges the concept of the sympathetic nervous system as a "mass action" system. Greater ipsilateral than contralateral extracranial vasodilatation was observed during immersion of the hand in extremely cold water. This asymmetric response was then blocked following pretreatment with guanethidine (a sympathetic noradrenergic neurotransmission blocker). Thus,

Drummond proposed that the sympathetic nervous system exerts separate control of distinct reflex pathways on either side of the body. These observations may help explain the mechanism of the asymmetric response observed in the present study (an ipsilateral release of sympathetic vasoconstrictor tone in extracranial vessels).

Pulse amplitude generally was comparable in both groups when the limb was painfully stimulated during OKS, though a constrictor response was evident in migraine sufferers during ice-water immersions. Furthermore, pulse amplitude was greater in migraine sufferers than in controls during painful stimulation of the limb before OKS, suggesting atypical autonomic vascular activity in this group.

Key points: faulty pain processing may have effected pulse amplitude

Findings suggest that limb pain evoked an autonomic (defense response) extracranial vasodilatation, particularly in migraine sufferers. Furthermore, blood flow was greater ipsilaterally than contralaterally for both groups, which may have been due to an ipsilateral release of sympathetic vasoconstrictor tone in extracranial vessels (Drummond, 2006).

13.3. General methodological issues associated with the project: strengths and limitations

Pre testing criteria

Participants needed to be 4 days headache-free, between periods of menstruation, and alcohol, nicotine and medication-free. They were also required to fast for 2 hours prior to testing. In addition to strict pre-testing criteria each session involved exposure to particularly uncomfortable procedures. Most participants returned and completed all 3 sessions despite the unpleasant nature of procedures and strict pre testing requirements. For some migraine sufferers, however, completion of the sessions was protracted due to their inability to meet testing criteria (e.g., 4 days headache-free). Additionally, some migraine sufferers developed a migraine attack post testing (refer to publications related to this book, Granston and Drummond, 2005). Consequently, for a number of these reasons some participants, particularly migraine sufferers, required considerable encouragement from the experimenter to return to complete the 3 sessions.

Extraneous procedural effects

Preliminary pilot research in the laboratory demonstrated that participants desensitized to OKS and painful procedures when the interval between repeated testing was too close. Therefore, the 3 sessions in the present study were spaced 3 to 4 weeks apart to reduce adaptation effects. This break also allowed for the time between menses required for female participants.

A shortcoming of the long interval between testing was that two subjects had to withdraw from the experiment as they commenced prophylactic anti-migraine medication between sessions (for participant details see Method, page 82-83).

Selection of procedures

Procedures used during testing were harmless and effects were transitory. To induce motion sickness OKS was selected, since exposure to the optokinetic drum is a well-established way of inducing symptoms of motion sickness in susceptible individuals (Cheung and Vaitkus, 1998). Participants were exposed to OKS for 15 minutes, a period found adequate to induce motion sickness during preliminary pilot research in the laboratory.

Ice was selected as a pain stimulus as it is harmless and also a vascular stimulus. Participants were exposed to ice for 30 seconds. This period was arbitrarily chosen as it appeared to be sufficient to induce pain. If exposure to the cold stimulus was longer or the pain stimulus was changed (e.g., heat or pressure) responses may have been different. This possibility may be useful to explore further, and is discussed shortly in section 13.4., Further research: Painful stimulation: procedural alternatives, pages 264-265.

Measurement of pulse amplitude

Recording procedures used to assess vasodilatation and constriction in the temple involved photoelectric plethysmography. This instrument measures the pumping action of the heart, and the recorded signal is commonly referred to as pulse volume or pulse amplitude (Stern, Ray and Davis, 1980). Absolute comparisons between subjects are not possible because of wide individual variations in skin characteristics. In addition, within individual variations make comparisons only relative (e.g., precise placement of the transducer from session to session may vary). Hence, changes in blood flow are commonly estimated from a baseline period, which is compared to a treatment period and is generally expressed as a percentage change from

baseline. Unfortunately, because of the relative nature of this measure, it cannot be ascertained whether or not blood vessel caliber of migraine sufferers and controls was equivalent at the commencement of the experiment. A lightproof headband was placeA lightproof headband was placed over the photoelectric pulse transducers to ensure that light transmitted from the instrument was not influenced by outside light. This covering could have influenced skin temperature from day to day depending on room temperature variations and individual responses. To minimize this possibility room temperature was maintained at a constant 22 degrees Celsius ($\pm$ 1.5^{o} C). Another limitation was that the precise placement of the transducers and headband may have varied from session to session, in turn influencing recordings. However, preparation of participants for testing was standard as the same researcher carried out procedures and recordings throughout the study.

Self-report issues

Migraine sufferers generally experienced more discomfort than controls in response to the procedures. However, due to the subjective nature of self-report data it is not certain if migraine sufferers tended to over report discomfort due to fear of developing symptoms associated with a migraine attack. It may be that there was a response bias in migraineurs; nevertheless the scales were explicit and well defined, including an option of "awareness" of symptom development. Headache developed during most procedures in migraine sufferers, apart from during limb pain before OKS, and also developed in some migraine sufferers post testing. As headache developed in response to painful cranial stimulation but not to painful limb stimulation, it did not appear to be a non-specific response to discomfort. Together, these findings suggest that headache experienced during the procedures was most likely a real account. In contrast, at no stage did headache, or even a head-awareness, develop in controls. Clearly, with regard to headache, migraine sufferers described a sensation that was not reported at all by controls.

Quantification of data

This research involved investigating many dependent variables that required the same measurements being taken several times on each subject. As a large number of statistical analyses were required, the General Linear Model (GLM) Repeated Measures procedure was selected using SPSS for Windows 11.5.0. Software. This statistic involves analysis of variance, and both univariate and multivariate analyses for repeated measures data. Between- and within-subjects factors demonstrated main effects and interactions of variables. The within-subjects design minimizes error variance (Grimm, 1993; Kerlinger, 1986) and strengthens power (Grimm, 1993). To minimize the possibility of chance findings, simple planned contrasts were used to investigate the mean of each level compared to the mean of the first or last category as the reference. Nevertheless, because of the large number of comparisons in the present study, some of the findings may still be chance effects. Therefore, important findings need to be confirmed in replication studies.

Organisation of sessions and conditions

The present project explored 6 experimental conditions over 3 sessions, 2 conditions per session. Condition 2, the application of ice to the temple after OKS, which explored painful stimulation in the presence of residual motion sickness, necessarily required the preceding procedure, OKS alone (Condition 1), to induce motion sickness. The remaining conditions did not necessarily require a preceding condition. OKS alone (Condition 1), ice to the temple before OKS (Condition 3) and hand immersion in ice-

water before OKS (Condition 5) were the first of 2 conditions conducted in separate sessions so were not preceded by another condition. The application of ice to the temple during OKS (condition 4) and the immersion of the hand in ice-water during OKS (condition 6) were preceded by a condition - ice to the temple before OKS (conditions 3) and hand immersion in ice-water before OKS (condition 5), respectively. It may be worthwhile exploring the 2 conditions involving painful stimulation during OKS independently, to minimize any possible carry-over effects from the preceding procedures. This would involve 2 further sessions on separate days which would extend the overall testing period for the entire experiment from 3 to 5 sessions.

13.4. Further research

Fear of pain

The present study provided insight into the effects of stress and pain on symptomatic and vascular responses in migraine sufferers and healthy controls. Anxiety and fear have been linked to the stress response but the relationship between anxiety sensitivity and fear of pain in determining somatic, affective and behavioural responses in recurrent headache sufferers, is poorly understood. Knowledge, specifically related to migraine sufferers, is even more limited (Asmundson, Norton and Veloso, 1999). Determining the impact of fear of pain on headache and lifestyle may be helpful in targeting treatment (e.g. cognitive-behavioural, medication management). Therefore, more research into the modulation of pain by fear in subgroups of headache sufferers is required.

The stress response

The stress response was not physiologically confirmed in this study. In order to validate the impact of stress in relation to the development of symptoms, it may be useful to measure the stress response in future research. Two possible measures might include monitioring galvanic skin responses, or respiration, possibly using techniques resembling those previously discussed employed by Yen Pik Sang, Billar, Golding and Gresty (2003) or Jokerst, Gatto, Fazio, Stern and Koch (1999).

Skin conductance activity during motion sickness appears to involve thermoregulatory mechanisms rather than emotional/arousal (Golding, 1992; Golding and Stott, 1997). It may be worthwhile exploring further these two types of skin conductance responses in relation to motion sickness in future research.

In the present study it may have been that stress associated with OKS exposure led to increased breathing and increased sympathetic nervous system activity, thereby contributing to the development of symptoms of motion sickness (as suggested by Jokerst et al., 1999). Alternatively, increased sympathetic nervous system activity might be determined by measuring the release of stress hormones, as Koch, Stern, Vasey, Seaton, Demers and Harrison (1990) found that levels of norepinephrine, epinephrine, cortisol and β-endorphin were elevated during OKS.

Neuropeptide release

In the present study headache developed comparably in migraine sufferers irrespective of whether the temple or hand was painfully stimulated during OKS. Neuronal events mediating the headache phase of migraine are believed to involve the trigeminovascular system and its central projections (Welch, 2003). As previously discussed, it may be that in the present study this circuitry was somehow activated in migraineurs during OKS in the absence of painful stimulation, and painful stimulation facilitated this response (Ashkenazi et al., 2005).

In addition to headache, vasodilatation was experienced in migraineurs in the present study. The vasoactive parasympathetic messenger vasoactive intestinal peptide (VIP) and the sensory trigeminal messenger CGRP have been detected during migraine headache and also during chronic paroxysmal hemicrania and cluster headache (Edvinsson and Goadsby, 1995; Edvinsson and Uddman, 2005; Goadsby and Edvinsson, 1996). However, while these peptides appear to be a marker for migraine activity, without a blood assay it cannot be be determined whether their release contributed to vasodilatation in the sub group of migraineurs in the present study.

Saito et al. (2006) found that levels of the neuropeptides calcitonin gene-related peptide (CGRP) and substance P (SP) were elevated during limb pain in childhood in a family of migraine sufferers. They suggested that an abnormal release of these transmitters in vascular walls in extremities might be crucial in the pathophysiology of limb pain, similar to the case of the trigeminovascular explanation for migraine.

Neuropeptide release in response to cold stimulation was not measured in this study. Nevertheless, the enhanced limb pain observed in migraine sufferers may reflect hyperexcitable nociception in the interictal period as Ashkenazi et al. (2005) observed. In addition, as headache ratings were greater during temple pain than during limb pain, it may be that neuropeptide release associated with the development of migraine headache was greater when the temple was painfully stimulated in migraine sufferers. In contrast, controls remained headache-free over all three conditions. It may be helpful to measure neuropeptide release in response to cold stimulation in future research to determine if indeed neuropeptide release associated with the development of migraine headache differs during both types of painful stimuli.

Quality of pain

In the present study, both groups anecdotally reported a dull aching cold pain consistent with the concept of Ochoa and Yarnitsky (1994), of dual activation of A and C fibres in the sensation of cold pain. The experience of pain was more intense and unpleasant in migraine sufferers, indicating hypersensitive nociception in this group but

the quality of pain was not formally measured. It may be worthwhile measuring pain quality in future research to determine if dual activation of A and C fibres in the sensation of cold pain (Ochoa and Yarnitsky, 1994) occurred, or if blocking A fibres left C-fibre activity unopposed. In turn, this may shed light on understanding the hypersensitive response to painfully cold stimuli observed in migraineurs in the present study, and the neural mechanisms involved in pain processing.

Painful stimulation: procedural alternatives

In the present study participants were exposed to painfully cold stimulation for periods of 30 seconds. A lengthier exposure time to painfully cold stimuli, or a different (e.g., mechanical, chemical, electrical, heat) or more intense painful stimulus, may have elicited a different response. For instance, if early warning nociceptive pain is overwhelmed, instead of a defense response (e.g., Carrive and Bandler, 1991) or a withdrawal response to prevent tissue damage, severe trauma may occur (Woolf, 2003). In this case, a retreat response to recover from injury is more probable.

Stress induced analgesia appears to be associated with intense and extended noxious stimuli. This response may lessen the impact of the stressor so that the organism may defend itself against potentially life threatening events. Bandura, Cioffi, Taylor and Brouillard (1988) found that individuals became more distressed and opioid activation increased when they perceived pain could not be managed effectively in response to a cold pressor task.

There are 2 kinds of pain, visceral and somatic, and 2 kinds of sensations, painful and non-painful (Bray et al., 1999; Nicolodi, Sicuteri, Coppola, Greco, Pietrini and Sicuteri, 1994). The present study involved painful stimulation of nociceptors in the skin - somatic pain. Nicolodi et al. injected hypertonic saline into the antecubital vein of the arm – visceral pain, which produced considerable, and in some cases unbearable, pain in migraine sufferers but not in controls. Based on these findings Nicolodi et al. suggested that migraine might be a visceral sensory disorder, consistent with the theory that migraine pain is due to central derangement of the viscerosensory system. Migraine is

thought, in part, to involve inflammatory pain processes within the cranial vasculature, which act on meningeal sensory fibres. Additional mechanisms involve alterations in the sensitivity of sensory terminals innervating blood vessels in the meninges, and also increased excitability of central pain relay, neurons, and central sensitization (Woolf, 2003).

Visceral versus somatic pain mechanisms, alternative pain stimuli, and differing intensities of exposure to painful stimulation, may be worth exploring in future research, in relation to effects of OKS. If mechanisms of pain are better understood, more rational and specific choices for effective therapy are possible. Consistent with this premise, Woolf proposed that a mechanism-based diagnosis of pain, rather than a disease-based focus, would help increase the understanding of how pain is generated and, in turn, more appropriate treatment could then be identified.

Diffuse noxious inhibitoy controls (DNIC)

Nociceptive stimulation of the hand possibly triggered DNIC in migraine sufferers in this study, thereby inhibiting certain symptoms of motion sickness, e.g., body temperature. It might be interesting to further explore specific symptoms of motion sickness in relation to DNIC and the implications in respect to the migrainous brain. Furthermore, investigating the simultaneous effect of painful stimulation of the temple and hand during OKS in relation to specific pain sources (temple or hand alone) during OKS, may help to more conclusively determine whether DNIC influence the development of symptoms of motion sickness. If DNIC are involved, simultaneous painful stimulation during OKS may inhibit the enhanced nausea, and possibly headache, observed in this study during painful stimulation of the temple during OKS. This of course would be an exploratory exercise, as hand pain did not generally inhibit motion sickness in the present study.

Loss of appetite

It is generally assumed that migraine sufferers are unable to eat or drink during an attack (Blau, 1993). Blau asked 109 sufferers if they could tolerate food or fluid during migraine. The number of migraineurs able to eat (particularly selected foods) in spite of nausea during migraine was unexpected (50 could, 59 could not). Furthermore, food consumption reduced nausea, headache and improved general wellbeing. Blau pointed out that cravings for sweet foods is a well documented prodrome of migraine and that delayed meals can precipitate an attack. He suggested that the hypothalamus or the brainstem could play a role in nausea but that cravings are more likely to originate from the hypothalamus. Therefore, it may be that simultaneous nausea and cravings derive from the hypothalamus, which would also account for tiredness and yawning during the premonitory and headache phase as well as after attacks (Blau, 1991). Blau (1993) proposed that the generation of migraine is not only dependent on the activation of neurotransmitters, but may also be a central neuronal metabolic disturbance.

The ability to eat or drink during migraine may be worth investigating further. So too might the loss of appetite in relation to head pain and nausea during migraine. Loss of appetite during a migraine attack has been associated with the development of head pain, often before the experience of nausea, or even in the absence of nausea (Malick, Jakubowske, Elmquist, Saper and Burstein, 2001), suggesting that loss of appetite is independent of nausea. Instead nausea appears to be driven by pain. Consistent with this association, Malik et al. (2001) also found that brief noxious stimulation of the dura in conscious rats suppressed food intake. Mapping of neuronal activation in rats indicated that certain hypothalamic neurons mediated the suppression of food intake by pain signals. Further study aimed at determining the progression of loss of appetite and nausea in relation to head pain may help to identify neural structures/processes involved in the development of a migraine attack.

Hyperventilation in relation to motion sickness and migraine

Breathing style in relation to motion sickness and migraine was not explored in the present study but may be worthy of further investigation. Research indicates that breathing style may determine whether nausea and other symptoms of motion sickness develop during OKS (Yen Pik Sang, Billar, Golding and Gresty, 2003; Jokerst, Gatto, Fazio, Stern and Koch, 1999). Before surgery anxious patients may involuntarily swallow large amounts of air which may contribute to distention/discomfort of the upper gastrointestinal tract and post-operative nausea and vomiting (Andrews, 1992). In regards to motion sickness, slow deep breathing (8 breaths per minute) was found to reduce the development of tachygastria and decrease symptoms of motion sickness. Jokerst and others point out that this breathing style is known to increase parasympathetic nervous system activity and may stimulate reflexes that control the autonomic nervous system (ANS) (particularly, the baroreflex system) leading to more efficient ANS control. Certainly, slow breathing ('respiratory training') has been used successfully to treat anxiety (Andrews, Crino, Hunt, Lampe and Page, 1995).

Koch, Stern, Vasey, Seaton, Demers and Harrison (1990) found that that the stress associated with OKS exposure led to increased breathing and increased sympathetic nervous system activity: norepinephrine and epinephrine (evidence of sympathetic activity) levels were raised during OKS in motion sick subjects. During recovery, epinephrine, cortisol and β-endorphin responses were elevated: further indication of the stress response. However, neuroendocrine levels did not change from baseline levels in asymptomatic subjects, indicating that the stress response was not triggered.

Sympathetic activation of the ANS (increased respiration, heart rate) has also been observed during rotating chair-induced motion sickness (Cowings, Suter, Toskcan, Kamiya and Naifeh, 1986; Cramptom, 1990). Cowings et al. (1986) observed a rapid return to pretest levels during post test recovery and put this down to a reduction in sympathetic tone or to a parasympathetic rebound, on cessation of the stimulus. Similarly, Sakai and Meyer (1978) suggest that nausea and vomiting during a migraine attack may be a parasympathetic reaction to prolonged sympathetic activity.

Respiration was not measured in the present study but it may be that the stress associated with OKS exposure led to increased breathing and increased sympathetic nervous system activity, thereby contributing to the development of symptoms of motion sickness (as suggested by Jokerst et al., 1999), particularly in migraine sufferers. This notion requires further investigation.

Serotonin and migraine

Serotonergic activity has been linked to migraine, during (Hasler, 1999; Ladabaum and Hasler, 1999; Silberstein, 1994) and outside (Afra, Proietti Cecchini, Sandor and Schoenen, 2000) attacks. However, the precise role of serotonin is not clear (Evers, Quibeldey, Grotemeyer, Suhr and Husstedt, 1999; Ferrari et al., 1993; Fontes Ribeiro et al., 1990). During a migraine attack the trigeminal sensory system presumably activates central nociceptive neurons within the brainstem, which relay signals to autonomic brainstem nuclei and higher cortical pain processing centres. These afferent impulses, in turn, lead to head pain and nausea while activation of efferent autonomic pathways are thought to trigger stomach disturbance and vomiting (Dahlof and Hargreaves, 1998). Nausea, headache, fatigue and thermoregulation have been linked with 5-HT release (Hasler, 1999; Ladabaum and Hasler, 1999; Silberstein, 1994). Silberstein (1994) explains that 5-HT modulates rather than mediates sensory responsiveness, and serotonergic receptors are distributed widely throughout the brain (Pascual, del Arco, Romon, del Olmo, Castro and Pazos, 1996; Waxman, 2003). Serotonergic neurons originating in the raphe nuclei of the brainstem have extensive projections to widespread areas of the brain including the cortex, hippocampus, basal ganglia, thalamus, cerebellum, and spinal cord. These neurons play a role in controlling levels of arousal and sleep. In addition they modulate sensory input, particularly for pain (Waxman, 2003). Serotonergic input to vestibular nuclei has been found to affect the firing rate of vestibular nucleus neurones (Kishimoto, Sasa and Takaori, 1991, 1994). In particular, in

experiments on cats, 5-HT inhibited the transmission of neural impulses in the lateral vestibular nuclei.

Furthermore, evidence exists for vestibular regulation of sympathetic activity (Ray, 2001). Ray found that muscle sympathetic nerve activity, arterial pressure and heart rate increased during head down rotation, which engages the vestibulosympathetic reflex in healthy volunteers. Cass et al. (1997) suggested that autonomic and somatic activity during a migraine attack may, in part, be generated from the interaction between vestibular and sympathetic junctions. Just as depleted 5-HT is believed to play a role in vasodilatation and pain observed during migraine (Supornsilpchai, Sanguanrangsirikul, Maneesre and Srikiatkhachorn, 2006; Silberstein, 1994), a decrease in serotonergic transmission during an attack might also contribute to the development of other symptoms of migraine. However, low serotonergic transmission during the migraine attack is somewhat controversial as there is evidence 5-HT levels increase ictally (Fontes Ribeiro, Cotrim, Morgadinho, Ramos, Seabra Santos and Macedo, 1990). Clearly, the exact role of 5-HT in the pathogenesis of migraine is under discussion (Evers et al., 1999; Ferrari et al., 1993; Fontes Ribeiro et al, 1990).

Pharmacological studies indicate that serotonin may be involved in migraine and also motion sickness. Pascual et al. (1996) suggest that triptans evoke analgesic antimigraine activity in the TNC and antiemetic effects in the NTS, by acting on the numerous 5-HT receptor sites in these locations. 5-HT agonists and antagonists have also successfully treated motion sickness (Yates, Miller and Lucot, 1998). Additionally, serotonin has been found to prevent motion-induced emesis in animals (Javid and Naylor, 2002; Okada, Saito and Matsuki, 1996). Baloh (1997) pointed out that antimigraine treatments, e.g., ergotamines or sumatriptan, are probably of little help for the treatment of migraine-associated vertigo, though he did anecdotally report that several patients found sumatriptan, if taken early in an attack, aborted vertigo (Evans and Baloh, 2001). Consistent with this observation, more recently Zolmitriptan was used successfully to treat migrainous vertigo in a small group of sufferers (Neuhauser, Radtke, Breven and Lempert, 2003).

