The Nociceptive Blink Reflex in Migraine:

An investigation of endogenous and exogenous modulators on the trigeminal nervous system in migraine sufferers.

Shiree Treleaven-Hassard

This thesis is presented for the degree of

Doctor of Philosophy

School of Psychology and Exercise Science, Murdoch University
Western Australia
2013
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.

______________________________
Shiree Treleaven-Hassard
The Nociceptive Blink Reflex in Migraine

Abstract

The purpose of this thesis was to determine whether the blink reflex in response to a supraorbital electrical stimulus was a useful marker of activity in central and peripheral nociceptive processing pathways during and between attacks of migraine. In particular, the blink reflex was used to assess trigeminal nociceptive activity in migraine sufferers and to investigate the influence of various exogenous and endogenous modulators on this reflex. It was hypothesized that migraine sufferers would be subjectively and physiologically hypersensitive to both environmental (exogenous) and internal (endogenous) factors. This hypersensitivity was investigated both through subjective ratings and physiologically with blink reflex parameters in response to trigeminal stimulation with and without administration of a noxious compound (ingestion of hypertonic saline) and various environmental stimuli (light, heterosegmental cold pain). Topical application of a local anaesthetic agent inhibited the nociceptive blink reflex measured in response to a concentric electrode stimulus in healthy controls. However, in headache-free migraine sufferers, the nociceptive blink reflex was less likely to be affected by the local anaesthetic. Migraineurs and controls were equally susceptible to peripherally induced nausea evoked by the ingestion of hypertonic saline. However, nausea increased headache and scalp tenderness in all participants, and trigeminal irritation increased headache. Migraine did not affect any blink reflex parameters evoked by a weak electrical stimulus to the forehead. However, symptoms of migraine, scalp tenderness and painfulness of conditioning stimuli were all rated as more intense during a migraine attack, suggesting that temporal summation of trigeminal nociceptive stimulation evoked supraspinal central sensitisation. Whilst there was some evidence of interictal sensitisation in migraine sufferers, this would be better investigated with test stimuli that strongly activate nociceptive afferent fibres in terms of spatial and temporal summation.
### Table of Figures

| Figure 1-1: Illustrative Model of Photophobia in Migraineurs | 10 |
| Figure 2-1: Sequence of procedures for nociceptive blink reflex after EMLA study. | 57 |
| Figure 2-2: The suppression of evoked responses after local anaesthetic. | 59 |
| Figure 2-3: The number of evoked responses after local anaesthetic. | 60 |
| Figure 3-1: Diagram of area of activation from vagal nerve stimulation | 77 |
| Figure 3-2: Nausea and blink reflex study aims. | 78 |
| Figure 3-3: Sequence of procedures for nausea & trigeminal nociceptive processing study. | 82 |
| Figure 3-4: Symptom ratings across conditions | 87 |
| Figure 3-5: Symptom ratings before and after drink in nausea groups | 88 |
| Figure 3-6: Dizziness and Headache ratings in migraine sufferers and controls | 89 |
| Figure 3-7: Scalp tenderness test pain ratings | 91 |
| Figure 3-8: Scalp tenderness test pain ratings condition by nausea group interaction | 91 |
| Figure 3-9: Fingertip tenderness test pain ratings | 92 |
| Figure 3-10: Algometer Pain Ratings across nausea groups | 92 |
| Figure 3-11: High current normal electrode stimulus condition x nausea group interaction | 94 |
| Figure 3-12: Concentric Electrode stimulus mean blink reflex count | 95 |
| Figure 3-13: Concentric electrode stimulus mean area under the curve of actual responses | 96 |
| Figure 3-14: Concentric Electrode stimulus mean latency of actual responses | 96 |
| Figure 3-15: Percent change from baseline in AUC data for the concentric electrode | 97 |
| Figure 3-16: Normal electrode low intensity stimulus mean blink reflex count | 98 |
| Figure 3-17: Normal electrode low intensity stimulus mean area under the curve | 99 |
| Figure 3-18: Normal electrode low intensity stimulus mean latency of actual responses | 99 |
| Figure 3-19: Percent change from baseline in AUC for the low intensity normal electrode | 100 |
| Figure 3-20: Normal electrode high intensity stimulus mean area under the curve | 101 |
| Figure 3-21: Normal electrode high intensity stimulus mean latency | 102 |
| Figure 3-22: Percent change from baseline in AUC for the high intensity normal electrode | 102 |
| Figure 4-1: Sequence of procedures for final studies. | 121 |
| Figure 5-1: Pain ratings to pressure applied to the forehead. | 127 |
| Figure 5-2: Pain ratings to pressure applied to the fingers. | 127 |
| Figure 5-3: Pain ratings in response to algometer pressure | 128 |
| Figure 5-4: Pain ratings at each intensity for those participants tested during a migraine. | 130 |
| Figure 6-1: Symptoms of Migraine after trigeminal stimulation | 142 |
Figure 6-2: Pain ratings to Electrical Stimuli. ................................................................. 144
Figure 6-3: Response count of blink reflexes during the baseline .......................... 146
Figure 6-4: Mean area under the curve of blink reflexes during the baseline .... 147
Figure 6-5: Mean latency of blink reflexes during the baseline .......................... 148
Figure 6-6: Response count of blink reflexes from each side ................................. 149
Figure 6-7: Response count of blink reflexes during the baseline and the final set .... 149
Figure 6-8: Mean AUC of blink reflexes during the baseline and the final set .... 150
Figure 6-9: Mean latency of blink reflexes during the baseline and the final set ... 150
Figure 7-1: Symptoms of Migraine after noxious conditioning stimulation. .......... 163
Figure 7-2: Pain ratings in response to noxious conditioning stimuli. ................. 165
Figure 7-3: Pain ratings to Electrical Stimuli. ............................................................. 167
Figure 7-4: Response count of blink reflexes during Noxious conditioning stimuli .... 169
Figure 7-5: Mean AUC of blink reflexes during noxious conditioning stimuli ....... 169
Figure 7-6: Mean latency of blink reflexes during noxious conditioning stimuli. ..... 170
Figure 8-1: Visual stimuli pain (a) and glare (b) ratings .......................................... 183
Figure 8-2: Auditory stimuli pain (a), loudness (b) and discomfort (c) ratings ....... 184
Figure 8-3: Symptoms of Migraine after noxious sensory stimulation. ................. 186
Figure 8-4: Pain ratings in response to noxious visual stimuli .............................. 189
Figure 8-5: Pain ratings to Electrical Stimuli. ............................................................... 190
Figure 8-6: Response count of blink reflexes during darkness and bright light ...... 192
Figure 8-7: Mean area under the curve of blink reflexes during darkness, and bright light. 193
Figure 8-8: Mean latency of blink reflexes during darkness and bright light ......... 193
Figure 9-1: Neural Processes that might contribute to migraine. .............................. 206
Table of Tables

Table 1-1: Standard Electrode Blink Reflex and Migraine Studies ........................................29
Table 1-2: Concentric Electrode Blink Reflex and Migraine Studies ...............................30
Table 2-1: Blink reflex frequency F Ratios for all stimuli .................................................60
Table 2-2: Mean frequency values for Baseline condition and Post Local Anaesthetic .......61
Table 2-3: Mean AUC and percent change from baseline values for Baseline and Post Local Anaesthetic ........................................................................................................62
Table 2-4: Mean latency values for Baseline condition and Post Local Anaesthetic .....63
Table 2-5: Blink reflex F Ratios at each intensity for 0.3ms stimuli ..................................64
Table 2-6: Blink reflex F Ratios at each intensity for 0.5ms stimuli to the experimental side65
Table 2-7: Blink reflex F Ratios at each intensity for 0.5ms stimuli to the control side ......66
Table 3-1: Correlations with nausea ..................................................................................86
Table 3-2: F ratios for each symptom ................................................................................86
Table 3-3: Algometer pain rating F ratio ..........................................................................90
Table 3-4: F ratios for pain ratings for each stimulus type ..............................................94
Table 3-5: Concentric Electrode stimulus F ratio ...............................................................95
Table 3-6: Normal electrode low intensity stimulus F ratios .........................................98
Table 3-7: Normal electrode high intensity stimulus F ratios .....................................101
Table 3-8: Summary of results .........................................................................................106
Table 5-1: F Ratios for all stimuli between groups ........................................................126
Table 5-2: F Ratios for all stimuli within groups .............................................................129
Table 6-1: Migraine Symptom Rating F ratios .................................................................143
Table 6-2: F ratios for pain ratings for the electrical stimulus ........................................144
Table 6-3: F ratios for the blink reflex for location comparison ......................................145
Table 6-4: F ratios for the blink reflex baseline vs. final stimuli .....................................145
Table 7-1: Migraine Symptom Rating F ratios (degrees of freedom) .............................164
Table 7-2: F ratios (d.f.) for pain ratings in response to noxious conditioning stimuli ......166
Table 7-3: Pain Ratings and Nociceptive Blink Reflex F ratios (degrees of freedom) ......168
Table 8-1: F Ratios for all stimuli ...................................................................................182
Table 8-2: Migraine Symptom Rating F ratios .................................................................187
Table 8-3: F Ratios for light evoked pain ratings .............................................................188
Table 8-4: Pain Ratings and Nociceptive Blink Reflex F ratios .......................................191
Table 8-5: Summary of Main Findings .............................................................................196
Table 9-1: Summary of Main Findings ........................................................................................................ 204
Table D-0-1: Ch. 3 Migraine Symptom Means ....................................................................................... 234
Table D-0-2: Ch. 3 Scalp and Fingertip Tenderness Ratings Means ..................................................... 234
Table D-0-3: Ch. 3 Electrical Stimuli Pain Ratings Means ..................................................................... 235
Table D-0-4: Ch. 3 Blink Reflex Frequency Means .................................................................................. 235
Table D-0-5: Ch. 3 Blink Reflex Area Under the Curve Means .............................................................. 235
Table D-0-6: Ch. 3 Blink Reflex Frequency Latency Means .................................................................... 236
Acknowledgements

The completion of this thesis would not have been possible without the academic support, guidance, help and patience of my Ph D supervisor and mentor Professor Peter Drummond. I would like to thank him for his expert scientific leadership and his knowledge that has shaped me as researcher. I will miss the mentor-student relationship that has developed over the years of working together and hope that it will transpire into a collaborative partnership in future years. I would also like thank Professor Drummond for giving me a fantastic opportunity and enlightening me to research.

I would sincerely like to thank the organisations that financially supported the research. This research was financially supported by the NHMRC and the UK Migraine Trust. Without financial aid from organisations such as these, research would not occur. Thank You.

I would also like to thank the staff within the School of Psychology, especially the Technicians (Man, Francis & David). Due to the technical calibre of this research, it would not have been possible without their expert technical assistance. Additionally, I am grateful for the fantastic help from Cath who chaperoned and assisted me during the migraine testing sessions which included being called upon with no notice. I would also like to thank my two informal proof-readers, Reece and Brendan, who diligently ticked and crossed and highlighted their way through my thesis draft.

I would also like to sincerely acknowledge the role of all participants that completed the research. None of the studies were a pleasant experience especially when participants volunteered themselves during a migraine attack. These altruistic people sacrificed their comfort and time during an episode of debilitating illness, without medication, to be studied in the name of science which left me in awe of their participation.
During my candidature I have had the privilege of sharing the Lab with many inspiring and intelligent colleagues including Kylie, Bruce, Ashley, Anna CG, Dean and Juanita. I have also shared my Ph D journey with other candidates that have eased the burden with support, help, conversation, hugs, encouragement, writing groups, coffee and wine including Nat, Heather, Clare, Kate, Darren, Hayley, Anna and Jen J. Thanks also to Duane & Steve from ITRI for the continuing support.

I am also very thankful for the efforts from the team at Thinkwell (Maria Gardiner and Hugh Kearns) who helped getting the final write-up over the line. This task however would not have been completed without the very much appreciated thesis whispering of Cecily Scutt.

My final but far from least heart-felt thanks go to my family and friends. My family has expanded over my candidature but we have also experienced loss with my Dad passing away earlier in my candidature. I know he would have been proud, if nothing else but for my perseverance. My husband Stu and children Zach and Sophie gave my life another purpose other than the research, and continued to give me love, hope and encouragement throughout this amazing journey. My Mum and sisters also deserve a thank you for keeping my feet firmly on the ground and ensuring I see the lighter and funnier side of life. My parents-in-law Mai and Hugh, also helped out emotionally and financially throughout my candidature for which I am very grateful. I am very grateful to my special friends Jacquie (who kept me sane with coffee, shopping and conversation) and Trina (who helped me out with my formatting and encouraged me to persevere).

What an amazing journey!
Chapter 1  Literature Review and Introduction

1.1 Migraine

Migraine is defined as a throbbing, often one-sided, headache of moderate or severe intensity. It is often accompanied by nausea and/or vomiting, and light and/or sound sensitivity (photophobia; phonophobia) (IHS, 2004).

According to a recent Australian Health Survey, over one million Australians suffer from migraine headaches (ABS, 2009). This complex disorder is not only debilitating but also costly in terms of lost productivity and costs of treatment (Bigal & Lipton, 2009). The cost of migraine is estimated to be approximately $1 billion in Australia (Headache, 2003). The neurophysiological disturbances that precede and accompany migraine remain unclear. By understanding the origins and neural mechanisms of migraine, treatments may be discovered that have fewer side effects than current treatments, or that may be more cost effective.

Migraine is unique in that it is a disorder with no identifiable pathologies (Lambert, 2010; Levy, 2010). Migraine is often described as an episodic disorder, and although the migraine attacks are by definition ‘episodic’, the central nervous system apparently is dysfunctional most of the time in people with frequent attacks. This dysfunction may play an important role in the pathogenesis of migraine (Schoenen, 2006). A neurophysiological approach was employed in the current thesis to clarify the nature of this central dysfunction and to investigate the major neural component involved in migraine – the trigeminal system.

The aim of this thesis was to explore the idea that the trigeminal system is sensitised in migraine. This chapter reviews theories and studies relating to migraine, and specifically focuses on the sensitisation of the trigeminal system in migraine. The symptoms of migraine will be reviewed followed by a discussion of the anatomy of migraine. After the nociceptive
blink reflex and how it is used in migraine research is reviewed, the aims and hypotheses of this research are presented.
1.2 Pathophysiology of Migraine

1.2.1 Theories of Migraine

Whether migraine has a vascular or neural origin has been long debated. The vascular theory of migraine originated from a study of temporal arteries during migraine which were found to be dilated (Graham & Wolff, 1938). Although migraine responds to vasoconstrictors such as ergotamine and sumatriptan, these substances also inhibit the release of inflammatory agents such as the vasodilator agent calcitonin gene-related peptide (CGRP) from trigeminal nerve terminals (Buzzi, Carter, Shimizu, Heath, & Moskowitz, 1991). Early studies established that acute attacks of migraine were aborted by intravenous administration of serotonin (Kimball, Friedman, & Vallejo, 1960). Importantly, serotonin inhibits trigeminal cell firing via 5HT$_{1B/1D}$ receptors (Goadsby & Hoskin, 1998), suggesting that 5HT$_{1B/1D}$ receptor agonists (triptans) alleviate migraine by inhibiting trigeminal nerve activity.

The neurogenic inflammation theory of migraine proposed that the nerves that surround blood vessels in the meninges release inflammatory mediators (substance P; CGRP; nitric oxide) at the primary sensory neuron terminals, which inflame and sensitize the dural membrane and inflame and dilate the blood vessels that are imbedded within the dura mater (Moskowitz, 1993). The pathway for pain signals from the dura projects via the trigeminal nerve into the brainstem (Goadsby, Zagami, & Lambert, 1991). When this pathway is stimulated or inflamed in humans, intense pain results (Moskowitz, 1993). When activated, primary sensory neurons located in the pia, arachnoid and dura mater release the neuropeptides substance P, CGRP and neurokinin A onto the dura mater tissue, resulting in neurogenic inflammation. Some researchers believe that this neurogenic inflammation can sensitize the primary sensory afferents, resulting in a decrease in the nociceptive threshold. It was proposed that the throbbing nature of the pain that is endured in headaches is due to
activation of sensitized meningeal sensory fibres by the usually harmless pulsating of the intracranial blood flow (Strassman, Raymond, & Burstein, 1996).

Migraine is now thought to be a centrally mediated phenomenon in which the headache is not caused solely by vascular mechanisms but relies on a neurovascular disturbance that starts centrally with a disruption of sensory processing leading to a ‘wind-up’ of pain and sensitivity to innocuous stimuli (Giffin & Kaube, 2002). The vascular theory of migraine was left unsupported when vasodilator agents such as glyceryl trinitrate failed to produce migraine headaches in healthy controls (people who don’t suffer from migraine). Furthermore, triptans have been shown to alter neural activity at a central level – at least in animal models (Hoskin, Kaube, & Goadsby, 1996). Fundamental imaging studies have illustrated that the brainstem is activated during spontaneous migraine headaches (Weiller et al., 1995), suggesting a role of the central nervous system in migraine generation. The neurovascular theory is analogous to the theory of central origin of migraine headache, which argues against the primacy of peripheral activation and postulates that the ultimate migraine generator is dysfunctional pain modulation circuits (Lambert, 2010). Lambert argues that the generator must be located within the central nervous system as only this location could account for the spectrum of symptoms (such as nausea, photophobia and phonophobia).

1.2.2 Symptons of Migraine

The International Headache Society (2004) systematically outlines the symptoms required for diagnosis of different classes of headache and, more specifically, migraine headache. A migraine headache is diagnosed when the pain is moderate to severe and throbbing (usually unilateral) and lasts for 4 to 72 hours. The headache is often accompanied by nausea and/or vomiting, photo and/or phonophobia and is exacerbated by physical activities. However, questions still remain about the involvement of sensory systems in the symptoms of migraine
as neural pathways involved in these phenomena have not been truly explored (Olesen, 2010).

In a large study in the USA, 1025 migraine sufferers were interviewed regarding typical symptoms of migraine (Kelman & Tanis, 2006). The common symptoms associated with migraine headache included but were not limited to: nausea (90.1%), vomiting (51.8%), photophobia (93.9%), phonophobia (91.4%), and dizziness (72.4%). This study also demonstrated a significant correlation between headache severity and the associated symptoms of nausea, vomiting, photophobia, phonophobia and dizziness, suggesting that as headache intensified the associated migraine symptoms also intensified. One limitation of this study is that ratings were collected retrospectively for a single attack, suggesting the possibility of recall bias.

In the first prospective study on the time course of untreated migraine attacks, Linde et al (2006) recruited 18 migraine sufferers to record their symptoms over the entire untreated migraine period. Their main finding was that migraines have a heterogeneous natural course both inter- and intra-individually that medication can influence only temporarily. The general symptoms of migraine (headache, nausea, phonophobias and photophobia) accompany each other in a very similar time course, suggesting that a mutual underlying mechanism may be responsible. The authors argued that migraine must be central in origin because other non-pain related symptoms such as light and sound sensitivity and nausea sometimes developed before the appearance of the pain. In agreement with Kelman and Tanis (2006), Linde et al (Linde, Mellberg, & Dahlof, 2006) also report the synchronicity of the intensity/temporal course of photo- and phonophobia and headache as well as photo- and phonophobia and nausea. The authors postulated that all incoming stimuli accentuated the headache (Riley, 1932, as cited in Linde et al, 2006). From their research investigating motion sickness and migraine, Drummond and Granston (Drummond & Granston, 2005) suggested that headache
may increase nausea and that nausea caused by motion sickness intensifies headache (Drummond & Granston, 2004). Although some migraine sufferers report a reduction in their headache after vomiting (because the nausea has decreased) empirical evidence suggests that not all migraine sufferers report a decrease in headache after vomiting (Linde, et al., 2006). Thus, the link between gastrointestinal disturbances and headache requires further clarification.

1.2.2.1 Autonomic Dysfunction

Autonomic symptoms such as nausea, vomiting, pallor and flushing are commonly associated with migraine. This autonomic dysregulation might be due to an imbalance between the sympathetic and parasympathetic nervous system (Havanka-Kanniainen, Tolonen, & Myllyla, 1988) which has been identified both in adults (Appel, Kuritzky, Zahavi, Zigelman, & Akselrod, 1992; Cortelli et al., 1991; Melek et al., 2007) and children with migraine (Yakinci, Mungen, Er, Durmaz, & Karabiber, 1999).

The hypothalamus projects to the brainstem periaqueductal grey, the locus coeruleus and the medial raphe nuclei (Cortelli & Pierangeli, 2007). Because these areas are involved in autonomic mechanisms, sleep and descending control of pain perception, it is suggested that the hypothalamus is involved in these processes. The hypothalamus and the associated brainstem areas could be the neural sites responsible for the time-sequenced symptoms which occur during migraines (Cortelli & Pierangeli, 2007).

1.2.2.2 Headache

At least two mechanisms contribute to headache. The first is the malfunction of the endogenous antinociceptive system (Raskin, Hosobuchi, & Lamb, 1987) and the second is a secondary activation of dural trigeminal nociceptors (Burstein, Yamamura, Malick, & Strassman, 1998; Strassman, et al., 1996). Nausea induced by optokinetic stimulation (motion
sickness) either sensitised trigeminal nociceptive afferents or released inhibitory controls on
trigeminal nociceptive discharge (Drummond, 2002). Because nuclei in the brainstem are the
likely origin of motion sickness symptoms, this finding supports the involvement of these
brainstem centres in migraine (Weiller, et al., 1995).

1.2.2.3 Nausea and Vomiting

Vomiting and nausea are common in migraine. Most (90.1%) migraine sufferers report
nausea during a migraine headache, with just over 50% reporting vomiting (Kelman & Tanis,
2006). Interictally, migraine sufferers are also more likely to experience greater motion
sickness (Drummond, 2002; Drummond & Granston, 2004), and suffer greater nausea after
apomorphine challenge (Cerbo et al., 1997) than people who do not suffer from migraine.

The different categories of the anti-emetic migraine medications are not only grouped into
specific sites of action such as dopamine receptors, serotonin receptors, histamine antagonists
and cholinergic blockers but also larger sites of action such as the chemoreceptor trigger
zone, the so-called “vomiting centre” in the nucleus tractus solitarius (NTS) and the
vestibular apparatus (MacGregor, 2001).

The most commonly prescribed treatment for migraine is sumatriptan, which is a 5-HT₁B/D
agonist. Although this selective serotonin receptor agonist is prescribed mainly for the pain of
migraine headache, it also has anti-emetic properties. Sumatriptan is used to treat a variety of
nausea and vomiting syndromes – namely cyclic vomiting syndrome (Hikita et al., 2011). In
migraine sufferers, treatment with sumatriptan may alleviate attacks by constricting blood
vessels in the dura mater (Benson, Zorn, & Book, 1995). Sumatriptan also binds to several
sites in the central nervous system including the nucleus tractus solitarius (Pascual, Del Arco,
Romon, Del Olmo, & Pazos, 1996) where it may act to alleviate nausea and vomiting
(Hasler, 1999).
1.2.2.4 Photophobia and Phonophobia

Migraine can be triggered and aggravated by different environmental stimuli, perhaps due to a sensory overload vulnerability (Ambrosini & Schoenen, 2006). This overload may be expressed as photophobia (sight), phonophobia (hearing), allodynia (touch), osmophobia (smell), and taste abnormalities.

1.2.2.4.1 Photophobia

Photophobia is an abnormal sensitivity to otherwise tolerable light. Photophobia is a defining criterion of migraine (Drummond, 1986; IHS, 2004) but can also be a symptom of other disorders. Aside from the association with eye injuries, it is also associated with cranial disorders such as encephalitis, meningitis, head injury and subarachnoid haemorrhage (Amini, Digre, & Couldwell, 2006). Some researchers suggest that acute meningeal irritation can cause photophobia specifically in aseptic meningitis (Lamonte, Silberstein, & Marcelis, 1995) and subarachnoid haemorrhage (Welty & Horner, 1990). This is particularly pertinent to migraine because the meninges are innervated by trigeminal nerves. Tumors in the region of the optic chiasm (pituitary adenomas and craniopharyngiomas) have also been shown to produce photophobia (Kawasaki & Purvin, 2002). Photophobia may involve activation of the trigeminal pathway with inputs from the thalamus, the occipital lobe and the pretectal nuclei (Amini, et al., 2006). The ophthalmic division of the trigeminal nerve innervates the surface of the eye but it has also been proposed that central trigeminal projections to the midbrain and the thalamus are involved in photophobia in addition to peripheral involvement (Stringham, Fuld, & Wenzel, 2004; Welch, 2003). This is also evident in those cases where pituitary adenomas and other optic chiasm region tumors are present with photophobia as a common complaint. The most likely area of the central nervous system to mediate photophobia is where the visual pathways and pain pathways converge (Amini, et al., 2006). Although it was originally thought that a functioning optic nerve and trigeminal nerve were required for
photophobia, Custer and Reistad (Custer & Reistad, 2000) demonstrated that a functioning optic nerve was not required. More recent research has demonstrated that trigeminal nociceptors which are densely populated in the pars plana of the ciliary body can be activated by the proximal axons of the associational ganglion cell axons that project to the retinal periphery, illustrating a photophobia pathway that is independent of the central visual pathways (Dolgonos, Ayyala, & Evinger, 2011). This could also be the reason why virtually-blind patients report symptoms of photophobia (Noseda & Burstein, 2011).

Amini et al (2006) presented a case study of a patient with extensive and progressive pituitary adenoma who was blind but suffered from photophobia. After reviewing the literature on photophobia they concluded that hyperexcitability of the trigeminal system and the pretectal nucleus is involved in photophobia. After pretectal nuclei lesioning in monkeys, the light-induced blink reflex was inhibited. This inhibition did not occur after destruction of the superior colliculi (Mukuno et al., 1983). Amini et al (2006) concluded that the light-induced blink reflex and perhaps the photophobia pathways could project through retinotectal pathways to the facial neurons via the tectum that do not involve the visual structures beyond the optic tract. Amini et al (2006) suggested two afferent pathways for photophobia. The first is the trigeminal afferent system that processes photophobia sensed at the eye level (Figure 1-1). The second is via the visual afferent tract which communicates the photophobic information to the pretectal nuclei where the trigeminal and visual systems interact. Irritation anywhere within the trigeminal system leads to hypersensitivity which can result in photophobia. If an intracranial irritation to the meninges is present, excitation within the trigeminal system can exert an excitatory influence on the pretectal nucleus (Amini et al, 2006). This hypersensitivity in the pretectal region, combined with light coming from the visual pathway (via the magnocellular pathways), could result in photophobia. Amini et al speculated that the retinal ganglion cells could act as photoreceptors in patients with no visual
photic perception and send the photic information to the over-sensitised trigeminal system. They conceded that the actual location of the interaction between the retinal ganglion cells and the trigeminal system is unknown, but suggested that perhaps it could be at the retinal level where the choroid and blood vessels of the retina are innervated by the ophthalmic branch of the trigeminal nerve.

![Illustrative Model of Photophobia in Migraineurs](image)

**Figure 1-1:** Illustrative Model of Photophobia in Migraineurs. The illustration represents the two pathways of photophobia in migraine including the activation of the hyperexcitable visual cortex (shown in green) and the activation of the trigeminal nociceptive system within the brainstem (shown in red). The additional trigeminal painful stimulation also increases sensitivity to bright light.
Denuelle et al (Denuelle et al., 2011) carried out a PET study of photophobia during spontaneous migraine attacks. They found that the visual cortex was hyperexcitable to intense luminous stimulation and this persisted after headache relief, suggesting that the modulation of the cortical excitability present during photophobia goes beyond trigeminal nociception and may be controlled by brainstem nuclei. This same group of researchers (Boulloche et al., 2010) also tested migraine sufferers interictally with concomitant trigeminal pain and compared the findings in age-matched controls. The visual cortex was activated interictally in migraine sufferers during bright light. When concomitant trigeminal heat pain was also applied, activity increased in these same areas in migraine sufferers and developed in controls, suggesting an integration of noxious sensory stimuli.

1.2.2.4.2 Phonophobia

Sensitivity to auditory stimuli (phonophobia) is a diagnostic criterion for migraine (2004). It is often reported during migraine attacks and has also been reported between attacks of migraine (Olsson, 1991). Researchers who have quantitatively tested sound-induced pain and discomfort thresholds support the view that phonophobia develops during migraine headaches (Drummond & Woodhouse, 1993; Vingen, Pareja, Storen, White, & Stovner, 1998; Woodhouse & Drummond, 1993). However, quantitative investigations of phonophobia between attacks of migraine have yielded conflicting results (Drummond & Woodhouse, 1993; Vingen, et al., 1998; Woodhouse & Drummond, 1993). Ashkenazi et al (Ashkenazi, Yang, Mushtaq, & Oshinsky, 2010) found that migraine sufferers (particularly those with allodynia) were averse to sound stimuli both between attacks and more so during a migraine headache, suggesting an association between allodynia and phonophobia. However, Drummond and Woodhouse (Drummond & Woodhouse, 1993) reported that the sound-evoked discomfort threshold did not decrease in migraine sufferers or controls after painful
trigeminal stimulation of the forehead with ice, implying that phonophobia was unrelated to trigeminal nerve discharge.

Both photophobia and phonophobia are present during a migraine which suggests a common pathway. Recent research suggests that neurons in the thalamus may be sensitised during migraine with this area being activated in patients with alldynia (Burstein et al., 2010). Since this is the location of convergence of sensory neurons from the visual, aural and ascending and trigeminal pain pathways, the sensitisation of these thalamic neurons during a migraine seems plausible (Lovati, D'Amico, & Bertora, 2009).

**1.2.2.5 Summary**

Headache during migraine is most likely caused by a malfunction of the endogenous antinociceptive system and secondary activation of dural trigeminal nociceptors. The most common associated symptoms of migraine are nausea, vomiting, photophobia, phonophobia, and dizziness.

Additionally, migraine sufferers are susceptible to nausea provocation interictally. Photophobia can also be elicited in migraine sufferers interictally but provocation of phonophobia during the headache free period yields conflicting results.

**1.2.3 The Anatomy of Migraine**

The theory that migraine headaches originate from a top-down dysfunctional process in a hyperexcitable but hypoenergetic brain has been supported by some biochemical studies (D'Andrea, D'Arrigo, Dalle Carbonare, & Leon, 2012; D’Andrea & Leon, 2010). This group of researchers suggest that biochemical imbalances in neuromodulators and neurotransmitters may trigger activity in the trigeminal system, causing the cascade of events that lead to the migraine attack (release of CGRP, formation of inflammatory soup, sensitisation of first order
trigeminal neurons and subsequent migraine). The following section will discuss the processes that occur in the development of a migraine headache.

Although migraine has no identifiable permanent pathologies, various sectors of the central nervous system have been identified as contributing to symptoms during attacks. The source of migraine is controversial with arguments both in favour of a central (Lambert, 2010) or peripheral origin (Levy, 2010). The initial trigger of the migraine can be endogenous such as the decrease in estrogen that occurs prior to the onset of menstruation (MacGregor, 2004; Somerville, 1972, 1975a, 1975b) or pain from cervical structures (Bartsch & Goadsby, 2002). Exogenous triggers are many and are not limited to, but can include: alcohol, smoke, odours, sleep disturbances or sleeping late, fasting, weather, food triggers (preservatives in red wine, oranges, chocolate) and stress or relaxation after stress (Kelman, 2007). Whether these internal and external triggers prompt an initial aberrant cranial vasodilator response or neurogenic response is still controversial, but Burstein and colleagues discuss the rather circular activation of the neurogenic trigeminal system and inflammatory soup with its vasodilator neuropeptides (Burstein, 2001; Burstein, Cutrer, & Yarnitsky, 2000; Burstein, et al., 1998). Recent research has suggested that proinflammatory cytokines such as Interleukin-6 (Yan, Melemedjian, Price, & Dussor, 2012) and Interleukin-1β (Zhang, Burstein, & Levy, 2012) are involved in the meningeal nociceptive activation. The release of pro-inflammatory neuropeptides by the trigeminovascular system is central in the manifestation of migraine, which adds some support to migraine being a ‘peripherally’ located event (Goadsby, Edvinsson, & Ekman, 1988). The introduction of sumatriptan for the treatment of migraine also lends support to this argument, as sumatriptan acts directly to inhibit the release of neuropeptides and cannot cross an intact blood-brain barrier (Humphrey et al., 1991). However, some studies have shown that central trigeminal neurones can be inhibited by sumatriptan when the blood-brain barrier has been disrupted (Kaube, Hoskin, & Goadsby,
1993). Zolmitriptan, on the other hand, has been shown to be dual acting on both the central and peripheral divisions of the trigeminovascular system (Martin, 1997).

Recent research has established the role of calcitonin gene-related peptide (CGRP) in migraine (see (Raddant & Russo, 2011) for review). The CGRP is released from primary sensory neurons in the meninges. Vasodilation, mast cell degranulation and plasma extravasation in the meninges is caused by CGRP binding to its receptors near the meningeal vessels. The release of CGRP is pro-inflammatory and pro-nociceptive in migraine pathology (Durham & Masterson, 2012). The discovery of the role of CGRP in migraine pathology led to the possibility of using CGRP antagonists in the treatment of migraine (Durham & Masterson, 2012; Edvinsson & Ho, 2010; Tfelt-Hansen, 2012). But in a recent review of current pharmaceutical treatments of acute migraine, Tfelt-Hansen (2012) reports that only 25% of migraine patients were pain free after 2 hours in phase III studies in the clinical trials of CGRP receptor antagonists (Tfelt-Hansen, 2012). He also reported that the development of the current CGRP antagonists has been halted.

The primary sensory fibres of the meninges and associated vasculature are pseudounipolar and originate from the trigeminal ganglion and project to the trigeminal nucleus caudalis (TNC) in the medulla (Strassman, Mason, Moskowitz, & Maciewicz, 1986) via the mesencephalic nucleus, the principal sensory nucleus, the interstitial nucleus of the spinal trigeminal tract and the spinal trigeminal nucleus (located in the pons) which then extends to the three subnuclei in the upper cervical spinal cord (medulla) of the subnucleus oralis, interpolaris and caudalis. Within these three sensory nuclei, neurons are classified into three groups according to their cutaneous receptive fields in response to mechanical stimulation (Sessle, Hu, Amano, & Zhong, 1986). Light touch stimuli activates both low-threshold mechanoreceptive neurons and wide dynamic range (WDR) neurons but WDR neurons are the only neurons to increase their discharge rate when the stimulus approaches nociceptive
intensities. The nociceptive neurons only discharge in response to noxious stimuli. These nociceptive neurons are located in the interstitial nucleus of the spinal trigeminal tract and the three subnuclei of the spinal trigeminal nucleus which indicates the involvement of these centres in pain processing. Studies with patients with Wallenberg’s Syndrome (brainstem stroke) have shown that the interpolaris and caudalis of the spinal trigeminal nuclei are involved in trigeminal nociceptive processing (Vallis-Sole et al., 1996). During headache, C-fibres relay nociceptive information to the brainstem – specifically the trigeminal nucleus caudalis (Aurora, Ahmad, Welch, Bhardhwaj, & Ramadan, 1998; Mitsikostas & Sanchez del Rio, 2001).

Brainstem activation during migraine has been illustrated with various scanning techniques. More specifically, the dorsal [rostral] pons (Bahra, Matharu, Buchel, Frackowiak, & Goadsby, 2001; Matharu et al., 2004) has consistently been shown to be activated. The lateralisation of pain during a migraine headache may reflect lateralised brainstem dysfunction (Afridi et al., 2005). Afridi et al (2005) used PET to investigate healthy controls and migraine sufferers before, during and after a migraine induced by glyceryl trinitrate. Activation in the dorsal pons generally reflected laterality of headache and persisted after pain had subsided following the administration of sumatriptan.

The hypothalamus may be involved in the generation of headache (Matharu, 2007), with the ascending and descending pathways connecting to the major structures implicated in migraine including the nucleus tractus solitarius, rostroventromedial (RVM) medulla, the periaqueductal gray, the raphe nucleus magnus and trigeminal brainstem nuclear complex (Matharu, 2007).

The sensitisation of thalamic neurons has been observed by fMRI during extracephalic allodynia in both rats and ictal migraine patients (Burstein, et al., 2010). The authors suggest that this hypersensitivity of thalamic neurons could also be responsible for hypersensitivity to
other nonnoxious stimuli (light, sound, odours) because this is the site of convergence of nociceptive input from the cranial meninges with other sensory information.

Burstein et al (Burstein, Jakubowski, & Rauch, 2011) theorised about the development of the cascade of events that lead to a migraine headache. The first-order neurons in the trigeminal ganglion are activated by the inflammatory soup and if this is not stopped in 10-20 minutes, molecular changes occur and they become hypersensitive to intracephalic pressure changes such as pulsations (throbbing). By 60-120 minutes, the second order neurons in the spinal trigeminal nucleus undergo molecular changes that sensitise them into an activity-independent state in which they depolarise independently of any stimuli. At this stage, homosegmental skin sensitivity occurs (cephalic cutaneous allodynia) (Burstein, et al., 2011). Beyond this time, thalamic neurons can also become hypersensitive leading to extracephalic cutaneous allodynia and sensitisation to other sensory stimuli such as light, sound and odours (Burstein, et al., 2010).

1.2.3.1 Neurotransmitters

Although the current thesis does not address any hypotheses regarding neurotransmitters, a short section summarising neurotransmitter involvement in migraine models is worthwhile to illustrate pain pathways that may be important in migraine. Only two neurotransmitters will be discussed – serotonin and dopamine.

1.2.3.1.1 Serotonin

The role of serotonin is important in the development of clinical features in migraine (Marcus, 1993). Marcus postulates that the changes in serotonin occur prior to the vascular changes during the migraine although it is unclear whether this serotonergic change initiates the subsequent cascade of pathophysiology or accompanies it (Marcus, 1993).
Serotonin 1B/1D receptor agonists (termed *triptans* because they are derived from tryptamine) are frequently used to treat migraine acutely. Currently there are seven triptans on the international market for routine clinical use (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan) (Pascual, Mateos, Roig, Sanchez-del-Rio, & Jiménez, 2007) although almotriptan and frovatriptan are not currently available in Australia on the pharmaceutical benefits scheme. Triptans (serotonin agonist 1B, 1D, 1F) inhibit the release of neurotransmitters from central endings of nerves in the trigeminal nucleus caudalis, and prevent the transmission of pain signals to the brainstem (Levy, Jakubowski, & Burstein, 2004). Furthermore, this compound prevents the release of vasoactive neuropeptides at the pre-synaptic junction of the C-fibre afferent and meningeal vessel wall because activation of these specific (1D and 1F) receptors results in inhibition of neural discharge. Post-synaptically the serotonin agonists work on the 1B receptors to induce vasoconstriction. Ideally the use of serotonin agonists for the 1D and 1F receptors only would benefit the treatment of migraine without the side-effects evoked by the vasoconstrictive action of the 1B receptor. In summary, triptans have been shown to constrict cerebral blood vessels and modulate nociception in the trigeminovascular system.

Low serotonergic activity in the migraine brain could also be responsible for the lack of central habituation to repeated stimuli. According to Ozkul and Ay (2007) serotonergic neurons of the raphe nuclei modulate cortical information processing (Jacobs and Azmitia, 1992). Additionally, Hegerl and Jacobs (1993) suggested that low serotonergic activity in the migraine brain could increase sensitivity to sensory stimuli.

1.2.3.1.2 *Dopamine*

Although controversial (Mascia, Afra, & Schoenen, 1998), the dopamine theory of migraine, originally proposed by Sicuteri (Sicuteri, 1977), suggests that the migraine brain is hypersensitive to dopamine. This is based on the finding that dopamine agonists can provoke
yawning, nausea and blood pressure changes which are suggested to be premonitory symptoms of migraine. Although Akerman and Goadsby (2007) question the involvement of dopamine in migraine pathophysiology, especially when compared to the other major contributing neurotransmission systems of serotonin, CGRP and nitric oxide, it is tempting to argue that the dopaminergic system is involved in symptoms such as nausea and dizziness (Fanciullacci, Alessandri, & Del Rosso, 2000).

Apomorphine is a dopamine agonist. When apomorphine was administered, the number of yawns, nausea, vomiting, dizziness and sweating increased in migraine sufferers when compared with controls (Blin, Azulay, Masson, Aubrespy, & Serratrice, 1991) suggesting a role of dopamine in the presentation of these symptoms.

1.2.3.2 Summary

Meningeal neurogenic inflammation may be a source of pain in migraine. The C-fibre endings that surround the meningeal vessels release vasoactive neuropeptides (CGRP, Substance P and neurokinin A; IL-6 and IL-1β). The antidromic release of these neuropeptides causes neurogenic vasodilation, an increase in blood flow and meningeal oedema. This inflammatory process then activates the pre-synaptic trigeminal nerve C-fibre again and the cycle continues, sensitising the first-order trigeminal neurons in the trigeminal ganglion. Second-order neurons then become sensitised and depolarise independently of any input activity. These neurons are located in the trigeminal subnucleus caudalis (also known as the medullary dorsal horn (Hockfield & Gobel, 1982). The brainstem is activated during migraine with the trigeminal nucleus caudalis playing a major role in the manifestation of migraine. From the trigeminal nucleus caudalis, this information is then projected to other brainstem nuclei and higher cortical structures for nociceptive processing and modulation which can include sensitised thalamic neurons leading to extracephalic cutaneous allodynia, photophobia and/or phonophobia. Low serotonergic activity has been implicated in
trigeminovascular activation pathways, and increased dopamine has been implicated in other autonomic symptoms of migraine such as nausea and dizziness.
1.3 Blink Reflex

1.3.1 Introduction

Wide dynamic range and nociceptive specific neurons have been found in the interstitial nucleus of the spinal trigeminal tract and the spinal trigeminal nucleus (all sub nuclei), suggesting an involvement in trigeminal pain processing (Ellrich, 2002). Trigeminal nociceptive neurons are involved in central multi-receptive brainstem reflexes, such as the blink reflex (Ellrich, 2000). The blink reflex has been used to examine the trigeminal system of migraine sufferers. Studies that used both the standard and nociceptive blink reflex tests will be presented in the subsequent section, followed by a discussion of the application of these tests to migraine sufferers.