Atypical sertonergic activity may persist interically in migraine sufferers (Afra et al., 2000). Afra et al. suggested that low interictal activity of brain stem nuclei projecting to

the cortex, e.g., the raphe-cortical serontonergic pathway, may be responsible for electrophysiological abnormalities observed in migraine sufferers. Afra et al. demonstrated lack of habituation of visual evoked potentials and a marked intensity dependence of auditory evoked cortical potentials in both migraine with or without aura between attacks compared to healthy controls. Deficient habituation of the P3a component of the passive "oddball" auditory event-related potential was also demonstrated in migraineurs between attacks of migraine (Wang and Schoenen, 1998).

Interestingly, Schoenen et al. (2003) observed ictal normalisation of evoked and event-related potentials amplitudes and habituation, implying there is an increase in cortical preactivation level. The understanding of the sequence of activation of cortical and brain stem structures, e.g., raphe cortical serotonergic pathways, remains open to much debate. However, Afra et al. (2000) speculated that the normalisation observed in their study might be due to a rise in activity of raphe-cortical serotonergic pathways, particularly in close proximity to the migraine attack.

Serotonergic activity was not assessed in the present study, though fluctuations in 5-HT may have played a role, at least partly, in the development of symptoms observed in migraine sufferers. Assay of serum or urine 5-HT levels in migraine sufferers in response to procedures used in this study, may be worthwhile exploring. Findings may shed further light on the role of this neurotransmitter in those with a migraine predisposition.

13.4. Conclusions

Consistent with the literature (Golding, 1998; Kuritzky, Ziegler & Hassanein, 1981), migraine sufferers in this study developed motion sickness more readily than controls. Symptomatic responses were enhanced during the three procedures involving OKS and during temple pain after OKS, in the presence of residual motion sickness.

During trigeminal stimulation independent of OKS, headache initially developed followed by nausea as the procedure progressed, implying that activation of the TNC triggered the NTS. This close functional relationship between the trigeminovascular system and NTS in the brainstem of migraine sufferers has been described elsewhere (Knight, 2005). Symptoms barely developed in controls during any of the six procedures except for slight dizziness, self-motion and visual-illusion during conditions involving OKS, and slight nausea when the temple was painfully stimulated during OKS and during OKS alone. Trigeminal stimulation during OKS intensified nausea and headache in migraine sufferers compared to during OKS alone or limb pain during OKS. However, the remaining symptomatic ratings were not altered following temple pain during OKS, suggesting a specific association between nausea and head pain. These findings further imply a mutual interaction between the TNC and NTS. If so, it may be that these cardinal symptoms compound one another during a migraine attack. Enhanced symptomatic responses in migraine sufferers may reflect activation of hypersensitive neural pathways that mediate symptoms of motion sickness or migraine. Furthermore, migraineurs found procedures generally more unpleasant, and ice-induced pain ratings more intense and unpleasant, than controls, which may further indicate hyperexcitable nociception in this group, or a difference in their criterion of discomfort.

Vascular responses, particularly during OKS alone, and during painful stimulation independent of OKS, were greater in migraine sufferers than in controls. The stress of painful stimulation during OKS (two tandem stressors) appeared to boost facial blood flow in controls to approach levels obtained in migraine sufferers. The stress response also probably contributed to the enhanced vasodilatation observed in migraineurs, even prior to painful stimulation before OKS. In addition, as headache was experienced in migraine sufferers in conjunction with vasodilatation, activation of the TNC may have been involved. Therefore, it may be that increased blood flow in migraineurs was also mediated by the release of vasoactive polypeptides (Edvinsson and Goadsby, 1995; Edvinsson and Uddman, 2005; Goadsby and Edvinsson, 1996).

For both groups, ipsilateral vascular responses were greater than contralateral responses when the hand was painfully stimulated, but side differences were not apparent during painful stimulation of the temple. This asymmetrical vascular response to limb

pain has also been observed by Drummond (2006) in healthy controls, which implies a normal reaction to immersion of the hand in ice-water. In the present study, asymmetry was greater during limb pain before OKS than during OKS, in migraine sufferers but responses were comparable in controls. It may be that atypical autonomic reactivity may partly account for the augmented vascular responses observed in migraineurs. During limb pain before OKS asymmetry was marginal in migraine sufferers but more apparent in controls. An enhanced stress response in migraineurs may have drawn ipsilateral and contralateral responses closer together.

13.5. Concluding Comments: findings of the present study in relation to contemporary understanding of migraine

Migraine is a widespread, chronic, sometimes progressive, and often incapacitating, neurovascular disorder (Goadsby, 2003; Lipton and Bigal, 2005; Silberstein, 2003). The personal burden of the disease and the socioeconomic costs of migraine are well documented (Lipton and Bigal, 2005). Knight (2005) pointed out that the present challenge regarding what causes migraine is long-standing and gradually evolving. Migraine is a complex neurological disorder characterized by headache and associated symptoms, including nausea. The neural events involved in the link between the initiation of a migraine attack and the associated trigger factors are poorly understood (Williamson and Hargreaves, 2001). Interestingly, in the present study migraine-like attacks were triggered in migraine sufferers following procedures, particularly after sessions that involved painful stimulation of the temple during or after OKS (refer to publications related to this book, Granston and Drummond, 2005). Migraine symptoms are remarkably similar to symptoms of motion sickness, so it may be that symptoms evoked during the procedures of the present study simulated a migraine attack in the

interictal period. As migraine-like attacks were triggered in migraineurs, and persisted, it may be that symptoms built upon each other in a vicious circle. The build up of symptoms may demonstrate a neural hypersensitivity/"wind-up" (Bray, Cragg, MacKnight and Mills, 1999) that amplifies responses. Migraine-like attacks did not develop in controls.

The development of symptoms during the procedures of this study provide an insight into how symptoms might develop sequentially in a migraine attack. Perhaps, once the headache is in motion, nausea and headache mutually exacerbate one another. In turn, trigeminovascular responses and stress appear to be linked to the migraine crisis. Thus, it may be more effective to target multiple symptoms rather than individual symptoms in prophylactic or immediate chemical and psychological interventions. This approach may help relieve the burden of migraine, not only for the sufferer but also for the community.

APPENDICES CONTENTS

APPENDIX 1

MURDOCH UNIVERSITY
PERTH, WESTERN AUSTRALIA

School of Psychology
Division of Health Sciences

Consent form
Ethics Permit No: 144/2000

Project Title:
Motion sickness, head pain and non-specific pain in the origin of migraine

I am a Doctor of Psychology student at Murdoch University investigating the relationship between motion sickness, head pain, and non-specific pain, and how this relates to susceptibility to migraine. The purpose of this study is to find out how particular symptoms of migraine contribute to the development of a migraine attack; if certain symptoms attenuate or exacerbate the severity of other symptoms or predispose the individual to repeated attacks. Additionally, this study aims to find out whether sensitivity to pain elsewhere in the body plays a role in the symptomatology of migraine. This information will assist in treatment and research aimed at reducing the likelihood of the individual suffering repeated attacks of migraine.

To conduct my study I require people who suffer from migraine and people who do not. You will be required for 3 sessions of approximately 1.5 hours each. During these sessions an attempt will be made to simulate some of the symptoms of migraine including nausea (motion sickness) and head pain. You will be required to sit with your head inside a striped, revolving drum, which may provoke nausea. One session involves you sitting inside the drum and also receiving ice to your temple, which may provoke head pain. To assess the role of pain elsewhere in the body in migraine, another session requires drum exposure and immersing your fingers in iced water. You will be asked to report your experience of these stimuli and some of your physiological reactions will be monitored from electrodes attached to your skin. These procedures are harmless if you are in good health, but if you have any problems with your heart, lungs, epilepsy or any other serious medical conditions you should not participate in this experiment.

If you are willing to participate in this research, please complete the details below. Any queries about this study can be directed to myself, Anna Granston on 93606735, my supervisor, Associate Professor Peter Drummond on 93602415, or Murdoch University's Research Ethics Committee on 93606483.

I (the participant) have read the information above. Any questions I have asked have been clarified to my satisfaction. I agree to take part in this study, however, I know that I may change my mind and stop at any time.

I understand that all information provided is treated as confidential and will not be released by the investigator unless required to do so by law.

I agree that research data gathered for this study may be published provided my personal identifying information is not used.

_____ _____
Participant Date

_____ _____
Investigator Anna Granston Date

APPENDIX 2

CONFIDENTIAL PERSONAL DETAILS

Participant code _____
Age _____
Sex _____
Time last ate _____

- Medical status

  I suffer from a chronic medical condition, eg. neurological (especially epilepsy), heart disease, gastric ulcer, ear problems

  Yes/No

  Medical history _____
  _____

  I am uncertain about my medical status and need to visit a General Practitioner for a medical clearance

  Yes/No

  If decided on medical visit, date of visit _____
  Result of visit _____
  _____

- Headache (including migraine) experience - Less than 12/year Yes/No
  - More than 12/year Yes/No

  Frequency of headaches _____
  How many headaches are severe _____
  Of these, how many are migraine _____
  Date most recent headache finished _____
  Was most recent headache a migraine Yes/No

- Migraine experience – discuss with the experimenter the following 2 categories of migraine below (with & without aura) and circle Yes or No to that which describes your experience.

1) Migraine without aura

A . At least 5 attacks fulfilling B – D.
B . Headache attacks lasting 4 – 72 hours (untreated or successfully treated)
C . Headache has at least 2 of the following characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe intensity
4. Aggravation by walking stairs or similar routine physical activity

D . During headache at least one of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia

*2) **Migraine with aura***

A. At least 2 attacks fulfilling B.

B. At least 3 of the following 4 characteristics:

1. One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem dysfunction
2. At least 1 aura symptom develops gradually over more than 4 minutes or, 2 or more symptoms occur in succession
3. No aura symptom lasts more than 60 minutes. If more than one aura symptom is present, duration is proportionally increased
4. Headache follows aura with a free interval of less than 60 minutes. (It may also begin before or simultaneously with the aura)

Migraine without aura Yes/No
Migraine with aura Yes/No

Has a Doctor diagnosed migraine Yes/No
Name and specialty of Doctor _____
_____

Detail medical investigation(s) of your headache _____
_____
_____

- Migraine location (non-migraineurs give headache location):

	Yes	No	Approximate number per 10 headaches
Left side			
Right side			
Both sides			
Other location			

- Does anyone in your immediate family (parents, siblings, proband relatives) suffer from migraine Yes/No
  If yes, give details _____

- Medication

  Prophylactic medication for headache relief Yes/No
  If yes, give details _____

  Medication as required for immediate headache relief Yes/No
  If yes, give details _____
  _____

  Medication for another condition, including oral contraceptive Yes/No
  If yes, give details _____
  _____

  Medication over past 7 days Yes/No
  If yes, give details (**what, when**) _____
  _____

- Menstruating or premenstrual Yes/No/Not Applicable

  Date of last menstruation _____
  Days in your cycle _____

- Do you regard yourself as susceptible to motion sickness – circle below

  Not at all Slightly Moderately Very much so

- Dizziness or vertigo not associated with headache – circle below

  Never Once in 6 weeks More than once in 6 weeks

  Other, give details _____

- Regardless of motion sickness, over the last 10 years, how often have you travelled/used the following – tick boxes

	Never	1- 4 trips	5 - 10 trips	11 or more trips
Cars				
Buses, coaches				
Trains				
Aircraft				
Small boats				
Ships, eg. channel ferries				
Swings				
Roundabouts: playgrounds				
Big dippers, funfair rides				
Omni theatre				
Simulators				
Reading in the car				

- Over last 10 years, how often you felt sick or nauseated – tick boxes

	Never	Rarely	Sometimes	Frequently	Always
Cars					
Buses, coaches					
Trains					
Aircraft					
Small boats					
Ships, eg. channel ferries					
Swings					
Roundabouts: playgrounds					
Big dippers, funfair rides					
Omni theatre					
Simulators					
Reading in the car					

- Over last 10 years, how often you vomited – tick boxes

	Never	Rarely	Sometimes	Frequently	Always
Cars					
Buses, coaches					
Trains					
Aircraft					
Small boats					
Ships, eg. channel ferries					
Swings					
Roundabouts: playgrounds					
Big dippers, funfair rides					
Omni theatre					
Simulators					
Reading in the car					

- Nature and duration of motion sickness symptoms after exposure – tick boxes

	Intensity during exposure (0-10)		Duration of symptoms after exposure		
			< 1 hour	1 – 6 hours	> 6 hours
Nausea					
Dizziness					
Sweating					
Drowsiness					
Headache					
Vomiting	Never				
	Rarely				
	Sometimes				
	Frequently				
	Always				

- Migraineurs - tick below Yes, No or Unsure and note relevant details for migraine triggers
  ` - asterix headache triggers
- Non-migraineurs - tick below Yes, No or Unsure and note relevant details for headache triggers

PSYCHOLOGICAL	Yes	No	Unsure	Relevant details		
Emotional or mental stress including anxiety				Exposure time		
				< 1 hour	1 hour - 1 day	More than 1 day
Relaxation after stress						
Depression						
Crying:				Exposure time		
				< 1 hour	1 hour – 1 day	More than 1 day
• when sad						
• when happy						
• other, eg. peeling onions						

PHYSIOLOGICAL	Yes	No	Unsure	Relevant details
Blow to the head (eg. during sport)				
Lack of food				
Oral contraceptives				
Other drugs including vitamin supplements (particularly Vitamin A)				Specify
Menstruation				
Fatigue				
Excessive exercise				
Insomnia				
Sleeping late				
Allergic reactions (eg. asthma, hay fever, dermatitis)				
Illness				
High blood pressure				
Head/neck pains				

EXTERNAL	Yes	No	Unsure	Relevant details		
* tick items <u>Foods</u>: wheat, yeast, rice				Small taste/ bite/sip	Average serve	More than average serve
citrus fruits, apple, pineapple, grapes, coconut, tomato						
sugar, corn						
tea, coffee						
chocolate, cocoa products						
cola drinks						
eggs, nuts, legumes/broad beans						
fat, milk, sour cream						
Aged, salty or other cheese						
fermented sausages, salted-processed meats (ham, salami, frankfurters, bacon, bologna), beef, pork, shellfish, pickled herring						
Monosodium glutamate containing foods (some Chinese or soya sauce)						
Pretzels, potato chips, other salty snacks/fast foods						
* tick items <u>Alcohol</u>: red wine, white wine, spirits, beer, other (specify)				Sip	1 glass	More than 1 glass
Taste aversion						
Weather changes/extremes of temperature				Specify : eg. seasonal (which season), very hot days, very cold days, air conditioned or heated rooms		
Stuffy atmosphere				< ½ hour exposure	More than ½ hour exposure	
Fumes/odours				Specify		
Travel/motion						
Noise						
Visual stimuli (glare, flicker, sunlight, eye strain, television, films, darkness)				Specify		
Change in routine (eg. weekend headaches)						

	Yes	No	Unsure	Relevant details
Other triggers (detail below)				

APPENDIX 3

Headache Diary and Headache Detail Forms

Booklets supplied to participants were A5 size

HEADACHE

DIARY

Complete daily, even if headache free

FILLOUT HEADACHE DIARY DAILY

If you have more than a mild headache also complete the
Headache Details Form

NOTE:

- Day.....Date.....Tick box if a headache free day
- Time of onset & end of headache
- Intensity (0-10) - If intensity >3(or mild) complete the ***Headache Details Form***
- Trigger (refer to list below)

  Psychological (specify eg. arguing)

  External factor (specify eg. red wine)

  Physiological factor (specify eg. overslept, flu symptom)

  No trigger observed

- Treatment – what you did including medication details

Day ..... Date ..... Tick box if a Headache free day			
Time	Intensity	Trigger	Treatment

Remaining pages of diary followed this format.

HEADACHE

DETAIL FORMS

HEADACHE DETAIL FORMS

Fill out this form if you have more than a mild headache

NOTE:

- Date and time

  Note start time of headache and record headache details

  Continue recording details every 8 hours (note time - morning, afternoon, evening) until headache goes

  * If headache goes within 8 hours, note time and peak rating

- Location of head pain
- Signs and symptoms (refer to list below)

Sensitivity to light	Dizziness
Sensitivity to sound	Drowsiness
Nausea	Headache
Vomiting	
Sweating or increase in body temperature	

Aura

Note intensity of each sign and symptom (0-10)

HEADACHE DETAILS

Date and time	Location of head pain	Signs and symptoms (intensity of each sign and symptom

Remaining pages of booklet followed this format.

APPENDIX 4

Examples of physiological output for pulse amplitude data using Acqknowledge programme software, see last page of Appendix 4. Also, refer to method, pages 86-88.

RATING SCALES

During the procedure you will be asked to rate your experience of the following sensations:

VISUAL ILLUSION - stripes in the drum appear to be changing shape or are distorting

SELF MOTION - you feel as though you are moving although you are actually still, and the drum appears still

Rating scale None Some Complete

NAUSEA

Rating scale

0	1	2	3	4	5	6	7	8	9	10
No Stomach Discomfort	Stomach awareness	Mild stomach discomfort		Moderate nausea			Somewhat severe nausea	Severe nausea		Close to vomiting

DIZZINESS

Rating scale

0	1	2	3	4	5	6	7	8	9	10
None	Awareness of slight dizziness	Mild dizziness		Moderate dizziness			Somewhat severe dizziness	Severe dizziness		Close to collapsing

BODY TEMPERATURE

Rating scale

10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10
Extremely cold		cold		Moderately cold			Mildly cold		Normal		Mildly warm			Moderately hot			hot		Extremely hot	

DROWSINESS

Rating scale

0	1	2	3	4	5	6	7	8	9	10
None	Awareness of drowsiness	Mild		Moderate			Somewhat severe	Severe		Close to sleep

HEADACHE

Rating scale

0	1	2	3	4	5	6	7	8	9	10
None	Head Awareness	Mild headache		Moderate headache			Somewhat severe headache	Severe headache		Extremely severe Headache

UNPLEASANTNESS – how you feel in relation to any change you may experience during this experiment

Rating scale

0	1	2	3	4	5	6	7	8	9	10
Not Unpleasant	Slight awareness	Mildly unpleasant		moderately unpleasant			severely unpleasant			Extremely unpleasant

RESPONSE TO ICE

Intensity

Rating scale

0	1	2	3	4	5	6	7	8	9	10
Not noticeable	Slight awareness	Mild intensity		Moderate intensity			severely intense			Extremely intense

Unpleasantness

Rating scale

0	1	2	3	4	5	6	7	8	9	10
Not Noticeable	Slight awareness	Mildly unpleasant		Moderately unpleasant			Severely unpleasant			Extremely unpleasant

RECORD SHEET

Participant code:

Date: START: time temperature humidity

FINISH: time temperature humidity

Test condition: OPD

		Start drum							End drum			
Minutes	Pre drum	2	4	6	8	10	12	14	15	16	18	20
Nausea												
Body temperature												
Dizziness												
Drowsiness												
headache												

Self motion							
Visual illusion							

Unpleasantness											

RECORD SHEET

Participant code:

Date: START: time temperature humidity

FINISH: time temperature humidity

Test condition: OPD & ICE (temple/fingers)

Time between conditions (ICE, OPD & ICE):

Ice placement: Right Left

START: ice-water temperature warm water temperature

FINISH: ice-water temperature warm water temperature

	Start drum								End drum			
Minutes	Pre drum & ice	2	4 30sec ice	6	8 30sec ice	10	12 30sec ice	14	15	16	18	20
Nausea												
Body temperature												
Dizziness												
Drowsiness												
headache												