1.3.2 Anatomy and Measurement of the Blink Reflex

Electrical stimulation of the trigeminal supraorbital nerve with normal electrodes (also known as standard electrodes - flat surface electrodes placed over the supra-orbital foramen and 2 cm rostral) commonly provokes three components of the blink reflex: the unilateral oligosynaptic R1, the ipsilateral and contralateral polysynaptic R2, and the R3. The earliest response is the R1 that occurs ipsilaterally between 9 and 24 ms after the stimulus (Ellrich & Treede, 1998). The pathway for this response consists of a pontine oligosynaptic arc that is mediated through one or two interneurons by fibres that project from the trigeminal principal sensory nucleus to the facial nucleus (Shahani & Young, 1973). The second response to an electrical stimulus delivered via normal electrodes is the R2. This response occurs between 27 and 87 ms and is a bilateral multisynaptic event (Ellrich & Treede, 1998). Nerve impulses enter the pons ipsilaterally at the principal trigeminal nucleus before descending to the caudal spinal trigeminal nucleus. A medullary pathway then ascends to the ipsilateral and contralateral facial nuclei (Kimura, 1973). Because the reflex arc of the R2 involves the trigeminal nerve
and brainstem the blink reflex has been used clinically to diagnose lesions in these regions (Kimura, 1973). The third, late, R3 response occurs between approximately 85 and 120 ms (Ellrich & Hopf, 1996), is not always present and is generally not present when the stimulus is announced, suggesting it may be part of the startle response (Ellrich, Katsarava, Przywara, & Kaube, 2001). The thin myelinated Aδ fibres can be electrically activated at stimulus intensities 5 times the detection threshold (Ellrich, 2002) but the unmyelinated nociceptive C-fibres need an intensity much higher (15 times the detection threshold) (Ellrich, Katsarava et al, 2001). Local anaesthetic agent applied under the electrodes did not change the detection threshold, or the BR components of the classic blink reflex, but did change the pain threshold (Ellrich, et al., 2001).

The R2 component of the blink reflex elicited by standard bi-polar electrodes is mainly (90%) modulated by the input of the Aβ fibres onto the wide dynamic range neurons of the caudal region of the spinal trigeminal nucleus (Kaube et al., 2002). Ellrich (2000) suggested that the R2 component of the blink reflex can indicate excitability of brainstem interneurons that mediate this reflex. Innocuous mechanical and electrical stimuli can elicit R1 and R2, implicating the Aβ afferents.

Because non-nociceptive and nociceptive input can elicit an R2, two reflex arcs are possible. The first is the Aβ (LTM) projecting on to LTM receptive neurons and the Aδ, nociceptive input projecting onto the nociceptive specific neurons. The second reflex arc involves both inputs converging onto common wide dynamic range (WDR) interneurons. That is, both reflexes share the same interneurons. This was tested by investigating if R2 was affected by activation of the diffuse noxious inhibitory controls system. Input from nociceptive afferents from anywhere in the body activated the nociceptive neurons in the subnucleus reticularis dorsalis in the brain stem, causing inhibition of the WDR neurons in the spinal cord and the trigeminal system (Ellrich & Treede, 1998). Therefore, if R2 was mediated by WDR neurons
then remote painful stimuli (DNIC) would suppress this reflex. Ellrich and Treede (Ellrich & Treede, 1998) found that pain in the extremities inhibited R2 but didn’t affect R1. They postulated that Aβ and Aδ afferents probably converge onto common WDR neurons within the medullary spinal trigeminal nucleus and R1 is probably mediated by pontine LTM neurons. When a painful stimulus was applied to the forehead, R2 increased but R1 wasn’t affected, suggesting that spatial summation facilitated the R2 (Ellrich, Andersen, Treede, & Arendt-Nielsen, 1998).

Cruccu et al (Cruccu et al., 2005) used the standard electrode blink reflex in association with magnetic resonance imaging (MRI) to investigate focal ischaemic brainstem lesions in a large number of patients. It has been suggested that the anatomical caudal limit of this blink reflex response extends to the Spinal Trigeminal Nucleus caudalis although post-mortem investigations on a small number of patients with R2 abnormalities revealed that their lesions were rostral to the sub-nucleus caudalis because the lesions did not extend below the olivary/hypoglossal nerve nuclei (Aramideh, Ongerboer de Visser, Koelman, Majoie, & Holstege, 1997; Ongerboer de Visser & Kuypers, 1978). Blink reflexes in response to the standard electrode electrical stimulus were differentiated from the corneal reflex in patients with focal ischaemic brainstem lesions (Cruccu, et al., 2005). Whilst the corneal reflex is purely nociceptive in nature, it is mediated by the Aδ fibres that project onto the nociceptive specific neurons in the outer lamina of the subnucleus caudalis (Cruccu, et al., 2005). In contrast, the late blink reflex response (R2) to the standard electrode stimuli is mediated by the Aβ fibres which project to the mechanoreceptive neurons in the deeper layers of the spinal trigeminal nucleus (medullary laminae III-IV). Both pathways also transmit to WDR neurons located in the deeper medullary reticular area. The late blink reflex response to innocuous stimuli is mediated by the subnucleus interpolaris (Cruccu, et al., 2005). The low-threshold mechanoreceptive neurons (Aβ) are activated by electrically or mechanically
elicited low-threshold mechanoreceptor stimuli. Nociceptive input, activated by painful heat pulses, projects onto the nociceptive specific neurons in the medullary dorsal horn. But both of these inputs may converge onto the WDR neurons. Remote noxious stimuli have been shown to suppress the R2 by inhibiting the WDR neurons both in the spinal cord and the trigeminal system (Bouhassira et al., 1994).

1.3.3 Nociceptive Blink Reflex

Delivering stimuli from a concentric electrode is a non-invasive method for investigating the human trigeminal system. The small cathode surface area produces a high current density which limits depolarisation to the Aδ fibres in the superficial layer of the skin at low current intensities. However, higher current intensities delivered via the concentric electrode penetrate deeper and activate Aβ fibres (Kaube, Katsarava, Kaufer, Diener, & Ellrich, 2000).

The blink reflex elicited by a concentric electrode, termed the nociceptive blink reflex, produces only an R2 response, with an onset latency of about 42 ms (Kaube, et al., 2000).

A functional block to nociceptors did not change any component of the blink reflex in response to an electrical stimulus delivered via normal electrodes. However, the pain threshold increased (Ellrich, et al., 2001). This suggests that the blink reflex components of this type of stimulation are mediated predominantly by non-nociceptive afferents (Aβ fibres).

The nociceptive blink reflex was however reduced by 85% after a block of Aδ and C-fibre function (Kaube, et al., 2000), suggesting that this type of stimulation is predominantly mediated by nociceptive afferent (Aδ) fibres. As stated by Ellrich in numerous papers (Ellrich, 2000, 2002), this suggests that there are two conceivable pathways for the reflex arcs; the Aβ pathway and the Aδ pathway. The difference in onset latency of the R2 between the two types of stimulation supports the notion that the R2 of the normal electrode blink reflex is mediated by the Aβ fibres (large myelinated) because it is faster (30 ms) (Aramideh
& Ongerboer de Visser, 2002) than the nociceptive blink reflex (at 42 ms) (Ellrich, 2002) which is mediated by the small myelinated Aδ fibres.

Attention may also play a part in the nociceptive blink reflex. Pain ratings to a nociceptive specific stimulus decreased during a cognitive task (serial subtraction) but the R2 of the blink reflex increased by almost 50% (Koh & Drummond, 2006). Other influences may also be responsible for changes in the blink reflex such as diffuse noxious inhibitory controls, discussed in the next section.

1.3.4 Diffuse Noxious Inhibitory Controls (DNIC)

Diffuse noxious inhibitory controls (DNIC) is a process by which WDR neurons are ‘selectively and powerfully inhibited’ by noxious stimuli to areas away from their excitatory receptive fields. Remote painful heat has been shown to suppress the R2 response to stimuli delivered from a standard electrode (Ellrich & Treede, 1998). However, local painful heat prior to trigeminal electrical stimulation causes a facilitation of this part of the blink reflex (Ellrich, et al., 1998), demonstrating a convergence of both low threshold mechanical (Aβ) neurons and nociceptive orofacial inputs (Aδ) onto the WDR neurons of the medullary dorsal horn (Ellrich, Andersen, Messlinger, & Arendt-Nielsen, 1999) indicating that both reflexes share the same interneurons (Ellrich & Treede, 1998). The analogue of DNIC in human studies is now sometimes termed conditioned pain modulation (CPM) (Yarnitsky et al., 2010). Studies in humans only indirectly examine the neurophysiological pathways that underlie DNIC. However the initial terminology of DNIC is used because this term is more widely recognised and less confusing (Michaux, Anton, Erpelding, & Streff, 2010).

The blink reflex was examined in 13 participants using a standard electrode low-intensity stimulus (2.3 mA) and a higher intensity stimulus (18.6 mA) before, during and after ice-induced pain in the ipsilateral and contralateral temple and during immersion of the hand in
ice-water (Drummond, 2003). Ipsilateral cold-induced pain to the same dermatomal segment increased the pain rating given in response to a high intensity electrical stimulus but inhibited the R2 component both of low and high intensity stimuli, suggesting the activation of DNIC.

The findings of Drummond’s study do not support the findings of others. Ellrich et al investigated the blink reflex to standard electrode stimuli (11-15 mA depending on individual pain and detection thresholds) after applying a heat pulse by laser to the same area of the forehead. These researchers found a facilitation of the R2 component of the blink reflex and suggested that the results showed a convergence of low threshold mechanoreceptors with nociceptive inputs onto interneurons in the medullary dorsal horn (Ellrich, et al., 1998). Differences in site and type of stimulation might explain the differences between these two studies. Drummond used a block of ice as the homosegmental noxious stimulus perhaps leading to greater spatial summation, whereas Ellrich et al. used a laser point.

Giffin et al. used hand immersion in ice-water as a conditioning stimulus (to evoke a DNIC effect) during trains of nociceptive specific stimuli to evoke blink reflexes (Giffin, Katsarava, Pfundstein, Ellrich, & Kaube, 2004). The R2 component of the nociceptive blink reflex was inhibited during hand immersion only in response to double and triple pulse trains (inter stimulus interval of 5 ms) suggesting that a higher number of interneurons in the medullary dorsal horn were recruited during the pulse trains due to temporal summation and that DNIC inhibited this effect.

Rehberg et al also used the cold pressor test as the noxious conditioning stimulus to investigate the DNIC effect on both the flexion reflex and nociceptive blink reflex in humans (Rehberg, Baars, Kotsch, Koppe, & von Dincklage, 2012). The authors reported a reduction in subjective pain ratings to the test stimuli and reduced amplitude for both reflexes suggesting that DNIC occurred.
1.3.5 Case Studies

During the process of this research program, various case studies were investigated in our laboratory using the blink reflex paradigm. The first case study is the result of an investigation of a patient suffering from Parry-Romberg syndrome (Appendix A, (Drummond, Hassard, & Finch, 2006)) and illustrated a hypersensitive response on the affected side of the forehead in both subjective pain rating and blink reflexes evoked by standard electrode stimuli and concentric electrode stimuli. The second case study (Appendix B, (Drummond & Treleaven-Hassard, 2008) is a report about a patient benefiting from the electrical stimulation used to evoke the blink reflexes. The electrical stimuli resulted in analgesia for persistent neuralgic jabs in all three trigeminal branch regions after trigeminal ganglion ablation even though sensation and blink reflexes were absent in response to the stimuli. The third case study is an unpublished (Appendix C) report regarding a patient with idiopathic trigeminal pain. The results of the case study using the blink reflex paradigm illustrated an abnormality of the nociceptive afferent system on the affected side.

1.3.6 Summary

The blink reflex has been used to investigate the trigeminal nervous system using electrical stimuli in the ophthalmic region and measuring the electromyography response of the orbicularis oculi muscle. This reflex arc involves the Aβ fibres (standard electrode) and Aδ fibres (concentric electrode), and possibly C-fibres at higher intensities; projecting from the periphery to the spinal trigeminal nuclei, then travelling ipsilaterally and contralaterally to the facial nuclei to produce the motor components of the reflex. The blink reflex can be measured with the early monosynaptic R1 (9-24 ms) (standard electrodes stimulus only), the multi-synaptic R2 (27-87ms) and the late response R3. The blink reflex can be influenced by attention, inhibited by remote stimuli (DNIC) or facilitated by homosegmental sensitization.
(due to temporal summation). This will be discussed in the following section in relation to migraine.

1.3.7 Blink Reflex and Migraine (Table 1-1)

The study of the blink reflex in migraine dates back to the work of Bank, Bense and Kiraly (1992) and Sand and Zwart (1994). Because of the involvement of the trigeminal nerve and brainstem in migraine, it was presumed that the R2 component of the blink reflex would be influenced by migraine. Numerous migraine researchers have used stimuli delivered from standard electrodes to evoke the blink reflex (Aktekin, Yaltkaya, Ozkaynak, & Oguz, 2001; Avramidis, Podikoglou, Anastasopoulos, Koutroumanidis, & Papadimitriou, 1998; Bank, Bense, & Kiraly, 1992; de Tommaso, Guido, Libro, Sciruicchio, & Puca, 2000a, 2000b; Sand & Zwart, 1994). However, this research has produced inconclusive results with some reporting a longer R2 latency in migraine sufferers (Bank, et al., 1992); no difference in R2 latency between migraineurs and controls (Sand & Zwart, 1994); a suppression of R2 during a migraine (Avramidis, et al., 1998); and no changes to the R2 during a migraine (de Tommaso, et al., 2000b).

Over a decade ago the blink reflex in response to a standard electrode stimulus was investigated in migraineurs, tension-type headache sufferers and healthy controls (Avramidis, et al., 1998). Tension-type headache and migraine sufferers were tested during a headache, with migraine sufferers also being tested three days after testing and after the administration of sumatriptan. The R2 area for both the ipsilateral and contralateral sides was significantly lower for migraine sufferers during a migraine when compared to controls with the R2 being restored on both sides 60 minutes after sumatriptan administration. There was no difference in R2 area between tension-type headache episodes and controls. The authors argue that because there was no difference between controls and tension-type headache sufferers during
the attack that activity in trigeminal and facial nerves and interneurons involved in the blink reflex arc was normal in these patients.

In a study by de Tommaso et al (2000), the effect of Zolmitriptan and Sumatriptan on the blink reflex was investigated in migraine without aura patients during an attack and healthy controls (de Tommaso, et al., 2000b). Participants received the same stimulus during the attack, 2 hours after drug administration and 72 hours after the end of critical symptoms. The authors found no difference between the migraine attack and after treatment for the R1 and R2 components. The R3 component was the only component affected by migraine attack when compared with the pain free session. The authors suggested that the facilitation of R3 during a migraine is the result of sensitization of the trigeminal nociceptive system.

The final event causing pain in migraine headache is the activation of the trigeminal system (de Tommaso et al., 2002). Blink reflex modulation in migraineurs and controls was investigated during manipulated attention and habituation trials (de Tommaso, et al., 2002). The authors found that anticipating the stimulus increased the R2 response in migraine with aura sufferers but not controls or migraine without aura sufferers, indicating that attentional modulation of the blink reflex is present for migraine with aura sufferers.

All of the previously discussed researchers in this section used standard electrodes to evoke the blink reflex. However, another group of researchers found a facilitation effect of migraine on the blink reflex using a concentric electrode. This will be discussed in the following section.
Table 1-1: Standard Electrode Blink Reflex and Migraine Studies

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Experimental Groups (n)</th>
<th>Procedures</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TTH=11 Cervicogenic H=10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>Avramadis, Podikoglou, Anastasopoulos, Koutroumanidis, Papadimitriou.</td>
<td>Controls=30 Migraineurs=19 (Ictal &amp; interictal)</td>
<td>Blink reflex tested during and between headache/migraine in all participants and after sumatriptan in half of the migraineurs during migraine.</td>
<td>↓R2 during migraine. R2 restored to normal by sumatriptan.</td>
<td>Standard blink reflex suppressed during migraine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TTH=10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Aktekin, Yaltkaya, Ozkaynak, Oguz.</td>
<td>Controls=20 Migraineurs=20 (Ictal)</td>
<td>Measured the latency, amplitude &amp; size of R1 &amp; R2 and compared all 3 groups.</td>
<td>No differences in migraine blink reflex components.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TTH=32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>de Tommaso, Murasecco, Libro, Guido, Sciruicchio, Specchio, Gallai, Puca.</td>
<td>Controls=35 Migraine with aura=20 (interictal) Migraine without aura=50 (interictal)</td>
<td>R2 &amp; R3 blink reflex components were investigated during mental activity, stimulus anticipation &amp; recognition of target numbers.</td>
<td>↑R2 during stimulus anticipation in migraine with aura.</td>
<td>Dysfunctional adaptation capacity to environmental conditions in migraine.</td>
</tr>
<tr>
<td>Year</td>
<td>Authors</td>
<td>Experimental Groups (n)</td>
<td>Procedures</td>
<td>Results</td>
<td>Conclusions</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
<td>-------------------------</td>
<td>------------</td>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>2002</td>
<td>Kaube, Katsarava, Przywara, Drepper, Ellrich, Diener.</td>
<td>Migraineurs=17 (Ictal &amp; interictal)</td>
<td>R2 latencies &amp; AUC measured during migraine, after treatment with aspirin or zolmitriptan and interictally.</td>
<td>AUC of nociceptive blink reflex R2 ↑680% suppressed by aspirin &amp; zolmitriptan.</td>
<td>Central trigeminal sensitisation during migraine.</td>
</tr>
<tr>
<td>2002</td>
<td>Katsarava, Lehnerdt, Duda, Ellrich, Diener, Kaube.</td>
<td>Migraineurs=14 (Ictal &amp; interictal) Controls with sinusitis headache=14</td>
<td>Examined the nociceptive blink reflex during migraine and sinusitis headache.</td>
<td>Nociceptive blink reflex was facilitated on headache side during migraine.</td>
<td>Facilitation is migraine specific not peripherally mediated.</td>
</tr>
<tr>
<td>2003</td>
<td>Kowacs, Giffin, Putzki, Goadsby, Kaube.</td>
<td>Controls=8</td>
<td>Examined the nociceptive blink reflex before, during and after GTN infusion.</td>
<td>No change in R2 after infusion.</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Katsarava, Limmroth, Baykal, Akguen, Diener, Kaube.</td>
<td>Controls=30 Migraineurs=28 (Ictal &amp; Interictal)</td>
<td>Examined the nociceptive blink reflex during migraine and after treatment with aspirin &amp; zolmitriptan.</td>
<td>Nociceptive blink reflex facilitation suppressed after both treatments during migraine but not interictally.</td>
<td>The medications inhibited the facilitated responses during migraine but not the resting trigeminal nociceptive system.</td>
</tr>
</tbody>
</table>
1.3.8 Nociceptive Blink Reflex and Migraine (Table 1-2)

Some research has used the blink reflex evoked by a nociceptive specific electrode to depolarize the Aδ nerve fibres of the human trigeminal system to investigate the location of sensitization in migraine sufferers (Kaube, et al., 2000). The authors investigated the nociceptive blink reflex during acute migraine attacks and found a facilitation of almost 700% compared with the non-headache nociceptive blink reflex. The researchers were unsure if this temporary sensitization was the result of sensitization of peripheral nociceptors in the meninges or second order neurons in the trigeminal nuclei. In a follow-up study the same group of researchers investigated the nociceptive blink reflex during an acute migraine attack and during sinusitis head pain (Katsarava et al., 2002). The findings suggested that trigeminal nociceptive sensitization during migraine was indeed the result of central sensitization rather than primary sensitization of the peripheral nociceptors because the blink reflex was unchanged during painful sinusitis despite peripheral nociceptor activation.

The nociceptive-specific blink reflex evoked with the concentric electrode and the blink reflex evoked by normal electrodes were investigated in migraine sufferers within 6 hours of migraine onset. The patients were tested in a pain free period, during the attack and post treatment (1000 mg lysine acetylsalicylate (n = 8); or 5 mg of zolmitriptan (n = 9)) (Kaube, et al., 2002). During the migraine attack, R2 AUC of the nociceptive specific blink reflex increased by 680% ipsilaterally on the headache side. After treatment the facilitation of the blink reflex was significantly reduced by both medications (zolmitriptan 45% and lysine acetylsalicylate 48%). There were no significant differences for the blink reflex elicited by the standard electrodes. The authors suggest that the increase in the nociceptive specific blink reflex area under the curve supports a facilitation of a spinal or medullary reflex (based on Steffens & Schomberg, 1993; Woolf, 1983). The authors suggested that the facilitation of the
R2 is the result of central sensitization at the spinal trigeminal nucleus because of the depolarisation of the cutaneous trigeminal axons.

In a follow-up study, glyceryl trinitrate (GTN) was used to induce a headache in healthy controls to test the hypothesis that the nociceptive blink reflex would be facilitated during the headache (F. Kowacs, Giffin, Putzki, Goadsby, & Kaube, 2003). This paper used the nociceptive specific electrode to investigate if GTN affects the brainstem pain system. Although six of the eight healthy volunteers developed a moderate bilateral headache during the GTN infusion, there was no nausea, photophobia or phonophobia. They concluded that the headache that develops secondary to the GTN-induced vasodilation does not affect trigeminal nociceptive transmission. The authors suggested that the headache that developed during the GTN infusion was probably secondary to the vasodilation that occurred intracranially but did not evoke the required dysfunctional central trigeminal transmission which is present during migraine.

The effect of zolmitriptan and aspirin on the nociceptive blink reflex was investigated in migraine sufferers during and between migraine and in healthy controls (Katsarava et al., 2004). Migraine patients were tested within 6 hours after onset of a unilateral migraine headache, 60 minutes after treatment and 90 minutes after treatment. Fourteen patients received acetylsalicylic acid (aspirin – 1000 mg) and 14 patients received zolmitriptan. Migraine patients were also tested interictally (three days outside of an attack) before, 60 minutes after and 90 minutes after the same drug administration. Healthy controls did not have a personal or family history of migraine. Fifteen controls received either aspirin or placebo and 15 received either zolmitriptan or placebo. Controls were also tested before, 60 minutes after and 90 minutes after drug administration. Both aspirin and zolmitriptan significantly reduced the intensity of the headache in the migraine patients 90 minutes after
administration of the medication. All patients had a significant reduction in their headache intensity after 90 minutes regardless of which drug was administered. The latency of the nociceptive blink reflex was increased and the area under the curve was suppressed after the administration of both drugs during the migraine headache but not during the interictal period. There was no difference between the drugs. For healthy participants there was a lack of significant differences between either drug or placebo effects on latency or area under the curve. The authors of this paper propose the parallel nature of the effect of the medications on both headache relief and suppression of the facilitated area under the curve of the nociceptive blink reflex. Zolmitriptan prevents the transmission of pain signals by inhibiting the release of neurotransmitters from the central endings of the TNC fibres (Levy, et al., 2004) and this compound also prevents the release of vasoactive neuropeptides at the pre-synaptic junction of the C-fibre afferent and meningeal vessel wall. Post-synaptically the serotonin agonists work on the 1B receptors to induce vasoconstriction. Aspirin, on the other hand, is a non-specific COX inhibitor and has been shown to inhibit neurogenic inflammation in the rat dura mater (Buzzi, Sakas, & Moskowitz, 1989), and nociceptive transmission in the brainstem of the cat was blocked after administration of aspirin and non-steroidal anti-inflammatory agents (Kaufe, et al., 1993). The COX pathway is a function of resident macrophages that produce pro-inflammatory molecules in the synapse of trigeminal afferents. So even though both zolmitriptan and aspirin inhibit neurogenic inflammation and block nociceptive transmission, they work in different ways at the junction between the central anti-nociceptive system and the trigeminal system (Katsarava, et al., 2004). The authors suggest that the medications suppress the facilitated responses but do not affect the resting trigeminal nociceptive system. Furthermore, they also suggest that arousal and expectation of pain relief may account for some of the suppression of the nociceptive blink reflex after administration of the medication.
The nociceptive blink reflex is not under conscious control, but it can be modulated by attention (Koh & Drummond, 2006). Perhaps paying attention to the stimulus during a migraine can facilitate the nociceptive blink reflex. Furthermore, more attention would be afforded to the stimulus during a migraine because of trigeminal sensitisation and allodynia. The blink reflex can also be modulated in migraine sufferers by other influences such as habituation and DNIC.

1.3.9 Blink Reflex and Migraine - Habituation

Habituation is compromised in various modalities in migraine sufferers but the lack of habituation of blink reflexes in migraine sufferers will be addressed specifically in this thesis. A lack of habituation may be an indication of increased excitability of the neurones contributing to the blink reflex.

Habituation by definition is the decrease in intensity of the response to a repeated stimulus. It is a simple form of learning. It is non-associative learning because it involves only a single type of stimulus. A non-habituated response can become larger after a strong stimulus. This is known as sensitization – that is the response is larger than baseline because of prior stimulation. Habituation of blink reflexes to repeated supraorbital stimulation can be indicative of reductions in blink circuit excitability (Basso, Strecker, & Evinger, 1993). Different physiological systems may have different habituating mechanisms. For example, habituation of the electrodermal system is different from the habituation mechanism of a spinal reflex such as the blink reflex because a) the spinal reflex is much faster than the electrodermal response (milliseconds versus seconds) and b) a muscle action is required in the spinal reflex.
Evoked potential studies consistently demonstrate that habituation is compromised interictally in migraineurs (Schoenen, Ambrosini, Sandor, & Maertens de Noordhout, 2003), and this has been suggested to be an endophenotypic marker of migraine (Sandor, Afra, Proietti-Cecchini, Albert, & Schoenen, 1999). This habituation deficit has been suggested to facilitate migraine and to stem from dysfunction in brain stem monoaminergic pathways that contribute to cortical excitability changes (Katsarava, Giffin, Diener, & Kaube, 2003). The most common finding in electrophysiological studies of cortical excitability in the migraine brain is the lack of habituation interictally which returns to normal just before or during a migraine (Giffin & Kaube, 2002). This change of cortical excitability may reflect a neurophysiological preparedness to generate an attack and increase susceptibility to other triggering factors (Giffin & Kaube, 2002) or it could be a sign of central sensitization that overcomes the previous lack of response.

The lack of habituation in migraine sufferers interictally could be the result of the inability of the migraine brain to adjust information processing to demands required to process all current relevant information (Giffin & Kaube, 2002). In healthy volunteers, habituation is likely to be the result of adaptation to protect the cortex against sensory overload and to screen out irrelevant information from conscious awareness.

The response behaviour to repeated presentations (habituation) of a nociceptive stimulus to the trigeminal system was investigated in healthy volunteers and in migraine sufferers (without aura) both interictally and during a migraine (Katsarava, Giffin, et al., 2003). Migraineurs were tested within six hours of onset of the migraine, and were also tested two hours after treatment had been administered. The authors found a significant difference in habituation between healthy volunteers and migraine sufferers between attacks. Significantly, there was no difference between healthy volunteers and migraine sufferers during an attack or
after drug treatment. The authors conclude that this interictal deficit is also present at the brain stem level – as evidenced by their findings from the nociceptive trigeminal system. Normal habituation of the nociceptive blink reflex during a migraine attack is consistent with other studies – at least for cortical habituation response behaviours.

The nociceptive blink reflex and Visual Evoked Potentials were investigated interictally in healthy volunteers and migraineurs (without aura) (Di Clemente et al., 2005). The authors wanted to investigate the intraindividual correlation between the cortical response (via pattern reversal visual evoked potentials) and the brain stem response (via the nociceptive blink reflex). The migraine participants in this study were migraine free for at least 2 days. Latency of the nBR was shorter for the migraineurs (36.55 ms) than for the healthy volunteers 40.74 ms) but this was not significant. Cortical responses were associated with brain stem reflexes in migraine sufferers. An interesting finding was the significant positive correlation between habituation of the ipsilateral nociceptive blink reflex and attack frequency in the three months preceding the study, suggesting that the greater the attack frequency the greater the habituation. Habituation of reflexes is known to normalise during an attack of migraine so the decrease of the habituation deficit with the increased attack frequency could be explained by the fact that those participants with a greater number of migraines could have been tested whilst the effects of the migraine were still present (within 2 days). The positive correlation between the habituation deficit for both cortical and brain stem reflexes in migraine sufferers suggests that there is a common pathophysiologic mechanism (Di Clemente, et al., 2005).

In a follow-up study, the interictal habituation deficit of the nociceptive blink reflex was investigated in migraine sufferers, healthy controls and first degree relatives of migraine sufferers (Di Clemente et al., 2007). Migraine sufferers were tested at least 2 days after or before an attack. Healthy volunteers had a decrease of 55% of the nBR between the first and
tenth blocks but the healthy volunteers with a first degree relative with migraine had a
decrease of only 26% and migraineurs had a decrease of only 25%. They also found a strong
positive correlation between attack frequency and habituation for migraine sufferers
(r=0.621) (the greater the number of attacks, the greater the habituation). The authors argue
that the lack of habituation in migraineurs and first degree relatives of migraineurs could be a
trait marker for the low serotonergic disposition of migraineurs.

During migraine the nociceptive blink reflex increases in amplitude but habituation
normalises, whereas interictally it shows a lack of habituation to repeated stimuli (Kaube, et
al., 2002). Conversely, habituation of the blink reflex elicited by stimuli delivered from a
standard electrode is normal interictally in migraine sufferers (Katsarava, Giffin, et al., 2003).
The neurobiological causes of the lack of habituation are currently unknown, but are
reversible as the habituation normalises just before and during the attack, and after treatment
with some prophylactic agents (Schoenen, 2006). Whilst some research suggests that sensory
cortices of the migraine brain have a lower pre-activation level (Afra, Proietti Cecchini,
Sandor, & Schoenen, 2000), other research, such as that which uses the Transcranial
Magnetic Stimulation (TMS), suggests that (particularly in the visual cortex) the
hyperexcitability of the central nervous system in migraine could be the result of
underactivity in inhibitory interneurons (Schoenen, 2006).

1.3.10 Blink Reflex and Migraine - DNIC

Although consistent findings exist in the literature regarding the blink reflex and DNIC,
research regarding migraine and DNIC is scarce. This is surprising given the anatomical
location of the possible dysfunctional trigeminal system in migraine and the location of
DNIC – the spinal trigeminal nucleus caudalis.
The cold pressor test was used as the noxious conditioning stimulus to test DNIC in migraine sufferers; chronic tension type headache sufferers and healthy controls (Sandrini et al., 2006). The RIII withdrawal reflex (a spinal nociceptive reflex) was used as the test stimulus. DNICs were dysfunctional both in migraine sufferers and the chronic tension type headache sufferers, suggesting that the development of central sensitization in headache may be linked to the dysfunction of supraspinal pain modulation systems.

The functioning of DNIC was investigated in chronic migraine sufferers, episodic migraine sufferers and healthy controls (de Tommaso et al., 2007). The authors used a standard bar electrode to stimulate the supra-orbital nerve and used the R2 component of the blink reflex as the dependent variable. The conditioning stimulus was the application of capsaicin to the back of the hand. R2 area increased during the conditioning stimulus only in the chronic migraine sufferers, suggesting that DNIC failed to control central components of the trigeminal reflex in this group. The authors linked this failure of DNIC to migraine frequency. However, this may be due to the increased likelihood of testing the patient close to or during an attack.

More specifically, the nociceptive blink reflex was DNIC-like-inhibited after a conditioning stimulus of forearm ischemia in controls but was not inhibited in severe headache sufferers, which included migraine sufferers (Vincent, Williams, Bartley, Kerr, & Rhudy, 2010).

In a recent review of DNIC, Yarnitsky uses the term conditioned pain modulation (CPM) to replace ‘diffuse noxious inhibitory control’ (Yarnitsky, 2010). Low CPM efficiency is reported for patients with idiopathic pain conditions suggesting low pain inhibitory modulation in these patients. This may be pertinent to migraine.
1.3.11 **Summary**

It appears that migraine can influence the blink reflex, with the nociceptive blink reflex being influenced (facilitated) reliably during a migraine headache. Trigeminal dysfunction/sensitization has also been observed in migraine sufferers in the headache-free period. A lack of interictal habituation in migraineurs in various modalities, including the blink reflex, is well established in the literature. DNIC in migraine sufferers has not been extensively studied.
1.4 Sensitisation in Migraine

Many studies have shown a lack of habituation to a repeated stimulus in both neurophysiological studies and nociceptive blink reflex studies in migraine, but whether this finding is due to a lack of habituation of neuronal responses or whether there is a neuronal hyperexcitability (Schoenen, 2006) still remains unanswered. Although some suggest that neuronal hyperexcitability is an oversimplified and misleading explanation for increased excitability in migrainous brains (Coppola, Pierelli, & Schoenen, 2007), sensitisation during migraine has been illustrated by various researchers in various modalities. Migraine sufferers are abnormally sensitive to sensory stimuli including light and sound, nausea and noxious tactile stimuli, and all of these stimuli can be related to central sensitisation in trigeminal nociceptive pathways (Drummond, 1987) (DaSilva et al., 2007). Drummond (1987) found that scalp tenderness, suggesting central sensitization, persisted for four days after a migraine attack.

Central sensitisation has been defined as hyperexcitability, increased spontaneous activity and increased receptive fields in central wide dynamic range neurons that is secondary to increased primary afferent activity (Dougherty & Lenz, 1994; Willis et al, 1996, as cited by Eide, 2000). This means that the increased responses in the wide dynamic range neurons occur after the increased activity in first order neurons due to nerve or tissue injury – or in the case of migraine after exposure to inflammatory agents.

The role of spinal structures in central sensitisation has been demonstrated specifically in lamina I and V in the dorsal horn (see Latremoliere & Woolf, 2009 for review) and the nucleus pars caudalis (Burstein, et al., 1998). Supraspinal structures such as the thalamus, amygdala and anterior cingulate cortex, PAG, superior colliculus and prefrontal cortex have
also been demonstrated to show changes as a result of central sensitisation in imaging studies (Staud, Craggs, Robinson, Perlstein, & Price, 2007).

Migraine sufferers were more likely to have trigger points located on the neck and head that evoke migraine-like pain interictally than healthy controls (Calandre, Hidalgo, García-Leiva, & Rico-Villademoros, 2006). Most of the trigger points (74%) were located in the temporal or suboccipital areas and were positively related to frequency of migraine headaches and duration of the disease. These results led the authors to suggest that migraine sufferers experience nociceptive peripheral sensitisation between attacks and that this could develop into central sensitisation in those who have more frequent attacks and have the disease longer.

Central sensitisation of the trigeminal and somatic nociceptive systems was examined in controls, episodic migraine, analgesic induced medication overuse headache and triptan-induced medication overuse headache (Ayzenberg et al., 2006). The authors of this study found no differences across any of the groups in the nociceptive blink reflexes for latencies or area under the curve. The authors suggest that the lack of difference between groups for the nociceptive blink reflex indicates that sensitisation of central nociceptive mechanisms occurs at the supraspinal level rather than the trigeminal system in the brainstem.

However, another group of researchers used imaging studies and found permanent changes interictally in migraine sufferers (DaSilva, et al., 2007). Diffusion tensor imaging (a form of MRI used to map neuronal tracts in the brain) was used to investigate migraineurs’ brains interictally and the authors found permanent changes in the trigeminal somatosensory system and pain modulatory circuits (DaSilva, et al., 2007). These changes were evident in the thalamocortical tract (ascending pain pathway) which the authors suggest corresponds to third order neurons. The changes were also associated with frequent attacks of migraine. In
patients without aura, changes in the periaqueductal grey could suggest a dysfunctional descending pathway which could cause a lack of inhibition and lower the threshold required to initiate a migraine attack.

Migraine patients have been shown to have lower pain thresholds to electrical corneal stimulation between attacks of migraine compared to controls (Sandrini et al., 2002). These lower thresholds were more obvious on the symptomatic side in unilateral migraine sufferers. The authors concluded that pain modulating systems at the trigeminal level are impaired in migraine sufferers. The increased trigeminal excitability interictally in migraine sufferers could suggest chronic sensitisation. Central nervous system abnormalities persist between migraine headaches suggesting the presence of an interictal neural excitation (Marcus, 2003).

Cortical excitability was examined in chronic migraine patients using transcranial magnetic stimulation and Positron Emission Tomography (Aurora, Barrodale, Tipton, & Khodavirdi, 2007). Findings from this study support the hypothesis that migraine sufferers (especially chronic migraine patients) have greater cortical excitability because of reduced inhibitory capacity in the cortex. It was suggested that this cortical excitability is the result of modulatory influences from intracortical inhibitory network activity. The authors inferred from this study that chronic migraine patients are more susceptible to triggers of migraine because of their high cortical excitability, resulting in a higher frequency of migraine attacks.

The brainstems of 12 interictal migraine participants and 12 age-gender-matched controls were investigated with fMRI (Moulton et al., 2008). Noxious heat (pain threshold +1°C) and 41°C was administered to the back of the hand or the affected side of the forehead (as reported during an attack by the migraineurs). Control participants exhibited greater activation in the nucleus cuneiformis, which is involved in pain modulatory circuits in the brainstem. These results suggest that migraine participants could have dysfunctional
descending pain modulation pathways, resulting in hyperexcitable trigeminovascular neurons because of the lack of inhibition or greater facilitation (Moulton, et al., 2008).

An animal model was used to investigate brainstem trigeminovascular neuronal modulation by cortical excitability disturbances (Noseda, Constandil, Bourgeais, Chalus, & Villanueva, 2010). The authors used tracers to identify pathways from cortical regions that project onto brainstem regions that include trigeminovascular neurons. The area in the brainstem that contains neurons from the ophthalmic branch of the trigeminal neve also has cortical projections from both the insular and primary somatosensory cortices, suggesting that top-down cortical influences modulate activity in this area. In further electrophysiological investigations, activation of the primary somatosensory projections inhibited cutaneous and meningeal evoked responses in the trigeminocervical complex area (in which neurons activated by fine and large diameter neuronal input are also located). However, activation of insular projections onto the superficial layer of the trigeminocervical complex facilitated both Aδ and C-fibre meningeal evoked responses, which the authors suggest could be a selective modulation of the nociceptive primary afferents.

In summary, sensitisation occurs during a migraine in many sensory modalities and pain processing systems. Ongoing sensitisation in the headache free period can also occur. Various imaging studies have shown that supraspinal influences can cause dysfunctional descending pain modulation, possibly resulting in hyperexcitable trigeminovascular neurons in migraine. Allodynia is a form of central sensitisation and is discussed in the following section.

1.4.1 Allodynia

Cutaneous allodynia is defined as pain evoked by innocuous heat, cold or pressure stimuli applied to normal skin (Burstein, Yarnitsky, Goor-Aryeh, Ransil, & Bajwa, 2000). Burstein et
al (2000) reported that 79\% of migraine patients reported some type of cutaneous allodynia either within the ipsilateral to the headache side of the head or in the forearms. A prospective study on a Turkish population of migraine patients revealed that 61.3\% of the migraine patients suffered cutaneous allodynia (Guven, Cilliler, & Comoglu, 2012). What was also notable about this study was that the allodynic migraine patients were more likely to suffer from nausea and phonophobia suggesting a common pathway (Guven, et al., 2012), perhaps via the thalamus.

In a series of studies to explain allodynia during migraine, Burstein and colleagues (Burstein, et al., 1998; Strassman, et al., 1996; Yamamura, Malick, Chamberlin, & Burstein, 1999) postulated the development of a progression of events that occurred within the cranium in an animal model of migraine. In the first study the dura was irritated with inflammatory chemicals such as histamine, serotonin, bradykinin and prostaglandin E2 (Strassman, et al., 1996). This process resulted in hyperexcitability of neurons to innocuous pressure. Allodynia may develop during migraine because peripheral first order neurons from the intracranial structures (such as intracranial blood vessel nociceptors) converge onto second order neurons in the medullary dorsal horn (Malick & Burstein, 2000). Also converging onto these second-order neurons are extracranial neurons from the facial area and the scalp. When the peripheral first-order neurons become hyperexcitable due either to activation by inflammatory mediators, or in the absence of any stimuli (due to previous activation), these signals bombard the central second-order neurons which results in spontaneous activity in the medullary dorsal horn (Burstein, et al., 1998). These hyperexcitable second-order neurons then project to the higher structures that can alter pain perception during a migraine (Yamamura, et al., 1999). This series of studies also suggests that scalp tenderness development in migraine is associated with central sensitisation (Malick & Burstein, 2000).
Allodynia between attacks was investigated using blink reflexes and pattern-reversal visual evoked potentials in healthy subjects and migraine sufferers (Shibata, Yamane, & Iwata, 2006). Amongst the migraineurs, 13 were diagnosed with alldynic migraine by clinical interview, questionnaire and by clinically detectable manifestations of cranial cutaneous alldynia. The authors report an enhanced R2 recovery in the alldynic migraine patients suggesting hyperexcitability of the brainstem interneurons. During central sensitization hyperexcitable peripheral nociceptors can induce long-lasting hyperexcitability in these second-order neurons (Burstein, Curter, Yarnitzky, 2000).

1.4.2 Wind-up

Wind-up is the progressive neuronal activity increase in response to repeated electrical stimuli tested in animal models (You, Dahl Morch, Chen, & Arendt-Nielsen, 2003), and temporal summation of repeated painful stimuli is its psychophysical correlate (Eide, 2000). Woolf suggested that wind-up and central sensitisation should be seen as two different phenomena (Woolf, 1996). Whilst wind-up can evoke central sensitisation, it isn’t enough to solely evoke central sensitisation (Eide, 2000).

In two studies, Woolf and colleagues established that pain processing pathway sensitisation facilitates temporal processing of painful stimuli (Latremoliere & Woolf, 2009; Woolf, 2007). Similar to this is the ‘wind-up’ phenomenon in animals that is the result of temporal summation of incoming stimuli producing prolonged and stronger responses (Eide, 2000; You, et al., 2003). A tool to investigate pain processing in the spinal cord is the nociceptive withdrawal reflex, as temporal summation of pain parallels the temporal summation of the withdrawal reflex (Perrotta et al., 2010; Serrao et al., 2004). In the present thesis pain ratings were used to examine temporal summation and the blink reflex parameters to examine wind-up.
In this thesis, the term ‘wind-up like pain’ is synonymous with the term ‘temporal summation’ (Eide, 2000), that is an increase in pain ratings to repeated stimuli. The role of supra-spinal descending pain mechanisms has been illustrated in both wind-up (Gozariu, Bragard, Willer, & Le Bars, 1997) and temporal summation (Eide, Jorum, & Stenehjem, 1996). The importance of wind-up in the pathophysiology of migraine has only recently been suggested (Lambert & Zagami, 2009). In particular, Lambert & Zagami posit that the trigeminovascular neurons responsible for the throbbing nature of vascular headache could amplify the vascular pulsation sensations because the frequency of the human heart rate is adequate to evoke wind-up of sensory signals.
1.5 Summary and Integration

In essence, the purpose of this thesis was to provide further clarification of the neural mechanisms involved in migraine.

Headache during migraine is most likely caused by a malfunction of the endogenous anti-nociceptive system and the activation of dura trigeminal nociceptors. The most common associated symptoms of migraine are nausea and vomiting, photophobia and phonophobia, and dizziness. The trigeminal system is integrally linked with many brainstem processes and reflexes that might contribute to these symptoms (Amini, et al., 2006).

The trigeminal nuclei send input to the thalamus and are in close communication with brain stem centres involved in the production of symptoms of migraine; in particular, the spinal trigeminal nucleus communicates with the vestibular nuclei which, in turn, communicate with the nucleus tractus solitarius (the sensory branch of the vagus nerve terminates here). Meningeal neurogenic inflammation may contribute to migraine headache. The C-fibre endings that surround the meningeal vessels release vasoactive neuropeptides which causes neurogenic vasodilation, an increase in blood flow and meningeal oedema. This inflammatory process then activates the pre-synaptic trigeminal nerve C-fibres and the cycle continues, sensitising the first-order trigeminal neurons in the trigeminal ganglion. Second-order neurons in the trigeminal subnucleus caudalis then become sensitised and depolarise independently of any input activity. From the trigeminal nucleus caudalis, this information is then projected to other brainstem nuclei and higher cortical structures for nociceptive processing and modulation, leading to some symptoms of migraine and some sensory sensitisation. Potentially, during attacks, trigeminal activation results in activation of the vestibular nuclei, causing dizziness, and the nucleus tractus solitarius, causing the subjective experience of nausea.
The blink reflex is a brainstem reflex that has been used to investigate the trigeminal system using electrical stimuli. This reflex arc involves the Aβ fibres (standard electrode) and Aδ fibres (concentric electrode), and possibly C-fibres at higher intensities; projecting from the periphery to the spinal trigeminal nucleus caudalis, then travelling ipsilaterally and contralaterally to the facial nuclei to produce the motor components of the reflex. The blink reflex can be influenced by attention, inhibited by remote stimuli (DNIC) or facilitated by homosegmental sensitization which occurs during migraine (due to temporal summation). The multi-synaptic R2 (27-87ms) window of the blink reflex was used in this thesis to assess the trigeminal system in migraine sufferers and to investigate the influence of various exogenous and endogenous modulators on this reflex.

The nociceptive blink reflex is facilitated during migraine, and trigeminal dysfunction/sensitization has also been observed in migraine sufferers in the headache free period. A lack of interictal habituation in migraineurs in various modalities, including the blink reflex, is well established. This hyperexcitability in the migraine brain could be the result of either lower activation levels in the sensory cortices or a hypoactivity of inhibitory interneurons. Although some suggest that neuronal hyperexcitability is an oversimplified and misleading explanation for migraine, sensitisation during migraine has been illustrated by various researchers in various modalities including pain processing pathways. Migraine sufferers are abnormally sensitive to sensory stimuli including light and sound, nausea and noxious tactile stimuli – all of which can be related to trigeminal sensory system dysfunction. Ongoing sensitisation in the headache free period can also occur. Various imaging studies have shown that supraspinal influences can cause dysfunctional descending pain modulation, resulting in hyperexcitable trigeminovascular neurons in migraine sufferers. Allodynia and wind-up are expressions of central sensitisation. Migraine sufferers may have low
conditioned pain modulation which may further support the postulate that they have dysfunctional descending pain inhibitory pathways.
1.6 Research Aims

The main aim of this research was to explore central and peripheral nociceptive processing in migraine and to determine whether the blink reflex in response to an electrical stimulus is a useful marker of activity in nociceptive pathways during migraine.

The postulate that migraine sufferers have an interictal disturbance/dysregulation/sensitivity that involves, but is not limited to, the central and peripheral trigeminal system was explored in this thesis. A major question of this research was the location of the systemic dysfunction during migraine. Is the location peripheral (only in the trigeminal system); unconscious central (occurring in the brainstem) or cortically central (occurring within the cortices).

The complex interaction between headache, nausea and trigeminal stimulation has been investigated by Drummond’s group in numerous studies (Drummond, 2002, 2004, 2006; Drummond & Granston, 2004, 2005; Granston & Drummond, 2005). The current research explored these complex interactions and answered the call for further research into understanding the underlying mechanisms of migraine and its associated symptoms (Olesen, 2010).

In particular, I investigated whether migraine sufferers are subjectively and physiologically hypersensitive to both environmental (exogenous) and internal (endogenous) factors. This hypersensitivity was investigated through subjective ratings and physiologically with blink reflex parameters in response to trigeminal stimulation, to a peripheral noxious compound and to various environmental stimuli. The current research adds to the body of literature regarding the nociceptive blink reflex and migraine (Magis et al., 2007) and uses this methodology to examine the effects of various conditioning stimuli and migraine symptom challenges.
The purpose of the first study of this research was to validate the use of a concentric electrode in investigating trigeminal nociceptive processing pathways in migraine sufferers between attacks. It was hypothesized that sensitisation within trigeminal nociceptive pathways in migraine sufferers would be reflected by heightened excitability in response to stimuli delivered by the concentric electrode.

Afferent fibres in the vagus nerve terminate at the nucleus tractus solitarius, which also receives input from the trigeminal nerve. The purpose of the second study in this research was to determine whether vagal nerve stimulation with hypertonic saline induces more nausea in migraine sufferers than controls and whether this stimulation modulates trigeminal nociceptive processing. Specifically, the aim was to determine whether migraine sufferers were more susceptible to peripherally induced nausea than healthy controls, and to investigate scalp tenderness and pain thresholds and blink reflex parameters to supraorbital electrical stimuli before and after vagal nerve stimulation.

In the final series of studies, symptoms of migraine, pain thresholds and blink reflex parameters to trigeminal stimulation were investigated both in healthy volunteers and during and between attacks of migraine.
Chapter 2  Nociceptive Blink Reflex after Local Anaesthetic

2.1 Introduction

The trigeminal system is known to play a pathogenic role in the development of migraine (Katsarava, Egelhof, Kaube, Diener, & Limmroth, 2003). Although some evidence suggests that the trigeminal system may be dysfunctional in migraine sufferers interictally (Sandrini, et al., 2002), most evidence points to a temporary sensitization of central trigeminal structures during migraine attacks (Katsarava, et al., 2002; Kaube, et al., 2002).

Electrically-evoked blink reflexes have been used to explore the pathogenic role of the trigeminal system in migraine. The blink reflex can be elicited electrically with standard bipolar electrodes in the peri-ocular region. Earlier blink reflex studies in migraine used two standard electrodes attached to the supraorbital region of the forehead to deliver electrical stimuli that activated both nociceptive and non-nociceptive fibres. The blink was measured via EMG activity of the orbicularis oculi using latencies and integral (AUC) measures.

Findings from the investigation of the trigeminal system in migraine sufferers interictally using the blink reflex elicited with standard electrodes were inconclusive (Bank et al, 1992; Sand & Zwart, 1994), but a delay in habituation occurred approximately three days prior to a migraine headache (De Marinis et al, 2003).

However, these results may be stimulation-specific because nociceptive trigeminal stimulation in migraineurs illustrated some trigeminal system dysfunction. A decreased nociceptive reflex (corneal reflex) threshold was identified in migraine sufferers interictally with the authors suggesting that trigeminal pain control systems and/or sensorimotor mechanisms could be impaired (Sandrini, et al., 2002). Additionally, because the thresholds were lower in migraine sufferers than controls, independently of the symptomatic side of
usual migraine, the authors hypothesized that the dysfunction was located centrally. Interictal lack of habituation to repeated electrical stimuli from the concentric electrode in migraine sufferers also suggested dysfunctional control of the trigeminal system (Katsarava et al, 2003; Di Clemente, 2007).

To determine whether blink reflexes could be evoked specifically by nociceptive stimulation, Kaube and colleagues developed a nociception specific electrode with a high current density and small anode to cathode distance that depolarized Aδ fibres and C-fibres within the superficial layers of skin in the supra-orbital area (Kaube, et al., 2000). Kaube et al. compared blink reflex responses evoked by the standard and concentric electrodes before and after topical application of local anaesthetic agent at the site of stimulation. The blink reflex evoked by the concentric electrode was inhibited almost 90% after topical application of local anaesthetic agent. The blink reflex evoked by the concentric electrode (the nociceptive blink reflex) lacks the short-latency R1 response mediated by Aβ-fibres usually seen in the standard blink reflex because the Aβ-fibres are not activated by a superficial nociceptive stimulus. There were no effects of topical local anaesthetic on the nociceptive blink reflex with intensities higher than 2 mA delivered via the concentric electrode or on blinks evoked by stimulation delivered via standard electrodes. The authors suggested that responses to current intensities higher than 2 mA were due primarily to Aβ-fibre activation rather than stimulation of nociceptive fibres.

During acute migraine attacks Kaube et al. (2002) found a facilitation of almost 700% of the nociceptive blink reflex compared with the response measured between attacks (Kaube, et al., 2002). The researchers were unsure if this temporary sensitization was the result of sensitization of peripheral nociceptors in the meninges or second order neurons in the trigeminal nuclei. In a follow-up study by the same group of researchers, the nociceptive
blink reflex was investigated during an acute migraine attack and during sinusitis head pain (Katsarava, et al., 2002). The findings suggested that trigeminal nociceptive sensitization during migraine was indeed the result of central sensitization rather than primary sensitization of the peripheral nociceptors because sinusitis head pain did not facilitate the nociceptive blink reflex.

Topical local anaesthetic works by inhibiting signal propagation by blocking sodium channels in the neuronal cell membrane. Nociceptive transmission is blocked first because local anaesthetic blocks small myelinated fibres (Aδ), and small unmyelinated fibres (C-fibres) because of their close proximity to the skin surface and then large myelinated fibres (Aβ) (Rang et al, 2003).

The aim of the present study was to use the concentric electrode to stimulate the nociceptive fibres of the extracranial trigeminal system to determine if migraine sufferers responded differently than healthy controls. If trigeminal nociception is more sensitive than usual in migraine sufferers, a greater response should occur to the nociceptive specific stimulus because of sensitization within the peripheral pathway and/or brainstem (Katsarava, et al., 2002; Sandrini, et al., 2002). In addition, local anaesthetic agent might suppress the nociceptive blink reflex less effectively in migraine sufferers than controls because of this heightened excitability.

Two stimulus durations and various intensities were used to investigate effects of local anaesthetic. Responses were measured before and after the application of the topical anaesthetic on one side of the forehead. The other side of the forehead served as an internal control.
2.2 Materials and Methods

2.2.1 Participants

The sample consisted of five male and 27 female university students ranging in age from 18 years to 52 years (m=28.1 yrs). Fifteen met IHS criteria for migraine with or without aura (IHS, 2003) which included a throbbing, unilateral, moderate to severe headache accompanied by nausea or vomiting, photophobia or phonophobia, and/or an increase in intensity during physical exertion. Migraine participants were symptom free for at least 3 days prior to the testing session. The remaining 17 participants were age-matched controls without a history of migraine who had suffered less than 12 tension-type headaches in the previous 12 months. Each participant provided informed consent for the procedure which was approved by the Murdoch University Human Research Ethics Committee.

2.2.2 Blink Reflex

Adhesive washers were used to attach two purpose-built concentric electrodes (thin 0.5mm wire cathode; stainless steel anode – outer diameter 20mm, inner diameter 10mm) to the supra-orbital skin prepared by cleaning with a pumice-infused preparation pad (Professional Disposables, Inc, N.Y., USA). The outer ring (anode) of the electrode was smeared with electrode gel to aid in electrical conductivity. The electrodes were placed so that the cathode (inner point) was placed above the supra-orbital foramen. The electrical stimuli were monopolar square wave pulses with a duration of 0.5 ms or 0.3 ms and mean intensities of 1 mA, 2 mA, 3 mA, 4 mA and 5 mA. An interstimulus interval of at least 10 seconds was used to minimize habituation of the blink reflex.

The blink reflex was measured bilaterally from the mid orbicularis oculi muscle via electromyography (EMG). After cleaning the skin, silver cup electrodes or modified neo-
nate ECG (ConMed, N.Y., USA) electrodes were attached to the lower mid orbicularis oculi and lower lateral orbicularis oculi. A ground electrode was placed on the left wrist to minimise electrical interference.

EMG data were acquired via a Polygraph Data Recording System (Model 79E, Grass Instrument Co., Quincy, Mass., U.S.A.) or via an EMG digital pre-amplifier (EMG100C, BIOPAC Systems, Inc. California, U.S.A.) before being transmitted to a personal computer via a 16-bit MP100 BIOPAC Systems Analogue/Digital Channel Receptor (BIOPAC Systems, Inc. California, U.S.A.) using AcqKnowledge software (Version 3.7.1, BIOPAC Systems, Inc. California, U.S.A.). Data were collected at a sampling rate of 1-2KHz for later off-line analysis. Signals were band-stop filtered at 49-51Hz and 99-101Hz to reduce electrical artifact. Signals were also high pass filtered with a cut-off frequency of 20Hz to reduce interference from the movement of eyeball roll, and rectified prior to analysis. The ipsilateral R2 component of the blink reflex in response to all stimuli was investigated in the time window of 27 to 87 ms after the onset of the stimulus (Ellrich & Treede, 1998). The R1 component of the blink reflex was not detected in the data in response to any stimulus intensity.

2.2.3 Procedure

Participants were instructed to look straight ahead with their eyes open. After skin preparation the concentric electrodes were attached and the concentric electrode on the non-dominant (experimental) side was traced around to allow exact repositioning after the application of local anaesthetic cream.

A baseline measurement was first obtained. A 0.5 ms stimulus was applied to the experimental side, starting at 1 mA and increasing to 5 mA in 1 mA increments. Five sets of
these intensities were administered in ascending or descending 1 mA steps. Five sets of each of the second (0.3 ms) and third (0.5 ms to the control side) type of stimulus were administered similarly to the first stimulus.

After the baseline measurements were obtained the concentric electrode on the experimental side was removed and a topical local anesthetic (lignocaine 25 mg/g; prilocaine 25 mg/g, EMLA cream, AstraZeneca, Australia) was applied over a diameter of 30 mm (i.e., greater than the diameter of the concentric stimulation electrode). The EMLA cream was then covered with an occlusive dressing (Hypafix, Smith and Nephew). After 60 minutes the dressing and local anaesthetic were removed and the skin was cleaned with an alcohol wipe. The area was brushed with a piece of soft material and penetrated with a hypodermic needle to investigate tactile sensation. No participant felt the penetration of the hypodermic needle. The concentric electrode was then re-attached in the same position and electrical stimulation was repeated. The sequence of procedures are summarised in Figure 2-1.

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Stimuli administered from concentric electrode</th>
<th>Local Anaesthetic applied + 1 hour wait</th>
<th>Stimuli administered from concentric electrode</th>
</tr>
</thead>
</table>

Figure 2-1: Sequence of procedures for nociceptive blink reflex after local anaesthetic study.
2.2.4 Data Reduction and Statistical Analysis

The data from each type of stimulus (experimental 0.5 ms, experimental 0.3 ms, control 0.5 ms) were averaged across the five trials for each stimulus intensity (1 mA, 2 mA, 3 mA, 4 mA, 5 mA). Area under the curve data were used to define the presence of a blink reflex (defined as a value above the artefact level of 0.0002V·Sec). The number of blink reflexes, the area under the curve (AUC), latency of these responses and percent change from baseline were analysed. The frequency data were analysed with a 2 (pre/post local anaesthetic) x 5 (intensity – repeated) x 2 (between groups) mixed design ANOVA for each stimulus type. Because of missing data from null responses in the analyses of AUC and latency, 2 (pre/post local anaesthetic) x 2 (between groups) mixed design ANOVA for each stimulus intensity were used. Percent change from baseline data were analysed with independent sample t-tests. Parametric statistics were not used when cell sizes were less than 10. Alpha levels of less than 0.05 were deemed to be significant. Only significant main effects and significant interactions were reported in the Results section.
2.3 Results

The mean values for the number of evoked blink reflexes (Table 2-2), AUC and percent change from baseline (Table 2-3) and latency (Table 2-4) are shown in the tables below. The number of evoked blink reflexes was suppressed more effectively by the local anaesthetic in healthy controls (0.5ms \( t(16)=4.3, p<.05 \); 0.3ms \( t(15)=5.06, p<.05 \)) than in migraine sufferers (0.5ms \( t(14)=1.53, \text{N.S.} \); 0.3ms \( t(14)=2.4, p<.05 \)) (Figure 2-3) (Time x Group: Experimental 0.5ms \( F(1,30)=4.81, p<.05 \); Experimental 0.3ms \( F(1,29)=5.06, p<.05 \); Control 0.5ms \( F(1,28)=.82, \text{N.S.} \); Table 2-1) (Figure 2-2). There was no difference in the effect of the local anaesthetic between migraineurs and controls on the AUC of the evoked responses at any intensity (Table 2-5; Table 2-6; Table 2-7). There was a trend for the more intense stimuli (0.5ms duration) to evoke a faster response in migraineurs (Table 2-6; Table 2-7).

![Graph showing the suppression of evoked responses after local anaesthetic.](image)

Figure 2-2: The suppression of evoked responses after local anaesthetic. The number of evoked responses decreased more in controls after local anaesthetic compared to migraineurs (Mig.) Error bars represent SEM. The blink reflex was more inhibited in the control group after the local anaesthetic.
Table 2-1: Blink reflex frequency F Ratios (degrees of freedom) for 2 X 5 X 2 ANOVA for all stimuli.

<table>
<thead>
<tr>
<th></th>
<th>Experimental Side</th>
<th>Control Side</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 ms</td>
<td>0.3 ms</td>
</tr>
<tr>
<td>Group</td>
<td>2.33 (1,30)</td>
<td>0.84 (1,29)</td>
</tr>
<tr>
<td>Time</td>
<td>17.53 (1,30)*</td>
<td>28.84 (1,29)*</td>
</tr>
<tr>
<td>Intensity</td>
<td>23.38 (2.45,73.4)*</td>
<td>34.55 (2.44,70.75)*</td>
</tr>
<tr>
<td>Time x Group</td>
<td>4.81 (1,30)*</td>
<td>5.06 (1,29)*</td>
</tr>
<tr>
<td>Intensity x Group</td>
<td>1.06 (2.45,73.4)</td>
<td>2.42 (2.44,70.75)#</td>
</tr>
<tr>
<td>Time x Intensity</td>
<td>3.7 (3.03,90.97)*</td>
<td>5.18 (2.69,77.98)*</td>
</tr>
<tr>
<td>Time x Intensity x Group</td>
<td>0.59 (3.03,90.97)</td>
<td>0.83 (2.69,77.98)</td>
</tr>
</tbody>
</table>

* Denotes significance at .05 alpha level; #p=.085

Figure 2-3: The number of evoked responses after local anaesthetic. White bars represent the baseline and the solid bars represent after the local anaesthetic. Error bars represent SEM. The blink reflex was more inhibited in the control group after the local anaesthetic.
Table 2-2: Mean frequency values for Baseline condition and Post Local Anaesthetic condition (SEM).

<table>
<thead>
<tr>
<th>Stimulus Type</th>
<th>Experimental Side 0.5ms *</th>
<th>Experimental Side 0.3ms *</th>
<th>Control Side 0.5ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Migraineurs (n=15)</td>
<td>Controls (n=17)</td>
<td>Migraineurs (n=15)</td>
</tr>
<tr>
<td><strong>Baseline Blink Reflex Response (max 5)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1mA</td>
<td>4.07 (0.4)</td>
<td>3.71 (0.37)</td>
<td>3.6 (0.41)</td>
</tr>
<tr>
<td>2mA</td>
<td>4.47 (0.24)</td>
<td>4.47 (0.23)</td>
<td>4.07 (0.4)</td>
</tr>
<tr>
<td>3mA</td>
<td>4.8 (0.15)</td>
<td>4.71 (0.14)</td>
<td>4.2 (0.36)</td>
</tr>
<tr>
<td>4mA</td>
<td>4.73 (0.11)</td>
<td>4.82 (0.1)</td>
<td>4.47 (0.26)</td>
</tr>
<tr>
<td>5mA</td>
<td>4.93 (0.11)</td>
<td>4.82 (0.1)</td>
<td>4.67 (0.22)</td>
</tr>
<tr>
<td>Mean across all intensities</td>
<td>4.6 (0.14)</td>
<td>4.51 (0.14)</td>
<td>4.2 (0.3)</td>
</tr>
</tbody>
</table>

| **Post Local Anaesthetic Blink Reflex Response (max 5)** |                            |                            |                   |
| 1mA                 | 3.4 (0.46)                | 2.12 (0.43)                | 2.67 (0.52)       | 1.12 (0.5)     |
| 2mA                 | 4.07 (0.46)               | 3 (0.43)                   | 3.4 (0.48)        | 2.25 (0.46)    |
| 3mA                 | 4.47 (0.38)               | 3.82 (0.36)                | 3.73 (0.44)       | 3.38 (0.43)    |
| 4mA                 | 4.67 (0.27)               | 4.18 (0.25)                | 4 (0.4)           | 3.88 (0.39)    |
| 5mA                 | 4.8 (0.26)                | 4.29 (0.24)                | 4.67 (0.3)        | 4.06 (0.3)     |
| Mean across all intensities | 4.28 (0.31)               | 3.48 (0.29)                | 3.69 (0.36)       | 2.94 (0.35)    |

* Indicates a significant time x group interaction
Table 2-3: Mean AUC and percent change from baseline values for Baseline condition and Post Local Anaesthetic condition (SEM, n).

<table>
<thead>
<tr>
<th>Stimulus Type</th>
<th>Experimental 0.5ms</th>
<th>Experimental 0.3ms</th>
<th>Control 0.5ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Migraineurs</td>
<td>Controls</td>
<td>Migraineurs</td>
</tr>
<tr>
<td><strong>Baseline Area Under the Curve (mV·Sec)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1mA</td>
<td>1.2 (0.21, 10)</td>
<td>1.21 (0.25, 7)</td>
<td>0.9 (0.21, 9)</td>
</tr>
<tr>
<td>2mA</td>
<td>1.31 (0.21, 14)</td>
<td>1.08 (0.22, 13)</td>
<td>1.21 (0.23, 11)</td>
</tr>
<tr>
<td>3mA</td>
<td>1.51 (0.22, 14)</td>
<td>1.13 (0.22, 14)</td>
<td>1.23 (0.23, 12)</td>
</tr>
<tr>
<td>4mA</td>
<td>1.44 (0.23, 15)</td>
<td>1.23 (0.22, 16)</td>
<td>1.3 (0.21, 14)</td>
</tr>
<tr>
<td>5mA</td>
<td>1.56 (0.22, 15)</td>
<td>1.38 (0.22, 15)</td>
<td>1.36 (0.19, 15)</td>
</tr>
<tr>
<td><strong>Post Local Anaesthetic Area Under the Curve (mV·Sec)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1mA</td>
<td>0.67 (0.13, 10)</td>
<td>0.65 (0.15, 7)</td>
<td>0.66 (0.16, 9)</td>
</tr>
<tr>
<td>2mA</td>
<td>0.98 (0.17, 14)</td>
<td>0.7 (0.18, 13)</td>
<td>0.81 (0.19, 11)</td>
</tr>
<tr>
<td>3mA</td>
<td>1.16 (0.16, 14)</td>
<td>0.84 (0.16, 14)</td>
<td>1.11 (0.2, 12)</td>
</tr>
<tr>
<td>4mA</td>
<td>1.16 (0.17, 15)</td>
<td>0.86 (0.17, 16)</td>
<td>1.11 (0.21, 14)</td>
</tr>
<tr>
<td>5mA</td>
<td>1.31 (0.19, 15)</td>
<td>1.05 (0.19, 15)</td>
<td>1.12 (0.17, 15)</td>
</tr>
<tr>
<td><strong>Percent change from Baseline (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1mA</td>
<td>-38.42 (9.48, 10)</td>
<td>-46.68 (5.32, 7)</td>
<td>-16.35 (11.64, 9)</td>
</tr>
<tr>
<td>2mA</td>
<td>-25.54 (7.4, 14)</td>
<td>-29.7 (9.42, 13)</td>
<td>-30.6 (8.7, 11)</td>
</tr>
<tr>
<td>3mA</td>
<td>-18.43 (5.35, 14)</td>
<td>-25.65 (4.68, 14)</td>
<td>-8.49 (11.89, 12)</td>
</tr>
<tr>
<td>4mA</td>
<td>-17.71 (5.1, 15)</td>
<td>-25.38 (7.52, 16)</td>
<td>-19.36 (6.48, 14)</td>
</tr>
<tr>
<td>5mA</td>
<td>-14.26 (3.89, 15)</td>
<td>-23.55 (5.59, 15)</td>
<td>-16.32 (5.69, 15)</td>
</tr>
</tbody>
</table>
Table 2-4: Mean latency values for Baseline condition and Post Local Anaesthetic condition (SEM, n).

<table>
<thead>
<tr>
<th>Stimulus Type</th>
<th>Experimental 0.5ms</th>
<th>Experimental 0.3ms</th>
<th>Control 0.5ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Migraineurs</td>
<td>Controls</td>
<td>Migraineurs</td>
</tr>
<tr>
<td><strong>Baseline Latency (ms)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1mA</td>
<td>45.69 (2.45, 13)</td>
<td>48.16 (2.36, 14)</td>
<td>45.66 (2.06, 13)</td>
</tr>
<tr>
<td>2mA</td>
<td>41.98 (2.28, 14)</td>
<td>43.87 (2.28, 14)</td>
<td>41.95 (1.89, 14)</td>
</tr>
<tr>
<td>3mA</td>
<td>38.56 (2.07, 14)</td>
<td>45.01 (1.93, 16)</td>
<td>41.98 (1.89, 14)</td>
</tr>
<tr>
<td>4mA</td>
<td>37.96 (1.82, 15)</td>
<td>41.91 (1.76, 16)</td>
<td>39.74 (2.3, 14)</td>
</tr>
<tr>
<td>5mA</td>
<td>37.14 (1.84, 15)</td>
<td>39.33 (1.78, 16)</td>
<td>38.76 (1.92, 14)</td>
</tr>
<tr>
<td><strong>Post Local Anaesthetic Latency (ms)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1mA</td>
<td>45.17 (2.27, 13)</td>
<td>46.33 (2.18, 14)</td>
<td>44.52 (2.03, 13)</td>
</tr>
<tr>
<td>2mA</td>
<td>42.31 (2.11, 14)</td>
<td>45.49 (2.11, 14)</td>
<td>44.1 (2.13, 14)</td>
</tr>
<tr>
<td>3mA</td>
<td>39.81 (2.48, 14)</td>
<td>45.89 (2.32, 16)</td>
<td>41.24 (1.99, 14)</td>
</tr>
<tr>
<td>4mA</td>
<td>37.92 (2.02, 15)</td>
<td>43.99 (1.95, 16)</td>
<td>39.38 (2.06, 14)</td>
</tr>
<tr>
<td>5mA</td>
<td>36.82 (2.1, 15)</td>
<td>42.13 (2.04, 16)</td>
<td>38.94 (2.03, 14)</td>
</tr>
</tbody>
</table>
Table 2-5: Blink reflex parameters F Ratios (degrees of freedom) for 2 X 2 ANOVA and T values at each intensity for 0.3ms stimuli to the experimental side.

<table>
<thead>
<tr>
<th></th>
<th>1mA</th>
<th>2mA</th>
<th>3mA</th>
<th>4mA</th>
<th>5mA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Area Under the Curve</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time x Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Latency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time x Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Percent Change from Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Denotes significance at .05 alpha level; #p=.082
Table 2-6: Blink reflex parameters F Ratios (degrees of freedom) for 2 X 2 ANOVA and T values at each intensity for 0.5ms stimuli to the experimental side.

<table>
<thead>
<tr>
<th></th>
<th>1mA</th>
<th>2mA</th>
<th>3mA</th>
<th>4mA</th>
<th>5mA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Area Under the Curve</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>0.97 (1,25)</td>
<td>1.78 (1,26)</td>
<td>0.92 (1,29)</td>
<td>0.6 (1,28)</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>12.1 (1,25)*</td>
<td>18.18 (1,26)*</td>
<td>14.21 (1,29)*</td>
<td>17.96 (1,28)*</td>
<td></td>
</tr>
<tr>
<td>Time x Group</td>
<td>0.06 (1,25)</td>
<td>0.19 (1,26)</td>
<td>0.25 (1,29)</td>
<td>0.27 (1,28)</td>
<td></td>
</tr>
<tr>
<td><strong>Latency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>0.33 (1,25)</td>
<td>0.74 (1,26)</td>
<td>4.45 (1,28)*</td>
<td>3.89 (1,29)#</td>
<td>2.02 (1,29)</td>
</tr>
<tr>
<td>Time</td>
<td>2.05 (1,25)</td>
<td>1 (1,26)</td>
<td>1.17 (1,28)</td>
<td>1.53 (1,29)</td>
<td>2.63 (1,29)</td>
</tr>
<tr>
<td>Time x Group</td>
<td>0.64 (1,25)</td>
<td>0.43 (1,26)</td>
<td>0.04 (1,28)</td>
<td>1.64 (1,29)</td>
<td>4.12 (1,29)#</td>
</tr>
<tr>
<td><strong>Percent Change from Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>0.35 (25)</td>
<td>1.02 (26)</td>
<td>0.83 (29)</td>
<td>1.36 (25)</td>
<td></td>
</tr>
</tbody>
</table>

* Denotes significance at .05 alpha level; #p=.085
Table 2-7: Blink reflex parameters F Ratios (degrees of freedom) for 2 X 2 ANOVA and T values at each intensity for 0.5ms stimuli to the control side.

<table>
<thead>
<tr>
<th></th>
<th>1mA</th>
<th>2mA</th>
<th>3mA</th>
<th>4mA</th>
<th>5mA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Area Under the Curve</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>.75 (1,24)</td>
<td>3.34 (1,29)#</td>
<td>1.88 (1,28)</td>
<td>1.95 (1,28)</td>
<td>1.5 (1,28)</td>
</tr>
<tr>
<td>Time</td>
<td>3.77 (1,24)#</td>
<td>6.61 (1,29)*</td>
<td>10.11 (1,28)*</td>
<td>3.23 (1,28)#</td>
<td>6.23 (1,28)*</td>
</tr>
<tr>
<td>Time x Group</td>
<td>0.03 (1,24)</td>
<td>0.16 (1,29)</td>
<td>0.66 (1,28)</td>
<td>0.05 (1,28)</td>
<td>1.87 (1,28)</td>
</tr>
<tr>
<td><strong>Latency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>1.48 (1,24)</td>
<td>3.97 (1,25)#</td>
<td>5.23 (1,27)*</td>
<td>5.82 (1,27)*</td>
<td>4.75 (1,27)*</td>
</tr>
<tr>
<td>Time</td>
<td>0.00 (1,24)</td>
<td>0.29 (1,25)</td>
<td>1.65 (1,27)</td>
<td>4.12 (1,27)#</td>
<td>3.32 (1,27)#</td>
</tr>
<tr>
<td>Time x Group</td>
<td>0.49 (1,24)</td>
<td>0.69 (1,25)</td>
<td>0.47 (1,27)</td>
<td>1 (1,27)</td>
<td>1.65 (1,27)</td>
</tr>
<tr>
<td><strong>Percent Change from Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>0.21 (24)</td>
<td>0.44 (27)</td>
<td>0.42 (28)</td>
<td>0.2 (28)</td>
<td>1.31 (28)</td>
</tr>
</tbody>
</table>

* Denotes significance at .05 alpha level; #p<0.1
2.4 Discussion

This research answers the call by Kaube et al. (2002) to further investigate trigeminal transmission interictally in migraine sufferers. This research is particularly pertinent because it has compared the effect of a local anaesthetic agent in interictal migraine sufferers and healthy controls on a subcortical reflex known to be affected by migraine.

Suppression of the blink reflex after topical local anaesthetic (expressed as the number of responses to electrical stimuli) was greater in healthy controls than in migraine sufferers. This finding suggests that the afferent limb of the trigeminal nociceptive blink reflex is hyperexcitable between attacks of migraine.

The data in the healthy control group clearly support the notion that the concentric electrode depolarised nociceptive fibres as demonstrated by a significant reduction in blink reflex frequency after the application of a local anaesthetic whilst there was no change in blink reflex parameters in response to the control stimulus. These results were similar to those reported previously (Kaube, et al., 2000) in that the nociceptive blink reflex was suppressed after the topical application of local anaesthetic agent. However, the effect of the local anaesthetic persisted up to 5 mA in the present study whereas Kaube et al (2000) detected a significant reduction in the blink reflex only for stimulus intensities up to 2 mA. The findings of this study concur with findings from another study that illustrated an interictal hypersensitivity of the trigeminal system in migraine sufferers using the corneal reflex (Sandrini, et al., 2002). The corneal reflex is activated by Aδ trigeminal nociceptive afferents that run close to the corneal surface. Our findings illustrate the effect of the local anaesthetic agent on stimuli up to 5mA, suggesting a greater involvement of the Aδ afferents at these intensities in this study than in previous studies entirely on healthy controls (Kaube, et al., 2000).
In contrast to these straightforward findings, in the migraine group the local anaesthetic did not completely inhibit the blink reflex, as illustrated by the lack of decrease in blink reflex frequency, especially with the longer stimuli.

Resistance to the effects of local anaesthetic agent at the site of electrical stimulation suggests that trigeminal nociceptive afferents were more excitable in migraine sufferers than controls. The local anaesthetic agent appeared to block cutaneous nerve fibres because none of the participants felt the prick of a hypodermic needle at the anesthetized site. Thus, penetration of the electrical field beyond the anesthetized zone apparently activated trigeminal nociceptive afferents more readily in migraine sufferers than controls. It seems unlikely that the electrical field activated myelinated Aβ fibres because the short-latency R1 component of the blink reflex was absent from the raw blink reflexes (Ellrich, 2002). However Aβ fibres may still contribute subclinically to the blink reflex evoked by the concentric electrode (de Tommaso, 2013).

Alternatively, the blink reflex may have been facilitated in migraine sufferers by excitable second order neurons in the spinal trigeminal nucleus (Borsook, Burstein, & Becerra, 2004). This explanation could be tested using NMDA antagonists to inhibit trigeminal second-order neuron sensitization (Welch, 2003). Previous work carried out by Katsarava et al. (Katsarava, Egelhof, et al., 2003; Katsarava, et al., 2002), suggests that sensitisation of the trigeminal system during attacks of migraine (Kaub, et al., 2002) is centrally located because sinusitis pain (thought to result from peripheral trigeminal irritation) had no effect on the nociceptive blink reflex, whereas a pontine cavernoma facilitated the nociceptive blink reflex. The central location of sensitisation of the trigeminal system can also possibly be supported by a series of imaging studies (May et al., 1998; Weiller, et al., 1995) in which the brain stem was activated during migraine attacks, but not during painful subcutaneous capsaicin injection in the forehead.
Although activation and sensitisation of the trigeminovascular pain pathway clearly is important during attacks of migraine, whether trigeminal sensitisation persists between attacks of migraine is still controversial. A lack of interictal trigeminal sensitivity in migraine sufferers as measured by the nociceptive blink reflex has been reported by various research groups (Coppola et al., 2007; Kaube, et al., 2002). Coppola et al (2007) used the nociceptive blink reflex paired with either segmental or heterosegmental stimuli with a recovery curve methodology and found no difference in R2 recovery curves between migraine sufferers or healthy controls. Kaube et al (2002) tested migraine sufferers during and between migraine headaches and found that the nociceptive specific blink reflex was facilitated during migraine but not in the pain free state.

But a lack of habituation in these studies and others (Di Clemente, et al., 2005) suggests that a neurophysiological deficit persists interictally in migraine sufferers (Coppola, Pierelli, & Schoenen, 2009). The deficit in interictal habituation has been attributed to dysrhythmic thalamo-cortical activity (Coppola, et al., 2009). The migraine sensory cortices have been labelled as hyperresponsive (Ambrosini & Schoenen, 2006; Coppola, Pierelli, et al., 2007) with abnormal hyperexcitability observed between migraine attacks in response to various stimuli in both subjective and electrophysiological measures, including light sensitivity (Boulloche, et al., 2010; Drummond, 1997); sound sensitivity (Ashkenazi, et al., 2010; Main, Dowson, & Gross, 1997; Vingen, et al., 1998); and odour sensitivity (Demarquay et al., 2006; Grosser et al., 2000; Snyder & Drummond, 1997). The trigeminovascular pain pathway is modulated by higher-order mechanisms that may influence the nociceptive blink reflex, but these modulatory influences would be expected to influence responses on both sides.

The frequency of evoked blink reflexes was a more sensitive index of trigeminal excitability than the AUC or latency of the blink reflexes. Perhaps this is a reason why it has been difficult in past studies that measured only the AUC or latency of blink reflexes to demonstrate interictal excitability in migraine sufferers. The persistence of the nociceptive
Blink reflex after local anaesthetic in migraine sufferers in the current research suggests that trigeminal sensitisation (a subcortical process) does persist between migraine attacks. Whether this persistence in interictal migraine sufferers is a centrally mediated sensitisation at the second-order neurons or peripherally mediated change in cutaneous nociception requires further research.
Chapter 3  Effect of Nausea on Trigeminal Nociceptive Processing in Migraine Sufferers

3.1 Introduction

Nausea is a defining feature of the migraine attack which sets it apart from a tension type headache. Drummond has proposed a cyclical neural theory where head pain and nausea build upon each other in a vicious cycle which can eventually lead to vomiting (Drummond, 2002, 2004; Drummond & Granston, 2004). The aim of the present study was to extend this research by investigating the effect of peripherally induced nausea evoked by the ingestion of hypertonic saline on symptoms of migraine, scalp tenderness, pain ratings to trigeminal electrocutaneous stimulation and blink reflex parameters.

Numerous visceral sensory afferents ascend to the central nervous system via the vagus nerve. Emesis can be induced by electrical stimulation of the vagal afferent nerves which, according to Andrews et al (1990), strongly suggests the necessity of this pathway for rapid gastric ejection. The abdominal vagal nerve has two types of sensory nerve fibres: the mechanoreceptors which are located in the muscles of the gut; and the chemoreceptors which are embedded in the mucosal wall of the upper gut (Andrews, 1992). The chemoreceptors respond to various substances including acid, mustard powder, cayenne pepper and hypertonic saline (Clarke & Davison, 1978). An increase in vagal efferent response was evoked by hypertonic solution, and possibly by increased hydrochloric acid in the stomach (which would stimulate the chemoreceptors). This was associated with the prodrome of vomiting in the ferret suggesting that stimulation of the chemoreceptors, via numerous substances, can evoke vagal efferent responses (Blackshaw, Grundy, & Scratcherd, 1987).