Self motion							
Visual illusion							

Unpleasantness											

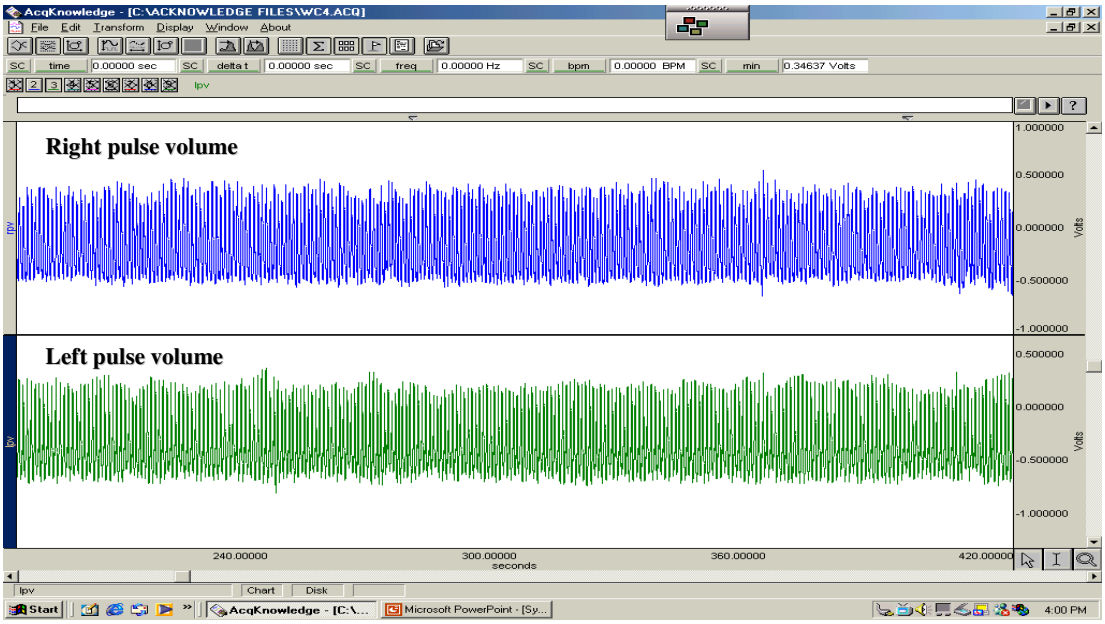
Ice Rating

Intensity										
Unpleasantness										

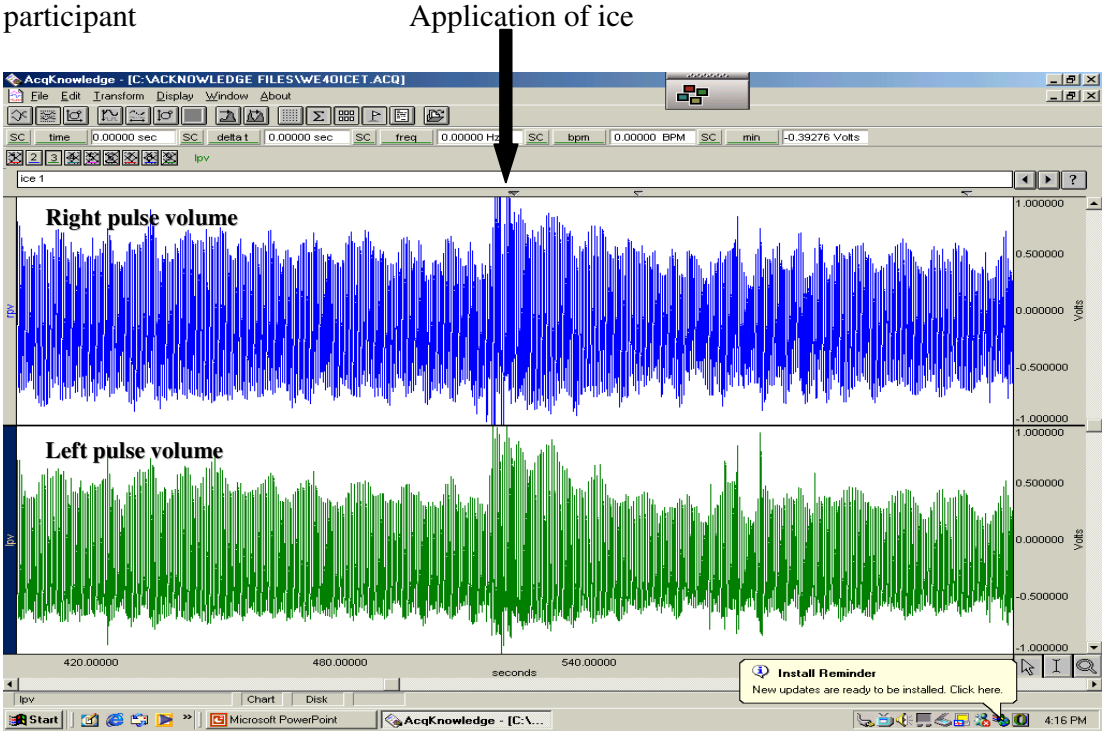
Examples of physiological output recorded throughout testing using AcqKnowledge programme software

(Refer to Chapter 3, Method, page 86-88)

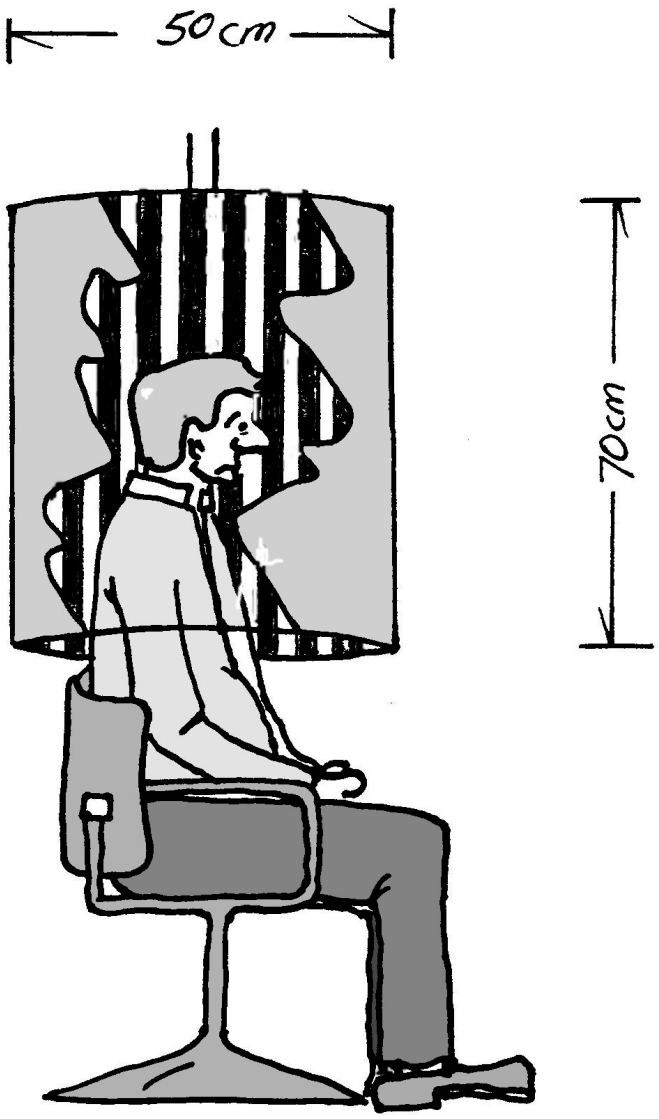
Baseline recording taken before exposure to optokinetic stimulation and/or ice.



Stimulation of right temple with ice during optokinetic stimulation in a migraine participant Application of ice



APPENDIX 5



The optokinetic drum and positioning of the participant

APPENDIX 6

Condition 1

Optokinetic stimulation (OKS) alone

SYPTOMATIC RATINGS

Table 6.1.1. Nausea

Nausea						
	Mean ± SD		Group t-tests (df)	Simple Contrasts F ratios (df = 1, 40)		
	Migraineurs (n=21)	Controls (n=21)		Level 1 vs.	Time	Group x time
Baseline	.119 ± .312	.048 ± .218	1.158 (40.958)			
Minute 2	.333 ± .677	.429 ± 1.363	.148 (45)	Level 2	3.326	.261
4	.714 ± 1.220 ^	.190 ± .680	2.170 (34.804) *	Level 3	5.737 *	2.155
6	1.476 ± 1.669 ^^^	.190 ± .512	3.919 (27.464) ***	Level 4	15.844 ***	10.383 **
8	1.905 ± 2.090 ^^^	.738 ± 1.513 ^	2.696 (36.775) *	Level 5	19.215 ***	3.759
10	2.476 ± 2.600 ^^^	.905 ± 1.751 ^	2.455 (38.253) *	Level 6	22.881 ***	4.983 *
12	3.143 ± 3.425 ^^^	.976 ± 1.933 ^	2.525 (31.570) *	Level 7	21.449 ***	6.028 *
14	3.500 ± 3.578 ^^^	.714 ± 2.083	3.084 (32.162) **	Level 8	20.564 ***	9.247 **
16	2.405 ± 2.681 ^^^	.429 ± 1.316	3.610 (35.288) ***	Level 9	16.479 ***	8.408 **
18	1.714 ± 2.125 ^^	.417 ± 1.335	2.982 (40.694) **	Level 10	12.586 ***	4.904 *
20	1.143 ± 1.534 ^^	.095 ± .436	3.367 (29.422) **	Level 11	8.980 **	7.455 **

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01, ^^^ p < .001)

Table 6.1.2. Body temperature

Optokinetic stimulation (OKS) alone

Body temperature						
	Mean ± SD		**Group**	**Simple Contrasts F ratios (df = 1, 40)**		
	Migraineurs (n=21)	**Controls (n=21)**	**t-tests (df)**	**Level 1 vs.**	**Time**	**Group x time**
Baseline	.024 ± .249	.214 ± .681	-1.202 (27.975)			
Minute 2	.714 ± 1.157 ^	.190 ± .512	1.058 (34.378)	Level 2	6.442 *	7.395 *
4	1.238 ± 1.617 ^^	.167 ± .483	2.279 (30.861) *	Level 3	10.738 **	12.563 ***
6	1.809 ± 1.997 ^^^	.226 ± .612	2.728 (30.789) **	Level 4	17.491 ***	17.031 ***
8	2.429 ± 2.276 ^^^	.393 ± .910	3.706 (39.368) ***	Level 5	25.093 ***	18.634 ***
10	3.238 ± 2.513 ^^^	.655 ± 1.652	3.262 (43) **	Level 6	34.307 ***	19.762 ***
12	3.357 ± 3.163 ^^^	.393 ± 1.131	4.044 (25.030) ***	Level 7	25.510 ***	20.585 ***
14	3.905 ± 3.296 ^^^	.369 ± .967	4.717 (23.417) ***	Level 8	31.413 ***	26.779 ***
16	3.119 ± 2.915 ^^^	.369 ± .914	4.238 (37.418) ***	Level 9	25.552 ***	20.916 ***
18	1.881 ± 2.371 ^^	.262 ± .700	3.289 (34.186) **	Level 10	13.364 ***	12.061 ***
20	1.500 ± 1.789 ^^^	.548 ± 1.532	2.494 (43.769) *	Level 11	12.864 ***	5.131 *

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01, ^^^ p < .001)

Table 6.1.3. Dizziness

OKS alone

Dizziness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 40)		
	Migraineurs (n=21)	Controls (n=21)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.048 ± .218	.000 ± .000	1.445 (24)			
Minute 2	1.000 ± 1.483 ^^	.452 ± 1.465	1.565 (45)	Level 2	9.428 **	1.194
4	1.381 ± 1.717 ^^	.619 ± 1.071 ^	2.326 (37.756) *	Level 3	19.615 ***	2.625
6	1.857 ± 2.157 ^^^	.881 ± 1.440 ^	2.577 (39.729) *	Level 4	22.489 ***	2.679
8	2.333 ± 2.431 ^^^	1.024 ± 1.820 ^	2.935 (41.373) **	Level 5	24.998 ***	3.634
10	2.762 ± 2.844 ^^^	1.214 ± 2.183 ^	2.381 (43) *	Level 6	25.166 ***	3.669
12	3.262 ± 3.176 ^^^	.952 ± 2.109	2.776 (34.763) **	Level 7	24.951 ***	7.353 *
14	3.333 ± 3.385 ^^^	.929 ± 2.215	2.724 (34.475) **	Level 8	22.678 ***	7.094 *
16	1.571 ± 2.111 ^^	.714 ± 1.908	2.062 (43.912) *	Level 9	13.147 ***	1.720
18	1.048 ± 1.857 ^	.548 ± 1.284	1.543 (41.976)	Level 10	9.771 **	.835
20	.643 ± 1.424	.214 ± .463 ^	1.480 (30.288)	Level 11	5.971 *	1.322

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01, ^^^ p < .001)

Table 6.1.4. Drowsiness

OKS alone

Drowsiness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 40)		
	Migraineurs (n=21)	Controls (n=21)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.190 ± .512	.214 ± .681	-.288 (45)			
Minute 2	.405 ± .944	.143 ± .478	1.296 (32.047)	Level 2	.594	2.376
4	.726 ± 1.000 ^	.286 ± .644	1.835 (36.510)	Level 3	6.149 *	3.596
6	1.012 ± 1.216 ^^	.357 ± .727	2.196 (36.801) *	Level 4	11.170 **	5.531 *
8	1.345 ± 1.450 ^^^	.405 ± .944	2.663 (40.047) *	Level 5	15.263 ***	7.842 **
10	1.690 ± 1.887 ^^^	.524 ± 1.078	2.522 (35.774) *	Level 6	17.805 ***	7.707 **
12	2.009 ± 2.358 ^^	.571 ± 1.207	2.487 (29.806) *	Level 7	16.839 ***	7.599 **
14	2.167 ± 2.517 ^^^	.571 ± 1.207	2.619 (28.740) *	Level 8	16.962 ***	8.167 **
16	1.976 ± 2.431 ^^	.381 ± 1.117	2.485 (35.182) *	Level 9	13.021 ***	8.954 **
18	1.750 ± 2.148 ^^	.190 ± .873	2.854 (33.246) **	Level 10	11.040 **	11.735 ***
20	1.655 ± 2.086 ^^	.333 ± 1.316	2.111 (41.479) *	Level 11	11.384 **	8.218 **

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01, ^^^ p < .001)

Table 6.1.5. Headache

OKS alone

Headache						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 40)		
	Migraineurs (n=21)	Controls (n=21)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.333 ± .577	.000 ± .000	3.206 (25.851) **			
Minute 2	.381 ± .590	.000 ± .000	3.342 (25.489) **	Level 2	.192	.192
4	.500 ± .742	.048 ± .218	2.908 (27.035) **	Level 3	1.416	.437
6	.762 ± 1.032	.048 ± .218	3.091 (25.472) **	Level 4	4.215 *	2.698
8	.881 ± 1.203 ^	.048 ± .218	3.228 (25.293) **	Level 5	5.333 *	3.763
10	1.357 ± 1.769 ^	.048 ± .218	3.649 (22.876) ***	Level 6	7.630 **	6.334 *
12	1.548 ± 2.132 ^	.048 ± .218	3.207 (20.419) **	Level 7	7.940 **	6.786 *
14	1.738 ± 2.427 ^	.119 ± .312	3.032 (20.663) **	Level 8	9.135 **	6.503 *
16	1.690 ± 2.305 ^^	.202 ± .367 ^	3.366 (25.532) **	Level 9	11.315 **	6.204 *
18	1.857 ± 2.600 ^^	.143 ± .322	3.512 (24.896) **	Level 10	10.722 **	7.361 *
20	1.786 ± 2.518 ^^	.048 ± .218	3.698 (24.434) ***	Level 11	9.051 **	7.938 **

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01)

Table 6.1.6. Unpleasantness

OKS alone

Unpleasantness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 40)		
	Migraineurs (n=21)	Controls (n=21)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.119 ± .312	.071 ± .239	.656 (45)			
Minute 2	1.429 ± 1.502 ^^^	.571 ± 1.434	1.933 (45)	Level 2	17.356 ***	3.474
4	1.905 ± 2.071 ^^^	.571 ± 1.399	2.639 (40.409) *	Level 3	19.033 ***	6.022 *
6	2.452 ± 2.397 ^^^	.631 ± 1.229	3.544 (34.136) ***	Level 4	25.487 ***	9.583 **
8	3.214 ± 2.727 ^^^	1.036 ± 1.854 ^	2.964 (45) **	Level 5	32.948 ***	9.089 **
10	3.738 ± 3.216 ^^^	1.274 ± 2.171 ^	2.771 (43) **	Level 6	33.248 ***	8.353 **
12	4.143 ± 3.627 ^^^	1.131 ± 2.185 ^	3.260 (32.825) **	Level 7	31.528 ***	10.721 **
14	4.786 ± 3.977 ^^^	.940 ± 2.142	3.901 (30.702) ***	Level 8	32.308 ***	15.205 ***
16	2.952 ± 2.819 ^^^	.548 ± 1.359	3.700 (40.412) ***	Level 9	24.352 ***	12.353 ***
18	2.071 ± 2.675 ^^	.679 ± 1.649	2.382 (42.777) *	Level 10	14.273 ***	3.943
20	2.071 ± 2.731 ^^	.405 ± 1.530	3.049 (39.147) **	Level 11	11.572 **	5.806 *

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01, ^^^ p < .001)

Table 6.1.7. Self-motion

OKS alone

Self motion						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 40)		
	Migraineurs (n=21)	Controls (n=21)	t-tests (df)	Level 1 vs.	Time	Group x time
Minute 2	1.048 ± .865	.619 ± .669	1.796 (45)			
4	1.452 ± .805	1.000 ± .837 ^^	2.157 (45) *	Level 2	10.912 **	.010
6	1.595 ± .664 ^^	.952 ± .805 ^	3.579 (45) ***	Level 3	15.077 ***	.892
8	1.286 ± .784	.857 ± .793	2.557 (45) *	Level 4	3.717	.000
10	1.286 ± .902	.952 ± .805 ^	1.732 (43)	Level 5	3.564	.099
12	1.333 ± .856	.762 ± .768	2.276 (40) *	Level 6	2.093	.233
14	1.190 ± .873	.857 ± .727	1.345 (40)	Level 7	1.882	.118

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01)

Ratings during the first 2 minutes of OKS were used as a point of comparison in a series of simple contrasts across subsequent time points.

Table 6.1.8. Visual-illusion

OKS alone

Visual illusion						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 40)		
	Migraineurs (n=21)	Controls (n=21)	t-tests (df)	Level 1 vs.	Time	Group x time
Minute 2	.762 ± .768	.476 ± .512	1.559 (45)			
4	1.000 ± .837	.429 ± .507	2.644 (45) *	Level 2	1.739	3.913
6	1.048 ± .805	.571 ± .598	2.430 (45) *	Level 3	3.368	.842
8	1.190 ± .814 ^^	.714 ± .717	2.403 (45) *	Level 4	9.849 **	.804
10	1.357 ± .793 ^^	.857 ± .727 ^^	2.210 (43) *	Level 5	21.332 ***	1.028
12	1.310 ± .844 ^	.762 ± .625 ^^	2.390 (36.866) *	Level 6	14.412 ***	1.424
14	1.333 ± .913 ^^	.786 ± .644 ^	2.247 (35.945) *	Level 7	16.818 ***	1.486

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01)

Ratings during the first 2 minutes of OKS were used as a point of comparison in a series of simple contrasts across subsequent time points.

PULSE AMPLITUDE

Table 6.2.1. Means and standard deviations for migraineurs and controls for changes in pulse amplitude (left, right) across 11 time points (30 second sample increments from baseline, at minutes 3 ½, 4, 4 ½, 7 ½, 8, 8 ½, 11 ½, 12, 12 ½, 14 ½, 19 ½).

OKS alone

Means ± SD						
	Migraineurs (n = 21)		Controls (n = 21)		Group t-tests (df)	
Time from baseline	Left	Right	Left	Right	Right	Left
Minute 3 ½	27.4 ± 31.0 ^^^	26.3 ± 23.6 ^^^	7.8 ± 15.6 ^	11.2 ± 16.5 ^^	2.056 (43.935) *	1.955 (45)
4	23.8 ± 31.5 ^^^	25.1 ± 23.3 ^^^	8.3 ± 16.2 ^	10.5 ± 19.0 ^^	1.936 (45)	1.568 (45)
4 ½	30.1 ± 35.1 ^^^	30.8 ± 29.0 ^^^	6.2 ± 16.1 ^	10.4 ± 19.2 ^	2.461 (42.451) *	2.498 (45) *
7 ½	36.7 ± 36.1 ^^^	39.5 ± 29.1 ^^^	9.6 ± 17.8 ^	10.2 ± 17.6	4.419 (40.191) ***	3.488 (35.529) ***
8	29.8 ± 36.0 ^^^	32.2 ± 29.6 ^^^	7.4 ± 16.3	8.4 ± 15.7	3.576 (37.904) ***	3.093 (32.397) **
8 ½	34.7 ± 34.4 ^^^	37.5 ± 27.8 ^^^	8.4 ± 15.6	9.5 ± 15.7	4.142 (43) ***	3.678 (33.790) ***
11 ½	33.6 ± 36.9 ^^^	44.1 ± 29.0 ^^^	10.5 ± 20.6 ^	11.5 ± 14.9 ^^	4.588 (29.836) ***	2.507 (31.322) *
12	35.4 ± 34.9 ^^^	43.7 ± 29.9 ^^^	9.2 ± 19.4 ^	11.3 ± 16.0 ^^	4.379 (30.599) ***	2.998 (31.269) **
12 ½	35.1 ± 38.1 ^^^	45.4 ± 30.5 ^^^	9.4 ± 18.9 ^	12.3 ± 14.8 ^^^	4.480 (28.934) ***	2.758 (29.291) **
14 ½	36.9 ± 39.3 ^^^	43.4 ± 27.7 ^^^	10.1 ± 19.8	11.3 ± 17.1 ^	4.079 (45) ***	3.204 (38.122) **
19 ½	22.6 ± 37.4 ^^	43.0 ± 61.5 ^^	.1 ± 16.1	6.9 ± 16.0	2.674 (30.346) *	2.918 (35.795) **

* statistically significant (* $p < .05$, ** $p < .01$, *** $p < .001$)
^ baseline *vs* subsequent levels within groups statistically significant (^ $p < .05$, ^^ $p < .01$, ^^^ $p < .001$)

PULSE AMPLITUDE

Table 6.2.2. Main effects, interactions and intercepts from a series of 2 (group: migraineurs, controls) x 2 (side: left, right) repeated-measures ANOVA's at each time point.

OKS alone

F ratios					
Main effects and Interactions (df)				Intercepts (df)	
Time from baseline	Group	Side	Side x Group	Migraineurs	Controls
Minute 3 ½	5.897(1,45) *	.156(1,45)	.052(1,45)	30.769(1,24) ***	15.860(1,21) **
4	4.453(1,45) *	.185(1,45)	.012(1,45)	25.006(1,24) ***	14.293(1,21) **
4 ½	8.420(1,45) **	.307(1,45)	.064(1,45)	27.887(1,24) ***	11.805(1,21) **
7 ½	21.174(1,44) ***	.149(1,44)	.134(1,44)	46.179(1,23) ***	8.269(1,21) **
8	14.393(1,43) ***	.007(1,43)	.000(1,43)	27.869(1,22) ***	3.995(1,21)
8 ½	19.807(1,43) ***	.017(1,43)	.002(1,43)	39.325(1,22) ***	5.011(1,21) *
11 ½	16.004(1,40) ***	1.706(1,40)	1.171(1,40)	35.540(1,20) ***	20.267(1,20) ***
12	18.875(1,40) ***	1.341(1,40)	.483(1,40)	40.741(1,20) ***	15.163(1,20) **
12 ½	16.392(1,40) ***	2.436(1,40)	.793(1,40)	34.145(1,20) ***	22.501(1,20) ***
14 ½	16.766(1,45) ***	.235(1,45)	.083(1,45)	37.323(1,24) ***	7.083(1,21) *
19 ½	9.464(1,45) **	2.807(1,45)	.384(1,45)	12.956(1,24) ***	.064(1,21)

* statistically significant (* $p < .05$, ** $p < .01$, *** $p < .001$)

APPENDIX 7

Condition 2

Ice on temple after OKS

SYMTOMATIC RATINGS

Table 7.1. 1. Nausea

Nausea						
	Mean ± SD		**Group**	**Simple Contrasts F ratios (df = 1, 43)**		
	Migraineurs (n=25)	**Controls (n=22)**	**t-tests (df)**	**Level 1 vs.**	**Time**	**Group x time**
Baseline	.760 ± 1.515	.091 ± .294	2.163 (26.048) *			
Before 1st ice	.760 ± 1.515	.091 ± .294	2.163 (26.048) *	Level 2	.	.
During 1st ice	.580 ± 1.222	.023 ± .107	2.270 (24.415) *	Level 3	.617	.125
Before 2nd ice	1.000 ± 1.548	.045 ± .147	3.068 (24.492) **	Level 4	1.475	3.175
During 2nd ice	1.100 ± 1.909	.023 ± .107	2.816 (24.170) **	Level 5	.458	1.032
Before 3rd ice	1.260 ± 2.092	.023 ± .107	2.952 (24.142) **	Level 6	2.416	4.182 *
During 3rd ice	1.500 ± 2.372	.000 ± .000	3.162 (24) **	Level 7	2.645	4.334 *
2 mins after 3rd ice	1.660 ± 2.388 ^^	.045 ± .213	3.365 (24.434) **	Level 8	8.278 **	10.133 **
4 mins after 3rd ice	1.460 ± 2.268 ^^	.023 ± .107	3.165 (24.120) **	Level 9	5.584 *	8.245 **
6 mins after 3rd ice	1.180 ± 2.025 ^^	.023 ± .107	2.853 (24.151) **	Level 10	4.499 *	8.662 **
8 mins after 3rd ice	1.140 ± 2.013 ^	.023 ± .107	2.771 (24.153) *	Level 11	4.004	8.272 **

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01)

In one case simple contrasts could not be computed because the matrix was singular.

Table 7.1.2. Body temperature

Ice on temple after OKS

Body temperature						
	Mean ± SD		**Group**	**Simple Contrasts F ratios (df = 1, 43)**		
	Migraineurs (n=25)	**Controls (n=22)**	**t-tests (df)**	**Level 1 vs.**	**Time**	**Group x time**
Baseline	.740 ± 1.234	.227 ± .685	1.787 (38.380)			
Before 1st ice	.740 ± 1.234	.227 ± .685	1.787 (38.380)	Level 2	.	.
During 1st ice	.540 ± 1.322	.182 ± .664	1.194 (36.333)	Level 3	4.256 *	1.687
Before 2nd ice	.580 ± 1.304	.204 ± .666	1.264 (36.665)	Level 4	2.171	1.225
During 2nd ice	.680 ± 1.626	.182 ± .664	1.405 (32.633)	Level 5	.306	.006
Before 3rd ice	.540 ± 1.224	.182 ± .664	1.266 (37.907)	Level 6	3.356	1.330
During 3rd ice	.680 ± 1.376	.136 ± .467	1.857 (30.119)	Level 7	.387	.016
2 mins after 3rd ice	.640 ± 1.141	.136 ± .538	1.971 (35.113)	Level 8	.968	.002
4 mins after 3rd ice	.440 ± 1.073	.091 ± .426	1.497 (32.194)	Level 9	3.843	.540
6 mins after 3rd ice	.480 ± 1.132	.091 ± .426	1.329 (32.238)	Level 10	4.200 *	.768
8 mins after 3rd ice	.065 ± .570	.045 ± .213	1.595 (31.433)	Level 11	2.614	.254

* difference between migraine sufferers and controls statistically significant (* $p < .05$)

In one case simple contrasts could not be computed because the matrix was singular.

Table 7.1.3. Dizziness

Ice on temple after OKS

Dizziness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=25)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.400 ± .913	.000 ± .000	2.191 (24) *			
Before 1st ice	.400 ± .913	.000 ± .000	2.191 (24) *	Level 2	.	.
During 1st ice	.360 ± 1.036	.000 ± .000	1.737 (24)	Level 3	.121	.121
Before 2nd ice	.760 ± 1.595	.000 ± .000	2.382 (24) *	Level 4	2.813	2.813
During 2nd ice	.320 ± .900	.000 ± .000	1.778 (24)	Level 5	.100	.100
Before 3rd ice	.480 ± 1.036	.000 ± .000	2.317 (24) *	Level 6	.111	.111
During 3rd ice	.740 ± 1.786	.000 ± .000	2.072 (24) *	Level 7	.808	.808
2 mins after 3rd ice	.580 ± 1.038	.000 ± .000	2.795 (24) **	Level 8	.671	.671
4 mins after 3rd ice	.300 ± .677	.000 ± .000	2.216 (24) *	Level 9	.351	.351
6 mins after 3rd ice	.340 ± .746	.000 ± .000	2.279 (24) *	Level 10	.134	.134
8 mins after 3rd ice	.400 ± .866	.000 ± .000	2.309 (24) *	Level 11	.000	.000

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01)

In one case simple contrasts could not be computed because the matrix was singular.

Table 7.1.4. Drowsiness

Ice on temple after OKS

Drowsiness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=25)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.720 ± 1.316	.341 ± 1.285	.996 (45)			
Before 1st ice	.720 ± 1.316	.341 ± 1.285	.996 (45)	Level 2	.	.
During 1st ice	.100 ± .408 ^^	.136 ± .640	-.235 (45)	Level 3	10.697 **	2.716
Before 2nd ice	.500 ± 1.275	.273 ± 1.077	.655 (45)	Level 4	2.880	.799
During 2nd ice	.240 ± .723	.182 ± .853	.253 (45)	Level 5	5.191 *	1.309
Before 3rd ice	.460 ± 1.338	.341 ± 1.285	.310 (45)	Level 6	1.578	1.578
During 3rd ice	.600 ± 1.581	.136 ± .640	2.072 (24) *	Level 7	.673	.046
2 mins after 3rd ice	.540 ± 1.338	.318 ± 1.287	.577 (45)	Level 8	.998	.601
4 mins after 3rd ice	.860 ± 1.510	.227 ± .869	2.216 (24) *	Level 9	.010	.922
6 mins after 3rd ice	.920 ± 1.612	.273 ± 1.077	1.595 (45)	Level 10	.237	.980
8 mins after 3rd ice	1.060 ± 1.787	.273 ± 1.077	1.853 (24)	Level 11	.828	1.866

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^^ p < .01)

In one case simple contrasts could not be computed because the matrix was singular.

Table 7.1.5. Headache

Ice on temple after OKS

Headache						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=25)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	1.220 ± 2.204	.250 ± .752	2.068 (30.168) *			
Before 1st ice	1.220 ± 2.204	.250 ± .752	2.068 (30.168) *	Level 2	.	.
During 1st ice	2.840 ± 3.558 ^	.545 ± 1.438	2.961 (32.463) **	Level 3	6.963 *	3.330
Before 2nd ice	1.380 ± 2.265 ^	.250 ± .612	2.397 (27.932) *	Level 4	2.774	2.774
During 2nd ice	2.750 ± 3.243 ^	.454 ± 1.371	3.226 (33.168) **	Level 5	6.222 *	3.633
Before 3rd ice	1.700 ± 2.341 ^	.295 ± .648	2.877 (28.124) **	Level 6	4.447 *	3.041
During 3rd ice	2.620 ± 2.927 ^^	.204 ± .570	4.040 (26.06) ***	Level 7	7.055 *	8.034 **
2 mins after 3rd ice	1.700 ± 2.179 ^^	.250 ± .593	3.195 (27.977) **	Level 8	4.807 *	4.807 *
4 mins after 3rd ice	1.500 ± 2.165	.295 ± .701	2.629 (29.584) *	Level 9	2.861	1.486
6 mins after 3rd ice	1.500 ± 2.184 ^	.454 ± .999	2.151 (34.535) *	Level 10	4.436 *	.108
8 mins after 3rd ice	1.480 ± 2.252 ^	.409 ± .895	2.189 (32.2) *	Level 11	4.352 *	.252

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01)

In one case simple contrasts could not be computed because the matrix was singular.

Table 7.1.6. Unpleasantness

Ice on temple after OKS

Unpleasantness						
	Mean ± SD		Group t-tests (df)	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=25)	Controls (n=22)		Level 1 vs.	Time	Group x time
Baseline	1.100 ± 2.150	.091 ± .294	2.322 (25.019) *			
Before 1st ice	1.100 ± 2.150	.091 ± .294	2.322 (25.019) *	Level 2	.	.
During 1st ice	5.100 ± 3.894 ^^^	2.045 ± 2.935 ^^	3.057 (44.023) **	Level 3	41.221 ***	4.864 *
Before 2nd ice	1.820 ± 1.973 ^	.250 ± .686	3.731 (30.386) ***	Level 4	6.287 *	2.559
During 2nd ice	5.040 ± 3.705 ^^^	1.818 ± 2.754 ^^	3.408 (43.845) ***	Level 5	39.934 ***	6.088 *
Before 3rd ice	2.160 ± 2.625 ^^	.409 ± .840	3.157 (29.455) **	Level 6	11.708 **	3.392
During 3rd ice	4.760 ± 3.443 ^^^	1.227 ± 2.562	4.019 (43.859) ***	Level 7	34.717 ***	9.611 **
2 mins after 3rd ice	2.140 ± 2.396 ^^^	.250 ± .703	3.765 (28.612) ***	Level 8	14.380 ***	7.761 **
4 mins after 3rd ice	1.640 ± 2.298 ^	.091 ± .294	3.339 (24.893) **	Level 9	5.125 *	5.125 *
6 mins after 3rd ice	1.400 ± 2.282	.045 ± .213	2.953 (24.476) **	Level 10	1.955	3.600
8 mins after 3rd ice	1.480 ± 2.252	.409 ± .895	2.722 (27.325) *	Level 11	5.913 *	.046

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01, ^^^ p < .001)

In one case simple contrasts could not be computed because the matrix was singular.

Table 7.1.7. Ice-induced intensity

Ice on temple after OKS

Ice-induced intensity						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=25)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
During 1st ice	7.020 ± 3.222	5.114 ± 2.572	2.220 (45) *			
Before 2nd ice	2.420 ± 2.271 ^^^	.932 ± .712 ^^^	3.107 (29.242) **	Level 2	114.149 ***	.259
During 2nd ice	7.260 ± 2.883	5.090 ± 2.715	2.644 (45) *	Level 3	.367	.536
Before 3rd ice	2.308 ± 2.103 ^^^	.786 ± .786 ^^^	3.361 (31.330) **	Level 4	118.119 ***	.214
During 3rd ice	6.968 ± 2.984	4.591 ± 2.706	2.845 (45) **	Level 5	1.424	.955
2 mins after 3rd ice	2.184 ± 2.010 ^^^	.664 ± .847 ^^^	3.449 (33.120) **	Level 6	114.438 ***	.198
4 mins after 3rd ice	1.300 ± 1.931 ^^^	.308 ± .391 ^^^	2.511 (26.223) *	Level 7	149.964 ***	1.131
6 mins after 3rd ice	.920 ± 2.014 ^^^	.086 ± .235 ^^^	2.054 (24.742)	Level 8	156.561 ***	1.455
8 mins after 3rd ice	.760 ± 1.937 ^^^	.000 ± .002 ^^^	1.960 (24)	Level 9	166.528 ***	1.693

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^^^ p < .001)

Ratings during the first application were used as a point of comparison in a series of simple contrasts across subsequent time points.

Table 7.1.8. Ice-induced unpleasantness

Ice on temple after OKS

Ice-induced unpleasantness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=25)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
During 1st ice	6.800 ± 3.096	3.409 ± 2.954	3.827 (45) ***			
Before 2nd ice	1.660 ± 2.144 ^^^	.273 ± .702 ^^^	3.054 (29.706) **	Level 2	84.803 ***	4.970 *
During 2nd ice	7.040 ± 2.772	3.659 ± 3.017	4.003 (45) ***	Level 3	1.633	.001
Before 3rd ice	2.088 ± 2.681 ^^^	.364 ± .743 ^^^	3.084 (28.126) **	Level 4	68.812 ***	3.176
During 3rd ice	6.428 ± 2.838	3.341 ± 2.834	3.723 (45) ***	Level 5	.819	.390
2 mins after 3rd ice	1.464 ± 2.068 ^^^	.409 ± .811 ^^^	2.353 (32.005) *	Level 6	79.594 ***	6.250 *
4 mins after 3rd ice	.880 ± 1.894 ^^^	.204 ± .367 ^^^	1.746 (26.037)	Level 7	101.920 ***	9.027 **
6 mins after 3rd ice	.670 ± 1.883 ^^^	.068 ± .234 ^^^	1.584 (24.839)	Level 8	107.698 ***	9.340 **
8 mins after 3rd ice	.500 ± 1.826 ^^^	.000 ± .000 ^^^	1.369 (24)	Level 9	110.973 ***	9.839 **

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^^^ p < .001)

Ratings during the first application were used as a point of comparison in a series of simple contrasts across subsequent time point.

PULSE AMPLITUDE

Table 7.2.1. Means and standard deviations for migraineurs and controls for changes in pulse amplitude (ipsilateral, contralateral to stimulation) across 11 time points (30 second samples, before {trial 1, 2 & 3}, during {trial 1, 2 & 3} and after {trial 1, 2 & 3} ice application to temple, and 3 and 8 mins after the 3rd application).

Ice on temple after OKS

	Means ± SD					
	Migraineurs (n = 25)		Controls (n = 22)		Group t-tests (df)	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral
Before 1st ice	-1.1 ± 16.7	6.2 ± 19.8	0.4 ± 7.0	-0.4 ± 6.6	-.412 (45)	1.503 (45)
During 1st ice	3.5 ± 28.4	6.7 ± 24.0	4.0 ± 20.0	2.5 ± 9.7	-.072 (43.062)	.799 (45)
After 1st ice	3.0 ± 22.1	11.8 ± 23.6 ^	2.3 ± 17.3	2.5 ± 10.0	.118 (44.395)	1.720 (45)
Before 2nd ice	-3.4 ± 24.0	0.2 ± 24.1	1.7 ± 10.2	0.1 ± 8.9	-.932 (45)	.007 (45)
During 2nd ice	-0.2 ± 29.1	3.8 ± 20.8	1.7 ± 24.2	-2.0 ± 10.4	-.245 (44.874)	1.184 (45)
After 2nd ice	-3.4 ± 25.4	9.3 ± 24.9	-2.0 ± 12.3	-2.8 ± 8.9	-.240 (45)	2.177 (45) *
Before 3rd ice	-7.1 ± 24.8	-1.6 ± 19.5	3.9 ± 18.6	-0.8 ± 10.1	-1.731 (43.970)	-.178 (45)
During 3rd ice	-4.3 ± 28.4	0.4 ± 21.3	3.9 ± 22.5	-2.3 ± 10.9	-1.106 (44.541)	.544 (45)
After 3rd ice	-0.5 ± 31.1	5.1 ± 23.3	0.1 ± 14.9	-1.7 ± 10.6	-.083 (35.450)	1.264 (45)
3 mins after 3rd ice	-6.3 ± 26.1	1.9 ± 25.7	1.7 ± 11.1	-2.1 ± 8.9	-1.334 (45)	.698 (45)
8 mins after 3rd ice	-8.6 ± 32.0	1.5 ± 28.1	1.7 ± 14.4	-2.9 ± 7.7	-1.386 (45)	.718 (45)

* statistically significant (* $p < .05$)

^ baseline *vs* subsequent levels within groups statistically significant (^ $p < .05$)

PULSE AMPLITUDE

Table 7.2.2. Main effects, interactions and intercepts from a series of 2 (group: migraineurs, controls) x 2 (side: ipsilateral, contralateral to stimulation) repeated-measures ANOVA's at each time point.

Ice on temple after OKS

F ratios					
	Main effects and Interactions (df = 1,45)			Intercepts (df)	
	Group	Side	Side x Group	Migraineurs (1,24)	Controls (1,21)
Before 1st ice	.510	2.210	3.630	.643	.000
During 1st ice	.127	.075	.497	1.254	1.759
After 1st ice	1.078	2.323	2.166	3.292	1.196
Before 2nd ice	.302	.125	.798	.158	.337
During 2nd ice	.128	.003	1.125	.162	.003
After 2nd ice	1.262	3.368	4.423 *	.482	2.437
Before 3rd ice	1.659	.015	2.440	1.340	.428
During 3rd ice	.293	.037	1.917	.216	.095
After 3rd ice	.361	.253	.981	.253	.184
3 mins after 3rd ice	.147	.639	4.640 *	.222	.011
8 mins after 3rd ice	.233	.760	5.382 *	.436	.093

* statistically significant (* $p < .05$)

APPENDIX 8

Condition 3

Ice on temple before OKS

SYMPTOMATIC RESPONSES

Table 8.1. 1. Nausea

Nausea						
	Mean ± SD		**Group t-tests (df)**	**Simple Contrasts F ratios (df = 1, 43)**		
	Migraineurs (n=25)	**Controls (n=23)**		**Level 1 vs.**	**Time**	**Group x time**
Baseline	.140 ± .339	.087 ± .245	.616 (46)			
Before 1st ice	.140 ± .339	.087 ± .245	.616 (46)	Level 2	.	.
During 1st ice	.140 ± .339	.087 ± .417	.485 (46)	Level 3	.000	.000
Before 2nd ice	.100 ± .289	.000 ± .000	1.732 (24)	Level 4	3.885	.531
During 2nd ice	.140 ± .396	.000 ± .000	1.769 (24)	Level 5	.863	.863
Before 3rd ice	.160 ± .374	.000 ± .000	2.138 (24) *	Level 6	.693	1.768
During 3rd ice	.440 ± .950	.000 ± .000	2.316 (24) *	Level 7	1.486	4.904 *
2 mins after 3rd ice	.420 ± 1.007	.022 ± .104	1.966 (24.559)	Level 8	1.172	3.027
4 mins after 3rd ice	.380 ± .869	.022 ± .104	2.045 (24.750)	Level 9	1.228	3.744
6 mins after 3rd ice	.320 ± .840	.011 ± .052	1.836 (24.201)	Level 10	.394	2.390
8 mins after 3rd ice	.280 ± .693	.011 ± .052	1.935 (24.295)	Level 11	.238	2.726

* difference between migraine sufferers and controls statistically significant (* p < .05)

In one case simple contrasts could not be computed because the matrix was singular.

Table 8.1.2. Body temperature

Ice on temple before OKS

Body temperature						
	Mean ± SD		**Group**	**Simple Contrasts F ratios (df = 1, 43)**		
	Migraineurs (n=25)	**Controls (n=23)**	**t-tests (df)**	**Level 1 vs.**	**Time**	**Group x time**
Baseline	.100 ± .500	.348 ± .790	-1.286 (36.652)			
Before 1st ice	.100 ± .500	.348 ± .790	-1.286 (36.652)	Level 2	.	.
During 1st ice	.160 ± .554	.283 ± .720	-.664 (46)	Level 3	.002	1.182
Before 2nd ice	.100 ± .289	.283 ± .720	-1.135 (28.414)	Level 4	.744	.744
During 2nd ice	.200 ± .595	.304 ± .703	-.557 (46)	Level 5	.131	.843
Before 3rd ice	.240 ± .459	.326 ± .701	-.507 (46)	Level 6	1.186	2.218
During 3rd ice	.280 ± .751	.304 ± .703	-.116 (46)	Level 7	.544	1.456
2 mins after 3rd ice	.240 ± .542	.304 ± .703	-.357 (46)	Level 8	.420	1.518
4 mins after 3rd ice	.140 ± .445	.304 ± .703	-.958 (36.666)	Level 9	.001	.369
6 mins after 3rd ice	.180 ± .476	.261 ± .619	-.510 (46)	Level 10	.003	1.881
8 mins after 3rd ice	.220 ± .502	.261 ± .619	-.252 (46)	Level 11	.067	2.632

In one case simple contrasts could not be computed because the matrix was singular.

Table 8.1.3. Dizziness

Ice on temple before OKS

Dizziness						
	Mean ± SD		Group t-tests (df)	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=25)	Controls (n=23)		Level 1 vs.	Time	Group x time
Baseline	.160 ± .473	.000 ± .000	1.693 (24)			
Before 1st ice	.160 ± .473	.000 ± .000	1.693 (24)	Level 2	.	.
During 1st ice	.080 ± .400	.000 ± .000	.958(46)	Level 3	1.917	1.917
Before 2nd ice	.140 ± .531	.000 ± .000	1.319 (24)	Level 4	.178	.178
During 2nd ice	.200 ± .645	.000 ± .000	1.549 (24)	Level 5	.298	.298
Before 3rd ice	.200 ± .645	.000 ± .000	1.549 (24)	Level 6	.298	.298
During 3rd ice	.320 ± .988	.000 ± .000	1.619 (24)	Level 7	1.056	1.056
2 mins after 3rd ice	.220 ± .914	.000 ± .000	1.204 (24)	Level 8	.277	.277
4 mins after 3rd ice	.200 ± .816	.000 ± .000	1.225 (24)	Level 9	.178	.178
6 mins after 3rd ice	.240 ± .831	.000 ± .000	1.445 (24)	Level 10	.604	.604
8 mins after 3rd ice	.200 ± .816	.000 ± .000	1.225 (24)	Level 11	.178	.178

In one case simple contrasts could not be computed because the matrix was singular.