Fos immunoreactivity is a marker for neuronal activity; this technique was used to investigate the mediating effect of the area postrema on the Nucleus Tractus Solitarius (NTS) in rats during high saline load. Fos responses were found in the NTS and the area postrema during
intragastric hypertonic load (Carlson, Collister, & Osborn, 1998), suggesting that hypertonic solution ingestion activates the NTS.

The NTS is a structure in the brainstem that is sometimes known as the vomiting centre. This centre is the terminating site for the vagus nerve. If this is the area of activation during vomiting, and nausea is the prodrome of vomiting, then we should be able to evoke nausea by activating this area via vagal gastrointestinal pathways. Participants in the current study ingested hypertonic saline to stimulate the chemoreceptors in the mucosal wall of the stomach and thereby activate the NTS (Figure 3-1).

3.1.1 Nausea in Migraine

Nausea is defined by Andrews (1992) as an unpleasant sensation in the upper abdomen and thorax preceding vomiting or associated with the desire to vomit. From an evolutionary perspective, vomiting occurs to rid the body of toxins, or poisonous foods that have entered the body and surpassed the front line of toxin defence (sight, taste and smell) (Andrews, 1992). Horn (2008) suggested that nausea and vomiting could be separate physiological processes as nausea persists after anti-emetic treatment for drug-induced emesis during cancer treatment (Horn, 2008). Unfortunately most authors view both of these phenomena together and Horn (Horn, 2008) himself places nausea as a prodrome of emesis in his neurobiological model of nausea and vomiting. Because of the subjective nature of nausea in humans, and the difficulty of testing nausea in animals, nausea is difficult to investigate physiologically.

Most migraine sufferers (90%) report nausea during a migraine attack (Kelman & Tanis, 2006) and migraine sufferers are more susceptible than controls to symptoms of motion sickness (primarily nausea and vomiting) over the life span and during provocation with optokineti con stimulation (Drummond, 2002, 2004; Marcus, Furman, & Balaban, 2005). Additionally, they are more susceptible to the dopaminergic effects of apomorphine,
including nausea and vomiting (Cerbo, et al., 1997). Drummond (Drummond, 2002) suggested that the structures involved in gastrointestinal disturbances are more responsive than normal in migraine sufferers. Based on this proposition, it was hypothesised that migraine sufferers would be more susceptible to the nauseating effects of ingesting hypertonic saline solution than controls.

3.1.2 Trigeminal Nociception in Migraine

Migraine sufferers are abnormally sensitive to noxious tactile stimuli, possibly due to central sensitisation in trigeminal nociceptive pathways (Drummond, 1987); (DaSilva, et al., 2007). Migraine patients have been shown to have lower pain thresholds to electrical corneal stimulation between attacks of migraine compared to controls (Sandrini, et al., 2002) suggesting increased trigeminal excitability interictally in migraine sufferers.

Drummond (1987) found that scalp tenderness and decreased scalp pressure-pain threshold, suggesting central sensitization, persisted for four days after a migraine attack.

Whether scalp tenderness during a migraine is specific to the trigeminal nervous system or is part of the well documented generalized allodynia (central) that occurs during migraine (Burstein, Yarnitsky, et al., 2000) is unknown. Scalp tenderness before and after the ingestion of the hypertonic saline and fingertip tenderness as a comparison was investigated in the current study. If the effect of hypertonic saline on nociception was limited to the scalp then the scalp tenderness could be attributed to the sensitisation of the trigeminal system and perhaps central mechanisms. Conversely, if the fingertips were also tender after the hypertonic saline, then allodynia could be mediated by a more general sensitisation of nociceptive pathways or failure of inhibitory pain control.

The use of the blink reflex as a trigeminal reflex testing paradigm in headache sufferers is becoming more popular and is sometimes cited as a neurophysiological test in migraine
sufferers (Magis, et al., 2007). Three different types of stimulation were used in the current study: a low intensity stimulus (2 mA) from standard electrodes that is thought to activate the Aβ fibres; a high intensity stimulus (18 mA) from standard electrodes which activates Aβ, Aδ and C-fibres; and a nociceptive specific stimulus which stimulates superficial Aδ fibres due to a high current density and small anode-cathode distance (Kaube, et al., 2000).

The R2 blink reflex area and amplitude evoked by standard electrodes at 10-12 mA did not differ in migraine sufferers studied between attacks compared with controls (Sand, Moll-Nilsen, & Zwart, 2006) although it is unclear which nerve fibres this intensity activated as pain ratings were not reported. However, it is likely that Aδ fibres would have been activated in addition to Aβ fibres. At intensities high enough to activate all fibres, de Tommaso, Guido, Libro, Sciruicchio, Losito et al (2000) found no differences in blink reflexes between controls and migraine sufferers between migraine attacks. Migraine sufferers and controls were used to investigate the effect of supraorbital and heterotopic conditioning stimuli on the R2 component of the nociceptive blink reflex (Coppola, Di Clemente, et al., 2007). Inhibition of the R2 was similar in migraine sufferers and controls and the authors concluded that interictal sensitisation of the trigeminal system was absent in migraine sufferers. Nevertheless, sensitisation may develop quickly after provocation in migraine sufferers. If migraine sufferers do have an interictal sensitisation of the trigeminal system, blink reflexes may differ between migraine sufferers and controls.

3.1.3 Interaction Between Trigeminal Nociception and Nausea in Migraine

We know from Drummond and Granston’s research that facial pain can cause nausea (Drummond & Granston, 2005) and that facial pain can intensify nausea, especially in migraine sufferers (Drummond & Granston, 2004). However, a symptomatic functional connection between nausea and headache remains speculative because the link between nausea and the trigeminal system has not been investigated physiologically in humans.
Scalp and fingertip tenderness was investigated with an algometer before and after motion sickness provocation (optokinetic stimulation) in 21 migraine sufferers and 15 controls (Drummond, 2002). Scalp tenderness developed in both groups during optokinetic stimulation but, surprisingly, did not differ between the groups although nausea was greater in migraine sufferers than controls. Nausea intensified in migraine sufferers during a painful stimulus applied to the temple before and during motion sickness induced by optokinetic stimulation (Drummond & Granston, 2004). Fingertip tenderness increased in migraine sufferers after optokinetic stimulation (Drummond, 2002), suggesting two hypotheses. The first is that nausea can increase scalp tenderness and the second is that migraine sufferers may develop pain hypersensitivity at distal sites after activation of brainstem circuits involved in gastrointestinal reflexes. In the current study nausea was evoked via a peripheral route to determine whether these findings could be replicated by nausea that is not centrally driven.

To investigate the effect of nausea on the trigeminal nervous system, 20 healthy volunteers were used to investigate the electrocutaneous blink reflex to stimulation of the supra-orbital region from both standard electrodes (high and low intensity) and the concentric electrode during optokinetic stimulation (Drummond, 2004). The R2 component of the blink reflex evoked by low intensity stimuli from both the standard and concentric electrodes was suppressed most during optokinetic stimulation in those who did not develop motion sickness symptoms. Interestingly, there was no difference between the blink reflexes evoked by the concentric electrode or the low intensity standard electrode (2 mA) during optokinetic stimulation. It was unclear if the effect on R2 was mediated by optokinetic stimulation or nausea, or reflected differences in psychological state between those with and without symptoms of motion sickness. After optokinetic stimulation, the R2 component to moderate and intense stimuli from the standard electrodes was more inhibited in those participants who felt nauseated. Drummond speculated that DNIC may be occurring with nausea being the aversive sensation, but he also suggested further research to consolidate this speculation as
responses to certain intensities were not affected by nausea. Inducing nausea peripherally could clarify whether the effect of the motion sickness on the blink reflex R2 was the result of the nausea or the result of the optokinetic stimulation, and whether DNIC can be evoked when nausea is generated via a peripheral route. In the current study DNIC would be discernible if the blink reflex was suppressed only in the nauseated group.

As numerous researchers have found no evidence of differences between migraine sufferers and controls in blink reflex parameters either to standard electrode stimuli (de Tommaso, et al., 2000b; Sand, et al., 2006) or nociceptive electrode stimuli (Coppola, Di Clemente, et al., 2007; Katsarava, et al., 2002) when at rest, this study explored the question of whether migraine sufferers might have a greater response to this and other forms of trigeminal stimulation after the induction of nausea.

It is unclear how ingesting the hypertonic solution would affect headache, dizziness and drowsiness during trigeminal nerve stimulation. If the cyclical neural theory of nausea and headache building upon each other in migraine is correct, nausea should increase headache.

The current study investigated the effect of nausea induced peripherally on other symptoms of migraine during trigeminal nerve activation. Since symptoms of motion sickness are evoked more readily in migraine sufferers than controls (Drummond & Granston, 2004), it was hypothesized that migraine symptoms would be greater in migraine sufferers than controls after the ingestion of hypertonic saline.

3.1.4 Study Aims

The aims of this study were two-fold (Figure 3-2). The first was to investigate the effect of ingesting hypertonic saline (i.e., vagal afferent activation) on ratings of scalp tenderness (using finger algometer pain ratings as a control), pain ratings of the three different types of brief electrical stimuli, the R2 component of the blink reflex evoked by these electrical
stimuli and whether this differed between migraine sufferers and controls. Because all participants ingested the hypertonic saline, it was accepted that all had some degree of vagal nerve activation.

The second aim was to investigate the effect of nausea, induced by peripheral activation, on the dependent variables. To investigate this aim, participants were separated into those who developed nausea and those who did not after ingestion of the hypertonic saline.

Figure 3-1: Diagram of area of activation from Vagal Nerve Stimulation upon the blink reflex neurological pathway. (Adapted from Majoie et al., 1999, p 1120, used with Author's permission) (1) interneurons subserving the ipsilateral early components; (2) interneurons subserving the bilateral late component; Vm indicates trigeminal motor nucleus; Sp V co, spinal trigeminal complex; Sp V tr, spinal trigeminal tract; VI, abducens nucleus; VII, facial nucleus; VII, facial nerve; VN, trigeminal sensory root; XII, hypoglossal nucleus; Lat tegm field, lateral tegmental field; Med tegm field, medial tegmental field.
Figure 3-2: Nausea and blink reflex study aims. (nBR evoked with concentric electrode; Aβ BR evoked with low intensity standard electrode; All fibre BR evoked with high intensity standard electrode.)
3.2 Method

3.2.1 Participants

The control sample consisted of 12 females and six males (mean age ± SD, 21.56 ± 4.82) who reported less than 12 headaches per year that did not meet the criteria for migraine. The migraine sample consisted of 16 females and 1 male (mean age ± SD, 26.59 ± 8.9) who met the International Headache Society (IHS, 2004) criteria for migraine without aura (thirteen participants) or with aura (four participants). Migraine participants were free from migraine headache for at least four days before the experiment and none of the participants had a history of any serious medical illness. Participants were alcohol, drug and medication free for at least 24 hours and were asked to fast for three hours prior to the testing session.

Volunteers were awarded course credit and a small remuneration for participation. They gave written informed consent for the procedures which were approved by the Murdoch University Human Research Ethics Committee.

3.2.2 Experimental Design

This study used a mixed design with between groups factors of migraine (Controls; Migraine sufferers) and nausea (those who became nauseated after the ingestion of a hypertonic saline solution versus those who did not) and a within subject variable of condition (Baseline; after ingestion of hypertonic saline).

3.2.3 Blink Reflex

Participants sat with their eyes open during the study. The blink reflex was measured bilaterally from the mid orbicularis oculi muscle below the eyelids via electromyography (EMG). The skin was lightly abraded with a skin preparation pad (Professional Disposables, Inc. NY, USA) before
being wiped with an alcohol wipe (Kendall, MA, USA) prior to attaching the electrodes with micropore tape (3 M, MN, USA). The silver cup electrodes were filled with conductive adhesive gel (Parker, USA) and the reference electrode was placed over the cheek bone. A disposable ground electrode was placed on the left wrist to minimise electrical interference.

The blink reflex was elicited by electrical stimuli to the supra-orbital nerve delivered via a concentric electrode (to the right forehead) and a standard electrode (to the left forehead). There was no relationship between side of stimulation and side of usual headache in migraine sufferers. The concentric electrode is a replication of the concentric electrodes described by Kaube et al (2000) which primarily stimulate superficial Aδ fibres due to a high current density and small anode-cathode distance. The concentric electrode consisted of a 0.5mm copper wire cathode with a stainless steel round anode with an external diameter of 20mm and internal diameter of 10mm. The concentric electrode was attached (with an adhesive washer) to the skin of the forehead prepared with an abrasive skin preparation pad. The outer ring (anode) of the electrode was smeared with electrode gel to aid electrical conductivity. The electrode was placed so that the cathode (inner point) was placed above the supra-orbital foramen. The concentric electrode stimuli had a mean intensity of 1.98 mA (.23 SD).

The normal bipolar electrodes (10mm diameter flat circular electrodes) were smeared with electrolyte gel and attached to the similarly prepared skin with adhesive washers. The cathode was attached to the supra-orbital foramen whilst the anode was attached 2cm rostral to the supra-orbital foramen. The lower intensity stimuli of 2.1 mA (.16 SD) were delivered with the intention of preferentially stimulating the Aβ touch fibres whilst the higher intensity stimuli of 17.98 mA (2.16 SD) were delivered with the intention of stimulating all fibres.

Electrical stimuli were monopolar square wave pulses with a duration of 0.3 ms. An interstimulus interval of at least 10 seconds was used to minimise habituation of the blink reflex. Each different
type of stimulus was delivered four times in three sets in a set random order before and after a saline drink (total of 12 deliveries per type in each condition).

EMG data were acquired via an EMG digital pre-amplifier (EMG100C, BIOPAC Systems, Inc. California, U.S.A.) before being transmitted to a personal computer via a 16-bit MP100 BIOPAC Systems Analogue/Digital Channel Receptor (BIOPAC Systems, Inc. California, U.S.A.) using AcqKnowledge software (Version 3.7.1, BIOPAC Systems, Inc. California, U.S.A.). Data were collected at a sampling rate of 1KHz for later off-line analysis. Signals were high pass filtered with a cut-off frequency of 10Hz to reduce interference from the movement of eyeball roll, and rectified prior to analysis. The R1 component of the blink reflex was not used in this study because it is a monosynaptic response that is relatively stable (Esteban, 1999) and therefore not susceptible to modulation by the independent variables. The R3 component was not used because of the controversial nature of its origin. Area under the curve (AUC) for the R2 component was assessed in the time window of 27 to 87 ms after the onset of the stimulus (Ellrich & Treede, 1998).

3.2.4 Procedures

Participants were briefly interviewed on their headache history before being briefed about rating scales and the electrodes were attached. A set of stimuli was first delivered to reduce the stimulus novelty and to help the participant feel comfortable rating the pain of the stimuli. The participant was required to rate every stimulus on an 11 point pain rating scale (0 – no sensation; 1 – painless sensation to 10 – intolerable pain). All pain ratings were later modified to fit a 10 point pain rating scale (0 – no pain; 1 – pain awareness; 9 – intolerable pain). In the baseline condition approximately 60 grams, 140 grams and 220 grams of pressure were applied from an algometer (2 mm diameter hemispheric metal tip) to the tips of the first, middle and ring fingers respectively (finger tenderness test) and to the forehead (scalp tenderness test). The participant rated how
painful each pressure was at each site on the 11-point pain rating scale. After the scalp and finger tenderness tests, the electrical stimuli were applied four times each in three sets (a total of 12 shocks per set). After each set the participant rated nausea, body temperature, dizziness, drowsiness, headache and unpleasantness on an 11 point scale (0 – none, 1 – awareness; 2 – mild; 10 – extreme).

After the baseline, participants drank a saline mixture which consisted of 16 grams of table salt and 30 grams of sodium drink powder (Staminade, Sterick, Pty Ltd, Australia) in 600 ml of water. The sodium chloride content was 30,522 parts per million (which is equivalent to sea water) as tested by flame photometer. There was no time limit on the time taken to drink the saline mixture but most participants took only a few minutes to drink it. Participants were required to drink as much of the mixture as they could, preferably all of it. As soon as the drink was consumed participants rated nausea and the unpleasantness of internal sensations every minute for 4 minutes.

Five minutes after completion of the drink, the pressure stimuli and the electrical stimuli were delivered in the same order as the baseline, with all stimuli being rated and symptom ratings being taken after each set. The sequence of the procedure are summarised in Figure 3-3.

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Algometer applied to fingertips and forehead</th>
<th>Concentric electrode stimuli and normal electrode stimuli administered</th>
<th>Hypertonic solution ingested orally + 5 minute wait</th>
<th>Algometer applied to fingertips and forehead</th>
<th>Concentric electrode stimuli and normal electrode stimuli administered</th>
</tr>
</thead>
</table>

Figure 3-3: Sequence of procedures for nausea and trigeminal nociceptive processing study.
3.2.5 Data Reduction and Statistical Analysis

Because a nausea rating of ‘2’ indicated mild nausea, the average nausea rating was used to classify two groups - those who reported nausea after the drink (an average nausea rating of two or more) and those who did not.

3.2.5.1 Statistical Analyses

All variables were averaged across trials and/or all three sets and analysed with a migraine group (controls vs. migraineurs) X condition (baseline vs. after drink) mixed design ANOVA and a nausea group (no nausea vs. nausea) X condition (baseline vs. after drink) mixed design ANOVA using the univariate approach with a Huynh-Feldt epsilon applied where necessary. Nausea ratings were also investigated in a migraine group (controls vs. migraineurs) X condition (baseline vs. after drink) mixed design ANOVA. Each location (forehead; finger) for the algometer was individually analysed and a third factor (pressure) was used in the mixed design ANOVA. Migraine x nausea cell sizes were too small to include both factors simultaneously in statistical analyses.

3.2.5.2 Blink Reflex Data

The ipsilateral blink reflex data for each type of stimulus (Concentric Electrode – 2 mA; Normal electrode low intensity – 2 mA; Normal Electrode high intensity – 18 mA) was used to simplify analyses. Area under the curve data was used to define the presence of a blink reflex response in which a value above the artefact level (0.0002V·Sec) defined a response. The number of blink reflexes, the area under the curve and latency of these responses was analysed. Additionally, the percentage change from baseline to after the hypertonic solution was analysed. Only significant main effects and significant interactions were reported in the Results section.
3.3 Results

3.3.1 Symptoms of Migraine (Table 3.2)

3.3.1.1 Effects of ingesting hypertonic saline

Nausea ratings increased after the ingestion of the saline mixture ($F(1,34)=52.24$, $p<.001$, $\eta^2_p=.61$). All other symptoms were significantly affected by ingestion of the saline mixture.

Dizziness ($F(1,33)=14.9$, $p<.05$), drowsiness ($F(1,33)=21.75$, $p<.001$), headache ($F(1,33)=13.76$, $p<.05$) and unpleasantness ($F(1,33)=29.11$, $p<.001$) all increased after the drink but ratings of body temperature decreased ($F(1,33)=7.47$, $p<.05$) (Figure 3-4).

3.3.1.2 Effects of nausea

Those who reported at least mild nausea after the drink rated greater dizziness ($F(1,33)=4.19$, $p<.05$, $\eta^2_p=.11$), unpleasantness ($F(1,33)=16.9$, $p<.05$, $\eta^2_p=.34$) and headache (approaching significance $F(1,33)=3.94$, $p=.055$, $\eta^2_p=.11$) overall than those who reported no nausea (Table 3.2 and Figure 3.3). Perceived body temperature was not significantly affected by nausea. Nausea group by condition interactions for dizziness ($F(1,33)=6.08$, $p<.05$, $\eta^2_p=.16$), headache ($F(1,33)=7.4$, $p=.05$, $\eta^2_p=.18$), unpleasantness ($F(1,33)=13.47$, $p<.05$, $\eta^2_p=.29$) and drowsiness (approaching significance $F(1,33)=3.81$, $p=.06$, $\eta^2_p=.1$), were investigated with independent and repeated measures t-tests. For those participants who reported nausea, symptom ratings increased after the drink for dizziness ($t(22)=3.86$, $p<.05$), drowsiness ($t(22)=4.45$, $p<.05$), headache ($t(22)=3.86$, $p<.05$) and unpleasantness ($t(22)=6.6$, $p<.05$) (Figure 3-5). In contrast, symptoms did not increase in the participants who reported no nausea. The electrical stimuli were rated as more unpleasant during baseline by those in the nausea group ($t(33)=2.5$, $p<.05$), suggesting that the stimuli could have contributed to the severity of the nausea after the ingestion of the mixture. An alternative explanation could be that participants who became nauseated after drinking the
hypertonic saline had a lower threshold for discomfort either in a physiological or psychological sense than the remainder of participants.

As a whole, most of the symptom ratings correlated positively with nausea (dizziness $r(33) = .58$, $p < .01$; drowsiness $r(33) = .51$, $p < .01$; headache $r(33) = .56$, $p < .01$; unpleasantness $r(33) = .89$, $p < .01$) (Table 3-1). In general these effects were stronger in the migraine group than the control group.

### 3.3.1.3 The effect of migraine

Greater dizziness was reported by migraineurs than controls (main effect for migraine group $F(1,33)=8.95$, $p<.05$, $\eta_p^2 = .21$) with migraineurs reporting a greater increase in dizziness after the ingestion of the drink (migraine group by condition interaction, $F(1,33)=4.29$, $p<.05$, $\eta_p^2 = .12$) (Figure 3-6). Headache was greater overall in migraineurs than controls ($F(1,33)=17.79$, $p<.001$, $\eta_p^2 = .35$) with migraineurs reporting a greater increase in headache after the drink than controls (migraine group by condition interaction $F(1,33)=7.59$, $p<.05$, $\eta_p^2 = .19$) (Figure 3-6). In addition, baseline ratings for dizziness ($t(16.95)=2.48$, $p<.05$) and headache ($t(18.58)=3.05$, $p<.05$) were significantly greater in migraine sufferers than controls.
Table 3-1: Correlations with nausea

<table>
<thead>
<tr>
<th>Correlations with Nausea</th>
<th>All (n=35)</th>
<th>Controls (n=18)</th>
<th>Migraineurs (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body temperature</td>
<td>-.028</td>
<td>.387</td>
<td>-.400</td>
</tr>
<tr>
<td>Dizziness</td>
<td>.578**</td>
<td>.453</td>
<td>.620**</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>.509**</td>
<td>.410</td>
<td>.527*</td>
</tr>
<tr>
<td>Headache</td>
<td>.559**</td>
<td>.201</td>
<td>.676**</td>
</tr>
<tr>
<td>Unpleasantness</td>
<td>.889**</td>
<td>.871**</td>
<td>.898**</td>
</tr>
<tr>
<td>Scalp tenderness (150)</td>
<td>.374*(n=33)</td>
<td>.379 (n=17)</td>
<td>.307 (n=16)</td>
</tr>
<tr>
<td>Finger tenderness (150)</td>
<td>.336 (n=33)</td>
<td>.217 (n=17)</td>
<td>.352 (n=16)</td>
</tr>
<tr>
<td>Concentric Electrode</td>
<td>.298</td>
<td>.132</td>
<td>.344</td>
</tr>
<tr>
<td>Low Intensity Standard Electrode</td>
<td>.247</td>
<td>-.028</td>
<td>.407</td>
</tr>
<tr>
<td>High Intensity Standard Electrode</td>
<td>.456**</td>
<td>.260</td>
<td>.595*</td>
</tr>
</tbody>
</table>

*p<.05; **p<.01

Table 3-2: F ratios (d.f.) for each symptom.

<table>
<thead>
<tr>
<th>Effect of Ingestion</th>
<th>Nausea</th>
<th>Dizziness</th>
<th>Drowsiness</th>
<th>Headache</th>
<th>Body Temp.</th>
<th>Unpleasantness</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Condition)</td>
<td>52.24 (1,33)*</td>
<td>14.9 (1,33)*</td>
<td>21.75 (1,33)*</td>
<td>13.76 (1,33)*</td>
<td>7.47 (1,33)*</td>
<td>29.11 (1,33)*</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.19 (1,33)*</td>
<td>1.16 (1,33)</td>
<td>3.94 (1,33)*</td>
<td>0.12 (1,33)</td>
<td>16.9 (1,33)*</td>
<td></td>
</tr>
<tr>
<td>Condition x Nausea</td>
<td>6.08 (1,33)*</td>
<td>3.81 (1,33)*</td>
<td>7.4 (1,33)*</td>
<td>0.04 (1,33)</td>
<td>13.47 (1,33)*</td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>3.00 (1,33)#</td>
<td>8.95 (1,33)*</td>
<td>2.25 (1,33)</td>
<td>17.89 (1,33)*</td>
<td>1.52 (1,33)</td>
<td>0.73 (1,33)</td>
</tr>
<tr>
<td>Condition x Migraine</td>
<td>0.7 (1,33)</td>
<td>4.29 (1,33)*</td>
<td>0.33 (1,33)</td>
<td>7.59 (1,33)*</td>
<td>0 (1,33)</td>
<td>0.54 (1,33)</td>
</tr>
</tbody>
</table>

* Denotes significance at .05 alpha level; #p=.092; ^p=.055; `p=.06
Figure 3-4: Symptom ratings across conditions (±SEM). n=35. Body temperature significantly decreased and all other symptoms significantly increased after ingesting the hypertonic solution.
Figure 3-5: Symptom ratings before and after drink in nausea groups (No Nausea n=12; Nausea n=23). Error bars represent SEM. a=headache ratings; b=dizziness ratings; c=drowsiness ratings; d=perceived body temperature ratings; e=unpleasantness ratings. Headache, dizziness, drowsiness and unpleasantness ratings all significantly increased in the nausea group after the drink.
3.3.2 Scalp and Fingertip Tenderness (Table 3-3)

3.3.2.1 Effects of ingesting hypertonic saline

Scalp tenderness increased in some participants after the ingestion of the hypertonic saline mixture but the results only approached significance in the group as a whole (Figure 3-7) (main effect for condition $F(1,29)=4.08$, $p=.053$, $\eta_p^2=.12$). All participants rated fingertip tenderness as more painful after the ingestion of the drink (Figure 3-9) (main effect for condition $F(1,29)=11.35$, $p<.05$, $\eta_p^2=.28$). Fingertip tenderness to the highest pressure increased significantly after the ingestion of the drink ($t(32)=5.24$, $p<.05$) (condition by pressure interaction $F(2,58)=7.13$, $p<.05$, $\eta_p^2=.2$) (Figure 3-9).

3.3.2.2 Effects of nausea

A condition by nausea group interaction ($F(1,29)=6.86$, $p<.05$, $\eta_p^2=.19$) suggests that those who reported nausea also reported greater scalp tenderness ($t(21)=3.99$, $p<.01$) after the ingestion of the drink.
drink (Figure 3-8). Those who reported nausea also reported a significantly greater scalp tenderness to the highest pressure than those who did not report nausea \((t(30.77)=2.77, \ p<.05)\). As shown in Figure 3-10, and investigated with an independent samples t-test, this was also the case for the highest pressure applied to the finger \((t(29.85)=2.84, \ p<.05)\), whereas the lower pressures were not \((\text{nausea group by pressure interaction } F(1.44, 41.66)=4.36, \ p<.05, \eta_p^2 = .13)\).

Scalp tenderness for the strongest pressure increased as nausea increased and this moderate correlation existed for the sample as a whole \((r(33)=.37, \ p<.05)\).

### 3.3.2.3 The effect of migraine

There was no significant difference between migraine sufferers and controls in scalp or fingertip tenderness.

<table>
<thead>
<tr>
<th></th>
<th>Scalp Tenderness F (d.f.)</th>
<th>Fingertip Tenderness F (d.f.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>2.43 (1,29)</td>
<td>0.86 (1,29)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.56 (1,29)#</td>
<td>3.51 (1,29)^</td>
</tr>
<tr>
<td>Migraine * Nausea</td>
<td>0 (1,29)</td>
<td>0.33 (1,29)</td>
</tr>
<tr>
<td>Condition</td>
<td>4.08 (1, 29)^</td>
<td>11.35 (1, 29)*</td>
</tr>
<tr>
<td>Condition * Migraine</td>
<td>0 (1, 29)</td>
<td>1.28 (1, 29)</td>
</tr>
<tr>
<td>Condition * Nausea</td>
<td>6.86 (1, 29)*</td>
<td>2.72 (1, 29)</td>
</tr>
<tr>
<td>Pressure</td>
<td>52.95 (1.41, 41.02)*</td>
<td>25.81 (1.44, 41.66)*</td>
</tr>
<tr>
<td>Pressure * Migraine</td>
<td>2.96 (1.41, 41.02)</td>
<td>0.67 (1.44, 41.66)</td>
</tr>
<tr>
<td>Pressure * Nausea</td>
<td>3.44 (1.41, 41.02)</td>
<td>4.36 (1.44, 41.66)*</td>
</tr>
<tr>
<td>Condition * Pressure</td>
<td>0.58 (2, 58)</td>
<td>7.13 (2, 58)*</td>
</tr>
<tr>
<td>Condition * Pressure * Migraine</td>
<td>1.14 (2, 58)</td>
<td>0.03 (2, 58)</td>
</tr>
<tr>
<td>Condition * Pressure * Nausea</td>
<td>1.1 (2, 58)</td>
<td>1.22 (2, 58)</td>
</tr>
</tbody>
</table>

\*\(p<.05\); \^\(p=.069\); \^\(p=.07\); \^\(p=.053\)
Figure 3-7: Scalp tenderness test pain ratings (+SEM). \( n = 33 \).

Figure 3-8: Scalp tenderness test pain ratings condition by nausea group interaction (+SEM). No Nausea \( n = 11 \); Nausea \( n = 22 \).
Figure 3-9: Fingertip tenderness test pain ratings (+SEM). \( n=33 \). Fingertip tenderness significantly increased after the drink.

Figure 3-10: Algometer Pain Ratings across nausea groups (+SEM). No nausea \( n=11 \); Nausea \( n=22 \). In the group that reported nausea, scalp tenderness significantly increased after the drink.
3.3.3 Pain Ratings to Electrical Stimulation (Table 3-4)

3.3.3.1 Effects of ingesting hypertonic saline

There was no effect of the ingestion of the hypertonic saline on the pain ratings for the concentric electrode or the low intensity standard electrode stimulus. All participants rated the high intensity normal electrode stimulus as more painful after the ingestion of the drink than at baseline (baseline 4.99, after drink 5.2) (main effect of condition F(1,31)=4.98, p<.05, $\eta_p^2 = .14$).

3.3.3.2 Effects of nausea

Nausea did not affect the ratings for the low intensity normal electrode stimulus. Those who did not report nausea rated the high intensity standard electrode stimulus as more painful after the drink (t(11)=2.68, p<.05) whereas nauseated participants did not (condition x nausea group interaction (F(1,31)=6, p<.05, $\eta_p^2 = .16$) (Figure 3-11).

3.3.3.3 The effect of migraine

Pain ratings to the concentric electrode stimulus and the low intensity standard electrode stimulus did not differ between migraine sufferers and controls.
Figure 3-11: High current normal electrode stimulus condition by nausea group interaction (+SEM). No Nausea n=12; Nausea n=23. Pain ratings were significantly increased in the group that did not report nausea.

Table 3-4: F ratios (d.f.) for pain ratings for each stimulus type.

<table>
<thead>
<tr>
<th>Effect of Ingestion (Condition)</th>
<th>Concentric Electrode</th>
<th>Low intensity Standard Electrode</th>
<th>High intensity Standard Electrode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0.38 (1,31)</td>
<td>0.08 (1,31)</td>
<td>4.98 (1,31)*</td>
</tr>
<tr>
<td>Condition x Nausea</td>
<td>0.23 (1,31)</td>
<td>0.42 (1,31)</td>
<td>0.54 (1,31)</td>
</tr>
<tr>
<td>Migraine</td>
<td>0.54 (1,31)</td>
<td>0.22 (1,31)</td>
<td>6 (1,31)*</td>
</tr>
<tr>
<td>Condition x Migraine</td>
<td>0.7 (1,31)</td>
<td>0.96 (1,31)</td>
<td>0.46 (1,31)</td>
</tr>
</tbody>
</table>

* Denotes significance at .05 alpha level

3.3.4 Blink Reflex

3.3.4.1 Effects of ingesting hypertonic saline

3.3.4.1.1 Concentric Electrode Stimulus (Table 3-5)

Ingestion of the hypertonic saline did not affect blink reflex frequency (Figure 3-12) or area under the curve of these responses (Figure 3-13). Latency of the blink reflex to the concentric electrode stimulus was shorter after the ingestion of the hypertonic solution (M=43.42 ms, SEM=.96) than the response evoked during the baseline condition (M=44.31, SEM=1.07) (F(1,30)=4.94, p<.05,
$\eta_p^2 = .14$) (Figure 3-14). This finding suggests that ingestion of the hypertonic solution facilitated the nociceptive blink reflex, although this must remain speculative in the absence of a control condition that did not involve ingestion of hypertonic saline.

Table 3-5: Concentric Electrode stimulus F ratios and degrees of freedom (ipsilateral side only).

<table>
<thead>
<tr>
<th>Condition</th>
<th>BR Count F (d.f.)</th>
<th>Mean AUC actual responses F (d.f.)</th>
<th>Mean Latency F (d.f.)</th>
<th>% Change from Baseline F (d.f.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>0.42 (1,30)</td>
<td>0.1 (1,30)</td>
<td>0.2 (1,30)</td>
<td>0.41 (1,29)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.19 (1,30)</td>
<td>0.48 (1,30)</td>
<td>0.25 (1,30)</td>
<td>0.74 (1,29)</td>
</tr>
<tr>
<td>Condition * Migraine</td>
<td>0.21 (1, 30)</td>
<td>0.32 (1, 30)</td>
<td>0.76 (1, 30)</td>
<td></td>
</tr>
<tr>
<td>Condition * Nausea</td>
<td>0.39 (1, 30)</td>
<td>0.27 (1, 30)</td>
<td>0.92 (1, 30)</td>
<td></td>
</tr>
</tbody>
</table>

*p<.05;
Figure 3-13: Concentric electrode stimulus mean area under the curve of actual responses for the both groups for the ipsilateral side. Error bars represent SEM. (No Nausea n=12; Nausea n=22; controls n=17; migraineurs n=17).

Figure 3-14: Concentric Electrode stimulus mean latency of actual responses for all groups for the ipsilateral side. Error bars represent SEM. (No Nausea n=12; Nausea n=22; controls n=17; migraineurs n=17). Latency significantly decreased after the ingestion of the drink.
3.3.4.1.2  **Low Intensity Normal Electrode (Table 3-6)**

There was no effect of ingestion of the hypertonic solution on blink reflex frequency (Figure 3-16) or area under the curve (Figure 3-17) in response to the normal electrode low intensity stimulus. The blink reflex latency was shorter after the ingestion of the solution ($M=40.36$ ms, $SEM=.85$) compared to the baseline latency ($M=42.01$ ms, $SEM=.88$) ($F(1,30)=9.84$, $p<.05$, $\eta^2_p=.25$) (Figure 3-18). The facilitation of the response is similar to the findings for the nociceptive specific blink reflex evoked by stimuli delivered from the concentric electrode.
Table 3-6: Normal electrode low intensity stimulus F ratios and degrees of freedom (ipsilateral side only).

<table>
<thead>
<tr>
<th>Condition</th>
<th>BR Count F (d.f.)</th>
<th>Mean AUC actual responses F (d.f.)</th>
<th>Mean Latency F (d.f.)</th>
<th>% Change from Baseline F (d.f.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>2.23 (1,31)</td>
<td>0.24 (1,31)</td>
<td>5.49 (1,30)*</td>
<td>4.4 (1,31)*</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.11 (1,31)</td>
<td>1.67 (1,31)</td>
<td>0.03 (1,30)</td>
<td>1.54 (1,31)</td>
</tr>
<tr>
<td>Condition</td>
<td>1.94 (1, 31)</td>
<td>0.21 (1, 31)</td>
<td>9.84 (1, 30)*</td>
<td></td>
</tr>
<tr>
<td>Condition * Migraine</td>
<td>1.47 (1, 31)</td>
<td>2.93 (1, 31)^</td>
<td>3.04 (1, 30)#</td>
<td></td>
</tr>
<tr>
<td>Condition * Nausea</td>
<td>0.04 (1, 31)</td>
<td>2.06 (1, 31)</td>
<td>1.21 (1, 30)</td>
<td></td>
</tr>
</tbody>
</table>

*p<.05; #=.092; ^p=.097

Figure 3-16: Normal electrode low intensity stimulus mean blink reflex count for the ipsilateral side. Error bars represent SEM. (No Nausea n=12; Nausea n=23; controls n=18; migraineurs n=17).
Figure 3-17: Normal electrode low intensity stimulus mean area under the curve of actual responses for the both groups for the ipsilateral side. Error bars represent SEM. (No Nausea n=12; Nausea n=23; controls n=18; migraineurs n=17).

Figure 3-18: Normal electrode low intensity stimulus mean latency of actual responses for the ipsilateral side. Error bars represent SEM. (No Nausea n=12; Nausea n=22; controls n=17; migraineurs n=17). Latency significantly decreased after the ingestion of the drink.
Figure 3-19: Percent change from baseline in AUC data for the low intensity normal electrode for the ipsilateral side for all groups (±SEM). Baseline is indicated at the zero point. (No Nausea n=12; Nausea n=23; controls n=18; migraineurs n=16).

3.3.4.1.3 **High Intensity Normal Electrode (Table 3-7)**

The number of blink reflexes was not analysed for the high intensity normal electrode stimulus because the maximum number of blinks was always evoked. The blink reflex area under the curve was significantly inhibited after the ingestion of the drink (M= 0.00418V·Sec, SEM= .00030) compared to baseline (M= 0.0045V·Sec, SEM= .00033) (F(1,31)=6.6, p<.05, ηp² = .18) (Figure 3-20). This inhibition could be the result of inhibitory influences triggered by ingestion of the hypertonic solution but is also consistent with habituation. Latency of the blink reflex in response to the high intensity normal electrode stimulus was not affected by ingestion of the hypertonic solution (Figure 3-21), possibly because the stimulus was so intense.
Table 3-7: Normal electrode high intensity stimulus F ratios and degrees of freedom.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mean AUC actual responses F (d.f.)</th>
<th>Mean Latency F (d.f.)</th>
<th>% Change from Baseline F (d.f.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>1.12 (1,31)</td>
<td>0 (1,31)</td>
<td>3 (1,31)^</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.01 (1,31)</td>
<td>1.14 (1,31)</td>
<td>2.96 (1,31)#</td>
</tr>
<tr>
<td>Condition</td>
<td>6.6 (1, 31)*</td>
<td>1.29 (1, 31)</td>
<td></td>
</tr>
<tr>
<td>Condition * Migraine</td>
<td>2.35 (1, 31)</td>
<td>0.35 (1, 31)</td>
<td></td>
</tr>
<tr>
<td>Condition * Nausea</td>
<td>1.33 (1, 31)</td>
<td>0.1 (1, 31)</td>
<td></td>
</tr>
</tbody>
</table>

*p<.05;^p=.093; #p=.096

Figure 3-20: Normal electrode high intensity stimulus mean area under the curve of actual responses for the both groups for the ipsilateral side. Error bars represent SEM. (No Nausea n=12; Nausea n=23; controls n=18; migraines n=17). The blink reflex AUC was significantly inhibited after the ingestion of the hypertonic solution.
Figure 3-21: Normal electrode high intensity stimulus mean latency of actual responses for the ipsilateral side. Error bars represent SEM. (No Nausea n=12; Nausea n=23; controls n=18; migraineurs n=17).

Figure 3-22: Percent change from baseline in AUC data for the high intensity normal electrode for the ipsilateral side for all groups (±SEM). Baseline is indicated at the zero point. (No Nausea n=12; Nausea n=23; Controls n=18; Migraineurs n=17).
3.3.4.2 Effects of nausea

3.3.4.2.1 Concentric Electrode

The number of blink reflex responses to the concentric electrode stimulus was not affected by nausea (Figure 3-12). Neither was the strength of the EMG activity of these responses (area under the curve), (Figure 3-13), latency (Figure 3-14) or percent change from baseline (Figure 3-15) affected by nausea.

3.3.4.2.2 Low Intensity Normal Electrode

There was no effect of nausea on blink reflex frequency (Figure 3-16), area under the curve (Figure 3-17), latency (Figure 3-18) or percent change from baseline (Figure 3-19) in response to the normal electrode low intensity stimulus.

3.3.4.2.3 High Intensity Normal Electrode

There was no effect of nausea on the area under the curve (Figure 3-20) or latency (Figure 3-21).

3.3.4.3 The effect of migraine

3.3.4.3.1 Concentric Electrode

The number of blink reflex responses, area under the curve data, latency and percent change from baseline to the concentric electrode stimulus were similar in migraine sufferers and controls.

3.3.4.3.2 Low Intensity Normal Electrode

There was no effect of migraine on blink reflex frequency (Figure 3-16) or area under the curve data (Figure 3-17) in response to the normal electrode low intensity stimulus. Latency was shorter in controls (M=39.25 mS; SEM=1.12) than migraine sufferers (M=43.12 ms; SEM=1.22) (F(1,30)=5.49, p<.05, ηp² =.16). This finding is unexpected because if the trigeminal system is
hyperexcitable in migraine sufferers interictally, one would expect a faster response in the migraine group. Percent change from baseline area under the curve data increased in controls after they ingested the drink (M=8%; SEM=3.22) but decreased in the migraine sufferers (M=-2.05%; SEM=3.55) (F(1,31)=4.4, p<.05, ηp² =.12) (Figure 3-19).

3.3.4.3.3 High Intensity Normal Electrode

There was no effect of migraine on area under the curve data (Figure 3-20) or latency data (Figure 3-21).
3.4 Blink Reflex and Nausea Discussion (Table 3-8)

Nausea was evoked by the ingestion of the hypertonic solution in the current study. Pain, some sights and smells can also evoke nausea (Mitchelson, 1992). Nausea may be a subjective experience that is triggered by stimulation of the NTS (Horn, 2008). The occurrence of nausea is correlated with the neuronal activation of the inferior frontal gyrus after vestibular stimulation and ingestion of ipecac syrup (Miller, Rowley, Roberts, & Kucharczyk, 1996).

All symptoms of migraine were affected by the ingestion of the hypertonic saline. Ratings of nausea, headache, dizziness, drowsiness and unpleasantness all increased significantly whilst subjective body temperature ratings decreased significantly. This finding can be interpreted in two ways. The first is that the increase in intensity of the symptoms is the result of repeated administration of the electrical stimuli and the second is that ingestion of the hypertonic solution resulted in nausea which then resulted in an increase in the other symptoms. It is plausible that the increase in intensity of these symptoms is in fact a combination of both influences. That is, that the repeated administration of the electrical stimuli to the trigeminal system combined with the nausea (resulting from the hypertonic saline ingestion) intensified these symptoms. Headache and dizziness increased more in migraine sufferers than controls after ingestion of the hypertonic saline, but these ratings were also elevated in migraine sufferers during the baseline condition. This result suggests either a rating bias (although there is no evidence in the literature that migraineurs over-rate somatic symptoms) or a susceptibility to these symptoms by migraine sufferers during trigeminal nerve activation (Table 3-8).
Symptoms of headache, dizziness, drowsiness and unpleasantness all increased in those participants who reported nausea after the drink. These findings concur with those of Drummond (2004) who reported that nausea and headache were evoked by optokinetic stimulation. When nausea is induced peripherally, such as in the current study, pain is more severe in response to trigeminal nerve stimulation. This finding supports the cyclical neural theory of nausea and headache building upon each other in migraine (Drummond & Granston, 2004).

Migraine sufferers reported a greater increase in headache and dizziness after the ingestion of the drink than the control group. These findings are similar to Drummond and Granston’s findings of an increase in headache and dizziness in migraine sufferers during optokinetic stimulation and cold induced temple pain (Drummond & Granston, 2004). However, their finding of the greater
increase in nausea in migraine sufferers during nausea provocation and trigeminal nerve activation (optokinetic stimulation and cold-induced temple pain) was not replicated in the current study. Perhaps the lack of replication of this finding could be explained by the different methods of nausea provocation. Optokinetic stimulation is centrally mediated whilst the hypertonic saline ingestion paradigm was developed to provoke nausea via a peripheral route. Alternatively, the nausea evoked during optokinetic stimulation could be more intense than the nausea evoked during hypertonic saline ingestion. Together, these findings suggest that migraine sufferers are more susceptible to centrally induced nausea but not peripherally induced nausea.

There is also the possibility that stimulation of nociceptive visceral afferents during induction of nausea could evoke the DNIC effect whereby the sensation of nausea suppresses scalp and fingertip tenderness (Bouhassira, et al., 1994). However, scalp tenderness and fingertip tenderness both increased after the ingestion of the hypertonic saline solution, suggesting an increase in pain sensitivity both for brainstem input (because trigeminal pain pathways enter the brain stem at the medullary level) and spinal pain input, indicating that this sensitivity is centrally driven.

Nausea influenced scalp tenderness with scalp tenderness increasing more for those participants in the nausea group after the ingestion of the hypertonic saline; this signifies that nausea induced via a peripheral route increased scalp tenderness. These findings are in agreement with Drummond’s (Drummond, 2002) results which illustrated an association between nausea evoked by optokinetic stimulation and increased scalp tenderness. The current findings suggest that regardless of whether nausea is evoked centrally or peripherally there is possibly a disruption to descending pathways of pain modulation during nausea. This could imply that during a migraine attack descending pain inhibitory pathways could be disrupted. Alternatively, disruption of descending pain modulation pathways might contribute to nausea.
There were no differences between controls and migraine sufferers in scalp tenderness after the ingestion of the hypertonic solution. Migraine sufferers rated fingertip pain as more intense after optokinetic stimulation (Drummond, 2002) and Drummond suggested that this could reflect a disruption to descending pathways of pain modulation in the migrainous brain. However, in the current study, fingertip tenderness did not differ between migraine sufferers and controls. There is the possibility that the stimulus used in the current study was not as painful or did not cover as much area as Drummond’s stimulus. Alternatively, the difference could be that optokinetic stimulation disrupted inhibitory pain control in migraine sufferers whereas ingestion of hypertonic saline did not.

In response to the high intensity standard electrode stimulus, ingestion of the hypertonic solution increased the painfulness of this stimulus both in migraine sufferers and controls. However, pain ratings to the concentric electrode stimulus and the low intensity normal electrode stimulus were not affected by ingestion of the hypertonic saline, presumably because of floor effects. This finding suggests that the pain processing pathway for the high intensity electrical stimulus, which would activate all fibre types (β, Aδ and C), was sensitised after ingestion of the hypertonic saline. One can also suggest the presence of extraneous influences that could modulate the rating (if one is feeling uncomfortable, everything else will be regarded as unpleasant) as symptoms also intensified after the ingestion of the hypertonic solution.

After hypertonic saline ingestion participants without nausea reported a greater pain rating in response to the high intensity electrical stimulus. This could suggest that nausea may inhibit subjective pain because the nausea group had consistent ratings across the conditions but overall after the ingestion of the hypertonic solution, pain ratings increased in response to the high intensity stimulus in participants without nausea. There were no significant findings for the other types of stimuli (concentric electrode or the low intensity standard electrode).
This result is interesting because it opposes the results presented for the effect of nausea on scalp tenderness, in which nausea increased scalp tenderness whereas it appears that nausea inhibited pain in response to the high intensity electrical stimulus. Both the supra-orbital electrical stimulation and the algometer used in the scalp tenderness test should activate the trigeminal system, whether it be via nociceptors or mechanoreceptors. As already discussed in the Introduction, the scalp tenderness test has a longer duration than the electrical stimuli and temporal summation may play a role in the increased severity of scalp tenderness during nausea. The algometer used in the scalp tenderness test is more likely to activate the C-fibres and temporal summation and wind-up are mechanisms that only involve C-fibres (You, et al., 2003).

It was hypothesized that migraine sufferers would rate the electrical stimuli as more painful than controls based on evidence that suggests that the trigeminal system in migraine is more sensitive than usual (Sandrini, et al., 2002). However, pain ratings to the electrical stimuli were not affected by migraine. The reason for this is unknown; however, it is worth noting that electrical stimuli simultaneously activate a wide array of nociceptive and non-nociceptive nerve fibres whereas other more natural forms of stimulation (e.g., deep pressure) evoke activity in specific subsets of fibres. Hence, it is tempting to speculate that sensitization of trigeminal afferents in migraine is limited to discrete nerve fibre categories (e.g., those that signal deep pressure-pain).

Pain ratings to deep pressure were affected by nausea, possibly due to cortical processes as both pain and nausea are known to require cognitive input. This is important because in accordance with Koh and Drummond (2006) it would suggest that subjective pain ratings were mediated by psychological influences that did not influence brainstem processing. Koh and Drummond (2006) found that pain ratings to the nociceptive blink reflex stimulus decreased during a cognitive task but also found that the R2 component of the blink reflex was facilitated during the task, suggesting that the two variables could be independent processes. There was no evidence of an effect of nausea evoked by optokinetic stimulation on pain ratings of electrical stimuli for either the
concentric electrode or the standard electrodes at either high or low intensity (Drummond, 2004). Electrical stimuli differ from the scalp tenderness stimuli in that they are brief. Scalp tenderness, on the other hand, has a longer duration and temporal summation may play a role.

In the current study, ingesting a hypertonic solution affected some elements of the blink reflex but this was not necessarily driven by nausea as there was little or no link between the presence of nausea and blink reflex indices. Given the anatomical location of these phenomena, with vagal nerve input in the NTS and nausea involving the cortex (activation of the inferior frontal gyrus during nausea (Miller, et al., 1996)), this finding is not surprising. Perhaps the influence of nausea on pain ratings for scalp tenderness (increase) and the high intensity electrical stimulus is a top-down process which is modulated by the cortex. Self ratings are a top down process where extraneous influences can modulate the rating (if one is feeling uncomfortable, everything else will be regarded as unpleasant).

In the current study, the latency of the blink reflex evoked by the concentric electrode and the normal electrode low intensity stimulus was shorter after the ingestion of the hypertonic solution than the response evoked during the baseline condition. Latency of the blink reflex in response to the high intensity normal electrode stimulus was not affected by ingestion of the hypertonic solution but area under the curve was inhibited after the ingestion of the drink compared to baseline in all participants. Blink reflex frequency and area under the curve in response to the concentric electrode stimulus and the low intensity standard electrode stimulus were not affected by hypertonic saline ingestion. These findings present a complicated story and raise questions about methodologies used in the blink reflex literature. What dependent variable represents facilitation or inhibition? Does a decrease in latency (faster responding) represent facilitation of the blink reflex? Does a decrease in area under the curve represent inhibition of the blink reflex? Area under the curve measures the amount of electrical energy produced by the orbicularis oculi muscles, which may be moderated by various extraneous phenomena such as habituation or
fatigue of the muscle. In contrast, latency could represent facilitation of trigeminal pathways because although the speed of the neuronal transmission through the communication pathway can be affected by habituation, more neuronal depolarisation has to be occurring for the faster response. The nociceptive blink reflex was faster after ingestion of the hypertonic saline in all participants, concurring with findings that acid and pepsin applied to the cat oesophagus sensitised brainstem neurons (Medda, Sengupta, Lang, & Shaker, 2005).

Nausea did not affect any component of the blink reflexes in response to the high intensity electrical stimulus. As blink reflexes were not disproportionately suppressed in the nauseated group in the current study, this finding indicates that DNIC was not triggered by the nausea evoked via the peripheral route. This suggests that the inhibition of the blink reflexes to moderate or intense electrical stimuli during motion sickness (Drummond, 2004) was mediated by another central source apart from nausea. It also suggests that the gastrointestinal disturbance evoked by hypertonic saline ingestion is different to the gastrointestinal disturbance caused by optokinetic stimulation.

A decrease in area under the curve for the high intensity standard electrode blink reflexes in the current study, combined with an increase in latency, would have been consistent with an inhibitory process evoked by ingestion of the hypertonic solution; however, in the absence of this combination, the minimal decrease in area under the curve is more likely to be a sign of habituation. It would be tempting to suggest that DNIC occurred in the current study because the high intensity stimulus blink reflex area under the curve data decreased. However, if present at all, the DNIC effect was not robust because the suppression was only 6% less than baseline and, subjectively, ratings of pain actually increased after ingestion of the hypertonic solution. Given this finding, the current study has provided no evidence of DNIC. Although there is evidence of WDR neurons in the medullary dorsal horn in the brainstem (Drummond, 2003; Ellrich & Treede, 1998), the results of the current study do not provide support for brainstem WDR neuron
suppression by noxious vagal stimulation. If C-fibre activation was the only type of activation evoked via the high intensity standard electrode then perhaps more evidence of DNIC would be forthcoming. However, the high intensity standard electrode stimulus activates tactile (such as A-β mechanoreceptors) and pain fibres, and the opposing reactions (inhibition versus facilitation) might cancel each other out. This dualism has been found in other blink reflex and migraine studies (Sand, et al., 2006).

There was no difference in blink reflexes in response to the high intensity standard electrode stimulus between controls and migraineurs in the current study. This finding is similar to that of other blink reflex and migraine studies that also found no difference in blink reflex parameters between migraine sufferers and healthy controls for standard electrode stimulation (de Tommaso, et al., 2000b; Sand, et al., 2006) and nociceptive specific stimulation (Coppola, Di Clemente, et al., 2007; Katsarava, et al., 2002). Thus, under the conditions of the present experiment, there was no evidence of interictal hypersensitivity in blink reflex pathways in migraine sufferers.

3.4.1 Limitations

The sample number in this study was relatively low, increasing the risk of Type 2 errors. Additionally, although the migraine participants met the required criteria for a migraine headache, they were from a convenience community sample, with the healthy controls recruited from within the university. Thus, the findings might not generalize to other samples (e.g., migraine sufferers who attend neurology or pain clinics).

Another limitation of the current study was that nausea was the only gastrointestinal rating recorded. Perhaps the gastrointestinal discomfort could have been painful or experienced as burning as chemical irritation in the viscera is known to activate nociceptive reactions.
The gastrointestinal sensation after the ingestion of the hypertonic saline could have differed from the nausea generated by a rotating optokinetic drum, the nausea felt during a migraine attack and possibly other forms of nausea (e.g., during the first trimester of pregnancy). Further research into peripherally induced nausea is needed to test other nausea inducing compounds that stimulate the stomach receptors, do not activate the area postrema and evoke nausea that is similar to the nausea sensation experienced during migraine, motion sickness and pregnancy. The migraine and apomorphine study (Cerbo, et al., 1997) could be considered as an investigation of a centrally induced nausea because apomorphine crossed the blood brain barrier and activated the area postrema because of its subcutaneous delivery. The area postrema would not have been activated in the current study due to the short time interval after hypertonic solution ingestion.

Future research should also include a control condition, in which a placebo oral solution is administered to control for non-specific effects of the procedure.

3.4.2 Conclusion

Ingestion of the hypertonic solution may have a sensitising influence on headache and other types of trigeminal pain processing such as scalp tenderness and high intensity electrical stimuli. Ingestion of a hypertonic solution but not nausea had a physiological effect in the trigeminal system by facilitating nociceptive trigemino-facial pathways.

In the current study, the scalp tenderness test and the high intensity standard electrode stimulus evoked a greater pain rating after the ingestion of the hypertonic solution. Both the scalp tenderness test and the high intensity standard electrode stimulus activate trigeminal nociceptors, the major difference being temporal summation (scalp tenderness test is longer than the brief electrical stimulus). After chemoreceptor excitation in the mucosal wall of the stomach, pain ratings to both of these stimuli increased, suggesting sensitisation. Our findings suggest that only stimuli that recruited larger numbers of afferent fibres were affected by heterotopic unpleasant
stimuli because pain ratings to the concentric electrode stimuli (brief, weak stimulation) and the low intensity standard electrode stimuli (mainly Aβ stimulation) were not affected by vagal nerve stimulation or nausea. Physiologically, the latency of the nociceptive blink reflex and the low intensity blink reflex was shorter after ingestion of the hypertonic solution in all participants, suggesting a physiological sensitisation in the blink reflex pathway.

There was some weak evidence to suggest an interaction between nausea and headache in humans but the results of this research lead me to speculate that higher cortical influences play a role in the impact of nausea on headache in migraine attacks. At the physiological level in the brainstem, migraineurs and healthy volunteers did not differ in their responses to the electrocutaneous trigeminal stimuli. Activation of the NTS via the vagus nerve had some facilitatory effect on the Aδ blink reflex and a marginal inhibitory effect was also seen in the high intensity electrode response but this could also have been due to habituation or fatigue. Nausea did not influence the blink reflex but increased scalp tenderness and other symptoms of migraine. The facilitation of the Aδ blink reflex response fits with the human model of migraine, and the effect of nausea on pain ratings concur with previous research but it is my understanding from the results of the current research that the effect of nausea on these subjective ratings is a process that occurs in the higher cortical regions superior to the brainstem.
Chapter 4  General Method

The next four chapters were written about a series of studies conducted on migraine sufferers between and during migraine and compared with a group of healthy controls. The aim was to determine whether migraine sufferers are subjectively and physiologically hypersensitive to both environmental (exogenous) and internal (endogenous) factors. This hypersensitivity was investigated both through subjective ratings and physiologically with blink reflex parameters in response to trigeminal stimulation and to various environmental stimuli by using the nociceptive blink reflex to examine the effects of various conditioning stimuli.

In the first study, scalp tenderness to pressure-pain stimuli was investigated in healthy controls and migraine sufferers between and during migraine. The aim of the second study was to determine whether signs of trigeminal sensitization could be detected in nociceptive pathways subserving the nociceptive blink reflex interictally and during attacks of migraine. The classic symptoms of migraine such as headache, nausea, dizziness, drowsiness, sensitivity to bright light, sound sensitivity, perceived body temperature and feelings of unpleasantness in healthy controls, interictal migraine sufferers and ictal migraine sufferers after trigeminal nociceptive stimulation were also investigated.

The effects of local and remote pain on the nociceptive blink reflex were investigated in the third study. The nociceptive blink reflex was also used in the fourth study to determine the effects of complete darkness, bright light and intense sound in healthy controls, between migraine and during migraine. Each of these studies will be addressed in more detail following the General Method section.
4.1 Method

4.1.1 Participants

The control sample consisted of 15 females and five males (mean age ± SD, 31.8 ± 9.15) who reported less than 12 headaches per year that did not meet the criteria for migraine. The migraine sample consisted of 21 females and 1 male (mean age ± SD, 34.32 ± 11.69) who met the International Headache Society (2004) criteria for migraine without aura (14 participants) or with aura (seven participants). Migraine participants were free from migraine headache for at least four days during the headache free session and none of the participants had a history of any serious medical illness. For the migraine testing session, participants (n=10) informed the researcher as soon as they knew that a migraine was developing. On average, during migraine, participants were 5.5 hours into their migraine attack. Participants were alcohol-, drug- and medication-free for at least 24 hours and were asked to fast for three hours prior to the test session. Volunteers were awarded course credit and a small remuneration for participation. They gave written informed consent for the procedures which were approved by the Murdoch University Human Research Ethics Committee.

4.1.2 Design

Test sessions for the control participants and most of the migraine sufferers between attacks were conducted in the laboratory. Participants who suffered from migraine were instructed to call the researcher as soon as they knew that an attack was developing. This then required the mobilisation of lab equipment; researcher and research assistant to the participants’ homes. In a few instances, the test session during migraine occurred in the university laboratory. The participants who were tested during migraine were also tested between migraine and in some instances test sessions between migraine attacks were also conducted at participants’ homes.
4.1.3 Dependent Variables

4.1.3.1 Nociceptive Blink Reflex

The blink reflex was elicited by electrical stimuli to the supra-orbital nerve delivered via a concentric electrode. The concentric electrode consisted of a 0.5mm copper wire cathode with a stainless steel round anode with an external diameter of 20mm and internal diameter of 10mm. The concentric electrode is a replication of the concentric electrodes described by Kaube et al (2000) which stimulate superficial Aδ-fibres due to a high current density and small anode-cathode distance. The concentric electrode was attached (with an adhesive washer) to the skin of the forehead prepared with an abrasive skin preparation pad (Professional Disposables, Inc. NY, USA). The outer ring (anode) of the electrode was smeared with electrode gel to aid in electrical conductivity. The electrode was placed so that the cathode (inner point) was placed above the supra-orbital foramen. The concentric electrode stimuli had an intensity of 2mA (± 0.2).

Electrical stimuli were monopolar square wave pulses with a duration of 0.3 ms. Six stimuli were delivered in each set at an inter-stimulus interval of at least 10 seconds to minimise habituation of the blink reflex.

Participants sat with their eyes open during the study. The blink reflex was measured bilaterally from electrodes placed over the mid orbicularis oculi muscle below the eyelids. The skin was wiped with an alcohol wipe (Kendall, MA, USA) prior to attaching trimmed neonate ECG (ConMed, N.Y., USA) electrodes to the lower mid orbicularis oculi and lower lateral orbicularis oculi. A disposable ground electrode was placed on the left wrist to minimise electrical interference.

EMG data were acquired via an EMG digital pre-amplifier (EMG100C, BIOPAC Systems, Inc. California, U.S.A.) before being transmitted to a personal computer via a 16-bit MP100 BIOPAC
Systems Analogue/Digital Channel Receptor (BIOPAC Systems, Inc. California, U.S.A.) using AcqKnowledge software (Version 3.7.1, BIOPAC Systems, Inc. California, U.S.A.). Samples were collected at a rate of 1KHz for later off-line analysis. Some signals were band-stop filtered to remove electrical interference (49-51 Hz; 99-101 Hz). All signals were high pass filtered with a cut-off frequency of 20 Hz to reduce interference from movement of the eyeball, and rectified prior to analysis. The latency and area under the curve (AUC) for the R2 component of the blink reflex was assessed in the time window of 27 to 87 ms after the onset of the stimulus (Ellrich & Treede, 1998).

4.1.3.2 Ratings

The participant was required to rate every stimulus on an 11 point pain rating scale (0 – painless sensation to 10 – intolerable pain). All pain ratings were later modified to fit a 10 point pain rating scale (0 – no sensation or a painless sensation; 1 – pain awareness; 9 – intolerable pain). After each exposure to the various conditions the participant rated headache, nausea, dizziness, drowsiness, body temperature, sound sensitivity, light sensitivity and unpleasantness on an 11 point scale (0 – none, 1 – awareness; 2 – mild; 10 – extreme). These ratings were also collected before and after the testing session.

4.1.4 Procedures

The sequence of procedures are summarized in

4.1.4.1 Mechanical Hyperalgesia

Prior to the presentation of any electrical stimuli, approximately 50 grams, 100 grams and 150 grams of pressure was applied from an algometer (2 mm diameter hemispheric metal tip) to the tips of the first, middle and ring fingers respectively on both hands (finger tenderness test) and to
both sides of the forehead (scalp tenderness test). The participant rated how painful each pressure
was at each site on the 11-point pain rating scale.

4.1.4.2 Electrical Stimulation

A threshold set of stimuli (1-5mA, repeated on both sides) was first delivered to reduce the
stimulus novelty and to help the participant feel comfortable rating the pain of the stimuli.

The stimulated side was determined randomly in the control sample – with half of the control
sample being stimulated on the left side of the forehead. For the migraine sample, the usual side of
headache was stimulated except during the first of six sets of electrical stimuli (contralateral to
headache side stimulation, baseline, during cold-evoked pain to the temple, during remote cold-
evoked pain, during bright light, during complete darkness). There was no difference between
frequencies of side of stimulation by group (control; between migraine) as analysed by chi square
($\chi^2(1, N = 42) = .336, p > .05$).

4.1.4.3 Conditioning Stimuli

The participant put their ipsilateral (same side as headache/stimulated side) index finger in a
vessel of ice-water for 90 seconds or held an ice cube (20mm x 30mm) on the ipsilateral temple
$posterior to the external angular process, external to the sphenoid area$ for 60 seconds. The order
of these conditions was randomised. Participants rested between each condition until stimulus-
evoked sensations disappeared. At the end of the condition, participants rated the cold-induced
pain and then rated other symptoms (headache, nausea, dizziness, drowsiness, body temperature,
sound sensitivity, light sensitivity and unpleasantness). In the ice on temple condition, electrical
stimuli were administered 10 seconds after the application of the ice. In the finger in ice water
condition, the electrical stimuli were administered after 30 seconds. As well as rating each
stimulus, participants rated the pain at the temple or finger then the other symptoms.
4.1.4.4 *Effect of Darkness*

To test the participant in complete darkness, a hood was constructed to fully encase the participant’s head with plenty of room to allow for electrodes and cables. Participants were instructed to keep their eyes open and the regular set of stimuli was administered. Participants rated each electrical stimulus and with the hood on, rated any discomfort in darkness as well as the other symptoms.

4.1.4.5 *Photophobia Thresholds*

To determine thresholds of light-induced pain and glare, participants stared at an illuminated screen that emitted light at various intensities (100, 200, 300, 400, 500, 600 lux). The screen was 30cm x 30cm and opaque light was equally diffused across the screen. The screen was positioned approximately 70cm from the face. Light intensity was measured with a lux meter held at the participant’s face level. Participants were required to sit for 30 seconds with their eyes closed, before opening their eyes and staring at the centre of the illuminated screen for 10 seconds, at which point they closed their eyes. They were then required to rate light-induced pain and glare, and then rate the other symptoms of migraine.

4.1.4.6 *Trigeminal Stimulation and Bright Light*

Once light-evoked sensations had disappeared, participants stared at the screen illuminated at 500 lux, and a set of six electrical stimuli was administered starting 10 seconds later. Participants rated each stimulus and after closing their eyes after the light exposure, rated light-induced pain and glare as well as the other symptoms.
4.1.4.7 Phonophobia Thresholds

Phonophobia thresholds were determined by delivering four different decibel intensities (70, 80, 90, 100) of a 20 millisecond white noise burst with a minimal rise time in a random order. Each stimulus was repeated three times. Participants rated the pain, loudness and discomfort of each noise burst before the next stimulus was presented. At the end of the presentation, participants were required to rate the full set of symptoms.

4.1.4.8 Conclusion

A final set of six stimuli was administered with each stimulus being rated as well as the other symptoms. In addition, mechanical hyperalgesia was reassessed in the forehead and finger.

Figure 4-1: Sequence of procedures for final studies. Migraine sufferers completed two sessions – one during a migraine (n=10) and one between migraine (n=21). A control group also completed a session (n=20).
4.1.5 Data Reduction

4.1.5.1 Nociceptive Blink Reflex

Blink Reflexes were analysed in terms of area under the curve and latencies. For area under the curve data, the baseline value (a 60ms period of data within the condition but without a stimulus) was subtracted from the absolute area under the curve values to control for artifact present during that condition. Any values that were negative (implying that there was no response (area under the curve was less than baseline) were replaced with a zero for the blink magnitude analyses. For the values used in the blink count and mean area under the curve analyses, any value under .0002 V X sec (representing electrical noise artefact) was replaced with a missing value. The nociceptive blink reflex was analysed with three dependent variables – blink reflex count (out of six); area under the curve of actual responses and latency of those responses.

To simplify analyses, only the blink reflexes ipsilateral to stimulation (the headache side in the migraine sufferers) were used in these analyses. In preliminary analyses the contralateral blink reflexes did not add any new information or insight into hypothesis testing. In general, the contralateral blink reflexes were fewer, weaker and slower than the ipsilateral blink reflexes.
Chapter 5  Mechanical Hyperalgesia and Migraine

5.1 Introduction

Signs of trigeminal nociceptive sensitisation have been detected both in animal models of migraine and during attacks of migraine. Both peripheral and central sensitisation may develop during migraine (Burstein, 2001). As previously stated, cutaneous allodynia is present in most migraine patients (Burstein, Yarnitsky, et al., 2000) and the development of scalp tenderness during a migraine is associated with central sensitisation (Malick & Burstein, 2000).

Scalp tenderness is often reported during a migraine attack. Whether this symptom of migraine is specific to the trigeminal nervous system or is part of the well documented generalized allodynia (central) that occurs during migraine (Burstein, Yarnitsky, et al., 2000) is unknown.

Muscle tenderness as measured by palpation of the scalp during headache is well-recognised (Lous & Olesen, 1982; Olesen, 1978; Tfelt-Hansen, Lous, & Olesen, 1981). However, the use of an algometer (Wolff, Tunis, & Goodell, 1953) standardises the pressure of palpation and more reliably measures scalp tenderness in headache patients (Drummond, 1987, 2002).

Additionally, scalp tenderness has also been investigated between migraine attacks after brain stem disturbances such as motion sickness induced by optokinetic stimulation (Drummond, 2002). Scalp tenderness increased after optokinetic stimulation only in nauseated participants whereas fingertip tenderness was unrelated to nausea but increased in migraine sufferers but not controls after optokinetic stimulation. Drummond suggested that pain hypersensitivity may develop at distal sites after brainstem disturbances in migraine sufferers. This hypersensitivity could be due to a disruption of descending pain modulation pathways (Drummond, 2002).

In research presented previously in this thesis, scalp tenderness and fingertip tenderness both increased after the ingestion of the hypertonic saline solution, suggesting that chemoreceptor
excitation of the stomach mucosa increases pain sensitivity both for brainstem input (because trigeminal pain pathways enter the brain stem at the medullary level) and at distal sites. This distribution suggests that the heightened sensitivity to pain is centrally driven. Nausea, on the other hand, only influenced scalp tenderness and fingertip tenderness at the highest stimulus intensity, with scalp tenderness increasing more for those participants in the nausea group after the ingestion of the hypertonic saline. There were no differences between controls and migraine sufferers in scalp tenderness.

5.1.1 Study Aims

Scalp tenderness, as measured by mechanical hyperalgesia, was investigated in healthy control participants and migraine sufferers between and during migraine in this study. Fingertip tenderness was used as a comparison to explore the mechanism of the tenderness. If the effect was limited to the scalp then the scalp tenderness should be attributed to the sensitisation of the trigeminal system (which could be peripheral or central), whereas if the fingertips were also tender then the sensitisation could be mediated by a more general sensitisation of nociceptive pathways or failure of inhibitory pain control. In essence, we wanted to find out whether scalp or finger tenderness increased over the course of the session in migraine sufferers as this would indicate that peripheral and/or central sensitization developed readily; if so, this might increase vulnerability to migraine. Based on previous research and previously presented findings in this thesis, it was hypothesized that scalp tenderness would be similar in controls and migraine sufferers between attacks and that scalp tenderness would increase during a migraine attack.
5.2 Method

5.2.1 Participants

Please see Section 4.1.1.

5.2.2 Procedure

Prior to other procedures (presented in the General Method in Chapter 4), approximately 50 grams, 100 grams and 150 grams of pressure was applied from an algometer to the tips of the first, middle and ring fingers respectively on both hands (finger tenderness test) and to both sides of the forehead (scalp tenderness test). The participant rated how painful each application was at each site on the 11-point pain rating scale. Mechanical hyperalgesia was reassessed in the forehead and finger at the end of the session.

5.2.3 Data Reduction and Analysis

To simplify analyses, only the side of stimulation ipsilateral to the site of headache was analysed in migraine sufferers and was compared with the side of nociceptive stimulation in controls. Pain rating data were analysed in a time (pre and post session) x location (forehead and finger) x level (50gm; 100gm; 150gm) x groups (healthy controls and migraine sufferers between migraine) mixed design ANOVA. The effect of migraine was also investigated in the 10 migraine sufferers who were tested during a migraine with a time x location x level x migraine repeated measures ANOVA. A Huynh-Feldt epsilon correction was used when the assumption of sphericity was violated. An alpha level of .05 was used an indication of significance. Only significant main effects and significant interactions were reported in the results.
5.3 Results

5.3.1 Algometer Pain Ratings between Migraine

Pain ratings increased in response to increasing pressure at the forehead and fingers (main effect of intensity $F(1.47, 58.68) = 80.28, p<.001, \eta_p^2 = .67$; linear contrast $F(1,40)=94.74,p<.001, \eta_p^2 = .7$) (Table 5-1; Figure 5-1; Figure 5-2). The pressure applied to the forehead was rated as more painful ($M=1.5; \text{SEM}=0.156$) than the pressure applied to the fingers ($M=0.65; \text{SEM}=0.095$) ($F(1,40)=46.51,p<.001, \eta_p^2 = .54$) and this difference increased at all intensities (location x level interaction $F(1.86, 74.44) = 14.89, p<.001, \eta_p^2 = .27$). There were no overall group differences in pain ratings ($F(1,40)=.027, \text{N.S.}$). Ratings increased across the session when pressure was applied to the forehead in migraine sufferers but decreased in the healthy controls, whilst ratings increased for both groups in response to pressure applied to the fingers (time x location x group interaction $F(1,40)=5.26, p<.05, \eta_p^2 = .12$) (Figure 5-3).

Table 5-1: F Ratios (degrees of freedom) for 2 X 2 X 2 X 3 ANOVA for all stimuli between groups.

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>F Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>0.03 (1,40)</td>
</tr>
<tr>
<td>Time</td>
<td>1.04 (1,40)</td>
</tr>
<tr>
<td>Location</td>
<td>46.51 (1,40)*</td>
</tr>
<tr>
<td>Intensity</td>
<td>80.28 (1.47,58.68)*</td>
</tr>
<tr>
<td>Time x Group</td>
<td>.38 (1,40)</td>
</tr>
<tr>
<td>Location x Group</td>
<td>3.17 (1,40)</td>
</tr>
<tr>
<td>Intensity x Group</td>
<td>.7 (1.47,58.68)</td>
</tr>
<tr>
<td>Time x Location</td>
<td>.94 (1,40)</td>
</tr>
<tr>
<td>Time x Intensity</td>
<td>3.05 (1.29,51.62)</td>
</tr>
<tr>
<td>Location x Intensity</td>
<td>14.89 (1.86,74.44)*</td>
</tr>
<tr>
<td>Time x Location x Group</td>
<td>5.26 (1,40)*</td>
</tr>
<tr>
<td>Time x Intensity x Group</td>
<td>.04 (1.29,51.62)</td>
</tr>
<tr>
<td>Location x Intensity x Group</td>
<td>1.03 (1.86,74.44)</td>
</tr>
<tr>
<td>Time x Location x Intensity</td>
<td>.9 (1.68,67.06)</td>
</tr>
<tr>
<td>Time x Location x Intensity x Group</td>
<td>.06 (1.68,67.06)</td>
</tr>
</tbody>
</table>

* Denotes significance at .05 alpha level
Figure 5-1: Pain ratings to pressure applied to the forehead. Error bars represent SEM. Ratings were significantly more painful during migraine.

Figure 5-2: Pain ratings to pressure applied to the fingers. Error bars represent SEM.
Figure 5-3: Pain ratings in response to algometer pressure averaged across all intensities for each group. a. forehead site. b. finger. Error bars represent SEM.
5.3.2 Algometer Pain Ratings during Migraine

Pain ratings increased as pressure applied to the forehead and fingers increased (main effect of intensity $F(1.24, 11.14) = 23.41, p<.001, \eta^2_p = .72$; linear contrast $F(1,9)=25.2, p=.001, \eta^2_p = .74$) (Figure 5-1; Figure 5-2). The pressure applied to the forehead was rated as more painful ($M=2.04; \text{SEM}=0.36$) than the pressure applied to the fingers ($M=0.68; \text{SEM}=0.25$) ($F(1,9)=14.73, p<.05, \eta^2_p = .62$) and again this difference increased at all intensities (location x level interaction $F(2, 18) = 9.43, p<.05, \eta^2_p = .51$). The pressure was more painful during migraine ($F(1,9) = 8.13, p<.05, \eta^2_p = .47$) but this effect was moderated by time, intensity and location of pressure (4 way interaction $F(2, 18) = 3.9, p<.05, \eta^2_p = .3$) (Figure 5-4). Ratings increased across the session when the higher intensity pressure was applied to the forehead during migraine ($t(9)=2.42, p<.05$) compared with ratings between attacks ($t(9)=.08, \text{N.S.}$) and when the same intensity pressure was applied to the finger between migraine ($t(9)=.26, \text{N.S.}$) and during migraine ($t(9)=.64, \text{N.S.}$).

Table 5-2: F Ratios (degrees of freedom) for 2 X 2 X 2 X 3 ANOVA for all stimuli within groups.

<table>
<thead>
<tr>
<th>Migraine</th>
<th>8.13 (1,9)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>.53 (1,9)</td>
</tr>
<tr>
<td>Location</td>
<td>14.73 (1,9)*</td>
</tr>
<tr>
<td>Intensity</td>
<td>23.41 (1.24,11.14)*</td>
</tr>
<tr>
<td>Time x Migraine</td>
<td>.86 (1,9)</td>
</tr>
<tr>
<td>Location x Migraine</td>
<td>2.65 (1,9)</td>
</tr>
<tr>
<td>Intensity x Migraine</td>
<td>3.99 (2,18)*</td>
</tr>
<tr>
<td>Time x Location</td>
<td>1.25 (1,9)</td>
</tr>
<tr>
<td>Time x Intensity</td>
<td>3.74 (2,18)*</td>
</tr>
<tr>
<td>Location x Intensity</td>
<td>9.43 (2,18)*</td>
</tr>
<tr>
<td>Time x Location x Migraine</td>
<td>.8 (1,9)</td>
</tr>
<tr>
<td>Time x Intensity x Migraine</td>
<td>11.46 (2,18)*</td>
</tr>
<tr>
<td>Location x Intensity x Migraine</td>
<td>1.37 (1.41,12.68)</td>
</tr>
<tr>
<td>Time x Location x Intensity</td>
<td>.92 (1.38,12.44)</td>
</tr>
<tr>
<td>Time x Location x Intensity x Migraine</td>
<td>3.9 (2,18)*</td>
</tr>
</tbody>
</table>

* Denotes significance at .05 alpha level
Figure 5-4: Pain ratings at each intensity for those participants tested during a migraine. * indicates a significant increase in pain rating during a migraine across the session when 150 grams of pressure was applied to the forehead. 

a. 50 grams; b. 100 grams; c. 150 grams. Error bars represent SEM.
5.4 Discussion

5.4.1 Summary

Pain ratings increased across the session when pressure was applied to the forehead in migraine sufferers between migraine attacks but decreased in the healthy controls. In contrast, ratings increased for both groups in response to pressure applied to the fingers. All pressures were rated as more painful during migraine, and ratings increased across the session when the higher intensity pressures were applied to the forehead during migraine.

5.4.2 Previous Research

5.4.2.1 Healthy Controls and Migraine Sufferers Between Migraine

The lack of a significant difference between healthy controls and migraine sufferers between attacks in response to scalp tenderness provocation supports previous research (Drummond, 2002) and the previous study in this thesis. A surprising finding in this study was the increase in pain ratings in migraine sufferers between migraines across the session when pressure was applied to the forehead. This new finding could be explained by the increased excitation of the trigeminal system after nociceptive electrical activation by the concentric electrode and/or repeated testing with the algometer or painful cooling of scalp tissue. As this is the first reported study that looked at scalp tenderness after trigeminal nociceptive activation, it could be an interesting and important finding.

5.4.2.2 During Migraine

The increase in scalp tenderness during migraine is consistent with other research in this domain (Burstein, Cutrer, et al., 2000; Burstein, Yarnitsky, et al., 2000; Drummond, 1987; Wolff, et al., 1953). Even though the previous research used thresholds as dependent variables, this effect was detected in the present study to a fixed range of stimuli. As with the between groups analyses,
scalp tenderness increased during migraine after trigeminal nociceptive stimulation. Again, as this is the first reported study to investigate scalp tenderness after trigeminal nociceptive activation during migraine, it could be an important finding.

5.4.3  **Theoretical Implications**

Migraineurs had greater scalp tenderness after trigeminal irritation during and between migraine attacks. This finding implies that sensitization develops more rapidly than usual in migraine sufferers. This finding supports Burstein’s model of sensitization during migraine (Burstein, et al., 1998; Malick & Burstein, 2000; Strassman, et al., 1996; Yamamura, et al., 1999). During migraine, peripheral first-order neurons that surround the intracranial blood vessels are activated by inflammatory mediators. This barrage of signals then converges onto the second-order medullary dorsal horn neurons, resulting in spontaneous activity in the medullary dorsal horn that is also the converging point of the facial and scalp skin leading to hypersensitivity in these regions. Sensitization could also have been initiated by stimulation of the Aδ fibres that were activated by the concentric electrode stimuli and other noxious stimuli in the present study. Vulnerability to sensitization in migraine sufferers could be related to interictal changes that have been observed in the trigeminal somatosensory and modulatory pain systems (DaSilva, et al., 2007). There was no consistent evidence in this study of increased heterosegmental sensitisation because fingertip tenderness was similar in migraine sufferers and controls throughout the study. Sensitisation of third-order neurons projecting to the thalamus (Borsook, et al., 2004) would be required for disinhibition of descending pain pathways which would produce greater tenderness at the fingertips. Perhaps sensitization did not progress to the third (thalamic) or fourth order (somatosensory cortex) neurons in migraine sufferers in the present study because of the limited period of trigeminal stimulation.

In summary, this study supports the theory of trigeminal sensitization during migraine, and of “latent hyperexcitability” of the trigeminal nociceptive system between attacks of migraine. It
also supports the possibility that pain pathways are likely to be activated in a cascade of sensitization involving the trigeminal system.

5.4.4 Limitations

Both Drummond (1987) and Burstein et al. (2000) assessed pain sensitivity by way of thresholds. The method used in this thesis was different to the methods used previously because participants were required to rate pain evoked by fixed pressures. There is a possibility that this method does not include individual ranges of pain thresholds. But this limitation did not mask increases in scalp tenderness during migraine. As scalp tenderness is a subjective measure and can be affected by higher cortical influences such as affective and cognitive control, further research with objective measures should be carried out to re-examine these hypotheses and theoretical implications.

5.4.5 Future Studies

Further investigation into trigeminal hypersensitivity measured objectively could also add to this research. The nociceptive blink reflex has been used to investigate sensitization of the trigeminal system (Katsarava, Egelhof, et al., 2003; Katsarava, et al., 2002; Kaube, et al., 2000; Kaube, et al., 2002). The next presented study in this thesis addressed this issue. If a barrage of signals within the peripheral trigeminal system triggers sensitisation, then we may see this same increase in sensitivity (indicated by nociceptive blink reflex facilitation) across the session.