Table 8.1.4. Drowsiness

Ice on temple before OKS

Drowsiness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=25)	Controls (n=23)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.160 ± .374	.152 ± .351	.075 (46)			
Before 1st ice	.160 ± .374	.152 ± .351	.075 (46)	Level 2	.	.
During 1st ice	.000 ± .000 ^	.000 ± .000 ^		Level 3	8.836 **	.006
Before 2nd ice	.120 ± .440	.065 ± .229	.534 (46)	Level 4	1.309	.179
During 2nd ice	.080 ± .400	.000 ± .000 ^	.958 (46)	Level 5	4.530 *	.438
Before 3rd ice	.200 ± .645	.196 ± .653	.023 (46)	Level 6	.214	.000
During 3rd ice	.280 ± .891	.043 ± .208	1.290 (26.841)	Level 7	.004	1.548
2 mins after 3rd ice	.380 ± 1.184	.196 ± .653	.660(46)	Level 8	1.125	.505
4 mins after 3rd ice	.320 ± .900	.217 ± .654	1.225 (24)	Level 9	1.140	.202
6 mins after 3rd ice	.480 ± 1.046	.304 ± 1.052	.580 (46)	Level 10	2.721	.344
8 mins after 3rd ice	.540 ± 1.098	.283 ± 1.251	.759 (46)	Level 11	2.344	.560

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05)

In one case t could not be computed because the standard deviation of both groups was 0

In one case simple contrasts could not be computed because the matrix was singular.

Table 8.1.5. Headache

Ice on temple before OKS

Headache						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=25)	Controls (n=23)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.290 ± .538	.000 ± .000	2.693 (24) *			
Before 1st ice	.290 ± .538	.000 ± .000	2.693 (24) *	Level 2	.	.
During 1st ice	.876 ± 2.133	.000 ± .000	2.053 (24)	Level 3	1.861	1.861
Before 2nd ice	.470 ± .953	.000 ± .000	2.466 (24) *	Level 4	1.156	1.156
During 2nd ice	1.440 ± 1.827 ^^	.130 ± .625	3.374 (29.972) **	Level 5	10.710 **	6.790 *
Before 3rd ice	.610 ± 1.000 ^	.000 ± .000	3.049 (24) **	Level 6	4.536 *	4.536 *
During 3rd ice	1.900 ± 2.411 ^^	.174 ± .834	3.367 (24) **	Level 7	11.824 **	7.662 **
2 mins after 3rd ice	1.140 ± 1.611 ^^	.000 ± .000	3.539 (24) **	Level 8	7.477 **	7.477 **
4 mins after 3rd ice	1.040 ± 1.689 ^	.000 ± .000	3.079 (24) *	Level 9	4.979 *	4.979 *
6 mins after 3rd ice	.984 ± 1.849	.000 ± .000	2.661 (24) *	Level 10	3.528	3.528
8 mins after 3rd ice	.970 ± 1.786	.000 ± .000	2.716 (24) *	Level 11	3.778	3.788

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01)

In one case simple contrasts could not be computed because the matrix was singular.

Table 8.1.6. Unpleasantness

Ice on temple before OKS

Unpleasantness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=25)	Controls (n=23)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.170 ± .373	.109 ± .300	.624 (46)			
Before 1st ice	.170 ± .373	.109 ± .300	.624 (46)	Level 2	.	.
During 1st ice	2.840 ± 3.300 ^^^	1.283 ± 1.814 ^^	2.047 (37.898) *	Level 3	25.472 ***	3.859
Before 2nd ice	.540 ± 1.258	.065 ± .229	1.855 (25.722)	Level 4	2.037	3.266
During 2nd ice	4.160 ± 3.236 ^^^	1.326 ± 1.910 ^^	3.729 (39.452) **	Level 5	48.836 ***	13.845 **
Before 3rd ice	.660 ± 1.188 ^	.196 ± .494	1.793 (32.616)	Level 6	7.928 **	3.869
During 3rd ice	3.190 ± 3.344 ^^^	.783 ± 1.223 ^^	3.363 (30.777) **	Level 7	28.104 ***	11.336 **
2 mins after 3rd ice	1.080 ± 1.712 ^^	.130 ± .458	2.671 (27.692) *	Level 8	8.095 **	7.357 **
4 mins after 3rd ice	.740 ± 1.508 ^	.065 ± .229	2.210 (25.200) *	Level 9	3.603	4.892 *
6 mins after 3rd ice	.710 ± 1.667	.000 ± .000	2.129 (24) *	Level 10	2.040	4.299 *
8 mins after 3rd ice	.680 ± 1.682	.000 ± .000	2.021 (24)	Level 11	1.481	3.832

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01, ^^^ p < .001)

In one case simple contrasts could not be computed because the matrix was singular.

Table 8.1.7. Ice-induced intensity

Ice on temple before OKS

Ice-induced intensity						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=25)	Controls (n=23)	t-tests (df)	Level 1 vs.	Time	Group x time
During 1st ice	6.600 ± 2.278	4.435 ± 2.586	3.084 (46) **			
Before 2nd ice	1.680 ± 1.224 ^^^	.630 ± .757 ^^^	3.604 (40.479) ***	Level 2	189.176 ***	3.094
During 2nd ice	6.720 ± 2.525	4.630 ± 2.573	2.838 (46) **	Level 3	1.277	.073
Before 3rd ice	2.140 ± 1.715 ^^^	.674 ± .614 ^^^	4.025 (30.589) ***	Level 4	143.568 ***	1.038
During 3rd ice	6.780 ± 2.492	4.261 ± 2.486	3.503 (46) ***	Level 5	.000	.990
2 mins after 3rd ice	2.160 ± 1.586 ^^^	.609 ± .768 ^^^	4.366 (35.295) ***	Level 6	127.002 ***	.701
4 mins after 3rd ice	1.100 ± 1.099 ^^^	.193 ± .319 ^^^	3.947 (28.341) ***	Level 7	179.528 ***	2.997
6 mins after 3rd ice	.600 ± .898 ^^^	.098 ± .176 ^^^	2.738 (25.997) *	Level 8	198.875 ***	5.148 *
8 mins after 3rd ice	.330 ± .656 ^^^	.104 ± .315 ^^^	1.537 (35.126)	Level 9	213.913 ***	7.161 *

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^^^ p < .001)

Ratings during the first application were used as a point of comparison in a series of simple contrasts across subsequent time points.

Table 8.1.8. Ice-induced unpleasantness

Ice on temple before OKS

Ice-induced unpleasantness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=25)	Controls (n=23)	t-tests (df)	Level 1 vs.	Time	Group x time
During 1st ice	6.260 ± 2.582	3.239 ± 2.558	4.067 (46) ***			
Before 2nd ice	.820 ± 1.282 ^^^	.174 ± .387 ^^^	2.403 (28.696) *	Level 2	132.734 ***	10.348 **
During 2nd ice	6.160 ± 2.794	3.478 ± 2.543	3.467 (46) ***	Level 3	.138	.818
Before 3rd ice	1.280 ± 1.601 ^^^	.304 ± .559 ^^^	2.863 (30.197) **	Level 4	106.249 ***	7.095 *
During 3rd ice	6.180 ± 2.817	3.196 ± 2.553	3.834 (46) ***	Level 5	.067	.006
2 mins after 3rd ice	1.440 ± 1.523 ^^^	.217 ± .518 ^^^	3.783 (29.910) ***	Level 6	100.645 ***	5.293 *
4 mins after 3rd ice	.590 ± .856 ^^^	.087 ± .288 ^^^	2.771 (29.774) **	Level 7	138.770 ***	11.303 **
6 mins after 3rd ice	.304 ± .593 ^^^	.022 ± .104 ^^^	2.340 (25.606) *	Level 8	148.351 ***	13.222 ***
8 mins after 3rd ice	.180 ± .476 ^^^	.000 ± .000 ^^^	1.890 (24)	Level 9	155.490 ***	14.450 ***

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01, ^^^ p < .001)

Ratings during the first application were used as a point of comparison in a series of simple contrasts across subsequent time points.

PULSE AMPLITUDE

Table 8.2.1. Means and standard deviations for migraineurs and controls for changes in pulse amplitude (ipsilateral, contralateral to stimulation) across 11 time points (30 second samples, before {trial 1, 2 & 3}, during {trial 1, 2 & 3} and after {trial 1, 2 & 3} ice application to temple, and 3 and 8 mins after the 3rd application).

Ice on temple before OKS

	Means ± SD					
	Migraineurs (n = 25)		Controls (n = 23)		Group t-tests (df)	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral
Before 1st ice	21.0 ± 24.0 ^^^	17.1 ± 21.1 ^^^	0.5 ± 5.1	-0.9 ± 7.3	4.163 (26.356) ***	4.001 (30.154) ***
During 1st ice	22.9 ± 28.7 ^^^	17.0 ± 28.1 ^^	4.5 ± 16.1	1.0 ± 9.9	2.712 (46) **	2.675 (30.353) *
After 1st ice	25.2 ± 33.0 ^^^	21.2 ± 40.4 ^	3.5 ± 11.1	1.0 ± 15.7	3.102 (29.793) **	2.314 (31.563) *
Before 2nd ice	20.8 ± 23.1 ^^^	15.5 ± 23.9 ^^	6.6 ± 9.6 ^^	7.3 ± 15.8 ^	2.819 (32.640) **	1.419 (41.951)
During 2nd ice	23.0 ± 28.1 ^^^	19.1 ± 31.5 ^^	1.5 ± 13.9	5.2 ± 15.3	3.404 (35.674) **	1.974 (35.325)
After 2nd ice	24.7 ± 30.3 ^^^	26.4 ± 40.5 ^^	3.6 ± 10.4	4.3 ± 17.5	3.275 (29.994) **	2.490 (33.298) *
Before 3rd ice	25.6 ± 24.3 ^^^	26.9 ± 30.8 ^^^	6.7 ± 16.7	6.8 ± 14.0 ^	3.111 (46) **	2.955 (34.100) **
During 3rd ice	30.1 ± 35.8 ^^^	26.5 ± 35.1 ^^^	8.8 ± 23.5	8.7 ± 15.2 ^	2.408 (46) *	2.308 (33.292) *
After 3rd ice	30.8 ± 36.1 ^^^	28.4 ± 39.0 ^^^	11.8 ± 27.0 ^	9.9 ± 22.4 ^	2.042 (46) *	1.991 (46)
3 mins after 3rd ice	31.4 ± 35.8 ^^^	33.1 ± 34.5 ^^^	11.2 ± 19.1 ^^	12.0 ± 21.3 ^	2.402 (46) *	2.580 (40.513) *
8 mins after 3rd ice	37.4 ± 40.1 ^^^	34.1 ± 38.2 ^^^	16.4 ± 25.7 ^^	15.0 ± 28.0 ^	2.140 (46) *	1.980 (43.902)

* statistically significant (* $p < .05$, ** $p < .01$, *** $p < .001$)

^ baseline *vs* subsequent levels within groups statistically significant (^ $p < .05$, ^^ $p < .01$, ^^^ $p < .001$)

PULSE AMPLITUDE

Table 8.2.2. Main effects, interactions and intercepts from a series of 2 (group: migraineurs, controls) x 2 (side: ipsilateral, contralateral to stimulation) repeated-measures ANOVA's at each time point.

Ice on temple before OKS

F ratios					
	Main effects and Interactions (df = 1,46)			Intercepts (df)	
	Group	Side	Side x Group	Migraineurs (1,24)	Controls (1,22)
Before 1st ice	19.813 ***	1.316	.295	22.155 ***	.036
During 1st ice	9.607 **	1.980	.129	16.373 ***	1.569
After 1st ice	7.833 **	.975	.053	11.454 **	.948
Before 2nd ice	5.429 *	.690	1.151	18.444 ***	11.859 **
During 2nd ice	8.313 **	.000	1.502	14.875 **	1.906
After 2nd ice	9.298 **	.108	.019	15.553 **	3.269
Before 3rd ice	12.603 **	.046	.028	31.275 ***	6.722 *
During 3rd ice	6.757 *	.232	.214	18.758 ***	7.060 *
After 3rd ice	4.924 *	.317	.003	18.139 ***	5.851 *
3 mins after 3rd ice	7.676 **	.108	.017	26.181 ***	9.966 **
8 mins after 3rd ice	5.158 *	.310	.053	26.539 ***	8.997 **

* statistically significant (* $p < .05$, ** $p < .01$, *** $p < .001$)

APPENDIX 9

Condition 4

Ice on temple during OKS

Table 9.1.1. Nausea

Nausea						
	Mean ± SD		Group t-tests (df)	Simple Contrasts F ratios (df = 1, 38)		
	Migraineurs (n=18)	Controls (n=22)		Level 1 vs.	Time	Group x time
Baseline	.278 ± .647	.045 ± .213	1.869 (29.085)			
Before 1st ice	.972 ± 1.684	.023 ± .107	2.690 (24.474) *	Level 2	2.988	3.406
During 1st ice	1.389 ± 2.125 ^	.277 ± .753	2.403 (38.407) *	Level 3	7.916 **	3.394
Before 2nd ice	1.944 ± 2.639 ^	.500 ± 1.134 ^	2.609 (40.086) *	Level 4	11.213 **	3.662
During 2nd ice	2.361 ± 2.806 ^^	.832 ± 1.584 ^	2.767 (44.003) **	Level 5	17.662 ***	3.608
Before 3rd ice	3.083 ± 3.318 ^^	.773 ± 1.771 ^	3.388 (29.971) **	Level 6	20.288 ***	7.021 *
During 3rd ice	3.417 ± 3.414 ^^^	1.273 ± 2.359 ^	2.807 (32.145) **	Level 7	24.665 ***	4.728 *
2 mins after 3rd ice	3.917 ± 3.392 ^^^	.727 ± 1.541	3.690 (22.701) ***	Level 8	28.821 ***	13.500 ***
4 mins after 3rd ice	2.944 ± 2.437 ^^^	.579 ± 1.204 ^	4.397 (40.712) ***	Level 9	30.824 ***	13.683 ***
6 mins after 3rd ice	1.611 ± 1.819 ^^	.123 ± .433	3.873 (35.436) ***	Level 10	13.887 **	10.861 **
8 mins after 3rd ice	1.356 ± 1.893 ^	.045 ± .147	3.281 (37.503) **	Level 11	8.321 **	8.231 **

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01, ^^^ p < .001)

Table 9.1.2. Body temperature

Ice on temple during OKS

Body temperature						
	Mean ± SD		**Group t-tests (df)**	**Simple Contrasts F ratios (df = 1, 38)**		
	Migraineurs (n=18)	**Controls (n=22)**		**Level 1 vs.**	**Time**	**Group x time**
Baseline	.056 ± .820	.227 ± .528	-.555 (46)			
Before 1st ice	.528 ± 1.091	.295 ± .630	.880 (46)	Level 2	4.012	2.243
During 1st ice	1.028 ± 2.075	.341 ± .643	1.390 (35.544)	Level 3	5.531 *	3.458
Before 2nd ice	1.222 ± 2.257 ^	.364 ± .726	2.242 (36.245) *	Level 4	6.483 *	4.047
During 2nd ice	1.667 ± 2.294 ^^	.409 ± .734	2.827 (37.886) **	Level 5	12.216 ***	7.754 **
Before 3rd ice	1.667 ± 2.491 ^	.409 ± .854	2.462 (23.432) *	Level 6	9.990 **	6.349 *
During 3rd ice	1.667 ± 2.739 ^	.704 ± 1.453	1.942 (26.733)	Level 7	9.943 **	2.931
2 mins after 3rd ice	2.167 ± 3.106 ^^	.482 ± .849	2.234 (19.086) *	Level 8	12.449 ***	7.668 **
4 mins after 3rd ice	1.750 ± 2.427 ^^	.386 ± .770	3.248 (33.249) **	Level 9	13.357 ***	9.165 **
6 mins after 3rd ice	.750 ± 1.801	.227 ± .612	2.067 (32.645) *	Level 10	3.387	3.387
8 mins after 3rd ice	.917 ± 2.315	.250 ± .612	1.885 (32.726)	Level 11	3.260	2.933

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01)

Table 9.1.3. Dizziness

Ice on temple during OKS

Dizziness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 38)		
	Migraineurs (n=18)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.278 ± .752	.000 ± .000	1.549 (24)			
Before 1st ice	1.944 ± 2.261 ^^	.614 ± 1.090 ^	2.517 (31.238) *	Level 2	17.316 ***	3.693
During 1st ice	2.667 ± 3.010 ^^	.591 ± 1.054 ^	3.117 (29.665) **	Level 3	21.468 ***	7.816 **
Before 2nd ice	2.861 ± 3.377 ^^	.727 ± 1.307 ^	3.294 (31.241) **	Level 4	20.413 ***	6.416 *
During 2nd ice	2.944 ± 3.244 ^^	.773 ± 1.412 ^	3.233 (33.226) **	Level 5	22.491 ***	6.820 *
Before 3rd ice	2.722 ± 3.286 ^^	.886 ± 1.573 ^	2.806 (27.239) **	Level 6	20.620 ***	4.512 *
During 3rd ice	3.583 ± 3.482 ^^^	1.227 ± 2.424 ^	2.812 (33.597) **	Level 7	25.516 ***	5.364 *
2 mins after 3rd ice	3.694 ± 3.722 ^^^	.877 ± 1.785 ^	2.945 (23.334) **	Level 8	25.215 ***	8.819 **
4 mins after 3rd ice	1.944 ± 2.338 ^^	.341 ± 1.189	2.942 (34.294) **	Level 9	12.883 ***	5.618 *
6 mins after 3rd ice	1.083 ± 1.611 ^	.182 ± .664	2.642 (29.303) *	Level 10	8.000 **	3.193
8 mins after 3rd ice	.906 ± 1.521	.136 ± .467	2.601 (28.083) *	Level 11	6.351 *	2.627

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01, ^^^ p < .001)

Table 9.1.4. Drowsiness

Ice on temple during OKS

Drowsiness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 38)		
	Migraineurs (n=18)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.333 ± .840	.295 ± 1.278	.249 (46)			
Before 1st ice	1.250 ± 1.240 ^	.500 ± 1.739	1.539 (46)	Level 2	11.987 ***	4.835 *
During 1st ice	1.417 ± 1.987 ^	.477 ± 1.721	1.648 (45.566)	Level 3	8.040 **	4.082 *
Before 2nd ice	1.444 ± 2.175 ^	.659 ± 1.873	1.392 (46)	Level 4	8.318 **	2.137
During 2nd ice	1.694 ± 2.515 ^	.682 ± 1.836	1.761 (43.891)	Level 5	9.426 **	2.933
Before 3rd ice	1.889 ± 2.581 ^	.818 ± 1.973	2.172 (34.498) *	Level 6	11.717 ***	2.894
During 3rd ice	1.806 ± 2.834 ^	.364 ± .953	2.652 (22.677) *	Level 7	5.936 *	4.931 *
2 mins after 3rd ice	2.083 ± 2.809 ^	.636 ± 1.529	1.961 (25.050)	Level 8	12.021 ***	5.460 *
4 mins after 3rd ice	1.861 ± 2.519 ^	.409 ± 1.140	2.874 (33.474) **	Level 9	9.455 **	7.018 *
6 mins after 3rd ice	1.500 ± 2.407 ^	.364 ± 1.497	2.430 (39.118) *	Level 10	6.061 *	4.796 *
8 mins after 3rd ice	.944 ± 1.552	.295 ± 1.076	2.300 (39.061) *	Level 11	4.565 *	4.565 *

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05)

Table 9.1.5. Headache

Ice on temple during OKS

Headache						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 38)		
	Migraineurs (n=18)	Controls (n=22)	t -tests (df)	Level 1 vs.	Time	Group x time
Baseline	.722 ± 1.320	.000 ± .000	2.864 (24) **			
Before 1st ice	.861 ± 1.370	.000 ± .000	3.636 (24) ***	Level 2	1.480	1.480
During 1st ice	1.528 ± 1.802 ^^	.045 ± .213	4.116 (24.902) ***	Level 3	11.582 **	9.240 **
Before 2nd ice	1.528 ± 2.104 ^^	.000 ± .000	3.917 (24) ***	Level 4	12.475 ***	12.475 ***
During 2nd ice	2.556 ± 2.999 ^^	.000 ± .000	4.473 (24) ***	Level 5	16.421 ***	16.421 ***
Before 3rd ice	2.566 ± 2.770 ^^^	.011 ± .053	4.464 (20.014) ***	Level 6	25.320 ***	24.700 ***
During 3rd ice	2.556 ± 2.940 ^^^	.000 ± .000	4.231 (19) ***	Level 7	18.872 ***	18.872 ***
2 mins after 3rd ice	2.444 ± 2.828 ^^^	.045 ± .213	3.591 (17.158) **	Level 8	22.577 ***	20.315 ***
4 mins after 3rd ice	2.361 ± 2.611 ^^^	.023 ± .107	4.702 (24.087) ***	Level 9	24.076 ***	22.777 ***
6 mins after 3rd ice	2.250 ± 2.475 ^^^	.004 ± .021	5.089 (24.004) ***	Level 10	25.794 ***	25.489 ***
8 mins after 3rd ice	2.292 ± 2.685 ^^^	.023 ± .107	4.881 (24.100) ***	Level 11	20.748 ***	19.580 ***

* difference between migraine sufferers and controls statistically significant (** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^^ p < .01, ^^^ p < .001)