5.4.6 Conclusion

The development of scalp tenderness in migraine participants could be interpreted as a subjective response. However, as fingertip tenderness did not increase, supra-spinal influences apparently were not involved. Additionally, if a purely subjective response was responsible for the increase in scalp tenderness, this should also have been reflected in pain ratings to the electrical stimuli.
Pain ratings increased across the session when pressure was applied to the forehead in migraine sufferers between migraine attacks but decreased slightly in the healthy controls, whilst ratings increased for both groups in response to pressure applied to the fingers. All pressures were rated as more painful during migraine, and ratings increased across the session when the higher intensity pressures were applied to the forehead. These new findings could be due to repetitive excitation of the trigeminal system after nociceptive activation, which supports the theory of trigeminal sensitization during migraine.
Chapter 6  Trigeminal Pain, Nociceptive Blink Reflex and Migraine

6.1 Introduction

The first study in this thesis investigated the effectiveness of a concentric electrode for evoking blink reflexes and if there was a difference between controls and migraine sufferers. That study investigated whether there was a dysfunction within the trigeminal system in migraine sufferers interictally and whether the concentric electrode could be used to examine the trigeminal nociceptive system. The findings in the control group supported the hypothesis that the concentric electrode depolarised the Aδ free nerve endings as demonstrated by a significant reduction in blink reflex frequency and area under the curve after the application of a local anaesthetic; in contrast, there was no change in blink reflex parameters in the control condition that did not involve application of local anaesthetic agent. Whilst the area under the curve was inhibited by local anaesthetic agent in the migraine group, blink reflex frequency remained unchanged, consistent with interictal trigeminal hypersensitivity.

In the second presented study in this thesis, the latency of the blink reflex to the concentric electrode stimulus was shorter after the ingestion of the hypertonic solution than the response evoked during the baseline condition in all participants. This finding suggested that the nociceptive blink reflex was facilitated after ingesting a hypertonic solution.

In the study presented in Chapter 5, scalp tenderness increased during migraine and ratings increased across the session when the higher intensity pressures were applied to the forehead during migraine. This could be explained by the increased excitation of the trigeminal system after nociceptive electrical activation by the concentric electrode, thus supporting the theory of trigeminal sensitization during migraine. It also supports the possibility that the migrainous brain is more likely to be activated in a cascade of progressing sensitization of the trigeminal system.
6.1.1 Study Aims

The aim of this study was to determine whether signs of trigeminal sensitization could be detected in pathways subserving the nociceptive blink reflex interictally and during attacks of migraine. It was hypothesized that sensitization would develop in migraine sufferers between attacks at the end of the session due to excitation of the trigeminal system during the session. It was also hypothesized, based on previously presented literature (Kaube, et al., 2000; Kaube, et al., 2002), that the nociceptive blink reflex would be facilitated during an attack of migraine on the side affected by headache, and that this facilitation would be greater at the end of the testing session.

The classic symptoms of migraine such as headache, nausea, dizziness, drowsiness, bright light sensitivity, sound sensitivity, perceived body temperature and feelings of unpleasantness were also investigated in the current study to determine whether symptoms intensified after trigeminal nociceptive stimulation. It was hypothesised that symptoms would intensify in migraine sufferers during a migraine and that the intensity would be greater at the end of the test session in migraine sufferers both during and between attacks.
6.2 Method

6.2.1 Participants

Please see Section 4.1.1.

6.2.2 Procedure

6.2.2.1 Blink Reflex

Please see Section 4.1.3.1.

6.2.2.2 Electrical Stimulation

The first set of six electrical stimuli was administered contralaterally as a comparator and thereafter ipsilaterally. A final set of six stimuli was then administered ipsilaterally. The participant was required to rate every stimulus on the pain rating scale. Participants rated symptoms of migraine after each set of electrical stimuli.

6.2.3 Data Reduction and Analysis

6.2.3.1 Symptoms of Migraine

All symptoms were analysed in separate Condition (start [before any stimulation]; baseline [after initial set of stimuli]; final [after final nociceptive stimulation]) X Group (healthy controls; migraine sufferers between migraine) mixed design ANOVAs. The effect of migraine on the symptoms was investigated in similar analyses.

6.2.3.2 Pain Ratings to the Electrical Stimuli

Pain ratings were averaged across trials in each condition. Means were analysed in an ipsilateral/contralateral x controls/between migraine mixed design ANOVA, and baseline versus
final condition x group mixed design ANOVA for measures that were repeated on the same side. The effect of migraine on pain ratings was investigated in similar analyses.

6.2.3.3 The Nociceptive Blink Reflex

6.2.3.3.1 Stimulation to the non-headache side

The baseline was the only condition where the non-headache side in migraine sufferers and the non-experimental side in the control group was stimulated by the 2 mA stimuli. The contralateral side to these stimuli is actually the headache side. From this perspective, it is important to investigate what happened to the blink reflexes on the headache side. This is the only analysis that investigated blink reflexes contralateral to the stimuli. The three dependent variables of the nociceptive blink reflex (count; area under the curve; latency) were analysed in a stimulated side (headache side/non headache side) x measurement side (ipsilateral/contralateral to the stimuli) x group (healthy controls/migraine sufferers between migraine) mixed design ANOVA; and a stimulated side (headache side/non headache side) x measurement side (ipsilateral/contralateral to the stimuli) x migraine (between migraine/during migraine) repeated measures ANOVA on the data from the 10 migraine participants tested during migraine.

6.2.3.3.2 Stimulation to the headache side at baseline and end of session

To simplify analyses, only blink reflexes from the side ipsilateral to stimulation (the headache side) were used. The three dependent variables of the nociceptive blink reflex were analysed in a time (baseline/final stimuli) x group (healthy controls/migraine sufferers between migraine) mixed design ANOVA and a time (baseline/final stimuli) x migraine (between migraine/during migraine) repeated measures ANOVA on the data from the 10 migraine participants tested during migraine.
6.3 Results

Unreported main effects and interactions were not significant.

6.3.1 Symptoms of Migraine (Table 6-1)(Figure 6-1)

Most symptoms of migraine except body temperature and drowsiness increased after noxious trigeminal stimulation for both healthy controls and migraine sufferers in the headache-free interval. Similarly, all symptoms of migraine increased during a migraine headache, except for perceived body temperature.

6.3.2 Pain Ratings to Electrical Stimuli (Figure 6-2)(Table 6-2)

There were no overall group differences in pain ratings to the electrical stimuli at any location (ipsilateral versus contralateral to headache side F(1,40)=.98, N.S.) or point in time (baseline versus final stimuli F(1,39)=.65, N.S.). Pain ratings did not increase across the session for the migraine sufferers between migraine (time x group interaction F(1,39)=1.95, p=.17, $\eta^2_{p}=.048$). The stimuli were rated as more painful during a migraine but this effect was more evident when the stimuli were applied to the headache side (presence versus absence of headache for ratings averaged across ipsilateral and contralateral stimuli F(1,9)=1.95, p=.082, $\eta^2_{p}=.299$; presence versus absence of headache for ratings averaged across initial and final stimuli presented ipsilaterally F(1,9)=6.47, p<.05, $\eta^2_{p}=.42$). Pain ratings to the electrical stimuli did not change across the session during a migraine (time x migraine interaction F(1,9)=.04, N.S.).

6.3.3 Nociceptive Blink Reflex

6.3.3.1 Stimulation on the non-headache side (Table 6-3)

None of the blink reflex parameters differed significantly between the healthy controls and the migraine sufferers between attacks (Blink Reflex count F(1,40)=.64, N.S., Figure 6-3; area under the curve F(1,34)=.05, N.S., Figure 6-4; latency F(1,29)=.01, N.S., Figure 6-5). The blink
reflex count increased during attacks (headache free period M= 5, SEM= .59; during migraine M= 5.35, SEM= .59; F(1,9)=3.5, p=.094, η_p^2 =.28) with less blinks evoked on the contralateral side between attacks (t(9)=2.12, p=.063) (migraine x side of blink reflex F(1,9)=5.62, p<.05, η_p^2 =.38) (Figure 6-6). More blinks were evoked during a migraine compared to the control group for all stimulation sites and measurement sites (Exploratory t-tests – control vs. during migraine Ipsilateral to Headache Stimulation (Headache Side Response) t(21.05)=2.79, p<.05; Ipsilateral to Headache Stimulation (Non-Headache Side Response) t(19)=3.49, p<.05; Contralateral to Headache Stimulation (Headache Side Response) t(20.69)=3.38, p<.05; Contralateral to Headache Stimulation (Non-Headache Side Response) t(19)=2.83, p<.05). There was no effect of migraine on the area under the curve data (headache free period M= 0.00119 V·Sec, SEM=.000152; during migraine M= 0.00192 V·Sec, SEM=.000504; F(1,8)=1.84, N.S., η_p^2 =.19), or the latency data (headache free period M= 44 ms, SEM= 2; during migraine M= 44 ms, SEM= 2; F(1,6)=.01, N.S.). There was no facilitation when the headache side was stimulated during migraine as indicated by no interactions between migraine and side stimulated for any blink reflex parameter (Blink Reflex count F(1,9)=2.04, N.S., η_p^2 =.18; area under the curve F(1,8)=2.68, N.S., η_p^2 =.25.; latency F(1,6)=1.04, N.S., η_p^2 =.15).

6.3.3.2 Stimulation on the headache side at baseline compared with end of session (Table 6-4)

Sensitization was not detected to stimuli presented at the end of the session for any blink reflex parameter during migraine (migraine x time interaction – blink reflex count F(1,9)=.38, N.S.; area under the curve F(1,8)=1.37, N.S.; latency F(1,5)=2.38, N.S., η_p^2 =.32) or in migraine sufferers between attacks (time x group interaction – Blink Reflex count F(1,39)=.11, N.S.; area under the curve F(1,34)=.99, N.S.; latency F(1,24)=.001, N.S.). Instead, when averaged across groups, all blink reflex parameters decreased significantly to the final set of stimuli (main effect of time – Blink Reflex count F(1,39)=10.53, p<.05, η_p^2 =.21, Figure 6-7; area under the curve F(1,34)=17.59, p<.001, η_p^2 =.34, Figure 6-8; latency F(1,24)=6.61, p<.05, η_p^2 =.22, Figure 6-9).
a. Headache Rating (0-10)
   - Healthy Controls (n=20)
   - Between migraine (n=21)
   - During migraine (n=10)

b. Nausea Rating (0-10)

c. Dizziness Rating (0-10)

d. Drowsiness Rating (0-10)
Figure 6-1: Symptoms of Migraine after trigeminal stimulation. a. = headache; b.=nausea; c.=dizziness; d.=drowsiness; e.=perceived body temperature; f.=sound sensitivity; g.=light sensitivity; h.=unpleasantness. Error bars represent SEM. All symptoms of migraine (except perceived body temperature) were significantly greater during migraine. All symptoms except perceived body temperature and drowsiness increased after trigeminal stimulation.
Table 6-1: Migraine Symptom Rating F ratios (degrees of freedom).

<table>
<thead>
<tr>
<th></th>
<th>Headache</th>
<th>Nausea</th>
<th>Dizziness</th>
<th>Drowsiness</th>
<th>Perceived Body Temperature</th>
<th>Sound Sensitivity</th>
<th>Light Sensitivity</th>
<th>Unpleasantness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Between Groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>4.86</td>
<td>2.27</td>
<td>3.66</td>
<td>2.85</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.52,59.43)*</td>
<td>(1.14,44.55)</td>
<td>(1.2,46.81)</td>
<td>(1.47,57.16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>.72 (1.39)</td>
<td>.005 (1.39)</td>
<td>.08 (1.39)</td>
<td>.00 (1.39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.52,59.43)</td>
<td>(1.14,44.55)</td>
<td>(1.2,46.81)</td>
<td>(1.47,57.16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition x Group</td>
<td>1.94</td>
<td>.07</td>
<td>.39 (1.2,46.81)</td>
<td>1.78</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.52,59.43)</td>
<td>(1.14,44.55)</td>
<td>(1.2,46.81)</td>
<td>(1.47,57.16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>During Migraine</strong></td>
<td>3.02</td>
<td>1.31</td>
<td>1.21</td>
<td>3.45 (2.18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>(1.13,10.15)</td>
<td>(1.14,44.55)</td>
<td>(1.2,46.81)</td>
<td>(1.47,57.16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>87.22 (1.9)*</td>
<td>9.98 (1.9)*</td>
<td>5.97 (1.9)*</td>
<td>11.56 (1.9)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition x Migraine</td>
<td>2.48 (2,18)</td>
<td>1.31 (2,18)</td>
<td>1.25 (1,14,10.25)</td>
<td>.54 (2,18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.13,10.15)</td>
<td>(1.14,44.55)</td>
<td>(1.2,46.81)</td>
<td>(1.47,57.16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* *p<.05

Table 6-1b: Migraine Symptom Condition comparisons p values.

<table>
<thead>
<tr>
<th></th>
<th>Headache</th>
<th>Nausea</th>
<th>Dizziness</th>
<th>Drowsiness</th>
<th>Perceived Body Temperature</th>
<th>Sound Sensitivity</th>
<th>Light Sensitivity</th>
<th>Unpleasantness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Between Groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start &amp; Baseline</td>
<td>.009*</td>
<td>.041*</td>
<td>.204</td>
<td>.112</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparison (α)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start &amp; Final</td>
<td>.006*</td>
<td>.054</td>
<td>.043*</td>
<td>.056</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparison (α)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* *p<.05

143
Figure 6-2: Pain ratings to Electrical Stimuli. The ratings were significantly greater during a migraine.

Table 6-2: F ratios (d.f.) for pain ratings for the electrical stimulus.

<table>
<thead>
<tr>
<th></th>
<th>Between Groups</th>
<th>During Migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location (headache vs. non-headache side)</td>
<td>0.88 (1,39)</td>
<td>0.56 (1,9)</td>
</tr>
<tr>
<td>Group</td>
<td>0.98 (1,39)</td>
<td>3.83 (1,9)</td>
</tr>
<tr>
<td>Location x Group</td>
<td>0.76 (1,39)</td>
<td>0.01 (1,9)</td>
</tr>
<tr>
<td>Condition (baseline vs. final)</td>
<td>2.59 (1,39)</td>
<td>.001 (1,9)</td>
</tr>
<tr>
<td>Group</td>
<td>0.65 (1,39)</td>
<td>6.47 (1,9)*</td>
</tr>
<tr>
<td>Condition x Group</td>
<td>1.95 (1,39)</td>
<td>0.04 (1,9)</td>
</tr>
</tbody>
</table>

* Denotes significance at .05 alpha level
Table 6-3: F ratios (d.f.) for the blink reflex parameters for location comparison (headache side vs. non-headache side in migraineurs; stimulated vs. non-stimulated side in controls).

<table>
<thead>
<tr>
<th>Between Groups</th>
<th>BR Count</th>
<th>Mean AUC</th>
<th>Mean Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>0.02 (1,40)</td>
<td>.01 (1,34)</td>
<td>.002 (1,29)</td>
</tr>
<tr>
<td>Side (Measurement)</td>
<td>17.2 (1,40)*</td>
<td>34.92 (1,34)*</td>
<td>38.33 (1,29)*</td>
</tr>
<tr>
<td>Group</td>
<td>0.64 (1,40)</td>
<td>0.05 (1,34)</td>
<td>.01 (1,29)</td>
</tr>
<tr>
<td>Location x Side</td>
<td>0.19 (1,40)</td>
<td>0.34 (1,34)</td>
<td>0.05 (1,29)</td>
</tr>
<tr>
<td>Location x Group</td>
<td>0.1 (1,40)</td>
<td>0.61 (1,34)</td>
<td>.4 (1,29)</td>
</tr>
<tr>
<td>Side x Group</td>
<td>0.18 (1,40)</td>
<td>0.2 (1,34)</td>
<td>1.38 (1,29)</td>
</tr>
<tr>
<td>Location x Side x Group</td>
<td>0.4 (1,40)</td>
<td>0.27 (1,34)</td>
<td>0.5 (1,29)</td>
</tr>
</tbody>
</table>

* Denotes significance at .05 alpha level

Table 6-4: F ratios (d.f.) for the blink reflex parameters for time comparison (baseline vs. final stimuli).

<table>
<thead>
<tr>
<th>Between Groups</th>
<th>BR Count</th>
<th>Mean AUC</th>
<th>Mean Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition</td>
<td>10.53 (1,39)*</td>
<td>17.59 (1,34)*</td>
<td>6.61 (1,24)*</td>
</tr>
<tr>
<td>Group</td>
<td>0.8 (1,39)</td>
<td>0.01 (1,34)</td>
<td>.16 (1,24)</td>
</tr>
<tr>
<td>Condition x Group</td>
<td>0.11 (1,39)</td>
<td>0.99 (1,34)</td>
<td>.001 (1,24)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>During Migraine</th>
<th>BR Count</th>
<th>Mean AUC</th>
<th>Mean Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition</td>
<td>1.82 (1,9)</td>
<td>2.51 (1,8)</td>
<td>0.23 (1,5)</td>
</tr>
<tr>
<td>Migraine</td>
<td>0.26 (1,9)</td>
<td>1.87 (1,8)</td>
<td>1.76 (1,5)</td>
</tr>
<tr>
<td>Condition x Migraine</td>
<td>0.38 (1,9)</td>
<td>1.37 (1,7)</td>
<td>2.38 (1,5)</td>
</tr>
</tbody>
</table>

* Denotes significance at .05 alpha level
Figure 6-3: Response count of blink reflexes during the baseline and stimulation to the non-headache side (null responses not included). Error bars represent standard error of the mean.
Figure 6-4: Mean area under the curve of blink reflexes during the baseline and stimulation to the non-headache side (null responses as missing values). Error bars represent standard error of the mean.
Figure 6-5: Mean latency of blink reflexes during the baseline and stimulation to the non-headache side. Error bars represent standard error of the mean.
Figure 6-6: Response count of blink reflexes from each side (null responses not included) averaged over stimulation side between and during migraine. The number of blink reflexes decreased on the non-headache side between migraine. Error bars represent standard error of the mean.

Figure 6-7: Response count of blink reflexes during the baseline and the final set of stimuli (null responses not included). Error bars represent standard error of the mean. Frequency significantly decreased to the final set of stimuli.
Figure 6-8: Mean area under the curve of blink reflexes during the baseline and the final set of stimuli (null responses as missing values). Error bars represent standard error of the mean. AUC significantly decreased to the final set of stimuli.

Figure 6-9: Mean latency of blink reflexes during the baseline and the final set of stimuli. Error bars represent standard error of the mean. Latency significantly decreased to the final set of stimuli.
6.4 Discussion

6.4.1 Summary

Symptoms of migraine increased after noxious trigeminal stimulation both in healthy controls and in migraine sufferers between attacks. In particular, headache intensity increased in migraine sufferers over the course of the session both during and between attacks (Table 6-1).

Neither pain ratings to the electrical stimuli nor the nociceptive blink reflex differed between controls and migraine sufferers during the headache-free interval. Pain ratings did not increase and blink reflexes were not facilitated at the end of the session for migraine sufferers between attacks, which did not support the hypothesised interictal sensitisation after trigeminal system excitation. In support of sensitisation during migraine, the stimuli were rated as more painful during than between attacks and this effect was most apparent when stimuli were applied to the headache side. The blink reflex count increased contralateral to headache during attacks.

6.4.2 Previous Research

6.4.2.1 Healthy Controls and Migraine Sufferers Between Attacks

Neither pain ratings to the electrical stimuli nor nociceptive blink reflexes differed between controls and migraine sufferers between attacks. This finding is consistent with the nociceptive blink reflex studies previously presented in this thesis.

Pain ratings did not increase and blink reflexes were not facilitated at the end of the session for migraine sufferers between attacks, which did not support the hypothesised interictal sensitisation after trigeminal system excitation. This result is interesting because it does not support previously presented findings regarding the increase in scalp tenderness after trigeminal excitation in migraine sufferers between attacks. As previously discussed in Chapter 3, the scalp
tenderness test is likely to evoke temporal summation and wind-up which are mechanisms that primarily involve C-fibres (You, et al., 2003).

6.4.2.2 During Migraine

The nociceptive blink reflex was more easily evoked during migraine than interictally; in particular, the blink contralateral to the headache was less likely to be evoked between attacks. These findings do suggest a more sensitized trigeminal system, with a residual sensitization ipsilateral to the headache between attacks of migraine. However, the data from this study did not emulate previous findings by others (Katsarava, et al., 2002) in that the area under the curve was not consistently facilitated (by 700% in the Kaube et al research and approximately 250% in the Katsarava et al research). Additionally, there was no evidence that sensitization facilitated the nociceptive blink reflex to the final set of stimuli. Koh and Drummond (2006) found that psychological arousal facilitated the nociceptive blink reflex. Perhaps fatigue after the current testing session reduced psychological arousal and therefore a facilitation of the blink reflex was counteracted with an inhibition. Additionally, the current findings do not support Burstein and colleague’s (Burstein, et al., 1998; Malick & Burstein, 2000; Strassman, et al., 1996; Yamamura, et al., 1999) model of sensitisation during migraine. One explanation for this could be that different pain pathways were active during nociceptive stimulation and migraine as the concentric electrode depolarises Aδ fibres whereas C-fibres most likely are active during migraine (Silberstein, 2004).
6.4.3 Theoretical Implications

The first major theoretical implication to consider for this study is the lack of strong facilitation of the nociceptive blink reflex during migraine headache. Although most studies using participants with naturally occurring migraine often use a small sample size (Katsarava et al 2002 = 14; Kaube et al 2002 = 17), the useable data sample size for the current study was small (N = 6 to 10 for different parameters of the blink reflex). Whilst the AUC means suggested a facilitation of the blink reflex during migraine, this effect was not significant possibly due to high individual variability.

Another major theoretical implication of this study is the lack of facilitation of the trigeminal nociceptive reflex in migraine sufferers after trigeminal excitation. If trigeminal Aδ fibres are subject to central sensitization, as inferred by Kaube et al (2002) and Katsarava et al (2002), the nociceptive specific blink reflex should have been facilitated at the end of the session both during and between attacks of migraine. It is plausible that the concentric electrode and stimulus parameters (which was 1.5 x the individual pain threshold) used by Kaube and colleagues stimulated sensitized Aδ and/or C-fibres during attacks of migraine (Kaube, et al., 2000).

The parameters of the electrode and stimuli used in this thesis were very similar to that used by Kaube et al (2002) and Katsarava et al (2002). The only parameter that differed was that this thesis research used a 2mA stimulus to elicit the nociceptive blink reflex, whereas the Kaube et al (2002) and Katsarava et al (2002) used an intensity 1.5 x the individual pain threshold. The other difference was the chronicity of the participant’s migraines with the current research using a community sample whereas Kaube and colleagues may have recruited participants from an outpatient’s clinic. Their patients could have had a more intense headache which could have evoked greater central sensitisation; a greater WDR response resulting in a greater nociceptive blink reflex.
If Kaube and colleagues activated C-fibres in addition to Aδ fibres, signs of central sensitization in their studies could be the result of C-fibre sensitization. C-fibres are activated via neurogenic inflammation when the cerebral blood vessels are dilated during migraine headache (Silberstein, 2004). This fits with Burstein’s (Burstein, et al., 1998; Malick & Burstein, 2000; Strassman, et al., 1996; Yamamura, et al., 1999) model of sensitization during migraine. During migraine trigeminal nociceptive C-fibres may be activated by inflammatory mediators in intracranial blood vessels (Silberstein, 2004). According to Burstein et al (Burstein, et al., 1998; Malick & Burstein, 2000; Strassman, et al., 1996; Yamamura, et al., 1999) this barrage of signals then converges onto the second-order medullary dorsal horn neurons, resulting in spontaneous activity in the medullary dorsal horn that is also the converging point of the nociceptive supply of facial and scalp skin, leading to a hypersensitivity in these regions. Thus, the facilitation of the nociceptive blink reflex during migraine detected by Kaube and colleagues (Katsarava, et al., 2002; Kaube, et al., 2002) may have been the result of central sensitization. A similar mechanism may be responsible for the development of allodynia (Burstein, Yarnitsky, et al., 2000) and scalp tenderness during attacks (Drummond, 1987).

Previously presented research in this thesis also fits the theory that nociceptor excitation is required for central sensitization. The results of the first study suggested a persistence of central sensitisation between attacks of migraine because the nociceptive blink reflex was less suppressed by local anaesthetic in migraine sufferers than in healthy controls. The lack of inhibition of the nociceptive blink reflex in the migraineurs after the local anaesthetic could be explained by the sensitisation model previously discussed and proposed by Burstein (Burstein, et al., 1998; Malick & Burstein, 2000; Strassman, et al., 1996; Yamamura, et al., 1999). The first study procedure involved a one hour wait time between the baseline and the post-anaesthetic conditions. This waiting may have resulted in less fatigue than the current study. Additionally,
the range of intensities used in the first study could have avoided habituation of both pain ratings and blink reflex parameters.

The effects of drinking a hypertonic solution on blink reflexes and scalp tenderness in migraine sufferers between attacks and healthy controls were investigated in the second presented study.

There was no demonstrated sensitization in migraine sufferers in the nociceptive blink reflex. The lack of nociceptive blink reflex facilitation in the migraine sufferers over the session could be explained by physiological fatigue (because there was no lengthy rest period between conditions) or habituation (because only the 2 mA intensity was used for the concentric electrode). Alternatively, diffuse noxious inhibitory controls (the suppression of one painful stimulus when another painful stimulus is being administered at another remote body site) evoked by gastrointestinal discomfort could be responsible for the absence of blink reflex facilitation in migraineurs after the consumption of the hypertonic solution.

There was little or no evidence of this cascade of progressing sensitization for the nociceptive blink reflex in migraine sufferers either interictally or during attacks in the current study. Physiological and psychological fatigue might have inhibited the nociceptive blink reflex (Koh & Drummond, 2006) because there were no lengthy rest breaks within the testing session.

Drowsiness did increase from the baseline to the final set of stimuli, indicating that the participants were tiring. Habituation could also have occurred because only one intensity was used as a stimulus parameter (2 mA). Perhaps both of these inhibiting factors counteracted any sensitization effect.

6.4.4 Limitations

Although the migraine participants used in this study met the required criteria for a migraine headache, they were from a convenience community sample. They were not outpatients of a medical headache clinic, which suggests that their migraine severity was not intense enough to
seek medical treatment. Migraine participants in this study were required to be medication-free and this may have impacted on the data somewhat as participants could have chosen to be studied during a mild attack. Nevertheless, headache ratings averaged 5 during this session, indicating that headaches were moderate.

The sample number was relatively low, increasing the risk of Type 2 errors. Kaube et al (2002) used a deviation from baseline percentage for the AUC data to normalise it. However, an investigation of percent deviation from baseline in this study failed to replicate the strong findings presented by Kaube et al (between migraine percent deviation from baseline=-24.87\% (SD=25.32); during migraine percent deviation from baseline=-37.72, (SD=26.38); F(1,7)=2.6, N.S.).
Chapter 7  Nociceptive Blink Reflex and Noxious Conditioning

Stimulation during Migraine

7.1  Introduction

As previously stated, the nociceptive blink reflex has been used to investigate the nociceptive processing of the trigeminal system. The data presented in Chapter 5 illustrated sensitivity in the migrainous trigeminal system during a migraine attack but not the hypothesised interictal and ictal development of sensitisation after trigeminal excitation in migraine sufferers either in terms of pain ratings or blink reflexes to electrical stimuli.

Cold pain has been used as a noxious stimulus numerous times within our research group to investigate nociceptive processing during motion sickness (Drummond, 2002; Drummond & Granston, 2004, 2005; Granston & Drummond, 2005); and nociceptive processing during standard electrode blink reflexes (Drummond, 2003). The effect of homosegmental cold pain on the nociceptive blink reflex was investigated in the present study. It was hypothesized that the combination of cold-evoked nociception and concentric electrode stimulation to the trigeminal system would temporarily reduce the effect of psychological and physiological fatigue on the blink reflex.

7.1.1  Study Aims

The current study investigated symptoms of migraine such as headache, nausea, dizziness, drowsiness, bright light sensitivity, sound sensitivity, perceived body temperature and feelings of unpleasantness in healthy controls, and during and between attacks of migraine after evoking cold pain in the affected area and a remote area.

The effect of homosegmental cold pain on the nociceptive blink reflex was investigated in the current study. This combination of cold-evoked nociception and concentric electrode stimulation
to the trigeminal system earlier in the testing session may reduce the effect of psychological and physiological fatigue on the blink reflex. Whilst previous research has shown a facilitation of the blink reflex during homotopic noxious stimulation there should be greater facilitation in the migraine sufferers.

In particular, the effect of cold pain in the ipsilateral temple on the nociceptive blink reflex was compared with the effect of finger immersion in cold water on the nociceptive blink reflex. It was hypothesised that a homosegmental noxious stimulus would facilitate the nociceptive blink reflex (Ellrich, et al., 1998) but a remote noxious stimulus would inhibit the R2 component of the blink reflex via DNIC processes (Bouhassira, et al., 1994; Ellrich & Treede, 1998). Based on previously presented literature regarding scalp tenderness, it was hypothesised that a noxious stimulus administered to the headache region during a migraine headache would be rated as more painful than the same stimulus administered interictally or to a location remote from the site of headache.
7.2 Method

7.2.1 Participants

Please see Section 4.1.1.

7.2.2 Procedure

7.2.2.1 Blink Reflex

Please see Section 4.1.3.1.

7.2.2.2 Conditioning Stimuli

Please see Section 4.1.4.3.

7.2.2.3 Electrical Stimulation

In the finger-in-ice condition, electrical stimuli were first administered 30 seconds after immersion of the finger in the ice-water and then at least 10 sec intervals for 60 seconds, and participants rated each stimulus. At the end of the condition, participants rated the cold-induced pain and then rated other symptoms. In the ice on temple condition, electrical stimuli were administered first 10 seconds after the application of the ice on the temple and then at 10 second intervals. As well as rating each electrical stimulus, participants rated the pain at the temple then the other migraine symptoms.

7.2.3 Data Reduction and Analysis

7.2.3.1 Symptoms of Migraine

All symptoms were analysed in separate 4 (condition – start; after baseline nociceptive stimulation; after noxious remote stimulation; after noxious homosegmental stimulation) X 2
(group – healthy controls; migraine sufferers between migraine) mixed design ANOVAs. Four (condition) X 2 (migraine– between migraine; during migraine) repeated measure ANOVAs were used to investigate the effect of migraine on the symptoms.

7.2.3.2 Pain Ratings to the Noxious Conditioning Stimuli

Pain ratings in response to the finger in ice-water were compared to the pain ratings given in response to the ice on the temple. A 2 (location – remote; homosegmental) x 2 (group) mixed design ANOVA was used for the between groups analysis and a 2 (location) x 2 (migraine) mixed design ANOVA was used for the within groups analysis.

7.2.3.3 Pain Ratings to the Electrical Stimuli

Pain ratings were averaged across trials in each condition. Means were analysed individually with a 3 (condition – baseline; finger in ice water; ice on ipsilateral temple) x 2 (group – controls; between migraine) mixed design ANOVA with planned contrasts to baseline. Similar analyses were used to investigate the effect of migraine.

7.2.3.4 The Nociceptive Blink Reflex

The three dependent variables of the nociceptive blink reflex (count; area under the curve; latency) were analysed in a 3 (condition) x 2 (group: migraine versus controls) mixed design ANOVA and a 3 (condition) x 2 (migraine: during versus between) repeated measures ANOVA on the data from the 10 migraine participants tested during migraine.
7.3 Results

Unreported main effects and interactions were not significant.

7.3.1 Symptoms of Migraine (Figure 7-1) (Table 7-1)

All participants rated the painful conditioning stimuli as unpleasant and headache was rated as more intense after the combination of the ice on temple and trigeminal electrical stimuli. Although the presence of migraine increased most symptoms of migraine, there was no interaction between migraine and the painful conditioning stimuli.
**Start**

Baseline Stimuli

Finger in Ice

Ice on Temple

Healthy Controls (n=20)

Between migraine (n=21)

During migraine (n=10)

**Headache Rating (0-10)**

- **a.**

**Nausea Rating (0-10)**

- **b.**

**Dizziness Rating (0-10)**

- **c.**

**Drowsiness Rating (0-10)**

- **d.**
Figure 7-1: Symptoms of Migraine after noxious conditioning stimulation. a. = headache; b.=nausea; c.=dizziness; d.=drowsiness; e.=perceived body temperature; f.=sound sensitivity; g.=light sensitivity; h.=unpleasantness. Standard error bars represent SEM. Headache was significantly greater in all participants after the combination of ice on temple and trigeminal electrical stimuli.
### Table 7-1: Migraine Symptom Rating F ratios (degrees of freedom).

<table>
<thead>
<tr>
<th></th>
<th>Headache</th>
<th>Nausea</th>
<th>Dizziness</th>
<th>Drowsiness</th>
<th>Perceived Body Temperature</th>
<th>Sound Sensitivity</th>
<th>Light Sensitivity</th>
<th>Unpleasantness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Between Groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>6.62</td>
<td>1.58</td>
<td>2.74</td>
<td>1.37</td>
<td>2.53</td>
<td>1.38</td>
<td>2.3</td>
<td>66.57</td>
</tr>
<tr>
<td></td>
<td>(1.74,69.48)</td>
<td>(2.34,93.66)</td>
<td>(1.71,68.34)</td>
<td>(2.66,106.51)</td>
<td>(3, 120)</td>
<td>(1.62,63.11)</td>
<td>(2.52, 100.86)</td>
<td>(2.27,90.84)*</td>
</tr>
<tr>
<td>Group</td>
<td>1.11</td>
<td>1.25</td>
<td>.01</td>
<td>1.18</td>
<td>.1</td>
<td>.21</td>
<td>.08</td>
<td>.11</td>
</tr>
<tr>
<td></td>
<td>(1,40)</td>
<td>(1,40)</td>
<td>(1,40)</td>
<td>(1,40)</td>
<td>(1,40)</td>
<td>(1,39)</td>
<td>(1,40)</td>
<td>(1,40)</td>
</tr>
<tr>
<td>Condition x Group</td>
<td>.53</td>
<td>1.58</td>
<td>.56</td>
<td>.46</td>
<td>.75</td>
<td>.76</td>
<td>.99</td>
<td>.12</td>
</tr>
<tr>
<td></td>
<td>(1.74,69.48)</td>
<td>(2.34,93.66)</td>
<td>(1.71,68.34)</td>
<td>(2.66,106.51)</td>
<td>(3, 120)</td>
<td>(1.62,63.11)</td>
<td>(2.52, 100.86)</td>
<td>(2.27,90.84)</td>
</tr>
<tr>
<td><strong>During Migraine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>.08</td>
<td>.2</td>
<td>.48</td>
<td>1.09</td>
<td>.93</td>
<td>1.06(1.98,17.78)</td>
<td>1(1.94,17.45)</td>
<td>18.18(1.74,13.88)*</td>
</tr>
<tr>
<td></td>
<td>(3,27)</td>
<td>(3,27)</td>
<td>(3,27)</td>
<td>(3,27)</td>
<td>(3,27)</td>
<td>8</td>
<td></td>
<td>8)</td>
</tr>
<tr>
<td>Migraine</td>
<td>52.41</td>
<td>8.75</td>
<td>4.74</td>
<td>10.04</td>
<td>.03</td>
<td>6.32</td>
<td>14.74</td>
<td>6.84(1.8)*</td>
</tr>
<tr>
<td></td>
<td>(1,9)</td>
<td>(1,9)</td>
<td>(1,9)</td>
<td>(1,9)</td>
<td>(1,9)</td>
<td>(1,9)</td>
<td>(1,9)</td>
<td></td>
</tr>
<tr>
<td>Condition x Migraine</td>
<td>.8</td>
<td>.2</td>
<td>.43</td>
<td>.83</td>
<td>2.04</td>
<td>1.06</td>
<td>1.38</td>
<td>1.16</td>
</tr>
<tr>
<td></td>
<td>(3,27)</td>
<td>(3,27)</td>
<td>(1.22,11.02)</td>
<td>(3,27)</td>
<td>(3,27)</td>
<td>(1.98,17.78)</td>
<td>(3,27)</td>
<td>(3,24)</td>
</tr>
</tbody>
</table>

* p<.05

### Table 7-1b: Migraine Symptom Condition comparisons p values.

<table>
<thead>
<tr>
<th></th>
<th>Headache</th>
<th>Nausea</th>
<th>Dizziness</th>
<th>Drowsiness</th>
<th>Perceived Body Temperature</th>
<th>Sound Sensitivity</th>
<th>Light Sensitivity</th>
<th>Unpleasantness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Between Groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start &amp; Finger in Ice Comparison (α)</td>
<td>.046*</td>
<td>.158</td>
<td>.457</td>
<td>.358</td>
<td>.347</td>
<td>.269</td>
<td>.042</td>
<td>.000*</td>
</tr>
<tr>
<td>Start &amp; Ice on Temple Comparison (α)</td>
<td>.003*</td>
<td>.062</td>
<td>.069</td>
<td>.884</td>
<td>.541</td>
<td>.182</td>
<td>.079</td>
<td>.000*</td>
</tr>
</tbody>
</table>

* p<.05
7.3.2 Pain Ratings to Noxious Conditioning Stimuli (Figure 7-2) (Table 7-2)

Ice on the temple (M=6.11, SEM=.34) was rated as more painful than finger in iced water (M=5.46, SEM=.35) but this was only approaching significance (F(1,40)=3.08, p=.087, \( \eta_p^2 = .071 \)). The pain ratings given by the healthy controls in response to the noxious conditioning stimuli (M=5.84, SEM=.42) did not differ from the ratings given by migraine sufferers between migraine (M=5.73, SEM=.4) (F(1,40)=.04, N.S.). Exploratory paired t-tests results revealed that during a migraine, the ice on the temple was more painful than between migraine (t(9)=2.93, p<.05).

![Figure 7-2: Pain ratings in response to noxious conditioning stimuli. Remote Noxious Stimuli = finger in ice; Homosegmental Noxious Stimuli = ice on the temple. Ice on the temple was significantly more painful during a migraine.](image-url)
Table 7-2: F ratios (d.f.) for pain ratings in response to noxious conditioning stimuli.

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>3.08</td>
<td>(1,40)</td>
</tr>
<tr>
<td>Group</td>
<td>0.04</td>
<td>(1,40)</td>
</tr>
<tr>
<td>Location x Group</td>
<td>1.3</td>
<td>(1,40)</td>
</tr>
<tr>
<td>During Migraine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>3.01</td>
<td>(1,9)</td>
</tr>
<tr>
<td>Migraine</td>
<td>3.57</td>
<td>(1,9)</td>
</tr>
<tr>
<td>Location x Migraine</td>
<td>3.88</td>
<td>(1,9)</td>
</tr>
</tbody>
</table>

7.3.3 Pain Ratings to Electrical Stimuli (Figure 7-3)(Table 7-3)

There were no overall group differences in pain ratings to the electrical stimuli regardless of presence of noxious conditioning stimuli (main effect of group F(1,40)=.45, N.S.). Pain ratings decreased in response to the electrical stimuli administered during noxious conditioning stimuli when compared to baseline pain ratings (M=2.6, SEM=.25) regardless of site (finger in iced water M=2.05, SEM=.22, c.f. baseline p<.05; ice on ipsilateral temple M=1.95, SEM=.22, c.f. baseline p<.05). Pain ratings to the electrical stimuli administered at the same time as homosegmental noxious stimuli during a migraine did not differ from the pain ratings given in response to the electrical stimuli during remote noxious conditioning stimuli (condition x migraine interaction F(3,27)=.74, N.S.).
7.3.4 Nociceptive Blink Reflex (Table 7-3)

All parameters of the nociceptive blink reflex were significantly inhibited during noxious conditioning stimuli (Figure 7-4; Figure 7-5; Figure 7-6) regardless of location. The frequency, area under the curve or the latency of the nociceptive blink reflex during noxious conditioning stimuli were not affected by migraine.

Figure 7-3: Pain ratings to Electrical Stimuli. Remote Noxious Stimuli = finger in ice; Homosegmental Noxious Stimuli = ice on the temple. Pain ratings decreased during the noxious stimuli.
Table 7-3: Pain Ratings and Nociceptive Blink Reflex F ratios (degrees of freedom).