Table 9.1.6. Unpleasantness

Ice on temple during OKS

Unpleasantness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 38)		
	Migraineurs (n=18)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.672 ± 1.040	.091 ± .426	2.552 (33.361) *			
Before 1st ice	1.950 ± 2.707 ^	.568 ± 1.137	2.733 (31.671) **	Level 2	9.099 **	1.893
During 1st ice	3.728 ± 3.368 ^^^	1.614 ± 1.889 ^^^	3.185 (40.979) **	Level 3	35.732 ***	4.005
Before 2nd ice	3.283 ± 3.316 ^^^	.818 ± 1.296 ^^	3.947 (35.951) ***	Level 4	24.356 ***	7.756 **
During 2nd ice	4.478 ± 3.248 ^^^	1.795 ± 2.207 ^^^	3.502 (46) ***	Level 5	49.467 ***	7.192 *
Before 3rd ice	3.783 ± 3.412 ^^^	.932 ± 1.650 ^	3.823 (28.445) ***	Level 6	30.929 ***	10.206 **
During 3rd ice	4.533 ± 3.433 ^^^	1.977 ± 2.826 ^^	3.056 (40) **	Level 7	42.946 ***	5.070 *
2 mins after 3rd ice	4.756 ± 3.735 ^^^	1.023 ± 1.715 ^	3.916 (22.818) ***	Level 8	40.218 ***	15.881 ***
4 mins after 3rd ice	2.894 ± 2.511 ^^^	.545 ± 1.090 ^	4.463 (36.474) ***	Level 9	26.803 ***	11.689 **
6 mins after 3rd ice	2.117 ± 2.466 ^^	.250 ± .612	3.961 (31.709) ***	Level 10	13.503 ***	8.676 **
8 mins after 3rd ice	1.700 ± 2.452 ^	.136 ± .351	3.308 (32.820) **	Level 11	5.961 *	4.994 *

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01, ^^^ p < .001)

Table 9.1.7. Ice-induced intensity

Ice on temple during OKS

Ice-induced intensity						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 38)		
	Migraineurs (n=18)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
During 1st ice	5.444 ± 2.935	4.250 ± 2.608	2.210 (46) *			
Before 2nd ice	1.944 ± 1.822 ^^^	.695 ± .870 ^^^	3.849 (35.409) ***	Level 2	72.726 ***	.004
During 2nd ice	5.694 ± 3.015	4.182 ± 2.801	2.171 (43) *	Level 3	.161	.493
Before 3rd ice	2.125 ± 1.989 ^^^	.559 ± .904 ^^^	3.571 (25.444) ***	Level 4	65.813 ***	.185
During 3rd ice	5.917 ± 2.901	3.977 ± 2.851	2.594 (38) *	Level 5	.197	2.743
2 mins after 3rd ice	2.900 ± 2.151 ^^	.641 ± .819 ^^^	4.213 (21.029) ***	Level 6	48.044 ***	1.438
4 mins after 3rd ice	1.747 ± 1.825 ^^^	.252 ± .505 ^^^	4.022 (27.704) ***	Level 7	78.393 ***	.120
6 mins after 3rd ice	1.247 ± 1.849 ^^^	.104 ± .295 ^^^	3.451 (25.362) **	Level 8	86.571 ***	.003
8 mins after 3rd ice	.764 ± 1.346 ^^^	.002 ± .011 ^^^	3.448 (24.003) **	Level 9	104.388 ***	.245

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01, ^^^ p < .001)

Ratings during the first application were used as a point of comparison in a series of simple contrasts across subsequent time points.

Table 9.1.8. Ice-induced unpleasantness

Ice on temple during OKS

Ice-induced unpleasantness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 38)		
	Migraineurs (n=18)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
During 1st ice	5.167 ± 3.222	3.068 ± 2.669	3.255 (46) **			
Before 2nd ice	1.222 ± 1.700 ^^^	.364 ± .710 ^^^	3.363 (31.245) **	Level 2	58.815 ***	2.045
During 2nd ice	5.306 ± 3.241	3.045 ± 2.786	2.954 (43) **	Level 3	.045	.086
Before 3rd ice	1.306 ± 1.341 ^^^	.454 ± .912 ^^^	2.767 (26.732) **	Level 4	53.235 ***	1.975
During 3rd ice	5.583 ± 3.200	3.068 ± 2.925	2.594 (38) *	Level 5	.580	.580
2 mins after 3rd ice	1.928 ± 2.078 ^^^	.295 ± .549 ^^^	3.242 (18.947) **	Level 6	40.280 ***	.242
4 mins after 3rd ice	1.039 ± 1.303 ^^^	.136 ± .467 ^^^	3.483 (27.824) **	Level 7	63.246 ***	1.815
6 mins after 3rd ice	.514 ± .979 ^^^	.045 ± .213 ^^^	2.862 (25.169) **	Level 8	71.464 ***	3.223
8 mins after 3rd ice	.417 ± .974 ^^^	.000 ± .000 ^^^	2.804 (24) **	Level 9	71.242 ***	3.297

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01, ^^^ p < .001)

In one case simple contrasts could not be computed because the matrix was singular.

Ratings during the first application were used as a point of comparison in a series of simple contrasts across subsequent time points.

Table 9.1.9. Self-motion

Ice on temple during OKS

Self motion						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 38)		
	Migraineurs (n=18)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
Minute 2	1.111 ± .676	.682 ± .716	2.830 (46) **			
4	1.333 ± .686	.636 ± .789	3.862 (46) ***	Level 2	.651	1.492
6	1.444 ± .616 ^	.727 ± .702	3.856 (46) ***	Level 3	2.576	1.488
8	1.000 ± .767	.818 ± .853	1.206 (46)	Level 4	.008	.812
10	1.056 ± .184	.705 ± .766	1.844 (41)	Level 5	.021	.120
12	1.444 ± .705	.727 ± .827	3.097 (39) **	Level 6	3.184	1.839
14	1.444 ± .705	.750 ± .752	2.988 (38) **	Level 7	2.868	1.251

* difference between migraine sufferers and controls statistically significant (** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05)

Ratings during the first 2 minutes of OKS were used as a point of comparison in a series of simple contrasts across subsequent time points.

Table 9.1.10. Visual-illusion

Ice on temple during OKS

Visual illusion						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 38)		
	Migraineurs (n=18)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
Minute 2	.889 ± .758	.773 ± .612	.691 (46)			
4	1.167 ± .786	.682 ± .780	1.961 (46)	Level 2	.851	3.314
6	1.111 ± .758	.818 ± .733	1.668 (46)	Level 3	2.678	1.168
8	1.222 ± .732	.727 ± .702	2.249 (46) *	Level 4	2.085	3.609
10	1.222 ± .732	.773 ± .752	2.479 (41) *	Level 5	1.608	1.608
12	1.444 ± .705 ^	.818 ± .733	2.922 (39) **	Level 6	5.807 *	4.183 *
14	1.389 ± .608 ^^	.818 ± .644	2.807 (38) **	Level 7	7.242 *	5.029 *

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01)

Ratings during the first 2 minutes of OKS were used as a point of comparison in a series of simple contrasts across subsequent time points.

PULSE AMPLITUDE

Table 9.2.1. Means and standard deviations for migraineurs and controls for changes in pulse amplitude (ipsilateral, contralateral to stimulation) across 11 time points (30 second samples, before {trial 1, 2 & 3}, during {trial 1, 2 & 3} and after {trial 1, 2 & 3} ice application to temple, and 3 and 8 mins after the 3rd application).

Ice on temple during OKS

	Means ± SD					
	Migraineurs (n = 18)		Controls (n = 22)		Group t-tests (df)	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral
Before 1st ice	25.2 ± 34.1 ^^^	25.2 ± 31.3 ^^^	19.5 ± 35.9 ^^	13.5 ± 14.8 ^^^	.298 (46)	.885 (46)
During 1st ice	31.1 ± 38.7 ^^^	24.4 ± 42.9 ^	21.0 ± 42.7 ^	13.4 ± 14.0 ^^^	.710 (46)	.447 (46)
After 1st ice	30.7 ± 37.2 ^^^	27.9 ± 37.0 ^^	17.5 ± 44.1 ^	10.2 ± 15.8 ^^	.964 (46)	1.409 (36.459)
Before 2nd ice	32.2 ± 32.0 ^^^	25.0 ± 26.9 ^^^	12.0 ± 37.4	10.3 ± 11.0 ^^^	1.959 (42)	2.294 (28.549) *
During 2nd ice	35.7 ± 34.1 ^^^	33.5 ± 40.1 ^^^	8.0 ± 28.3	12.8 ± 14.1 ^^^	2.766 (42) **	2.006 (26.630)
After 2nd ice	22.9 ± 27.6 ^^^	25.6 ± 34.0 ^^	10.9 ± 32.1	12.0 ± 14.8 ^^^	1.539 (42)	1.674 (29.688)
Before 3rd ice	23.5 ± 27.1 ^^	22.1 ± 35.5 ^	11.8 ± 32.6	15.6 ± 14.6 ^^^	1.213 (38)	.727 (21.688)
During 3rd ice	31.5 ± 39.2 ^^	25.2 ± 37.3 ^	11.0 ± 35.1	16.4 ± 18.5 ^^^	1.739 (38)	.909 (23.744)
After 3rd ice	18.3 ± 27.4 ^	18.4 ± 32.1 ^	9.7 ± 35.8	12.1 ± 17.4 ^^	.846 (38)	.746 (24.976)
3 mins after 3rd ice	20.9 ± 29.4 ^^	19.0 ± 36.2 ^	11.3 ± 38.8	11.0 ± 16.4 ^^	.938 (45)	.857 (33.140)
8 mins after 3rd ice	1.1 ± 20.0	2.7 ± 27.0	-8.1 ± 17.4 ^	-0.9 ± 14.2	.940 (46)	-.071 (37.910)

* statistically significant (* $p < .05$, ** $p < .01$, *** $p < .001$)

^ baseline *vs* subsequent levels within groups statistically significant (^ $p < .05$, ^^ $p < .01$, ^^^ $p < .001$)

PULSE AMPLITUDE

Table 9.2.2. Main effects, interactions and intercepts from a series of 2 (group: migraineurs, controls) x 2 (side: ipsilateral, contralateral to stimulation) repeated-measures ANOVA's at each time point.

Ice on temple during OKS

F ratios					
	Main effects and Interactions (df = 1,46)			Intercepts (df)	
	Group	Side	Side x Group	Migraineurs (1,24)	Controls (1,22)
Before 1st ice	.367(1,46)	1.069(1,46)	.174(1,46)	18.775(1, 24) ***	14.171 (1, 22) ***
During 1st ice	.523(1,46)	1.899(1,46)	.113(1,46)	19.496(1, 24) ***	11.748 (1, 22) **
After 1st ice	1.771(1,46)	1.300(1,46)	.002(1,46)	18.278(1, 24) ***	7.674 (1, 22) *
Before 2nd ice	6.222(1,42) *	1.010(1,42)	.418(1,42)	34.369(1, 21) ***	5.597 (1, 21) *
During 2nd ice	8.698(1,42) **	.028(1,42)	.576(1,42)	26.688(1, 21) ***	7.604 (1, 21) *
After 2nd ice	3.632(1,42)	.010(1,42)	.015(1,42)	20.377(1, 21) ***	7.498 (1, 21) *
Before 3rd ice	1.374(1,38)	.065(1,38)	.322(1,38)	10.687(1,17) **	11.292 (1, 21) **
During 3rd ice	2.729(1,38)	.007(1,38)	1.071(1,38)	12.451(1, 17) **	9.068 (1, 21) **
After 3rd ice	.888(1,38)	.071(1,38)	.068(1,38)	7.742(1, 17) *	5.255 (1, 21) *
3 mins after 3rd ice	1.076(1,45)	.058(1,45)	.095(1,45)	8.777(1, 23) **	4.992 (1, 22) *
8 mins after 3rd ice	.232(1,46)	2.388(1,46)	1.133(1,46)	.538(1, 24)	4.282 (1, 22) *

* statistically significant (* $p < .05$, ** $p < .01$, *** $p < .001$)

APPENDIX 10

Condition 5

Hand in ice-water before OKS

Table 10.1.1. Nausea

Nausea						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=23)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.087 ± .288	.068 ± .234	.239 (43)			
Before 1st ice	.087 ± .288	.068 ± .234	.239 (43)	Level 2	.	.
During 1st ice	.043 ± .209	.068 ± .234	-.374 (43)	Level 3	.956	.956
Before 2nd ice	.065 ± .229	.011 ± .053	1.098 (24.484)	Level 4	2.425	.483
During 2nd ice	.043 ± .209	.137 ± .637	-.661 (43)	Level 5	.027	.543
Before 3rd ice	.130 ± .458	.000 ± .000	1.367 (22)	Level 6	.048	.988
During 3rd ice	.087 ± .288	.114 ± .533	-.210 (43)	Level 7	.106	.106
2 mins after 3rd ice	.130 ± .344	.000 ± .000	1.817 (22)	Level 8	.072	1.469
4 mins after 3rd ice	.152 ± .510	.000 ± .000	1.432 (22)	Level 9	.001	1.623
6 mins after 3rd ice	.152 ± .510	.000 ± .000	1.432 (22)	Level 10	.001	1.623
8 mins after 3rd ice	.152 ± .510	.000 ± .000	1.432 (22)	Level 11	.001	1.623

In one case simple contrasts could not be computed because the matrix was singular.

Table 10.1.2. Body temperature

Hand in ice-water before OKS

Body temperature						
	Mean ± SD		**Group**	**Simple Contrasts F ratios (df = 1, 43)**		
	Migraineurs (n=23)	**Controls (n=22)**	**t-tests (df)**	**Level 1 vs.**	**Time**	**Group x time**
Baseline	-.043 ± .474	.068 ± .444	-.814 (43)			
Before 1st ice	-.043 ± .474	.068 ± .444	-.814 (43)	Level 2	.	.
During 1st ice	.304 ± 1.259	.114 ± .486	.664 (43)	Level 3	1.693	1.001
Before 2nd ice	-.087 ± .668	.091 ± .294	-1.146 (43)	Level 4	.065	.663
During 2nd ice	.087 ± .288	.045 ± .213	.547 (43)	Level 5	.959	1.940
Before 3rd ice	-.022 ± .612	.045 ± .213	-.487 (43)	Level 6	.000	.386
During 3rd ice	.326 ± .820	.136 ± .351	1.016 (30.084)	Level 7	4.163 *	1.973
2 mins after 3rd ice	.109 ± .602	.045 ± .213	.474 (27.646)	Level 8	1.018	1.859
4 mins after 3rd ice	.065 ± .570	.045 ± .213	.153 (43)	Level 9	.495	1.157
6 mins after 3rd ice	.130 ± .742	.045 ± .213	.517 (43)	Level 10	.918	1.552
8 mins after 3rd ice	.065 ± .570	.045 ± .213	.153 (43)	Level 11	.495	1.157

* difference between migraine sufferers and controls statistically significant (* $p < .05$)

In one case simple contrasts could not be computed because the matrix was singular.

Table 10.1.3. Dizziness

Hand in ice-water before OKS

Dizziness						
	Mean ± SD		Group t-tests (df)	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=23)	Controls (n=22)		Level 1 vs.	Time	Group x time
Baseline	.000 ± .000	.000 ± .000				
Before 1st ice	.000 ± .000	.000 ± .000		Level 2	.	.
During 1st ice	.000 ± .000	.000 ± .000		Level 3	.	.
Before 2nd ice	.000 ± .000	.000 ± .000		Level 4	.	.
During 2nd ice	.000 ± .000	.000 ± .000		Level 5	.	.
Before 3rd ice	.152 ± .729	.000 ± .000	1 (22)	Level 6	.956	.956
During 3rd ice	.043 ± .208	.000 ± .000	1 (22)	Level 7	.956	.956
2 mins after 3rd ice	.043 ± .313	.000 ± .000	1 (22)	Level 8	.956	.956
4 mins after 3rd ice	.065 ± .313	.000 ± .000	1 (22)	Level 9	.956	.956
6 mins after 3rd ice	.065 ± .313	.000 ± .000	1 (22)	Level 10	.956	.956
8 mins after 3rd ice	.130 ± .458	.000 ± .000	1 (22)	Level 11	1.785	1.785

It could not be computed where the standard deviations of both groups was 0.

Simple contrasts could not be computed where the matrix was singular.

Table 10.1.4. Drowsiness

Hand in ice-water before OKS

Drowsiness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=23)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.239 ± .561	.114 ± .306	.936 (34.316)			
Before 1st ice	.239 ± .561	.114 ± .306	.936 (34.316)	Level 2	.	.
During 1st ice	.043 ± .208	.045 ± .213	-.031 (43)	Level 3	4.477 *	1.045
Before 2nd ice	.087 ± .288	.045 ± .213	.547 (43)	Level 4	4.826 *	.701
During 2nd ice	.087 ± .417	.045 ± .213	.417 (43)	Level 5	4.826 *	.701
Before 3rd ice	.109 ± .368	.045 ± .213	.701 (43)	Level 6	5.078 *	.499
During 3rd ice	.000 ± .000	.045 ± .213	-1 (21)	Level 7	5.650 *	1.748
2 mins after 3rd ice	.152 ± .411	.091 ± .294	.573 (43)	Level 8	.959	.329
4 mins after 3rd ice	.283 ± .654	.113 ± .306	1.118 (31.490)	Level 9	.102	.102
6 mins after 3rd ice	.456 ± .752	.136 ± .468	1.722 (37.025)	Level 10	1.840	1.209
8 mins after 3rd ice	.500 ± .866	.182 ± .664	1.386 (41.103)	Level 11	2.130	.730

* difference between migraine sufferers and controls statistically significant (* $p < .05$)

In one case simple contrasts could not be computed because the matrix was singular.

Table 10.1.5. Headache

Hand in ice-water before OKS

Headache						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=23)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.217 ± .518	.000 ± .000	2.011 (22)			
Before 1st ice	.217 ± .518	.000 ± .000	2.011 (22)	Level 2	.	.
During 1st ice	.043 ± .208	.000 ± .000	1 (22)	Level 3	2.002	2.002
Before 2nd ice	.174 ± .388	.000 ± .000	2.152 (22) *	Level 4	.184	.184
During 2nd ice	.130 ± .458	.000 ± .000	1.367 (22)	Level 5	.628	.628
Before 3rd ice	.178 ± .490	.000 ± .000	1.745 (22)	Level 6	.249	.249
During 3rd ice	.113 ± .425	.000 ± .000	1.277 (22)	Level 7	.876	.876
2 mins after 3rd ice	.324 ± .689	.000 ± .000	2.255 (22) *	Level 8	1.775	1.775
4 mins after 3rd ice	.363 ± 1.007	.000 ± .000	1.730 (22)	Level 9	.669	.669
6 mins after 3rd ice	.435 ± 1.048	.000 ± .000	1.990 (22)	Level 10	1.177	1.177
8 mins after 3rd ice	.413 ± 1.030	.000 ± .000	1.924 (22)	Level 11	1.008	1.008

* difference between migraine sufferers and controls statistically significant (* $p < .05$)

In one case simple contrasts could not be computed because the matrix was singular.

Table 10.1.6. Unpleasantness

Hand in ice-water before OKS

Unpleasantness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=23)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.217 ± .518	.091 ± .294	1.012 (35.138)			
Before 1st ice	.217 ± .518	.091 ± .294	1.012 (35.138)	Level 2	.	.
During 1st ice	5.022 ± 4.210 ^^^	3.045 ± 3.181 ^^^	1.783 (40.866)	Level 3	48.527 ***	2.758
Before 2nd ice	.413 ± 1.010	.091 ± .426	1.407 (29.914)	Level 4	.760	.760
During 2nd ice	4.913 ± 4.402 ^^^	3.159 ± 3.278 ^^^	1.520 (40.606)	Level 5	45.290 ***	1.990
Before 3rd ice	.610 ± 1.033	.136 ± .640	1.853 (36.950)	Level 6	3.489	2.188
During 3rd ice	5.196 ± 4.329 ^^^	3.250 ± 3.330 ^^^	1.694 (41.142)	Level 7	50.987 ***	2.548
2 mins after 3rd ice	.870 ± 1.254 ^	.136 ± .468	2.620 (28.233) *	Level 8	7.314 **	5.532 *
4 mins after 3rd ice	.630 ± 1.245	.045 ± .213	2.219 (23.346) *	Level 9	2.231	3.471
6 mins after 3rd ice	.565 ± 1.111	.045 ± .213	2.202 (23.690) *	Level 10	2.040	3.451
8 mins after 3rd ice	.500 ± 1.097	.045 ± .213	1.948 (23.731)	Level 11	1.481	2.833

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^^ p < .001)

In one case simple contrasts could not be computed because the matrix was singular.

Table 10.1.7. Ice-induced intensity

Hand in ice-water before OKS

Ice-induced intensity						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=23)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
During 1st ice	8.261 ± 2.050	6.409 ± 2.505	2.719 (43) **			
Before 2nd ice	1.239 ± 1.223 ^^^	1.068 ± 1.545 ^^^	.412 (43)	Level 2	304.817 ***	5.635 *
During 2nd ice	8.239 ± 2.286	6.727 ± 2.520	2.110 (43) *	Level 3	.691	.908
Before 3rd ice	1.456 ± 1.177 ^^^	1.100 ± 1.534 ^^^	.877 (43)	Level 4	279.315 ***	4.256 *
During 3rd ice	8.478 ± 2.014	6.841 ± 2.528	2.409 (43) *	Level 5	2.078	.227
2 mins after 3rd ice	1.696 ± 1.697 ^^^	1.009 ± 1.416 ^^^	1.470 (43)	Level 6	264.337 ***	2.507
4 mins after 3rd ice	.563 ± 1.001 ^^^	.318 ± .568 ^^^	1.003 (43)	Level 7	419.252 ***	5.694 *
6 mins after 3rd ice	.374 ± .827 ^^^	.136 ± .351 ^^^	1.264 (29.965)	Level 8	433.883 ***	5.639 *
8 mins after 3rd ice	.272 ± .537 ^^^	.068 ± .233 ^^^	1.659 (30.310)	Level 9	449.774 ***	5.950 *

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^^^ p < .001)

Ratings during the first application were used as a point of comparison in a series of simple contrasts across subsequent time points.

Table 10.1.8. Ice-induced unpleasantness

Hand in ice-water before OKS

Ice-induced unpleasantness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 43)		
	Migraineurs (n=23)	Controls (n=22)	t-tests (df)	Level 1 vs.	Time	Group x time
During 1st ice	8.087 ± 2.255	6.000 ± 3.043	2.622 (43) *			
Before 2nd ice	.565 ± .945 ^^^	.182 ± .588 ^^^	1.641 (37.068)	Level 2	269.294 ***	4.392 *
During 2nd ice	8.022 ± 2.656	6.114 ± 3.090	2.225 (43) *	Level 3	.015	.209
Before 3rd ice	.587 ± 1.030 ^^^	.318 ± .780 ^^^	.984 (43)	Level 4	255.541 ***	4.862 *
During 3rd ice	8.348 ± 2.107	6.091 ± 3.096	2.870 (43) **	Level 5	.635	.148
2 mins after 3rd ice	.870 ± 1.058 ^^^	.318 ± .780 ^^^	1.983 (43)	Level 6	247.401 ***	3.506
4 mins after 3rd ice	.313 ± .632 ^^^	.136 ± .468 ^^^	1.062 (43)	Level 7	293.723 ***	5.763 *
6 mins after 3rd ice	.174 ± .576 ^^^	.091 ± .294 ^^^	.604 (43)	Level 8	295.938 ***	6.221 *
8 mins after 3rd ice	.130 ± .458 ^^^	.045 ± .213 ^^^	.792 (43)	Level 9	295.717 ***	6.125 *

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^^^ p < .001)

Ratings during the first application were used as a point of comparison in a series of simple contrasts across subsequent time points.

PULSE AMPLITUDE

Table 10.2.1. Means and standard deviations for migraineurs and controls for changes in pulse amplitude (ipsilateral, contralateral to stimulation) across 11 time points (30 second samples, before {trial 1, 2 & 3}, during {trial 1, 2 & 3} and after {trial 1, 2 & 3} ice application to temple, and 3 and 8 mins after the 3rd application).
Hand in ice-water before OKS

Hand in ice-water before OKS

Means ± SD						
	Migraineurs (n = 23)		Controls (n = 22)		Group t-tests (df)	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral
Before 1st ice	8.4 ± 15.1 ^	7.7 ± 23.8	1.8 ± 13.6	-3.6 ± 8.8	1.530 (43)	2.124 (28.113) *
During 1st ice	17.2 ± 21.6 ^^^	19.7 ± 59.4	15.2 ± 33.2 ^	-4.1 ± 13.7	.244 (43)	1.873 (24.452)
After 1st ice	50.3 ± 47.2 ^^^	36.8 ± 46.1 ^^^	31.1 ± 34.6 ^^^	8.2 ± 23.3	1.556 (43)	2.648 (32.889) *
Before 2nd ice	19.6 ± 14.8 ^^^	14.9 ± 21.5 ^^	12.1 ± 16.0 ^^	1.4 ± 16.6	1.636 (43)	2.355 (43) *
During 2nd ice	22.6 ± 24.6 ^^^	22.6 ± 60.6	19.1 ± 26.7 ^^	-3.0 ± 17.3	.463 (43)	1.911 (43)
After 2nd ice	45.4 ± 29.7 ^^^	31.5 ± 43.2 ^^	33.1 ± 24.9 ^^^	6.4 ± 17.6	1.503 (43)	2.573 (29.40)) *
Before 3rd ice	21.8 ± 22.7 ^^^	17.1 ± 24.7 ^^	18.6 ± 20.7 ^^^	8.8 ± 17.3 ^	.481 (43)	1.303 (43)
During 3rd ice	25.3 ± 29.5 ^^^	26.1 ± 65.1	21.2 ± 20.8 ^^^	2.6 ± 22.6	.543 (43)	1.608 (43)
After 3rd ice	47.6 ± 36.1 ^^^	37.6 ± 44.0 ^^^	41.2 ± 34.3 ^^^	16.5 ± 31.2 ^	.613 (43)	1.843 (43)
3 mins after 3rd ice	29.8 ± 28.1 ^^^	22.7 ± 32.4 ^^	15.4 ± 17.8 ^^^	4.6 ± 16.8	2.044 (43) *	2.361 (33.349) *
8 mins after 3rd ice	32.1 ± 40.4 ^^^	25.1 ± 38.1 ^^	17.7 ± 20.5 ^^^	7.1 ± 18.3	1.524 (32.968)	2.034 (31.996) *

* statistically significant (* $p < .05$)
^ baseline *vs* subsequent levels within groups statistically significant (^ $p < .05$, ^^ $p < .01$, ^^^ $p < .001$)

PULSE AMPLITUDE

Table 10.2.2. Main effects, interactions and intercepts from a series of 2 (group: migraineurs, controls) x 2 (side: ipsilateral, contralateral to stimulation) repeated-measures ANOVA's at each time point.

Hand in ice-water before OKS

F ratios					
	Main effects and Interactions (df = 1,43)			Intercepts (df)	
	Group	Side	Side x Group	Migraineurs (1,23)	Controls (1,22)
Before 1st ice	5.185 *	1.127	.665	5.832 *	.198
During 1st ice	2.109	1.775	2.993	5.943 *	1.566
After 1st ice	5.398 *	10.883 **	.722	25.520 ***	12.875 **
Before 2nd ice	6.466 *	5.950 *	.906	33.547 ***	5.496 *
During 2nd ice	2.732	2.943	2.956	7.951 *	5.923 *
After 2nd ice	5.720 *	19.193 ***	1.904	31.841 ***	29.572 ***
Before 3rd ice	1.160	4.007	.509	23.030 ***	16.180 **
During 3rd ice	2.078	1.788	2.139	8.565 **	11.554 **
After 3rd ice	1.984	11.918 ***	2.114	34.183 ***	20.118 ***
3 mins after 3rd ice	7.252 *	4.341 *	.181	26.225 ***	10.993 **
8 mins after 3rd ice	4.192 *	3.279	.131	16.565 **	13.162 **

*

statistically significant (* $p < .05$, ** $p < .01$, *** $p < .001$)

APPENDIX 11

Condition 6

Hand in ice-water during OKS

Table 11.1.1. Nausea

Nausea						
	Mean ± SD		Group t-tests(df)	Simple Contrasts F ratios (df = 1, 37)		
	Migraineurs (n=19)	Controls (n=20)		Level 1 vs.	Time	Group x time
Baseline	.184 ± .560	.012 ± .056	1.317 (22.503)			
Before 1st ice	.658 ± 1.081	.000 ± .000	2.888 (22) **	Level 2	3.031	3.369
During 1st ice	.868 ± 1.526	.100 ± .447	2.599 (25.708) *	Level 3	4.425 *	2.646
Before 2nd ice	1.447 ± 1.978 ^	.050 ± .224	3.200 (25.954) **	Level 4	8.445 **	7.499 **
During 2nd ice	1.658 ± 2.698 ^	.450 ± .887 ^	1.763 (35.977)	Level 5	9.720 **	2.857
Before 3rd ice	2.053 ± 2.872 ^^	.300 ± .657	2.606 (36.408) *	Level 6	11.898 ***	6.398 *
During 3rd ice	2.579 ± 3.006 ^^	.350 ± .763	2.269 (43) *	Level 7	16.580 ***	9.400 **
2 mins after 3rd ice	2.895 ± 3.030 ^^^	.200 ± .523	3.822 (19.019) ***	Level 8	19.532 ***	14.804 ***
4 mins after 3rd ice	2.316 ± 2.964 ^^	.125 ± .319	2.519 (40.898) *	Level 9	13.182 ***	10.671 **
6 mins after 3rd ice	1.368 ± 1.706 ^^	.087 ± .337	3.274 (26.553) **	Level 10	13.374 ***	10.377 **
8 mins after 3rd ice	.947 ± 1.177 ^^^	.025 ± .112	3.649 (22.319) ***	Level 11	16.101 ***	15.041 ***

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01, ^^^ p < .001)

Table 11.1.2. Body temperature

Hand in ice-water during OKS

Body temperature						
	Mean ± SD		**Group t-tests (df)**	**Simple Contrasts F ratios (df = 1, 37)**		
	Migraineurs (n=19)	**Controls (n=20)**		**Level 1 vs.**	**Time**	**Group x time**
Baseline	-.132 ± .704	-.050 ± .224	-.449 (27.038)			
Before 1st ice	.184 ± .506 ^	.050 ± .224	1.268 (28.766)	Level 2	7.415 *	1.997
During 1st ice	.342 ± 1.155	.000 ± .000	1.660 (22)	Level 3	2.732	1.788
Before 2nd ice	.513 ± 1.069 ^	.100 ± .447	1.689 (30.078)	Level 4	9.704 **	3.761
During 2nd ice	.816 ± 1.346 ^	.100 ± .447	2.047 (37.647) *	Level 5	9.867 **	5.210 *
Before 3rd ice	.921 ± 1.465 ^^	.125 ± .319	1.788 (39.695)	Level 6	11.663 **	5.961 *
During 3rd ice	1.000 ± 1.453 ^^	.100 ± .308	1.301 (43)	Level 7	12.742 ***	7.475 *
2 mins after 3rd ice	1.316 ± 1.916 ^^	.200 ± .696	2.392 (22.458) *	Level 8	12.636 ***	6.288 *
4 mins after 3rd ice	1.184 ± 2.063 ^	.100 ± .528	1.625 (39.570)	Level 9	8.544 **	5.405 *
6 mins after 3rd ice	1.000 ± 1.893 ^	.012 ± .056	1.980 (31.550)	Level 10	7.301 **	5.852 *
8 mins after 3rd ice	.579 ± 1.493	.000 ± .000	1.988 (22)	Level 11	5.135 *	3.873

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01)

Table 11.1.3. Dizziness

Hand in ice-water during OKS

Dizziness						
	Mean ± SD		Group t-tests (df)	Simple Contrasts F ratios (df = 1, 37)		
	Migraineurs (n=19)	Controls (n=20)		Level 1 vs.	Time	Group x time
Baseline	.158 ± .501	.000 ± .000	1.367 (22)			
Before 1st ice	1.500 ± 2.075 ^	.100 ± .447	2.582 (30.263) *	Level 2	9.276 **	6.882 *
During 1st ice	1.526 ± 2.270 ^	.250 ± .786	2.339 (31.926) *	Level 3	9.065 **	4.329 *
Before 2nd ice	2.210 ± 2.720 ^^	.500 ± 1.000 ^	2.733 (33.523) **	Level 4	16.549 ***	6.123 *
During 2nd ice	2.474 ± 3.151 ^^	.600 ± .995 ^	2.337 (32.798) *	Level 5	17.326 ***	5.999 *
Before 3rd ice	2.395 ± 3.243 ^^	.550 ± 1.146 ^	1.936 (38.521)	Level 6	14.649 ***	5.367 *
During 3rd ice	2.605 ± 3.522 ^^	1.100 ± 2.360	1.893 (41.329)	Level 7	15.059 ***	2.173
2 mins after 3rd ice	2.895 ± 3.604 ^^	.850 ± 1.565 ^	2.277 (24.290) *	Level 8	18.244 ***	5.048*
4 mins after 3rd ice	1.895 ± 2.690 ^^	.350 ± .745 ^	1.623 (41.359)	Level 9	13.684 ***	6.043 *
6 mins after 3rd ice	1.158 ± 1.922 ^	.050 ± .224	2.243 (25.138) *	Level 10	7.801 **	6.386 *
8 mins after 3rd ice	.710 ± 1.475 ^	.050 ± .224	1.882 (23.125)	Level 11	5.479 *	3.811

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01)

Table 11.1.4. Drowsiness

Hand in ice-water during OKS

Drowsiness						
	Mean ± SD		Group t-tests (df)	Simple Contrasts F ratios (df = 1, 37)		
	Migraineurs (n=19)	Controls (n=20)		Level 1 vs.	Time	Group x time
Baseline	.553 ± .941	.250 ± .910	.880 (43)			
Before 1st ice	.921 ± 1.417	.425 ± 1.184	1.014 (43)	Level 2	4.617 *	.585
During 1st ice	.526 ± 1.429	.350 ± .745	.765 (43)	Level 3	.041	.121
Before 2nd ice	1.290 ± 2.400	.450 ± .887	1.579 (28.702)	Level 4	4.560 *	1.497
During 2nd ice	1.132 ± 2.344	.400 ± .995	1.919 (29.510)	Level 5	2.749	.952
Before 3rd ice	1.553 ± 2.793	.550 ± 1.317	2.095 (30.880) *	Level 6	6.236 *	1.808
During 3rd ice	1.474 ± 2.674	.500 ± 1.147	2.103 (28.378) *	Level 7	4.604 *	1.512
2 mins after 3rd ice	1.632 ± 2.985	1.000 ± 1.892 ^	.793 (37)	Level 8	8.411 **	.272
4 mins after 3rd ice	1.526 ± 2.855	.700 ± 1.342 ^	1.5 (32.152)	Level 9	7.116 *	.963
6 mins after 3rd ice	1.158 ± 2.141	.500 ± 1.433	1.334 (43)	Level 10	5.117 *	.883
8 mins after 3rd ice	1.026 ± 1.874	.400 ± .754	1.761 (29.558)	Level 11	3.063	.825

* difference between migraine sufferers and controls statistically significant (* $p < .05$, ** $p < .01$)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ $p < .05$)

Table 11.1.5. Headache

Hand in ice-water during OKS

Headache						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 37)		
	Migraineurs (n=19)	Controls (n=20)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.684 ± .946	.000 ± .000	3.510 (22) **			
Before 1st ice	.947 ± 1.223	.000 ± .000	3.693 (22) ***	Level 2	4.392 *	4.392 *
During 1st ice	.974 ± 1.317	.000 ± .000	4.029 (22) ***	Level 3	1.462	1.464
Before 2nd ice	1.421 ± 1.917 ^	.000 ± .000	3.973 (22) ***	Level 4	6.082*	6.082 *
During 2nd ice	1.237 ± 2.251	.000 ± .000	3.228 (22) **	Level 5	1.951	1.951
Before 3rd ice	1.684 ± 2.496 ^	.050 ± .224	3.764 (22.311) ***	Level 6	6.314*	5.169 *
During 3rd ice	1.553 ± 2.576	.200 ± .615	3.083 (23.759) **	Level 7	5.201 *	2.036
2 mins after 3rd ice	1.974 ± 2.638 ^	.250 ± .786	2.735 (21.026) *	Level 8	10.122 **	4.615 *
4 mins after 3rd ice	1.821 ± 2.464 ^	.262 ± .784	3.301 (25.944) **	Level 9	10.633 **	4.151 *
6 mins after 3rd ice	1.947 ± 2.560 ^^	.300 ± .801	3.223 (26.013) **	Level 10	12.427 ***	4.718 *
8 mins after 3rd ice	1.974 ± 2.653 ^^	.300 ± .801	3.006 (25.741) **	Level 11	11.624 **	4.504 *

* difference between migraine sufferers and controls statistically significant (** p < .01, ** p < .001,*** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01)

Table 11.1.6. Unpleasantness

Hand in ice-water during OKS

Unpleasantness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 37)		
	Migraineurs (n=19)	Controls (n=20)	t-tests (df)	Level 1 vs.	Time	Group x time
Baseline	.579 ± 1.017	.100 ± .308	2.420 (25.446) *			
Before 1st ice	1.684 ± 1.945 ^	.350 ± .489 ^	3.148 (32.269) **	Level 2	11.922 ***	4.748 *
During 1st ice	5.184 ± 4.134 ^^^	3.750 ± 2.953 ^^^	1.371 (40.430)	Level 3	58.519 ***	.784
Before 2nd ice	2.974 ± 3.360 ^^	.850 ± 1.348 ^	2.414 (39.114) *	Level 4	17.137 ***	4.688 *
During 2nd ice	5.526 ± 3.802 ^^^	3.275 ± 3.058 ^^^	2.190 (43) *	Level 5	59.152 ***	2.817
Before 3rd ice	3.553 ± 3.562 ^^^	.550 ± .887 ^	3.017 (39.515) **	Level 6	21.004 ***	11.413 **
During 3rd ice	6.158 ± 3.416 ^^^	3.500 ± 3.099 ^^^	2.580 (43) *	Level 7	80.640 ***	4.749 *
2 mins after 3rd ice	4.053 ± 3.659 ^^^	1.350 ± 2.621 ^	2.662 (37) *	Level 8	24.194 ***	5.362 *
4 mins after 3rd ice	2.789 ± 3.101 ^^	.450 ± 1.146	2.698 (39.525) **	Level 9	14.617 ***	7.717 **
6 mins after 3rd ice	2.053 ± 2.300 ^^	.350 ± .813	2.977 (32.566) **	Level 10	12.985 ***	6.544 *
8 mins after 3rd ice	1.579 ± 2.317 ^	.450 ± .999	2.343 (30.011) *	Level 11	7.591 **	1.760

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01, ^^^ p < .001)

Table 11.1.7. Ice-induced intensity

Hand in ice-water during OKS

Ice-induced intensity						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 37)		
	Migraineurs (n=19)	Controls (n=20)	t-tests (df)	Level 1 vs.	Time	Group x time
During 1st ice	8.316 ± 1.827	5.800 ± 2.546	2.944 (43) **			
Before 2nd ice	1.947 ± 1.343 ^^^	.725 ± 1.070 ^^^	1.687 (43)	Level 2	229.109 ***	2.927
During 2nd ice	8.210 ± 2.600	5.812 ± 2.754	2.777 (43) **	Level 3	.055	.088
Before 3rd ice	1.816 ± 1.474 ^^^	.625 ± .872 ^^^	1.655 (43)	Level 4	240.132 ***	3.093
During 3rd ice	8.421 ± 1.981	5.862 ± 2.832	3.253 (37) **	Level 5	.241	.016
2 mins after 3rd ice	1.737 ± 1.437 ^^^	.525 ± .752 ^^^	3.274 (26.853) **	Level 6	277.017 ***	3.352
4 mins after 3rd ice	.737 ± .872 ^^^	.265 ± .522 ^^^	1.760 (38.258)	Level 7	306.477 ***	7.445 **
6 mins after 3rd ice	.395 ± .591 ^^^	.125 ± .319 ^^^	1.616 (37.304)	Level 8	373.827 ***	10.202 **
8 mins after 3rd ice	.316 ± .582 ^^^	.075 ± .245 ^^^	1.563 (30.227)	Level 9	373.681 ***	10.267 **

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01, ^^^ p < .001)

Ratings during the first application were used as a point of comparison in a series of simple contrasts across subsequent time points.

Table 11.1.8. Ice-induced unpleasantness

Hand in ice-water during OKS

Ice-induced unpleasantness						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 37)		
	Migraineurs (n=19)	Controls (n=20)	t-tests (df)	Level 1 vs.	Time	Group x time
During 1st ice	8.342 ± 1.944	5.400 ± 2.663	3.558 (43) ***			
Before 2nd ice	1.105 ± 1.197 ^^^	.350 ± .727 ^^^	1.949 (43)	Level 2	251.232 ***	7.958 **
During 2nd ice	8.158 ± 2.656	5.350 ± 2.943	3.267 (43) **	Level 3	.465	.153
Before 3rd ice	.974 ± 1.086 ^^^	.225 ± .525 ^^^	1.669 (43)	Level 4	275.272 ***	8.417 **
During 3rd ice	8.447 ± 1.957	5.350 ± 3.078	3.769 (32.414) ***	Level 5	.028	.221
2 mins after 3rd ice	1.084 ± 1.413 ^^^	.350 ± .813 ^^^	1.976 (28.435)	Level 6	274.575 ***	8.836 **
4 mins after 3rd ice	.605 ± .826 ^^^	.250 ± .639 ^^^	1.532 (43)	Level 7	301.260 ***	12.139 ***
6 mins after 3rd ice	.263 ± .562 ^^^	.100 ± .308 ^^^	.911 (43)	Level 8	317.366 ***	13.692 ***
8 mins after 3rd ice	.263 ± .562 ^^^	.050 ± .224 ^^^	1.466 (29.501)	Level 9	328.881 ***	13.581 ***

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01, *** p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05, ^^ p < .01, ^^^ p < .001)

In one case simple contrasts could not be computed because the matrix was singular.

Ratings during the first application were used as a point of comparison in a series of simple contrasts across subsequent time points.

Table 11.1.9. Self-motion

Hand in ice-water during OKS

Self motion						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 37)		
	Migraineurs (n=19)	Controls (n=20)	t-tests (df)	Level 1 vs.	Time	Group x time
Minute 2	1.000 ± .882	.800 + .768	.739 (43)			
4	1.105 ± .936	.850 + .813	1.008 (43)	Level 2	.419	.053
6	1.368 ± .684	.950 + .686	1.606 (43)	Level 3	3.344	.594
8	1.263 ± .733	.800 + .768	1.510 (43)	Level 4	.663	.663
10	1.421 ± .768	.950 + .686	1.120 (43)	Level 5	4.669 *	1.052
12	1.105 ± .936	.900 + .788	.663 (43)	Level 6	.348	.000
14	1.526 ± .772 ^	.900 + .718	2.624 (37) *	Level 7	7.629 **	3.535

* difference between migraine sufferers and controls statistically significant (* p < .05, ** p < .01)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05)

Ratings during the first 2 minutes of OKS were used as a point of comparison in a series of simple contrasts across subsequent time points.