<table>
<thead>
<tr>
<th></th>
<th>Pain Ratings</th>
<th>BR Count</th>
<th>Mean AUC</th>
<th>Mean Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Between Groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>6.62 (1.49,59.66)*</td>
<td>8.06 (2.78)*</td>
<td>9.02 (2.64)*</td>
<td>4.14 (2.40)*</td>
</tr>
<tr>
<td>Group</td>
<td>.44 (1.40)</td>
<td>1.3 (1.39)</td>
<td>.76 (1.32)</td>
<td>1.79 (1.20)</td>
</tr>
<tr>
<td>Condition x Group</td>
<td>1.81 (1.49,59.66)</td>
<td>1.24 (2.78)</td>
<td>1.92 (2.64)</td>
<td>.78 (2.40)</td>
</tr>
<tr>
<td><strong>During Migraine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>4.32 (2,18)*</td>
<td>3.01 (2,18)</td>
<td>2.25 (1.04,8.34)</td>
<td>.28 (2.10)</td>
</tr>
<tr>
<td>Migraine</td>
<td>3.65 (1,9)</td>
<td>.57 (1,9)</td>
<td>2.37 (1,8)</td>
<td>.26 (1,5)</td>
</tr>
<tr>
<td>Condition x Migraine</td>
<td>.88 (2,18)</td>
<td>.12 (1.16,10.39)</td>
<td>2.25 (1.04,8.34)</td>
<td>.61 (2,10)</td>
</tr>
</tbody>
</table>

* p<.05

Table 7-3b: Pain Ratings and Nociceptive Blink Reflex Condition Comparison p-values

<table>
<thead>
<tr>
<th></th>
<th>Pain Ratings</th>
<th>BR Count</th>
<th>Mean AUC</th>
<th>Mean Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Between Groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline &amp; Finger in Ice Comparison (α)</td>
<td>.004*</td>
<td>.001*</td>
<td>.002*</td>
<td>.008*</td>
</tr>
<tr>
<td>Baseline &amp; Ice on Temple Comparison (α)</td>
<td>.005*</td>
<td>.001*</td>
<td>.001*</td>
<td>.029*</td>
</tr>
<tr>
<td><strong>During Migraine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline &amp; Finger in Ice Comparison (α)</td>
<td>.015*</td>
<td>.279</td>
<td>.197</td>
<td>.37</td>
</tr>
<tr>
<td>Baseline &amp; Ice on Temple Comparison (α)</td>
<td>.036*</td>
<td>.058</td>
<td>.151</td>
<td>.55</td>
</tr>
</tbody>
</table>

* p<.05
Figure 7-4: Response count of blink reflexes during the baseline and Noxious conditioning stimuli (null responses not counted). Error bars represent standard error of the mean. Blink reflex frequency was significantly inhibited during noxious conditioning stimuli.

Figure 7-5: Mean area under the curve of blink reflexes during the baseline and noxious conditioning stimuli (null responses as missing values). Error bars represent standard error of the mean. Blink reflex was significantly inhibited during noxious conditioning stimuli.
Figure 7-6: Mean latency of blink reflexes during the baseline and during the baseline and noxious conditioning stimuli. Error bars represent standard error of the mean. Latency was significantly increased during noxious conditioning stimuli.
7.4 Discussion

7.4.1 Summary

Even though migraine was associated with an increase in symptoms, the presence of a homosegmental and remote noxious conditioning stimulus did not affect these increases. The combination of a homosegmental noxious conditioning stimulus with the trigeminal electrical stimuli resulted in an increase in unpleasantness and a more intense headache for all participants.

The pain ratings given by the healthy controls to the noxious conditioning stimuli did not differ from the ratings given by migraine sufferers between attacks. A trend of a noxious conditioning stimulus applied to the temple during a migraine being rated as more painful than the increased rating given in response to the finger in iced water during migraine suggests a temporal summation of C-fibre activation in that the migraine pain facilitated the cold pain.

There were no overall group differences in pain ratings to the electrical stimuli regardless of the presence of noxious conditioning stimuli. Pain ratings to the electrical stimuli decreased during noxious conditioning stimuli when compared with baseline pain ratings regardless of site of noxious stimulation. Pain ratings to the electrical stimuli administered at the same time as homosegmental noxious stimuli during a migraine did not differ from the pain ratings given in response to the electrical stimuli during remote noxious conditioning stimuli. These findings do not support an additive effect of different forms of nociceptive trigeminal stimulation during a migraine. In addition, the lack of facilitation of the nociceptive blink reflex during ipsilateral noxious conditioning stimuli during migraine does not support the view that sensitisation develops after trigeminal excitation in migraine sufferers. The inhibition of the nociceptive blink reflex during noxious conditioning stimuli (regardless of location) supports the theory that DNIC processes were activated. The lack of an effect of migraine on these processes suggests
that DNIC was not compromised during migraine in these participants. This is interesting because pain modulation processes such as DNIC did not suppress symptoms of migraine even though they suppressed the pain ratings to the electrical stimuli.

7.4.2 Previous Research

The findings from this study do not support the findings of Ellrich et al (1998) of facilitation to an innocuous standard electrode stimulus by nociceptive laser stimulation of the forehead. Perhaps the inhibition illustrated in the current study differed from Ellrich’s findings because the laser beam stimulated a smaller area of skin than the iceblock in a blink-sensitive region (the forehead versus the temple).

Inhibition of both pain ratings and R2 response to a trigeminal electrical test stimulus during a competing noxious stimulus to the same dermatome partially supports Drummond’s finding (Drummond, 2003) that R2 was inhibited during a cold stimulus both to low and high intensity electrical stimuli. However, pain ratings increased in response to the electrical stimuli in Drummond’s research, but decreased in the current study. The high intensity stimulus used by Drummond may have activated all nerve fibre types including the Aβs, Aδs and C-fibres whereas the stimulus employed in the present study probably primarily activated Aδ fibres.

Giffin et al (2004) found that DNIC was activated during trains of triple pulses from the concentric electrode. Even though only a single pulse was used the current study, a train of pulses is more reliable at activating the nociceptive blink reflex due to a greater recruitment of neurons and wind-up at the second order neurons leading to a greater exposure of neurons to DNIC and a greater effect (Giffin, et al., 2004).

The use of cold therapy as a treatment for migraine headache has been reported in the empirical literature (as a clinical trial) with headache severity (as rated on a visual analogue scale) decreasing significantly 25 minutes after the application of a cold gel cap (Ucler, Coskun, Inan,
Migraine sufferers were more likely to try different manoeuvres to reduce the headache severity and these manoeuvres included the application of cold stimuli to the affected area (Bag & Karabulut, 2005). This finding could have some bearing on the results of the current study due to the relieving properties of the ice on the temple during migraine. However, as previously discussed, the ice on the temple was rated as more painful during migraine, indicating that it was not immediately therapeutic.

7.4.3 Theoretical Implications

Facilitation of the nociceptive blink reflex during a simultaneous homosegmental noxious stimulus was not detected. Diffuse noxious inhibitory controls could have been activated in the current study because both the subjective and physiological parameters of the blink reflex were inhibited during the application of a competing homosegmental noxious conditioning stimulus. Temporal summation can be illustrated by a facilitation of spinal reflexes such as the RIII reflex. This phenomenon is also known as ‘wind up’ and it occurs because of an increase in spinal cord neuron excitability because of a central temporal summation of nociceptive activity (Serrao, et al., 2004). The effect of DNICs and temporal summation is more pronounced in the second pain (C-fibre mediated) than in the first pain mediated by the Aδ fibres (Serrao, et al., 2004). During hypoalgesia evoked by heterotopic noxious conditioning stimulation, descending pain modulatory pathways were activated, suggesting that higher order brain regions could contribute to the heterotopic noxious conditioning stimulation and possibly DNIC (Okada-Ogawa, Porreca, & Meng, 2009).

Somatosensory evoked potentials were used to investigate DNICs by Kakigi (Kakigi, 1994). Kakigi found that DNIC inhibited second pain more than first pain, suggesting that unmyelinated nociceptive fibres were more affected than myelinated fibres. He concluded that C-fibre activation is more strongly inhibited during heterosegmental noxious stimuli. This
finding is also supported by other research whereby DNICs were reliably produced by an occlusion cuff on pressure algometry test stimuli – which both increase C-fibre nociceptive activity (Cathcart, Winefield, Rolan, & Lushington, 2009). Cathcart et al also reliably produced temporal summation (defined as an increased pain rating to a repeated stimulus) using pressure algometry. Perhaps the dysfunctional DNIC previously reported in migraine sufferers would be more obvious in a C-fibre activation stimulus than the cold-pain stimulus used in the present study (which activates cold-specific Aδ fibres in addition to nociceptors (Simone & Kajander, 1997)).

7.4.4 Conclusion

The hypothesized facilitation of the nociceptive blink reflex during application of homosegmental noxious conditioning stimulus did not occur. In fact, both subjective and physiological variables in response to the nociceptive trigeminal stimuli were inhibited in healthy controls and migraine sufferers between attacks, suggesting the occurrence of diffuse noxious inhibitory control mechanisms.
Chapter 8  Cross Modal Sensory Sensitivity and Trigeminal Irritation during Migraine

8.1  Introduction

Photophobia and phonophobia are present in migraine sufferers both during (Kelman & Tanis, 2006; Linde, et al., 2006) and between attacks (Ashkenazi, et al., 2010; Olsson, 1991).

Migraine sufferers had a low threshold for visual discomfort between and during migraines (Drummond, 1997; Drummond & Woodhouse, 1993; Vanagaite et al., 1997). Increased light and sound sensitivity has also been documented quantitatively during a migraine attack (Woodhouse & Drummond, 1993) with some authors suggesting a central cause for this hypersensitivity (Olesen, 2010). Drummond (Drummond, 1986, 1997) suggested that this low threshold of discomfort is mediated by disruption of inhibitory influences or promotion of facilitatory influences in migraine.

Painful trigeminal stimulation also decreases the visual discomfort threshold in migraine sufferers during cold pain to the forehead (Drummond & Woodhouse, 1993) and during painful mechanical stimulation of the face (Drummond, 1997). Conversely, discomfort to auditory stimuli did not differ between migraine sufferers and controls and did not decrease during cold pain to the forehead (Drummond & Woodhouse, 1993). Drummond and Woodhouse suggested that trigeminal discharge contributes to photophobia but not phonophobia. In the current study it was hypothesised that migraine sufferers would have greater light sensitivity than controls between migraine but not greater noise sensitivity. If trigeminal discharge contributes to photophobia then we would also expect light sensitivity to increase during trigeminal nociceptive stimulation with the concentric electrode.
Migraine sufferers have also reported a decreased pain threshold in the trigeminal region after exposure to intense light (P. A. Kowacs et al., 2001), suggesting that light could influence trigeminal pain thresholds. Therefore it was hypothesised in the current study that pain ratings to the trigeminal stimuli would increase during bright light conditioning stimuli in migraine sufferers.

Reflex circuitry has been identified in which bright light activated nociceptive neurons in the trigeminal subnucleus caudalis, thereby explaining why bright light is painful (Okamoto, Tashiro, Chang, & Bereiter, 2010). Additionally, the blink reflex was facilitated in response to bright light stimulation in rats with lesioned optic nerves (Dolgonos, et al., 2011), implying that the facilitation was due to heightened trigeminal nociceptive traffic. Therefore, it was expected that bright light would facilitate trigeminal-nociceptive blink reflexes in the current study.

8.1.1 Study Aims

The aim of the current study was to investigate the symptoms of migraine during complete darkness, bright light and intense sound. It was hypothesised that photophobia and phonophobia would be greater during migraine than between attacks. Additionally, it was hypothesized that photophobia but not phonophobia would persist during the headache-free interval in migraine sufferers.

The electrical stimuli were used to test the hypothesis that light sensitivity would increase during trigeminal nociceptive stimulation, particularly during migraine. The hypothesised increase in trigeminal pain in migraine sufferers after bright light exposure was investigated using the electrical stimulus as the test stimulus and the bright light as the conditioning stimulus.
8.2 Method

8.2.1 Participants

Please see Section 4.1.1.

8.2.2 Procedure

8.2.2.1 Blink Reflex

Please see Section 4.1.3.1.

8.2.2.2 Light induced Pain and Glare Thresholds

Please see Section 4.1.4.5.

8.2.2.3 Sound induced Pain, Loudness and Discomfort Thresholds

Please see Section 4.1.4.7.

8.2.2.4 Conditioning Stimuli (darkness and bright light)

Please see Section 4.1.4.4. and 4.1.4.6.

8.2.2.5 Electrical Stimulation

In both conditioning stimuli conditions, electrical stimuli were administered 10 seconds after the onset of the conditioning stimulus. Participants rated each stimulus and after closing their eyes after the light exposure, rated light-induced pain or discomfort in darkness (in the hooded condition) as well as symptoms of migraine.
8.2.3 **Data Reduction and Analysis**

8.2.3.1 **Sensory Thresholds**

Each rating (Light stimuli – Pain and Glare; Sound stimuli – Pain, Loudness, and Discomfort) was analysed with mixed design ANOVAs with repeated contrasts with the repeated component representing the intensities of the stimuli. Differences between controls and headache-free migraine sufferers were investigated in one set of analyses, and differences between and during migraine were investigated in a second set of analyses.

8.2.3.2 **Symptoms of Migraine**

All symptoms were analysed in separate 5 (condition – baseline; after baseline nociceptive stimulation; during complete darkness; after bright light exposure; after aversive sound stimuli) X 2 (group – healthy controls; between migraine) mixed design ANOVAs with repeated contrasts for condition. Five (condition) X 2 (migraine) repeated measure ANOVAs were used to investigate the effect of migraine on the symptoms.

8.2.3.3 **Light Evoked Pain Ratings during Trigeminal Nociception**

Pain ratings to the 500 lux intensity were compared to the pain ratings given for the bright light stimulus during the nociceptive blink reflex in a 2 (condition) x 2 (group) mixed design ANOVA. Similar analyses were used to investigate the effect of migraine.

8.2.3.4 **Pain Ratings to the Electrical Stimuli**

Pain ratings were averaged across trials in each condition. Means were analysed with a 3 (condition – baseline; noxious visual stimulation; no visual stimulation) x 2 (group) mixed design ANOVA. To investigate the effect of migraine on pain ratings, means were analysed in a 3 (condition) X 2 (migraine) repeated measures ANOVA.
8.2.3.5 The Nociceptive Blink Reflex

The three dependent variables of the ipsilateral nociceptive blink reflex (count; area under the curve; latency) were analysed in a 3 (condition) x 2 (group) mixed design ANOVA and a 3 (condition) x 2 (migraine) repeated measures ANOVA on the data from the 10 migraine participants tested during migraine.
8.3 Results

Unreported main effects and interactions were not significant.

8.3.1 Sensory Thresholds (Table 8-1)

Bright light was rated as more painful during a migraine headache \((M=3.45, \text{SEM}=.86)\) than between migraine (Figure 8-1) \((M=.99, \text{SEM}=.35)\) \((F(1,7)=9.15, p<.05, \eta^2 =.57)\). In addition, headache-free migraine sufferers rated the light as more painful \((M=2.29, \text{SEM}=.42)\) than controls \((M=1.02, \text{SEM}=.46)\) \((F(1,37)=4.18, p<.05, \eta^2 =.101)\). Migraine sufferers rated the light stimulus as having more glare during a migraine headache \((M=5.77, \text{SEM}=.77)\) compared to between migraines \((M=4.03, \text{SEM}=.56)\) \((F(1,7)=10.02, p<.05, \eta^2 =.59)\) but there was no difference between controls \((M=4.6, \text{SEM}=.53)\) and migraine sufferers between attacks \((M=4.93, \text{SEM}=.49)\) \((F(1,37)=.18, \text{N.S., } \eta^2 =.005)\).

Sound was rated as more painful during a migraine \((M=3.26, \text{SEM}=.7)\) compared to the non-headache period \((M=1.14, \text{SEM}=.3)\) \((F(1,9)=11.99, p<.05, \eta^2 =.57)\) but there was no difference in pain thresholds to the auditory stimulus between controls \((M=1.37, \text{SEM}=.35)\) and migraine sufferers between attacks \((M=1.93, \text{SEM}=.33)\) \((F(1,39)=1.33, \text{N.S., } \eta^2 =.03)\) (Figure 8-2).

Additionally, controls (Loudness \(M=3.3, \text{SEM}=.39\); Discomfort \(M=2.02, \text{SEM}=.39\)) and migraine sufferers (Loudness \(M=3.52, \text{SEM}=.37\); Discomfort \(M=2.27, \text{SEM}=.37\)) between attacks did not differ in their ratings of loudness and discomfort when ratings were averaged across the intensities. However, migraine sufferers rated the 100dB stimulus as more uncomfortable in comparison to the 90dB stimulus compared to controls (90dB vs. 100dB x group interaction \(F(1, 38)=11.99, p<.05\)).
8.3.2 Symptoms of Migraine (Figure 8-3)(Table 8-2)

Light sensitivity was greater during migraine headache regardless of conditioning stimuli (F(1, 8)=18.89, p<.05, ηp² =.57). Sound sensitivity was greater during a migraine headache except during the dark conditioning stimulation although the main effect for migraine was only approaching significance (main effect of migraine F(1, 8)=4.52, p.066, ηp² =.36; Start t(9)=2.86, p<.05; Baseline t(9)=2.29, p<.05; Dark t(9)=1.82, N.S.; Bright Light t(9)=2.46, p<.05). The inclusion of the bright light stimuli with the trigeminal stimulation resulted in an increase in all symptoms of migraine regardless of group. Migraine sufferers between migraine had a more intense headache after the bright light stimulation than controls (dark vs. light x group interaction F(1, 39)=7.49, p<.05). During migraine a dark environment decreased both light sensitivity (M=1.06) (condition x migraine interaction F(4,32)=3.14, p<.05) and unpleasantness (M=2.61) (condition x migraine interaction F(4,32)=3.14, p<.05) compared to the ratings collected at the beginning of the session (light sensitivity M=3.72; unpleasantness M=4.33).
Table 8-1: F Ratios (degrees of freedom) for ANOVA for all stimuli.

<table>
<thead>
<tr>
<th></th>
<th>Light Pain</th>
<th>Light Glare</th>
<th>Sound Pain</th>
<th>Loudness</th>
<th>Sound Discomfort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensity (Linear)</td>
<td>24.2 (1,37)*</td>
<td>100.6 (1,37)*</td>
<td>70.68 (1,39)*</td>
<td>271.01 (1,38)*</td>
<td>118.8(1,38)*</td>
</tr>
<tr>
<td>Group</td>
<td>4.18 (1,37)*</td>
<td>.18 (1,37)</td>
<td>1.33 (1,39)</td>
<td>.16 (1,38)</td>
<td>.21 (1,38)</td>
</tr>
<tr>
<td>Intensity x Group</td>
<td>1.51 (2.488.65)</td>
<td>1.51(2.69,99.58)</td>
<td>.85(1.69,66.12)</td>
<td>1.68(2.29,86.93)</td>
<td>3.81(1.9,72.23)*</td>
</tr>
<tr>
<td>During Migraine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensity (Linear)</td>
<td>8.75 (1,7)*</td>
<td>74.09 (1,7)*</td>
<td>59.65 (1,9)*</td>
<td>112.24 (1,9)*</td>
<td>147.67 (1,9)*</td>
</tr>
<tr>
<td>Migraine</td>
<td>9.15 (1,7)*</td>
<td>10.02 (1,7)*</td>
<td>11.99 (1,9)*</td>
<td>3.23 (1,9)</td>
<td>9.31 (1,9)</td>
</tr>
<tr>
<td>Intensity x Migraine</td>
<td>1.68 (2.4,16.77)</td>
<td>.38 (2.73,19.1)</td>
<td>2.52 (3,27)</td>
<td>.14 (3,27)</td>
<td>.69 (3,27)</td>
</tr>
</tbody>
</table>

* Denotes significance at .05 alpha level
Figure 8-1: Visual stimuli pain (a) and glare (b) ratings in controls and migraine sufferers between and during migraines. Error bars represent SEM. Bright light was rated as more painful during a migraine and by migraine sufferers between migraine.
Figure 8-2: Auditory stimuli pain (a), loudness (b) and discomfort (c) ratings in controls and migraine sufferers between and during migraines. Error bars represent SEM. Sound was rated as more painful during a migraine.
Start
Baseline Stimuli
Dark
Light
Sound

a. Headache Rating (0-10)
Healthy Controls (n=20)
Between migraine (n=21)
During migraine (n=10)

b. Nausea Rating (0-10)

Healthy Controls (n=20)
Between migraine (n=21)
During migraine (n=10)

Nausea Rating (0-10)

Healthy Controls (n=20)
Between migraine (n=21)
During migraine (n=10)

Dizziness Rating (0-10)

Healthy Controls (n=20)
Between migraine (n=21)
During migraine (n=10)

Dizziness Rating (0-10)

Healthy Controls (n=20)
Between migraine (n=21)
During migraine (n=10)

Drowsiness Rating (0-10)
Figure 8-3: Symptoms of Migraine after noxious sensory stimulation. a. = headache; b.=nausea; c.=dizziness; d.=drowsiness; e.=perceived body temperature; f.=sound sensitivity; g.=light sensitivity; h.=unpleasantness. Error bars represent SEM. Light and sound sensitivity (except during darkness) were significantly greater during a migraine headache.
Table 8-2: Migraine Symptom Rating F ratios (degrees of freedom).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Headache</th>
<th>Nausea</th>
<th>Dizziness</th>
<th>Drowsiness</th>
<th>Perceived Body Temperature</th>
<th>Sound Sensitivity</th>
<th>Light Sensitivity</th>
<th>Unpleasantness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>3.57 (2.08,81.33)*</td>
<td>2.97 (1.89,73.77)</td>
<td>3.28 (2.24,87.25)*</td>
<td>4.86 (2.27,88.8)*</td>
<td>2.82 (2.29, 89.16)</td>
<td>2.37 (1.72,67.09)</td>
<td>22.75 (1.72, 66.88)*</td>
<td>19.41 (2.76,107.55)*</td>
</tr>
<tr>
<td>Group</td>
<td>.001 (1.39)</td>
<td>.08 (1.39)</td>
<td>.12 (1.39)</td>
<td>.23 (1.39)</td>
<td>.38 (1.39)</td>
<td>.02 (1.39)</td>
<td>.66 (1.39)</td>
<td>.68 (1.39)</td>
</tr>
<tr>
<td>Condition x Group</td>
<td>5.46</td>
<td>.79</td>
<td>.24</td>
<td>2.26</td>
<td>.64</td>
<td>.32</td>
<td>2.57</td>
<td>.96</td>
</tr>
<tr>
<td>Group</td>
<td>(2.08,81.33)*</td>
<td>(1.89,73.77)</td>
<td>(2.24,87.25)</td>
<td>(2.27,88.8)</td>
<td>(2.29, 89.16)</td>
<td>(1.72,67.09)</td>
<td>(1.72, 66.88)</td>
<td>(2.76,107.55)</td>
</tr>
</tbody>
</table>

Table 8-2b: Migraine Symptom Condition Comparison p-values

<table>
<thead>
<tr>
<th>Condition</th>
<th>Headache</th>
<th>Nausea</th>
<th>Dizziness</th>
<th>Drowsiness</th>
<th>Perceived Body Temperature</th>
<th>Sound Sensitivity</th>
<th>Light Sensitivity</th>
<th>Unpleasantness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>.02*</td>
<td>.03*</td>
<td>.072</td>
<td>.003*</td>
<td>.002*</td>
<td>.035*</td>
<td>.457</td>
<td>.001*</td>
</tr>
<tr>
<td>Start &amp; Dark Comparison (α)</td>
<td>.004*</td>
<td>.019*</td>
<td>.017*</td>
<td>.005*</td>
<td>.017*</td>
<td>.035*</td>
<td>.000*</td>
<td>.000*</td>
</tr>
<tr>
<td>Start &amp; Sound Comparison (α)</td>
<td>.002*</td>
<td>.033*</td>
<td>.024*</td>
<td>.091</td>
<td>.068</td>
<td>-</td>
<td>.008*</td>
<td>.000*</td>
</tr>
</tbody>
</table>

* p<.05
8.3.3 Light Evoked Pain during Trigeminal Nociception (Figure 8-4)(Table 8-3)

Whilst trigeminal nociception did not affect the pain rating given in response to a 500 lux visual stimulus in healthy controls (500 lux stimulus M=1.85, SEM=.63; 500 lux stimulus during trigeminal nociception M=1.82, SEM=.52), migraine sufferers between attacks rated the visual stimulus as less painful during trigeminal nociception (500 lux stimulus M=3.09, SEM=.61; during trigeminal nociception M=2.29, SEM=.51) (group X condition interaction F(1,39)=4.47, p<.05, ηp^2 =.103). However a combination of a migraine headache and trigeminal nociception resulted in an increase in the light evoked pain rating in migraine sufferers during a migraine headache (500 lux stimulus M=4.44, SEM=.93; during trigeminal nociception M=4.94, SEM=1.02) (migraine X condition interaction F(1,8)=5.26, p=.051, ηp^2 =.397).

Table 8-3: F Ratios (degrees of freedom) for ANOVAs for light evoked pain ratings to noxious visual stimuli with no trigeminal stimulation and during trigeminal stimulation.

<table>
<thead>
<tr>
<th>Pain</th>
<th>Between Groups</th>
<th>Condition x Group</th>
<th>During Migraine</th>
<th>Condition x Migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5.06 (1,39)*</td>
<td>4.47 (1,39)*</td>
<td>5.26 (1,8)#</td>
</tr>
<tr>
<td>Condition</td>
<td>1.18 (1,39)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group x Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>.05 (1,8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>19.17 (1,8)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition x Migraine</td>
<td>5.26 (1,8)#</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p< .05; #p=.051
Figure 8-4: Pain ratings in response to noxious visual stimuli with no trigeminal stimulation and during trigeminal stimulation. Migraine headache and trigeminal stimulation significantly increased light evoked pain.

### 8.3.4 Pain Ratings to Electrical Stimuli (Figure 8-5) (Table 8-4)

Between attacks of migraine, there were no overall group differences in pain ratings to the electrical stimuli regardless of the presence of noxious sensory conditioning stimuli (main effect of group $F(1,39)=1.16$, N.S.). Pain ratings in response to the electrical stimuli did not differ between baseline ($M=2.63$, SEM=.25) and the presence of bright light ($M=2.46$, SEM=.23) but decreased during complete darkness ($M=1.92$, SEM=.19) (baseline vs. darkness post hoc comparison $p<.01$) (main effect of condition $F(1.34,52.14)=3.91$, $p<.05$). The electrical stimuli were not rated as more painful during a migraine headache during bright light exposure (condition X migraine interaction headache $F(1.25,11.27)=1.15$, N.S.).
Figure 8-5: Pain ratings to Electrical Stimuli. Error bars represent SEM. Pain ratings significantly decreased during darkness.
Table 8-4: Pain Ratings and Nociceptive Blink Reflex F ratios (degrees of freedom).

<table>
<thead>
<tr>
<th></th>
<th>Pain Ratings</th>
<th>BR Count</th>
<th>Mean AUC</th>
<th>Mean Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Between Groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>3.91 (1.34,52.14)*</td>
<td>4.28</td>
<td>3.97 (2,64)*</td>
<td>.44 (2,44)</td>
</tr>
<tr>
<td></td>
<td>(1.83,71.23)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>1.16 (1,39)</td>
<td>2.96 (1,39)</td>
<td>.04 (1,32)</td>
<td>1.3 (1,22)</td>
</tr>
<tr>
<td>Condition x Group</td>
<td>.86 (1.34,52.14)</td>
<td>2.63</td>
<td>.21 (2,68,076)</td>
<td>1.07 (2,44)</td>
</tr>
<tr>
<td></td>
<td>(1.83,71.23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>During Migraine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>5.01 (1.3,11.66)*</td>
<td>1.91 (1.28,10.2)</td>
<td>1.81 (1.02,7.17)</td>
<td>.66 (2,10)</td>
</tr>
<tr>
<td>Migraine</td>
<td>3.15 (1,9)</td>
<td>3.05 (1,8)</td>
<td>1.3 (1,7)</td>
<td>.16 (1,5)</td>
</tr>
<tr>
<td>Condition x Migraine</td>
<td>1.15 (1.25,11.27)</td>
<td>1.66 (2,16)</td>
<td>1.46 (1.05,7.32)</td>
<td>1.38 (2,10)</td>
</tr>
</tbody>
</table>

* p<.05

Table 8-4b: Pain Ratings and Nociceptive Blink Reflex Condition Comparison p-values.

<table>
<thead>
<tr>
<th></th>
<th>Pain Ratings</th>
<th>BR Count</th>
<th>Mean AUC</th>
<th>Mean Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Between Groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline &amp; Dark</td>
<td>.000*</td>
<td>.006*</td>
<td>.007*</td>
<td>.622</td>
</tr>
<tr>
<td>Comparison (α)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline &amp; Light</td>
<td>.603</td>
<td>.019*</td>
<td>.131</td>
<td>.304</td>
</tr>
<tr>
<td>Comparison (α)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dark &amp; Light</td>
<td>.06</td>
<td>.66</td>
<td>.23</td>
<td>.697</td>
</tr>
<tr>
<td>Comparison (α)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>During Migraine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline &amp; Dark</td>
<td>.001*</td>
<td>.051</td>
<td>.196</td>
<td>.401</td>
</tr>
<tr>
<td>Comparison (α)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline &amp; Light</td>
<td>.58</td>
<td>.126</td>
<td>.248</td>
<td>.377</td>
</tr>
<tr>
<td>Comparison (α)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dark &amp; Light</td>
<td>.038*</td>
<td>.45</td>
<td>.19</td>
<td>.98</td>
</tr>
<tr>
<td>Comparison (α)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p<.05
8.3.5 Nociceptive Blink Reflex (Table 8-4)

The number of nociceptive blink reflexes was significantly lower during noxious conditioning with bright light and complete darkness compared with baseline (Figure 8-6). The area under curve was significantly inhibited during complete darkness (Figure 8-7). Latency was not affected by bright light or darkness (Figure 8-8). There were no significant group interactions for any of the blink reflex parameters between the healthy controls and migraine sufferers between attacks. Migraine did not affect any of the parameters.

Figure 8-6: Response count of blink reflexes during the baseline, darkness, and bright light (null responses not counted). Error bars represent SEM. Frequency was significantly decreased during darkness and bright light exposure.
Figure 8-7: Mean area under the curve of blink reflexes during the baseline and during darkness, and bright light (null responses as missing values). Error bars represent SEM. AUC was significantly inhibited during darkness.

Figure 8-8: Mean latency of blink reflexes during the baseline, darkness, and bright light. Error bars represent SEM.
8.4 Discussion

The effect of bright light on the nociceptive blink reflex has not been tested previously. I used the nociceptive blink reflex during bright light stimulation to explore the mechanism of photophobia in migraine.

8.4.1 Summary (Table 8-5)

As hypothesised, photophobia and phonophobia increased during migraine headache. Photophobia was also greater in migraine sufferers during the headache-free interval than controls as they rated the bright light as more painful. However, there was no difference in phonophobia between the control group and the migraine sufferers between attacks. The combination of bright light with the trigeminal electrical stimuli resulted in an increase in all symptoms of migraine regardless of group. Between attacks, migraine sufferers had a more intense headache after the bright light stimulation than controls. As might be expected, exposure to a completely dark environment during a migraine headache reduced light sensitivity and ratings of unpleasantness.

Trigeminal nociceptive stimulation did not affect the pain rating to the bright light stimulus given by the control group but unexpectedly migraine sufferers between migraines rated the bright light as less painful during trigeminal nociceptive stimulation than controls. As hypothesised, during a migraine headache, further trigeminal nociceptive stimulation resulted in an increase in the pain rating given in response to the bright light.

The hypothesis that migraine sufferers would have a greater rating of pain to the electrical stimuli after bright light exposure, and that the presence of a migraine would make this effect even greater during bright light exposure, was not supported as there was no overall group differences in pain ratings to the electrical stimuli regardless of the presence of noxious
conditioning with bright light. Pain ratings in response to the electrical stimuli did not differ between baseline and the presence of bright light but decreased during darkness regardless of group. The electrical stimuli were only marginally rated as more painful during a migraine headache but bright light exposure did not affect these ratings.

The hypothesis of facilitation of nociceptive blink reflexes during exposure to bright light was not supported as there were no group differences during any of the conditioning stimuli for any of the blink reflex parameters. Furthermore, the presence of a migraine did not affect any of the parameters during any of the conditioning stimuli.

With regard to the hypothesised interictal and ictal development of sensitisation after trigeminal excitation in migraine sufferers, there was some evidence of sensory sensitisation in migraine sufferers during a migraine and between migraine headaches. Pain ratings given in response to the bright light during a migraine increased, suggesting that trigeminal stimulation like that involved in a migraine headache could heighten sensory discomfort.
### Table 8-5: Summary of Main Findings

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photophobia &amp; phonophobia would ↑ during migraine</td>
<td>Photophobia and phonophobia increased during migraine headache.</td>
</tr>
<tr>
<td>Photophobia but not phonophobia would persist between migraine.</td>
<td>Photophobia was greater in migraine sufferers during the headache-free interval and there was no difference in phonophobia between migraines.</td>
</tr>
<tr>
<td>Light sensitivity would ↑ during trigeminal irritation, particularly during migraine.</td>
<td>Migraine and trigeminal irritation increased photophobia.</td>
</tr>
<tr>
<td>Pain in response to the trigeminal irritation after bright light exposure would increase in migraineurs.</td>
<td>Not supported. There was no overall group differences in pain ratings to the electrical stimuli regardless of the presence of noxious conditioning with bright light.</td>
</tr>
<tr>
<td>Facilitation of nBR during bright light.</td>
<td>Not supported.</td>
</tr>
<tr>
<td>Interictal and ictal development of sensitisation after trigeminal excitation in migraine sufferers</td>
<td>Pain ratings in response to the bright light increased during a migraine, suggesting that trigeminal stimulation could heighten sensory discomfort.</td>
</tr>
<tr>
<td>Additional Findings</td>
<td>Bright light and trigeminal irritation increased migraine symptoms in all participants. Bright light and trigeminal irritation increased headache in migraine sufferers.</td>
</tr>
</tbody>
</table>

### 8.4.2 Previous Research

The quantitative support of the presence of phonophobia during migraine but not during the headache-free interval concurs with findings reported by Drummond and Woodhouse (Drummond & Woodhouse, 1993; Woodhouse & Drummond, 1993). The increase in photophobia after a bright light challenge in migraine sufferers during and between attacks in the current study supports the postulate put forward by Drummond that dysfunction in a central sensory processing mechanism is responsible for increased sensitivity to sensory stimulation in migraine sufferers. The increase in headache for both groups (controls and
interictal migraine sufferers) after both aversive light and sound stimuli suggests that incoming stimuli can accentuate headache (Riley, 1932, as cited in Linde et al, 2006).

The lack of effect of bright light on pain evoked by supraorbital electrical stimuli does not support the hypothesis that bright light stimulation increases pain in the distribution of the supraorbital nerve. This finding does not agree with the previously presented research that demonstrated a decrease in pain thresholds after a noxious visual stimulus (Drummond, 1997; Drummond & Woodhouse, 1993; P. A. Kowacs, et al., 2001). However, the stimuli used as the test stimuli in prior studies may have been more intense, widespread, or activated proportionally more C-fibres than A\(\delta\) fibres than the stimulus used in the current study. In particular, the test stimuli used in the current study were shorter and likely weaker than stimuli used in the other studies, so there may have been less trigeminal discharge and less opportunity for interaction with visual stimuli. This might also explain why none of the nociceptive blink reflex parameters were altered during exposure to bright light in migraine sufferers.

8.4.3 Theoretical Implications

The findings of the current study may help to clarify mechanisms of photophobia in migraine. The first pathway that has been well established is that of the hyperexcitable visual cortex in migraine sufferers to bright light both interictally and ictally (Bulloche, et al., 2010; Denuelle, et al., 2011). This is consistent with the present finding that, between attacks, migraine sufferers had a greater increase in light sensitivity after a bright light challenge than controls.

The other pathway for photophobia in migraine is the known relationship between visual discomfort to bright light and the trigeminal nociceptive system. Noseda et al (2010)
investigated 20 blind human participants who suffered from migraine related photophobia. In the six blind participants who suffered either optic nerve damage or bilateral enucleation of the eyes, deficient pupillary light responses were observed, suggesting that ictal photophobia in migraine patients is mediated by retino-thalamo-cortical-trigeminovascular pathway. Similarly, Dolgonos et al (2011) detected a facilitated supraorbital blink reflex in optic nerve lesioned rats during bright light stimulation. They suggested that the associational ganglion cells could be the intraretinal mechanism responsible for photophobia in patients without light perception. These associational ganglion cells are independent of the central visual pathways and do not converge on the optic nerve (Dolgonos, et al., 2011). Dolgonos et al suggested that trigeminal nociceptors which are densely populated in the pars plana of the ciliary body could be activated by the proximal axons of the associational ganglion cell axons that project to the retinal periphery, thereby sensitizing the spinal trigeminal nucleus neurons. Although in the current study the nociceptive blink reflex was not facilitated there were other indications of sensitized trigeminal nucleus neurons, such as an increase in headache after bright light exposure. Additionally, bright light was rated as more painful during attacks of migraine, possibly due to trigeminal sensitisation.

The mechanism of phonophobia during migraine can be explained not by peripheral or end-organ dysfunction but by the central sensitisation that occurs in the third order – thalamo-cortical neurons during migraine (Burstein, et al., 2010; Moulton, et al., 2008). This thalamo-cortical sensitisation could also provide an explanation for osmophobia which also occurs occasionally during migraine.

8.4.4 Conclusion

Photophobia and phonophobia were present during attacks of migraine. This study supports summative trigeminal activation during a migraine resulting in greater photophobia. Neither
subjective nor physiological responses to the nociceptive blink reflex stimulus were affected by bright light exposure. Although symptoms increased during migraine, trigeminal nociceptive stimuli delivered by the concentric electrode did not induce or aggravate these symptoms, presumably because they were intermittent, brief, and mild. An increase in headache after bright light exposure is consistent with sensitized trigeminal nucleus neurons that underlie a retino-trigemino pathway for photophobia.
Chapter 9  General Discussion

9.1  Summary (Table 9-1)

The main aim of this research was to explore the nociceptive processing pathways of migraine and to determine whether the blink reflex in response to an electrical stimulus is a useful marker of these pathways during migraine. The main findings are summarised in Table 9-1.

The purpose of the first study was to validate the use of a concentric electrode in investigating trigeminal nociceptive processing pathways in migraine sufferers and healthy controls. The nociceptive specific blink reflex electrode depolarised the Aδ and/or C-fibre free nerve endings as demonstrated by a significant reduction in blink reflex frequency and area under the curve after the application of a local anaesthetic, whilst there was no change in blink reflex parameters in response to the control stimulus. This effect was clearly present in the healthy controls. In the migraine group, blink reflex area under the curve was reduced but the local anaesthetic did not completely inhibit the blink reflex, as illustrated in the lack of significant decreases in blink reflex frequency. Taken together, these findings suggest that trigeminal hypersensitivity persists interictally in migraine sufferers. In contrast to blink reflexes, pain ratings to electrical stimuli were similar in migraine sufferers and controls before and after the application of local anaesthetic agent. Thus, trigeminal hyperexcitability apparently did not influence sensations evoked by the intermittent electrical stimuli.

The purpose of the second study was to determine whether ingestion of hypertonic saline would induce greater nausea in migraine sufferers than controls, and whether this would modulate trigeminal nociceptive processing. Headache increased in response to trigeminal stimulation after participants ingested the hypertonic saline, suggesting that vagal nerve
stimulation (and thereby pathways involved in processing gastrointestinal sensations in the nucleus tractus solitarius) may have a sensitising influence on trigeminal pain processing. This might explain why the hypertonic saline also augmented scalp tenderness and pain evoked by high intensity electrical stimuli applied to the supraorbital region. The findings provided weak evidence to suggest a trigemino-solitarii-trigemino feedback loop in humans, but it seems likely that cortical influences play a major role in the impact of nausea on headache during migraine attacks. Blink reflexes to electrocutaneous trigeminal stimuli were similar in migraineurs and healthy volunteers. Nausea did not influence blink reflexes but was associated with heightened scalp tenderness and other symptoms of migraine.

The final series of studies in this thesis investigated the symptoms of migraine, pain ratings and physiological parameters of the blink reflex during trigeminal stimulation with a nociceptive electrical stimulus to the supraorbital region both in healthy volunteers and during and between attacks of migraine. Scalp tenderness decreased in healthy controls across the session but increased in migraine sufferers between migraine attacks, whilst ratings increased for both groups in response to pressure applied to the fingers. All pressures were rated as more painful during migraine, and ratings increased across the session when the higher intensity pressures were applied to the forehead. These findings are consistent with increased excitability of the trigeminal system after nociceptive activation, which supports the theory of trigeminal sensitization during migraine. Neither pain ratings to the electrical stimuli nor nociceptive blink reflex parameters differed between controls and migraine sufferers between attacks. However, consistent with trigeminal sensitisation during migraine, the stimuli were rated as more painful during migraine headache. Possible temporal summation of pain ratings was identified in migraine sufferers during migraine headache when a painful noxious (cold) stimulus was applied to the same region as the migraine headache, supporting the postulate that headache is associated with activation of trigeminal
nociceptive fibres or their central destinations. However, the hypothesized facilitation of the nociceptive blink reflex during application of the homosegmental noxious conditioning stimulus did not occur. In fact, both subjective and physiological responses to the nociceptive trigeminal stimuli were inhibited in healthy controls and in migraine sufferers during the headache-free interval, suggesting the occurrence of diffuse noxious inhibitory control mechanisms. Photophobia and phonophobia were present during migraine. Photophobia increased in migraine sufferers during the headache-free interval after noxious sensory stimuli whereas phonophobia did not. Summative trigeminal activation during a migraine augmented photophobia. Neither subjective nor physiological responses to the nociceptive blink reflex stimulus were affected by bright light exposure. An increase in headache after bright light exposure is consistent with a retino-trigemino pathway for photophobia. Pain ratings to the electrical stimuli increased during migraine headache. There were no differences in any of the nociceptive blink reflex parameters between healthy controls and interictal migraine sufferers during any of the conditioning stimuli, suggesting that the electrical stimuli from the concentric electrode didn’t evoke signs of trigeminal hyperexcitability under the conditions employed in the experiment.