Table 11.1.10. Visual-illusion

Hand in ice-water during OKS

Self motion						
	Mean ± SD		Group	Simple Contrasts F ratios (df = 1, 37)		
	Migraineurs (n=19)	Controls (n=20)	t-tests (df)	Level 1 vs.	Time	Group x time
Minute 2	.895 ± .737	.550 + .510	1.125 (43)			
4	1.053 ± .705	.300 + .470 ^	3.657 (43) ***	Level 2	.249	4.886 *
6	1.105 ± .809	.550 + .605	1.788 (43)	Level 3	1.054	1.054
8	1.211 ± .713	.950 + .887	1.287 (43)	Level 4	5.977 *	.083
10	1.053 ± .848	.700 + .732	1.313 (43)	Level 5	1.792	.001
12	1.053 ± .911	.800 + .768	.890 (43)	Level 6	2.471	.126
14	1.211 ± .787	.600 + .680	2.595 (37) *	Level 7	2.291	1.210

* difference between migraine sufferers and controls statistically significant (* p < .05, ***p < .001)
^ simple contrasts: baseline *vs* subsequent levels within groups statistically significant (^ p < .05)

Ratings during the first 2 minutes of OKS were used as a point of comparison in a series of simple contrasts across subsequent time points.

PULSE AMPLITUDE

Table 11.2.1. Means and standard deviations for migraineurs and controls for changes in pulse amplitude (ipsilateral, contralateral to stimulation) across 11 time points (30 second samples, before {trial 1, 2 & 3}, during {trial 1, 2 & 3} and after {trial 1, 2 & 3} ice application to temple, and 3 and 8 mins after the 3rd application).

Hand in ice-water during OKS

	Means ± SD					
	Migraineurs (n = 19)		Controls (n = 20)		Group t-tests (df)	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral
Before 1st ice	22.4 ± 43.2 ^	14.6 ± 39.1	25.5 ± 29.9 ^^^	15.9 ± 18.4 ^^^	- .258 (43)	- .136 (43)
During 1st ice	18.6 ± 40.5 ^	11.2 ± 36.5	31.5 ± 33.3 ^^^	17.5 ± 20.4 ^^^	-1.328 (43)	- .924 (43)
After 1st ice	32.8 ± 39.2 ^^^	19.7 ± 37.5 ^	43.0 ± 43.5 ^^^	18.0 ± 19.9 ^^^	- .828 (43)	.284 (43)
Before 2nd ice	25.1 ± 53.5 ^	10.0 ± 33.1	31.1 ± 41.9 ^^	14.4 ± 16.1 ^^	- .161 (43)	- .131 (43)
During 2nd ice	22.0 ± 43.7 ^	6.5 ± 34.2	36.1 ± 43.6 ^^	16.0 ± 20.5 ^	- .839 (43)	- .846 (43)
After 2nd ice	32.8 ± 44.0 ^^	15.1 ± 38.7	42.6 ± 44.4 ^^^	18.9 ± 18.1^^	- .493 (43)	- .045 (43)
Before 3rd ice	33.5 ± 68.4 ^	13.4 ± 40.5	29.7 ± 38.3 ^^	14.4 ± 17.1 ^^^	.215 (37)	- .101 (24.003)
During 3rd ice	29.3 ± 71.6	5.9 ± 37.9	35.1 ± 48.7 ^^	16.9 ± 25.5 ^^	- .298 (37)	-1.066 (37)
After 3rd ice	40.3 ± 70.3 ^	16.4 ± 47.4	40.9 ± 51.4 ^^	15.6 ± 17.7 ^^^	- .034 (37)	.070 (22.740)
3 mins after 3rd ice	29.0 ± 68.2 ^	9.2 ± 43.4	26.3 ± 38.2 ^	8.1 ± 11.4	.346 (43)	.535 (28.259)
8 mins after 3rd ice	-.4 ± 41.6	-4.4 ± 34.5	1.2 ± 16.3	-2.0 ± 16.3	.031 (33.043)	- .187 (32.600)

^ baseline *vs* subsequent levels within groups statistically significant (^ $p < .05$, ^^ $p < .01$, ^^^ $p < .001$)

PULSE AMPLITUDE

Table 11.2.2. Main effects, interactions and intercepts from a series of 2 (group: migraineurs, controls) x 2 (side: ipsilateral, contralateral to stimulation) repeated-measures ANOVA's at each time point.

Hand in ice-water during OKS

F ratios					
	Main effects and Interactions (df = 1,46)			Intercepts (df)	
	Group	Side	Side x Group	Migraineurs	Controls
Before 1st ice	.046	9.930 **	.061	5.905 (1, 22) *	21.22 (1,21) ***
During 1st ice	1.479	12.084 ***	.858	34.70 (1, 22)	22.99 (1,21) ***
After 1st ice	.157	17.627 ***	1.817	13.33 (1,22) ***	27.44 (1,21) ***
Before 2nd ice	.025	11.210 **	.019	4.373 (1,22) *	9.430 (1,21) **
During 2nd ice	.784	17.581 ***	.211	3.121 (1, 22)	9.818 (1,21) **
After 2nd ice	.111	16.902 ***	.451	8.498 (1,22) **	14.89 (1,21) ***
Before 3rd ice	.011	8.787 **	.161	3.846 (1,18)	15.669 (1,19) ***
During 3rd ice	.349	10.503 **	.161	2.137 (1, 18)	10.95 (1,19) **
After 3rd ice	.000	12.034 ***	.011	4.953 (1,18) *	15.88 (1,19) ***
3 mins after 3rd ice	.198	8.404 **	.003	3.341 (1, 22)	7.020 (1,21) *
8 mins after 3rd ice	.006	.567	.094	.272 (1, 22)	.774 (1, 21)

* statistically significant (* $p < .05$, ** $p < .01$, *** $p < .001$)

APPENDIX 12

Condition 2

Ice on temple after OKS

Analyses using baseline from condition 1 (OKS alone)

Table 12. Main effect and interaction F, *p*, and df values from a 2 (group: migraineurs, controls) x 2 (side: ipsilateral, contralateral to stimulation) x 11 (time: 30 second samples, before {trial 1, 2 & 3}, during {trial 1, 2 & 3} and after {trial 1, 2 & 3} ice application to temple, and 3 and 8 mins after the 3rd application) repeated-measures ANOVA.

Main effect	*df*	F	P
Group	1, 45	2.771	.103
Side	1, 45	.115	.736
Time	10, 36	1.271	.283
Interaction			
Side x Time	10, 36	.654	.758
Side x Group	1, 45	.082	.776
Time x Group	10, 36	.981	.477
Side x Time x Group	10, 36	.995	.466

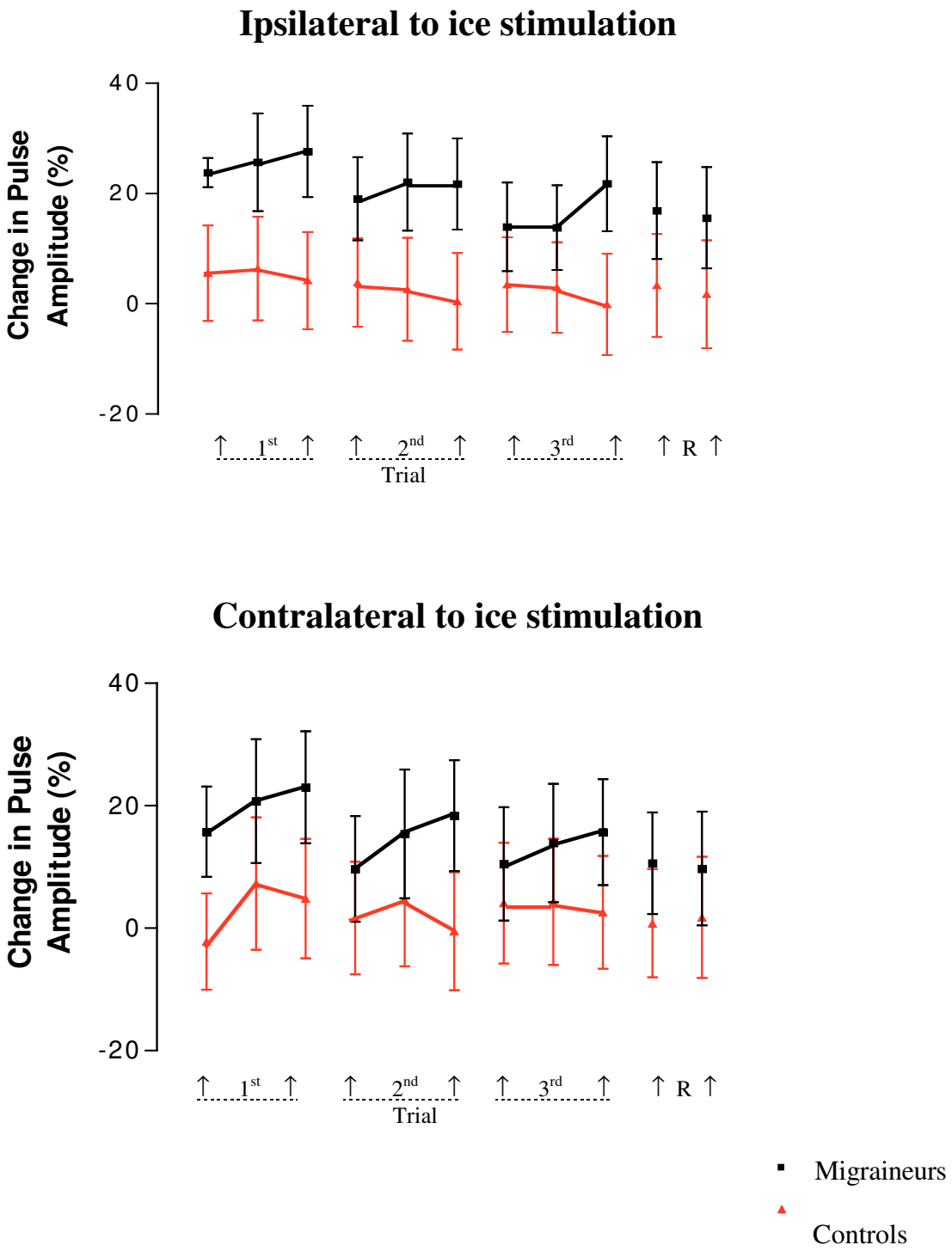


Figure 12. Pulse amplitude change (± SEM) for migraineurs (n = 25) and controls (n = 22) over 11 time points (30 second samples: before, during and after ice application {3 trials}, and after 3 and 8 minutes of recovery {R}). The first arrow in each trial represents pulse amplitude before the immersion, and the second arrow represents pulse amplitude after the immersion.

Appendix 13

Table 13. Number of subjects who withdrew from each procedure: OKS alone, stimulation of the temple with ice during OKS and stimulation of the hand in ice-water during OKS

Withdrawals from optokinetic stimulation

	Migraineurs	Controls	x^2	*p*
Drum alone	4/25 (16%)	1/22 (5%)	1.61	0.20
Temple-ice and drum	7/25 (28%)	1/23 (4%)	4.82	0.03
Hand-ice and drum	4/23 (17%)	2/22 (9%)	0.67	0.41

APPENDIX 14

Slides illustrating the content of PowerPoint platform presentation held at the 14th Migaine Trust international conference in London, United Kingdom.

Doctor of Psychology Research
Murdoch University

Anna Granston

Supervisor:
Associate Professor Peter Drummond

The Association between nausea, head pain, and vascular changes in migraine sufferers

Objectives

Investigate:

- whether head pain intensifies symptoms of motion sickness
- whether motion sickness intensifies head pain
- vascular changes during motion sickness

Participants

- ***Migraine sufferers*** – with/without aura, no other serious medical problems, no ongoing drug treatment. At least 1 migraine per month and headache free during baseline
- ***Controls*** – <12 headaches/year which did not meet the criteria for migraine
- Age 18– 62

Method

To investigate whether motion sickness intensifies head pain, motion sickness was induced by optokinetic stimulation:

3 separate occasions: 23 migraineurs
22 controls

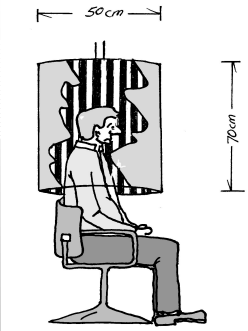
1 occasion: 4 migraineurs
1 control

Optokinetic stimulation

Sit with head inside striped, revolving drum 15 mins

Motion sickness : mismatch between visual & propriocecptive messages

eg. widescreen movies



The optokinetic drum and positioning of participant

Trigeminal stimulation

Ice applied to temple. Three applications 30s every 4mins

Stimulates the trigeminal nerve & provokes head pain

Non-specific painful stimulation

Non-dominant hand immersed in iced water. Three applications 30s every 4mins

Used to compare effects of trigeminal vs. non-specific painful stimulation elsewhere in the body

To investigate whether nausea intensifies head pain, the intensity of pain induced by ice applied to the temple was compared before & during optokinetic stimulation

Experimental design

Optokinetic stimulation alone

Trigeminal stimulation before optokinetic stimulation

Non-specific painful stimulation before optokinetic stimulation

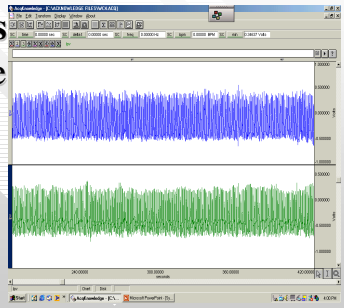
Trigeminal stimulation during optokinetic stimulation

Non-specific painful stimulation during optokinetic stimulation

Throughout testing:

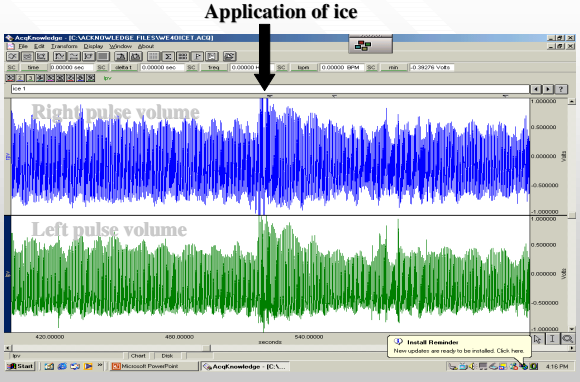
Verbal ratings
10 point scale

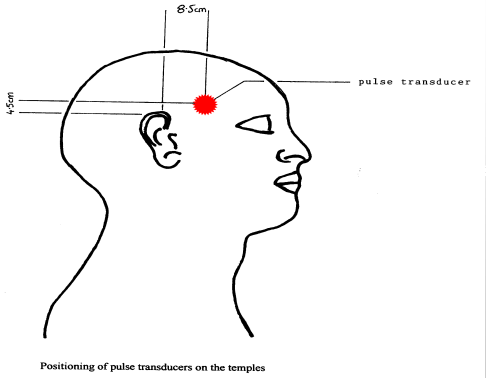
Changes in pulse amplitude



Stimulation of the right temple with ice during optokinetic stimulation in a migraine participant

Application of ice

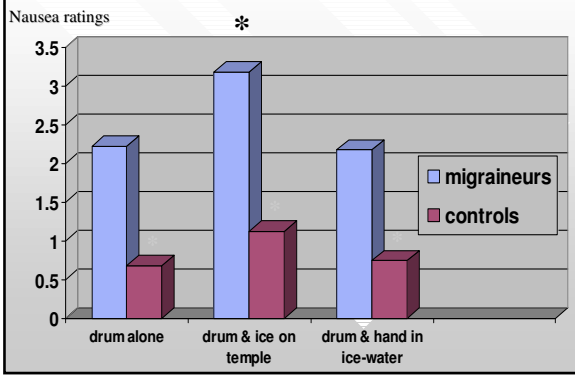




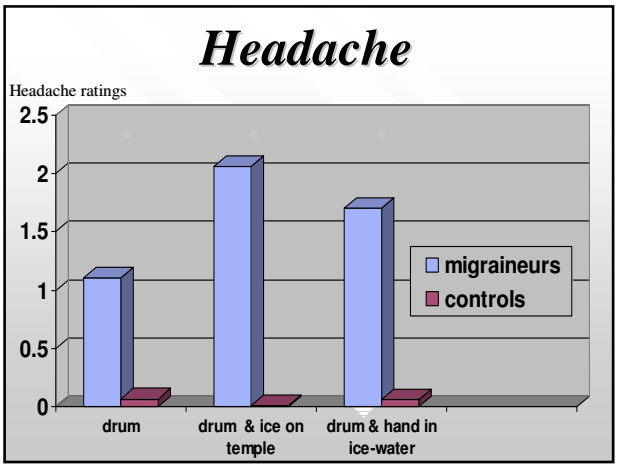
Positioning of pulse transducers on the temples

RESULTS

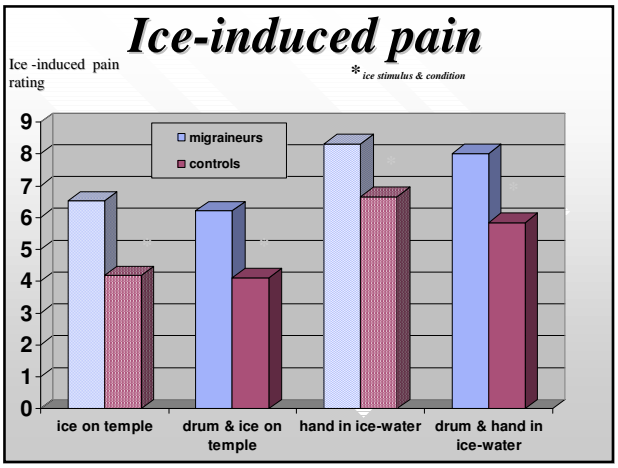
Nausea



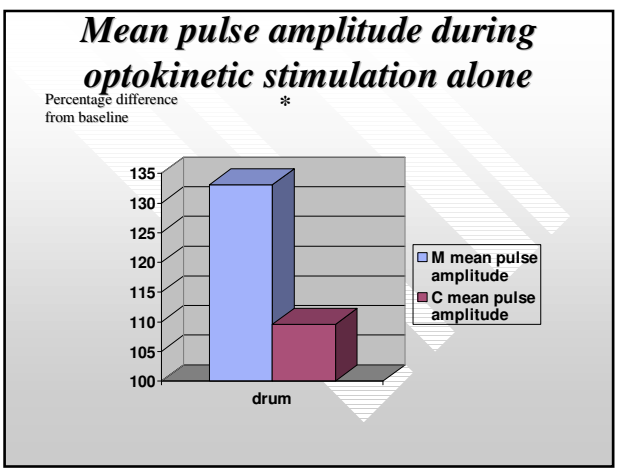
Headache



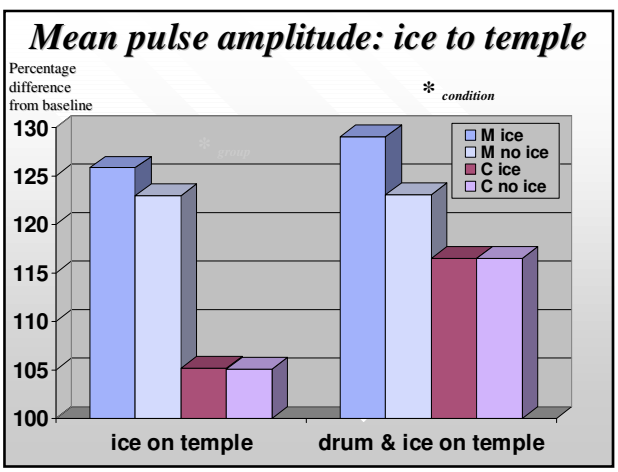
Ice-induced pain



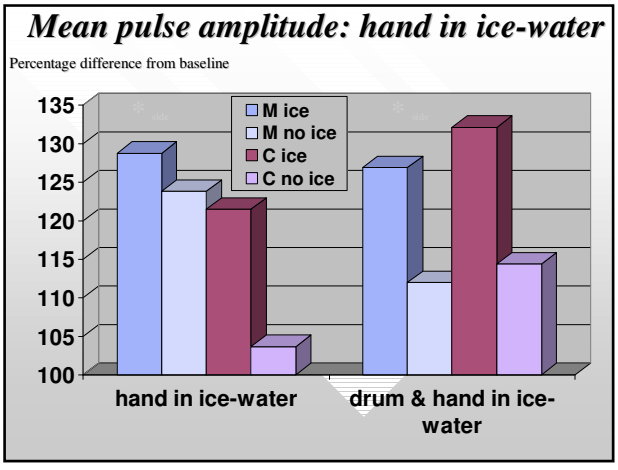
Mean pulse amplitude during optokinetic stimulation alone



Mean pulse amplitude: ice to temple



Mean pulse amplitude: hand in ice-water



Withdrawals from optokinetic stimulation

	Migraineurs	Controls
Drum alone	(25) 4	(22) 1
Temple-ice & drum	(25) 7	(23) 1
Hand-ice & drum	(23) 4	(22) 2

Summary of ratings

- Migraineurs were more susceptible to motion sickness induced by optokinetic stimulation than controls
- Ice to the temple intensified nausea during optokinetic stimulation
- However, optokinetic stimulation did not intensify ice induced pain

Summary of vascular changes

- Before & during optokinetic stimulation vascular responses were greater in migraineurs than controls
- However, painful stimulation and optokinetic stimulation reduced differences between the 2 groups.

Key points

- Findings have helped clarify the relationship between head pain & nausea
- Confirmed facial blood vessels are more reactive in migraineurs than controls to a range of stimuli

Goals

Continue to investigate cause-effect relationships in symptoms of migraine & vascular changes that accompany them

Identify new targets for treatment/approaches to reduce susceptibility to recurring attacks of migraine

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