Migraine increased the blink reflex count with there being less blinks evoked on the contralateral side between attacks but this finding was not strong enough to completely support the hypothesised nociceptive blink reflex facilitation during migraine. This might be due to the small sample size and the use of a community sample. The hypothesised progression of sensitisation after trigeminal excitation was not detected in migraine sufferers either in the subjective or physiological data in the final series of studies, either between or during attacks of migraine.
The experimental effects were more obvious with the self-report measures than the blink reflex results. Except for the finding from the first study (the effect of local anaesthetic on the nociceptive blink reflex), in general blink reflexes were similar in migraine sufferers and controls. A number of reasons could be responsible for the lack of findings in the nociceptive blink reflex data. Firstly, the blink reflex in response to a single, brief (0.3ms) and low-intensity (2mA) pulse may not have been a strong stimulus of trigeminal nociception. The nociceptive blink reflex to the stimuli used in the latter studies had large individual variability. A combination of the large individual variability of the blink reflex and the small sample sizes could be another reason for the lack of significant findings in this data. Additionally, the repetition of the same weak stimulus could possibly lead to an adaptation process, in which the stimulus no longer evokes a response – whether this be behavioural (in which the stimulus is no longer relevant) or neuronal (in which the neuron does not depolarise in response to the stimulus). Overall, the nociceptive blink reflex was not a correlate of the participant’s subjective experience.
Table 9-1: Summary of Main Findings

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Nociceptive blink reflexes less inhibited by local anaesthetic in migraineurs</td>
</tr>
<tr>
<td>3</td>
<td>Peripherally induced nausea increased headache in all participants</td>
</tr>
<tr>
<td></td>
<td>Peripherally induced nausea increased scalp tenderness in all participants</td>
</tr>
<tr>
<td>5</td>
<td>Migraine and trigeminal irritation increased scalp tenderness</td>
</tr>
<tr>
<td>6</td>
<td>Trigeminal irritation increased headache in all participants</td>
</tr>
<tr>
<td></td>
<td>Migraine increased pain ratings to trigeminal irritation</td>
</tr>
<tr>
<td></td>
<td>Migraine increased the number of evoked blink reflexes</td>
</tr>
<tr>
<td>7</td>
<td>Painful stimulus and trigeminal irritation increased headache in all participants</td>
</tr>
<tr>
<td></td>
<td>Painful homosegmental stimulus more painful during migraine</td>
</tr>
<tr>
<td>8</td>
<td>Bright light and trigeminal irritation increased migraine symptoms in all participants</td>
</tr>
<tr>
<td></td>
<td>Bright light and trigeminal irritation increased headache in migraine sufferers</td>
</tr>
<tr>
<td></td>
<td>Migraine and trigeminal irritation increased photophobia</td>
</tr>
</tbody>
</table>

**9.2 Theoretical Implications (Figure 9-1)**

Trigeminal dysfunction/sensitization has been observed during migraine and in migraine sufferers in the headache free period. Although some suggest that neuronal hyperexcitability is an oversimplified and misleading explanation of migraine pathophysiology (Coppola, Pierelli, et al., 2007), sensitisation during migraine has been detected by various researchers in various modalities, including the blink reflex. Migraine sufferers are abnormally sensitive to sensory stimuli including light and sound, nausea and noxious tactile stimuli, and all of these stimuli can be related to central sensitisation in trigeminal nociceptive pathways (DaSilva, et al., 2007; Drummond, 1987). Central sensitisation has been defined as hyperexcitability, increased spontaneous activity and increased receptive fields in central
wide dynamic range neurons that is secondary to increased primary afferent activity (Dougherty & Lenz, 1994; Willis et al, 1996, as cited by Eide, 2000). This means that the increased responses in the wide dynamic range neurons occur after the increased activity in first order neurons due to nerve or tissue injury – or in the case of migraine perhaps after exposure to inflammatory agents. Alternatively, release of inhibitory controls on activity in wide dynamic range neurons in trigeminal nuclei might contribute to migraine.

Temporal summation of painful stimuli is a common feature of nociceptive pathway sensitisation (Woolf, 2007). During nitric oxide donor (Glyceryl trinitrate) provocation, temporal summation of nociceptive inputs occurred at spinal level in migraine sufferers but not in controls (Perrotta et al., 2011). Thus, susceptibility to migraine could also be intrinsically related to dysfunction in trigeminal nociceptive transmission.

The trigeminal system and central sensitisation were investigated in nociceptive blink reflex (Ayzenberg, et al., 2006) and imaging studies (DaSilva, et al., 2007; Moulton, et al., 2008) in interictal migraine sufferers. Ayzenberg et al (2006) suggested that sensitisation of central nociceptive mechanisms occurs at the supraspinal level rather than the trigeminal system in the brainstem and DaSilva et al (2007) reported permanent changes in the trigeminal somatosensory system and pain modulatory circuits in migraine sufferers. This was also supported by Moulton et al (2008) who suggested that the sensitisation occurs beyond the first order neurons, in the second (trigemino-thalamic) and third order (thalamo-cortical) neurons.
Figure removed due to copyright restrictions

Figure 9-1: Neural Processes that might contribute to migraine. Adapted from Drummond (Drummond, 2012) and Bruining (Bruining, 2004).
The findings of the first study (the effect of local anaesthetic on the nociceptive blink reflex) in which interictal migraine sufferers’ blink reflexes were not as inhibited by a topical local anaesthetic as controls could be explained by the sensitisation of the second order rather than primary afferent neurons. Interestingly, when healthy controls were challenged with various migraine symptom provocations, they also reported increased headache and pain. This suggests that activating the somatosensory pathways with noxious conditioning stimuli could sensitise the second and third order neurons that are active during migraine. These findings could also lend support to Drummond’s cyclical theory of migraine in which symptoms build upon each other in a vicious cycle. Physiologically, this theory can also be supported by the findings of the current thesis that demonstrate summation of excitation via multiple stimuli that could recruit greater numbers of afferents causing more intense headache and pain.

The experimental effects that were observed during migraine (increased scalp tenderness, pain in response to the electrical stimuli and photophobia) could be explained by summation – whether it be temporal, spatial, or cross-modal, with the summation being demonstrated in the higher cortical regions by greater self report measures suggesting the sensitisation of second order neurons.

The present findings indicated that a single nociceptive stimulus of 2 mA from a concentric electrode was not sufficient to elicit signs of trigeminal sensitisation. A large number of trigeminal nociceptors are likely to be activated during migraine, whereas the electrical stimulus might have recruited fewer nociceptive afferents because the stimulus was brief and weak. The concentric electrode used in the current studies consisted of an anode (or outer ring) that surrounded a very small cathode, thereby allowing the current flow to penetrate the skin surface and stimulate dermal and epidermal free nerve endings (primarily nociceptors).
The present findings indicate that scalp tenderness and the nociceptive blink reflex are not synonymous because temporal summation was detected for pain ratings to scalp pressure but not for pain ratings to the nociceptive specific stimulus employed to evoke blinks. This may be an important finding because the deep pressure pain evoked by the algometer is similar to visceral pain experienced during migraine whereas the concentric electrode evokes a more superficial somatic pain.

The lack of the experimental effects on the nociceptive blink reflexes evoked by the brief, weak electrical stimulus has implications for migraine research. Important mechanisms may be overlooked if only this intensity of stimuli is used. More nociceptive fibres were activated by the conditioning stimuli in the final set of studies which might have resulted in temporal summation of pain during migraine and during the conditioning paradigms.
9.3 Limitations

One of the major limitations of this research was low sample numbers (especially during migraine). Linde et al (2006) commented that the low participation rate in their study was due to the reluctance of migraine sufferers to endure an attack without treatment. This could also apply in the current study because not only did participants have to endure the migraine attack untreated but they also had to undergo methodological protocols that could potentially intensify the attack (such as trigeminal pain, bright light and loud noise). However, Linde et al (2006) with the aid of Max (2002, as cited in Linde et al, 2006) pointed out the usefulness and importance of small populations in elucidating principles and pathophysiological mechanisms of migraine symptoms.

Another major limitation was the concentric electrode 2mA stimuli. The stimuli were not intense enough to evoke physiological signs of trigeminal sensitization. Although all of our migraine sufferers met the criteria for migraine headaches (2004), the migraine sample was recruited from the community rather than a hospital setting. In addition, a selection bias could have occurred because the research was undertaken at a university campus and used a convenience sample. This may have implications in terms of how far the findings generalize to clinical samples as it seems likely that frequent and/or intense headache episodes are associated with detrimental effects on central and peripheral nociceptive processing. The recruitment process may also explain why results varied from those reported in other major studies.

Gender and age could affect temporal summation in humans (Eide, 2000). However, this is unlikely to have affected differences between migraine sufferers and controls as all healthy control samples were age-matched to the migraine sample.
Extracephalic allodynia (e.g., development of tenderness in the fingertips in the present series of studies) must be mediated by structures other than the nucleus tractus caudalis because this structure does not have whole body receptive fields (Lovati, et al., 2009). The sensitisation of thalamic neurons has been observed by fMRI during extracephalic allodynia in both rats and ictal migraine patients (Burstein, et al., 2010). Burstein et al (2010) suggest that this hypersensitivity of the thalamic neurons could also be responsible for the location of hypersensitivity to other nonnoxious stimuli (light, sound, odours) because this is the location of the convergence of cranial meninges nociceptive input and other sensory information. This is particularly pertinent to the results in this thesis because subjective ratings to the more intense (second pain) evoking stimuli increased after provocation.
9.4 Future Research

Replicating these studies on a clinical sample of migraine patients would be worthwhile because headaches in the convenience migraine sample used in the current thesis may not have been as chronic as in participants used in other research. Chronicity may cause more hypersensitivity within the trigeminal and central pain modulating systems between migraine or constant trigeminal irritation because the trigeminal system is always activated (when one migraine just leads into another).

Unfortunately, symptoms of migraine were not recorded after the sets of stimuli in the first study. This meant that migraine symptoms could not be analysed after the barrage of high intensity concentric stimuli. Replicating the first study (nociceptive blink reflex after local anaesthetic) on a clinical sample of interictal migraine patients possibly using a triple train pulse (Giffin, et al., 2004) and adding migraine symptoms as another measured dependent variable would be valuable. Giffin et al (2004) found that the triple pulse from the concentric electrode was the most effective stimulus train to illustrate DNIC. But it is unknown as to whether the blink reflex elicited by a triple pulse is inhibited by a topical local anaesthetic (Kaube, et al., 2000). With a triple pulse stimulus recruiting a greater number of afferent fibres, it may be possible that this trigeminal irritation could be sufficient to sensitise the first order trigeminal neurons and trigger the sensitisation cascade in interictal migraine patients. Measuring migraine symptoms throughout this suggested paradigm could give greater clarity about the relationship between this process and other symptoms that occur during a migraine attack such as headache, nausea, photophobia and phonophobia.

It would be interesting to replicate the studies with C-fibre activating test stimuli as these stimuli would more closely resemble the neurophysiological properties (C-fibre activation) which occur during a migraine (Silberstein, 2004). Migraine research has been conducted
using laser stimuli measuring cortical reflexes, such as the laser evoked potential (LEP) (de Tommaso, 2008). The main findings from these studies is that using the LEP during migraine has illustrated an abnormal regulation of cortical pain processing in migraineurs (de Tommaso, 2008). However, the laser parameters can be adjusted such that only C-fibre activation occurs, resulting in an ultra-late potential in the electroencephalogram representing the conduction velocity of the unmyelinated pain fibres (Cruccu et al., 2003), and this is the most pertinent reason for recommending this paradigm. The LEP is facilitated in migraine patients (Romaniello, Iannetti, Truini, & Cruccu, 2003) but can the ultra-late potential be facilitated during migraine symptom challenges, similar to the ones used in the current thesis? Additionally, a reflex evoked in the orbicularis oculi (similar to the blink reflex) by the CO2 laser may be useful in specifically investigating a C-fibre reflex during symptom challenges.

Eide (2000) discussed the role of the NMDA receptor both in wind-up and temporal summation and suggested that pharmaceutical treatment of pain should target this mechanism. Future studies could include an NMDA receptor antagonist to test the hypothesis that the nociceptive blink reflex could be used as an indicator of wind-up in humans.
9.5 Conclusion

The current research adds to the body of literature regarding central sensitisation, the nociceptive blink reflex and migraine. A major finding from this series of studies was that sensitisation in migraine may best be investigated with test stimuli that strongly activate nociceptive afferent fibres in terms of spatial and temporal summation. Whilst there was some evidence of interictal sensitisation in migraine sufferers, another main finding of this research was the development of signs of trigeminal sensitisation in controls by temporal summation evoked by simultaneous multiple stimulation from various sources. Thus, with sufficiently intense stimulation, it might be possible to evoke symptoms of migraine in normal volunteers. If so, this would provide a convenient paradigm for testing potential migraine treatments, and for clarifying mechanisms that increase vulnerability to migraine.
Appendices
Appendix A Case Study 1

CLINICAL CORRESPONDENCE

Trigeminal neuralgia, migraine and sympathetic hyperactivity in a patient with Parry–Romberg syndrome

PD Drummond1, S Hasnal1 & PM Finch2
School of Psychology, Murdoch University, and 2North Pain Management Centre, Perth, Australia

Trigeminal neuralgia is a rare disorder of unknown aetiology that involves slowly progressive but self-limited wasting of subcutaneous tissues on one side of the face (1), usually in the distribution of a branch of the trigeminal nerve. In an internet survey of 205 people on the mailing list of the 'Parry-Romberg's Connection' site, 69% reported suffering from migraine and 46% from facial pain, almost always affecting the same side as the atrophy (2). Headaches and facial pain have also been associated with an increased frequency of migraine (8,9) and a reduced pain threshold (10,12).

We had the opportunity to examine a trigeminal and cervical sympathetic nerve function in a woman with right-sided Parry–Romberg syndrome, migraine and trigeminal neuralgia. We wished to determine whether trigeminal or cervical sympathetic hyperactivity was associated with the facial atrophy, because aberrant somatosensory function has been implicated in the pathophysiology of Parry–Romberg syndrome (11,12).

Case report

A 32-year-old woman with a long history of right hemifacial pain had developed trigeminal neuralgia in the right upper orbital region in childhood, which was diagnosed as Parry–Romberg syndrome. When she was 15 years old, scalp biopsy was removed from the right superior orbital region. Trigeminal pain started about 6 months after the cosmetic surgery. Initially, the headaches occurred every few minutes but the frequency increased progressively. When seen in June 2000, the headaches lasted around 3 days with only a few days a week of freedom before the next attack.

The patient reported that the headaches were strictly right-sided and began as an ache in the cheek, temple and supraorbital notch. The ache then gradually intensified into a stabbing sensation and eventually radiated to the right occipital region, down the right arm, and into the fifth finger. The headaches were associated with photophobia, phonophobia, nausea and vomitting. She reported that the right nostril became stuffy and the right eye felt heavy and drooping, usually during the attack. Alcohol triggered the headache within about 30 min. Other triggers included fatigue, stress, perfume, repetitive stimulation of the forehead, cold wind on the right side of her face, and light touch, particularly on the right cheek. The migrainous attacks did not respond to ergotamine or butalamine elimination.

The patient also described a continuous, jabbing neuralgia pain and tingling sensation in the right cheek and angle of the jaw, which was aggravated by cold wind and light touch on the right side of her face (e.g., shower water), particularly near the temples and cheek. She reported that these pain sensations produced a persistent ache which could last for 10 min or more and could intensify into a migraine headache. The neuralgia pain responded well to gabapentin and carbamazepine, but these drugs were discontinued because of severe side-effects. Approximately 1 month after attending the laboratory, lithium treatment was injected bilaterally above the ear, but the neuralgia pain remained unchanged.

Magnetic resonance imaging in 2001 and 2003 identified several isolated foci in the subcortical and periventricular white matter of the right frontal lobe, suggestive of deep white matter ischaemic change. No abnormality was seen in Fischel's scans along the course of the trigeminal nerves.

Sensory tests

Tactile sensitivity was investigated on each side of the face with graded cotton wool tests.

©Blackwell Publishing Ltd, Cephalalgia, 2006, 26, 1146-1149

The touch threshold was investigated on the right side of the forehead and on both sides of the face by placing a 2 mm diameter, 2 mm thick, and 3 mm long wooden pin on the forehead to elicit a sensation of touch. The pin was then moved slowly toward the face until the patient felt the sensation of touch. The touch threshold was then measured by moving the pin slowly away from the face until the patient no longer felt the sensation of touch. The touch threshold was measured on both sides of the face at 1 cm intervals.

As shown in Fig. 1, a smaller intensity of electrical current on the right side of the forehead than on the left was required to elicit the threshold of sensation (a sum of 1), the pain threshold (a sum of 2) and the unimodal component of the blink reflex, for stimulation both from multiple electrodes and from concentric electrodes. The R1 component of the blink reflex begins at around 1 ms for stimulation delivered from several electrodes, both on the affected and unaffected side.

Autonomic Tests

To investigate the autonomic response, the patient was asked to report the sensation of a cold sensation on the right side of the forehead and on both sides of the face. The cold sensation was rated as 1-5 on the right side of the forehead and 1-9 elsewhere on the face. In addition, a sensation of a warm sensation developed with the heat applied to the right forehead and chest.

Warmth and cold sensation thresholds were investigated on each side of the face with a sensor-controlled radiant heat lamp, which measured skin temperature at 3-6°C. The patient was asked to rate the warmth on the right side of the forehead as the heat intensified. A sensation was felt that developed around 42°C. In contrast, warmth was detected on the left side of the forehead at 37°C and on the right at 40°C. Warmth and heat thresholds were 4-5°C greater on the right than on the left, but all thresholds were symmetrical.

Discussion

The prevalence of Frey syndrome and facial pain appears to be greater in Frey–Romberg syndrome than in the general population. Moreover, it is well known that Frey syndrome is uncommon in the elderly, its association with Frey–Romberg syndrome is unlikely to be due to chance. Although sensory stimulation was increased with stimulation of the trigeminal nerve, thermal sensitivity was increased with stimulation of the trigeminal nerve. Taken together, these observations suggest a causal link between Frey–Romberg syndrome, Frey syndrome, and trigeminal neuralgia. This is interesting to note that semisaccharide was recorded bilaterally from the root and on the right side of the forehead, below the center of the orbit and off the superior part of the orbicularis oculi muscle.

©Blackwell Publishing Ltd, Cephalalgia, 2000, 26(1), 1196-1149
Loss of sensitivity to innocuous sensations (light touch, warmth and cold) was accompanied by heightened sensitivity to noxious pressure and heat in the atrophic region of the forehead and to a lesser extent on the cheek. Indeed, monosynaptic stimuli such as slight touch and cold induced abnormal pain sensations which spread from the site of stimulation. Furthermore, weak electrical stimulation of the supraorbital nerve evoked Jason and Frank responses-monosynaptic responses-on the affected and nonaffected side. Abnormal sensibility and sustained discharges of trigeminal nociceptive afferents are characteristic of trigeminal neuralgia. This may arise as a result of electrical or chemical cross-talk between Aβ touch afferents and nociceptive neurons in the trigeminal ganglion or trigeminal root due to denervation or axonal regrowth (15). Abnormal trigeminal sensitivity might also increase susceptibility to migraine headaches through a process of central sensitization (16).

Although sympathetic involvement in Parry-Romberg syndrome has been suggested for some time (1, 11, 12), from a practical viewpoint, this aspect of the syndrome is limited. In the present case, sympathetic activity appeared to be greater on the affected than on the unaffected side. Similarly, prolonged body heating augmented sweating on the affected side of the forehead, consistent with heightened sympathetic vasoconstrictor tone. Sympathetic activity was sustained in regions other than the affected side of the forehead, suggesting an association between sympathetic hyperactivity and subcutaneous atrophy.

Chronic sympathetic hyperactivity, possibly triggered by an inflammatory process which attacks...
An electrocardiogram (ECG) has been the mainstay in the diagnosis of coronary heart disease. However, it has been reported that patients with coronary artery disease may have normal ECGs. This has led to the development of other diagnostic tools, such as stress tests and coronary angiography, to accurately identify the presence of coronary artery disease.


diagnosis of coro

References

Appendix B Case Study 2

CLINICAL CORRESPONDENCE

Electrical stimulation decreases neuralgic pain after trigeminal deafferentation

PD Drummond & S Tekkesen-Hassel
School of Psychology, Murdoch University, Perth, WA, Australia

10.1002/ajp.2009.8.5.752

Ten years before the current investigation, a 35-year-old woman developed left facial numbness, decreased left eye closure with diplopia, an extreme left gaze, and mild left-sided contraction of the left side of the face. There was no associated numbness or pain. After the surgical procedure, the left side of the patient’s face remained numb from minor stimulation in the chin. However, most other and facial movements remained intact and peripheral byes were not required. She also had a peripherally small left pupil and partial left-sided facial tone, and the left side of her forehead did not sweat during 10-minute spells. When she was examined. After the numbness was removed, magnetic resonance imaging of the spinal cord showed increased residual tumour in the left sphenoid bone, causing pressure on the optic canal and Meckel’s cave that did not require further surgery or radiation treatment.

Several months after the meningiomas were removed, left-sided headache pain developed, all these structures of the trigeminal nerve. The pain initially responded to carbamazepine, sodium valproate and amitryptiline, but these drugs were discontinued because of unacceptable side effects. The pain continued over the next 10 years and at the time of investigation was described as a tic-like stabbing sensation above the left upper lip, in the left side of the nose, and along an indented area in the left frontal area where there had been meningiomas. The tic began as pains and needles, which quickly intensified into 5-10 painful stabs over the next 10 minutes every hour without any immediate identifiable trigger, but appeared to be aggravated by stress. The stabbing pain was superimposed on a constant dysaesthesia in the left chin, jaw and left side of the face, but neither side of the face was treated. The dysaesthesia and pains were accompanied by lacrimation, conjunctival injection or other autonomic disturbances. As few minutes later the dysaesthesia felt like tiny insects crawling around inside her face or like local anaesthesia wearing off. Asringer anaesthesia the dysaesthesia developed into a dull pain, which lasted a day, and then moved discontinuously from one side to another.

The patient provided informed consent for the investigations, which were approved by the Murdoch University Ethics Committee. Sensory testing with thin cotton wicks indicated complete loss of light touch sensation from the forehead to the chin on the left side, whereas deep pressure stimulation with thumb tickle or an algometer...
erected a dull painless sensation at each site that began at higher pressures than on the right. The patient could not detect 4 °C stimuli in the left forehead or cheeks, but could detect slight coolness in the chin. She could not detect warmth or heat pain in the left forehead, cheeks or chin when the skin was heated at 54 °C from 22 to 68 °C with a radiant heat lamp. To investigate the effect of cold on the facial pain, the patient immersed her right hand in 10 °C water for 1 min. Hand pain was rated as 6 (extremely painful) on a 0–10 scale of pain intensity, whereas facial dysesthesia decreased from 2 (mild pain) to 0 for 1–2 min. The dysesthesia gradually returned to the previous intensity over the next 10 min. Effects were similar after the patient immersed her left hand in the cold water.

On another occasion, concentric electrodes were attached to the supraorbital region on each side of the forehead, to stimulate bilateral trigeminal nociceptive afferents (13). Blink reflexes were recorded bilaterally from surface electrodes attached below the lower eyelids and 2–3 cm lateral to the lower eyelid. Current intensity (monopolar square waves: 0.3–0.6 ms duration, interstimulus interval > 15 s) was increased in 0.1–0.2 ms steps to identify the pain and blink responses. Right-side step was 1.2 ms (indicating that both facial nerves were intact) (Fig. 1). In contrast, the patient was unaware of any sensation on the left side of the forehead for stimuli up to 27 ms (the maximum intensity employed), and blink reflexes were absent (indicating that the trigeminal nerve was lesioned). At the start of the session, the left-sided stimulating pain and dysesthesia was rated at 5.2 on the 0–10 scale of pain intensity, and remained unchanged when the right side of the forehead was stimulated with electric current. However, pain decreased to 1 (mild pain) after left-sided stimulation, even though the patient did not detect any of the electrical stimuli. Pain was minimal for several hours afterwards.

Management

To determine whether the decrease in facial pain after electrical stimulation could be attributed to a phasence response, mild or strong stimuli were applied to the left side of the forehead on different occasions. Dysesthesia decreased from moderate (4) to slight (2) after 2–3 ms stimulation from the concentric electrode (monopolar square wave, 0.3 ms duration, interstimulus interval > 15 s). The patient was treated for several months with antidepressants and gabapentin, with little improvement.

Discussion

Our patient had developed neuralgia and dysesthesia dolentia several months after the left trigeminal ganglion was destroyed when a spheno-maxillary tumor was removed surgically. Although the origin of the neuralgia is unclear, one possibility is that the medial meningeal artery was compressed by the tumor, which in turn compressed the ophthalmic branch of the trigeminal nerve.
Electrical stimulation of the trigeminal ganglion sometimes alleviates dysaesthesia in patients with trigeminal neuralgia (8, 9), suggesting that different inputs inhibit the spontaneous neuronal discharge. In the present case, non-epileptic blink reflexes and most sensory modality were lost in the affected side of the face after removal of the trigeminal ganglion. Nevertheless, electrical stimulation of the affected forehead and cheek alleviated dysaesthesia and suppressed epileptic fits.

Although most facial sensations are conveyed to the central nervous system by the trigeminal nerve, certain sensations persist after section of the trigeminal sensory root (8-12). For example, Sydenham (12) has noted that sensitivity to deep pressure persisted in patients who had undergone section of the trigeminal ganglion when the trigeminal ganglion was infiltrated by an intraneural tumour or the ganglion was removed surgically. Pressure, tactile, two-point discrimination, and vibration thresholds are higher on the affected than unaffected side in patients with unilateral lower motor neuron facial nerve palsy (13), suggesting that the facial nerve distributes sensory fibres to facial tissues (most likely pressure receptors and proprioceptors in muscles) (14). However, electrical stimulation of different muscles produced no sensation. Therefore, electrical stimulation of different muscles produced no sensation. These findings suggest that the facial nerves carry a separate set of sensory fibres that project to the central nervous system after section of the trigeminal ganglion. Furthermore, the electrical stimulation of the facial nerve in patients with trigeminal neuralgia suggested that the facial nerve might provide an alternative pathway for trigeminal neuralgia (15), thereby offering an additional pathway to the nucleus that might increase or decrease in prominence in the absence of normal trigeminal input.

Electrical stimulation of the trigeminal ganglion sometimes alleviates trigeminal neuralgia in patients with trigeminal neuralgia, but it is less effective in patients with referred sympathetic pain (6, 7). Nevertheless, in the present case, electrical stimulation of the affected side of the face was beneficial despite virtually complete loss of facial sensation apart from deep pressure. Moreover, electrical stimulation of trigeminal cutaneous afferent fibres failed to reduce blink reflexes, even at stimulus intensities that would also be expected to evoke intracranial non-affective trigeminal afferents. Taken together, these findings suggest that electrical stimulation of trigeminal afferents that enter the trigeminal ganglion by a pathway that bypasses the trigeminal ganglion may be used to treat trigeminal neuralgia in patients with trigeminal neuralgia. However, this mechanism does not account for the therapeutic effect of electrical stimulation, because central stimulation of the trigeminal nerve by a peripheral nerve was ineffective.

Cursory, electrical stimuli that inhibited facial dysaesthesia produced no sensation. These findings suggest that sensation of pain and motor response to electrical stimuli are independent of the trigeminal nerve root, despite permanent loss of light touch sensations. In addition, an extremely low stimulus intensity (6-12 V) elicited a stringing or twitching sensation when applied to affected muscles or skin regions if the stimulus intensity was applied long enough for the patient to perceive it. Furthermore, this capacity was lost in patients who had undergone section of the trigeminal ganglion. Therefore, the electrical stimulation of the trigeminal ganglion by a pathway that bypasses the trigeminal ganglion may be used to treat trigeminal neuralgia in patients with trigeminal neuralgia. However, the electrical stimulation of the trigeminal ganglion by a peripheral nerve was ineffective.
Acknowledgements

The research was supported by National Health and Medical Research Council of Australia grants. 13792 awarded to P.D.M. We gratefully acknowledge the contribution of members of the Nerve Surgery Department at Royal North Shore Hospital who carried out the clinical procedures. Professor W. Lumsden commented on a draft of the manuscript, and Mr. J. Le Comte assisted with psychological testing.

References

Appendix C Case Study 3

Unpublished Case Study

Abnormal nociceptive blink reflex in a patient with episodic severe trigeminal pain.

Shiree Treleaven-Hassard

&

Peter Drummond

School of Psychology, Murdoch University, Western Australia
Introduction

The trigeminal nervous system has long been known to be involved in migraine. Our laboratory has recently investigated the trigeminal nervous system of a 53 year old who presented in an interictal period of severe idiopathic trigeminal pain. A constant sensation occurred behind her nose. Cruccu et al (1990) (Cruccu, Leandri, Feliciani, & Manfredi, 1990) suggests that trigeminal pain can be investigated with trigeminal reflexes and Cruccu et al (Cruccu et al., 2001) also suggested that the nociceptive afferent system of trigeminal neuralgia patients could possibly be dysfunctional on the painful side. Although our patient is not diagnosed with trigeminal neuralgia, a common link between our patient and trigeminal neuralgia patients may be present. Because the blink reflex arc involves nociceptive neurons, then trigeminal nociception can be investigated using the blink reflex as an investigative tool (Ellrich, 2000). It was decided that we would use the blink reflex response to two types of stimulation to investigate the patient’s trigeminal system – the normal electrode stimuli that activate the A-beta fibres and the concentric electrode stimuli that activate nociceptive specific fibres.

The blink reflex activated during supra-orbital stimulation with normal electrodes (flat surface electrodes placed over the supra-orbital foramen and 2cm dorsal) produces 3 possible responses. The earliest response is the R1 that occurs ipsilaterally between 9 and 24 msec after the stimulus (Ellrich & Treede, 1998). This pathway for this response consists of a pontine oligosynaptic arc that is mediated through one or two interneurons by fibres that project from the trigeminal principal sensory nucleus to the facial nucleus (Drummond, 2003). The second response to an electrical stimulus delivered via normal electrodes is the R2. This response occurs between 27 and 87 ms and is a bilateral multisynaptic event (Ellrich & Treede, 1998). Nerve impulses enter the pons ipsilaterally at the principal trigeminal nucleus before descending to the caudal spinal trigeminal nucleus. A medullary pathway then ascends to the ipsilateral and contralateral facial nuclei (Kimura, 1973). The third, late, R3 response occurs between approximately 85 and 120msec (Ellrich & Hopf, 1996) and is not always present and is especially not present when the stimulus is announced, suggesting it may be part of the startle response (Ellrich, et al., 2001).

The blink reflex elicited by a concentric electrode, termed the nociceptive blink reflex, only produces an R2 response, with an onset latency of about 42ms (Kaube, et al., 2000). This high current density (because the electrons flow from a small surface area) from low current intensity stimulus is delivered via a concentric electrode with small anode-cathode distance and stimulated only the superficial A-delta nerve fibres rather than the deeper A-beta fibres (Kaube, et al., 2000). Higher intensities from this electrode produces a deeper penetration of the current and therefore stimulates the A-β nerves as well (Kaube, et al., 2000).

A functional block to nociceptors did not change any component of the blink reflex in response to an electrical stimulus delivered via normal electrodes. However, the pain threshold increased (Ellrich, et al., 2001). This suggests that the blink reflex components of this type of stimulation are mediated predominantly by non-nociceptive afferents (A-Beta fibres). The nociceptive blink reflex was however reduced by 85% after a block of A-delta and C fibre function (Kaube, et al., 2000) suggesting that this type of stimulation is predominantly mediated by the nociceptive afferent system (A-delta fibres). As stated by Ellrich in numerous papers (Ellrich, 2000, 2002) this suggests that there are two conceivable pathways for the reflex arcs; the A-Beta pathway and the A-delta pathway. The difference in onset latency of the R2 between the 2 types of stimulation support the notion that the R2 of the normal electrode blink reflex is mediated by the A-Beta fibres (large myelinated) because
it is faster (30 msec) (Aramideh & Ongerboer de Visser, 2002) than the nociceptive blink reflex (at 42 msec) (Ellrich, 2002) which is mediated by the A-delta fibres (small myelinated fibres).

Ellrich and Treede (Ellrich & Treede, 1998) used the theory of Diffuse Noxious Inhibitory Controls (DNIC) to investigate if both inputs from the A-Beta and A-Delta fibres converge onto common Wide Dynamic Range (WDR) neurons (so that both reflexes share the same interneurons). WDR neurons in the spinal cord and trigeminal system are inhibited by activation of the nociceptive neurons in the subnucleus reticularis dorsalis, so remote painful stimuli would suppress the normal electrode R2 blink reflex. They found that the R2 was suppressed by 15% when a painful heat was applied to the extremities while R1 remain unchanged. However, in a similar study by Giffin et al (Giffin, et al., 2004), the nociceptive blink reflex (using the concentric electrode) in response to a single pulse stimulus was not inhibited by DNIC. This result suggests that A-Delta fibres do project onto nociceptive specific neurons rather than WDR neurons.

The aim of this case study was to investigate the patient’s trigeminal system with both the normal electrode blink reflex and nociceptive blink reflex to identify any anomalies in the afferent system. In a broader context, this case study can also identify the pathways used during both types of stimulation.

**Method**

The participant was a 53 year old post-menopausal female referred by a Pain Specialist to investigate paroxysmal severe trigeminal pain. The severe attacks had occurred at least 12 times in the previous 12 months with 75% of attacks occurring after the patient had supervised choir practice on Tuesday nights. The attacks are severe, last for approximately 3 hours, are accompanied by nausea and vomiting and are occasionally accompanied by paralysis. The pain begins on the left side of the soft palate and describes pain passing behind the nose on the left side and travels up behind her nose to the left supra-orbital region. The patient’s usual treatment is pregabalin.

The patient had previously suffered from migraines but reported that the current attacks were not similar to her migraine attack.

**Blink Reflex**

The patient sat with her eyes open during the data collection. The blink reflex was measured bilaterally from the mid orbicularis oculi muscle via electromyography (EMG) signals. The skin was wiped with an alcohol wipe prior to attaching modified neo-nate ECG (ConMed, N.Y., USA) electrodes to the lower mid orbicularis oculi and lower lateral orbicularis oculi. A disposable ground electrode was placed below the left ear to minimise electrical interference.

EMG data were acquired via an EMG digital pre-amplifier (EMG100C, BIOPAC Systems, Inc. California, U.S.A.) before being transmitted to a personal computer via a 16-bit MP100 BIOPAC Systems Analogue/Digital Channel Receptor (BIOPAC Systems, Inc. California, U.S.A.) using AcqKnowledge software (Version 3.7.1, BIOPAC Systems, Inc. California, U.S.A.). Data was collected at a sampling rate of 2KHz for later off-line analysis. Signals were band-stop filtered at 49-51Hz and 99-101Hz to reduce electrical artifact. Signals were also high pass filtered with a cut-off frequency of 10Hz to reduce interference from the
movement of eyeball roll, and rectified prior to analysis. The R1 component of the blink reflex from the ipsilateral side in response to the standard electrode stimuli and the R2 component of the blink reflex in response to all stimuli were investigated in this case study. The R3 component was not used because of the controversial nature of its origin. To avoid R3 contamination in the R2 component, specific time windows were used to calculate area under the curve (AUC). The R2 component was assessed in the time window of 27 to 87 ms after the onset of the stimulus (Ellrich, et al., 1998) whilst the presence of the R1 component was assessed in the window of 9-24ms after the onset of the stimulus.

Normal Electrode Blink Reflex

The normal bipolar electrodes were smeared with electrolyte gel and attached to the similarly prepared skin with adhesive washers. The first was attached to the supra-orbital foramen whilst the other was attached 2cm rostral to the supra-orbital foramen.

Electrical stimuli were monopolar square wave pulses with a duration of 0.3 ms with a starting intensity of 1.1mA increasing in approximately 0.5mA increments until reaching the patient’s tolerance limit of 8.6mA. The lower intensity stimuli were delivered with the intention of stimulating the A-beta touch fibres whilst the higher intensity stimuli were delivered with the intention of stimulating all fibres. An inter-stimulus interval of at least 10 seconds was used to minimise habituation of the blink reflex.

Nociceptive Blink Reflex

The nociceptive blink reflex was elicited by an electrical stimulus to the supra-orbital nerve delivered via a concentric electrode. The concentric electrodes are a replication of the concentric electrodes described by Kaube et al (2000) which stimulate superficial A-delta fibres due to a high current density and small anode-cathode distance. Adhesive washers attached two concentric electrodes to the supra-orbital skin prepared by cleansing with a pumice infused preparation pad (Professional Disposables, Inc, N.Y., USA). The outer ring (anode) of the electrode was smeared with electrode gel to aid in electrical conductivity. The electrodes were placed so that the cathode (inner point) was placed above the supra-orbital foramen. The electrical stimuli were monopolar square wave pulses with a duration of 0.3 ms and intensities began at 0.1mA and increasing at 0.1mA increments until 2.3mA. An interstimulus interval of at least 10 seconds was used to prevent habituation of the blink reflex.

Each different type of stimulus was delivered various times in a pseudo-staircase sequence depending on pain and blink reflex thresholds.

Habituation

Both types of stimuli were presented to both sides at 1Hz for 20seconds to evaluate habituation at the highest intensity tolerated by the patient. (normal electrode blink reflex left – 5.1mA; normal electrode blink reflex right – 8.1mA; nociceptive blink reflex left - 2.5mA; nociceptive blink reflex right - 2 mA). The last stimulus in the 20 stimulus series was rated on the 0-10 pain scale by the patient.
Procedure

The different stimuli were delivered on two different occasions separated by approximately one month. The procedure was similar on both occasions and the first session investigated the nociceptive blink reflex.

The patient sat in a shielded room to avoid electrical artifacts. She was instructed to keep her eyes open, and look at a fixated cross that was situated directly at eye level. The patient was asked to rate the pain intensity of every electrical stimulus on an 11-point scale (0 – no sensation, 1 – painless sensation, 2 – mild pain, 10 – extreme pain).

After skin preparation the stimulating and EMG electrodes were attached and the patient was asked to rate headache, nausea, dizziness, drowsiness, and unpleasantness on 11 point scales (0-none; 10-extreme) and body temperature on a 21 point scale (-10 – extremely cold; 0-normal; +10 – extremely hot) for a baseline measure. These ratings were also noted after each set of trials.

In the nociceptive blink reflex session the right side was stimulated first but in the normal electrode blink reflex session the left side (affected side) was investigated first.

The pain threshold was first established by beginning at the lowest intensity and increasing the stimulus intensity until a pain rating of ‘2’ (mild pain) was reached. If the pain rating was higher then the intensity was reduced until the mild pain rating was evoked. The blink reflex threshold was established in a similar fashion except the raw data were evaluated to ensure a blink had occurred. Once the threshold was established, values around the blink reflex threshold value were randomly presented to acquire more accurate data through averaging over more trials. It is interesting to note that on both occasions the patient was more inconsistent with the ratings for the stimuli presented to the right side, resulting in more trials to this side.

In the nociceptive blink reflex session the habituation testing occurred after the establishment of the pain and blink reflex thresholds on both sides. However in the normal electrode blink reflex session the habituation trials were presented after the threshold trials on each side.

Data Reduction

Pain ratings, R2 AUC and latency were averaged across all trials for each stimulus type and intensity. The habituation data were investigated independently of stimulus type, presented side and trial number.

Results

Pain Ratings

Normal Electrode Blink Reflex

As illustrated in Figure 1, stimuli presented to the right (unaffected) side were rated as more painful than the stimuli presented to the left (affected) side. The pain threshold was higher when the stimuli were presented to the left side (4.7mA) whereas the pain threshold was approximately 3mA when the stimuli were presented to the right side.
Nociceptive Blink Reflex

As depicted in Figure 2, when stimuli were presented to the right side, the lower intensities (less than 1mA) were rated as mildly painful, whereas when these same intensities were presented to the left side they were not rated as painful. The pain threshold was higher when the stimuli were presented to the left side (1.6mA).

Blink Reflex

The blink reflex in response to the normal electrode evoked a greater response when the left (affected) side was stimulated (Figure 3). In comparison, the blink reflex in response to the concentric electrode evoked a noticeable lack of response to stimuli presented to the left side (Figure 4). Whilst the stimuli presented to the right resulted in a blink reflex at about 1.1mA (the stronger blink reflexes at the lower intensities (0.4-0.6mA, could have been the result of either startle or novelty), the stimuli presented to the left did not result in a blink reflex until 1.6mA, therefore illustrating a higher blink threshold on the left side. On average, there was very little response from the right blink reflex to all stimuli presented to the left side.
Figure 3: Area under the curve for normal electrode. Key: lrbr – left side stimulated, right blink reflex; llbr – left side stimulated, left blink reflex; rrbr – right side stimulated, right blink reflex; rlbr – right side stimulated, left blink reflex.

Figure 4: Area under the curve for concentric electrode. Key: lrbr – left side stimulated, right blink reflex; llbr – left side stimulated, left blink reflex; rrbr – right side stimulated, right blink reflex; rlbr – right side stimulated, left blink reflex.
Habituation

Habituation for both types of stimuli appear relatively uniform with at least a 50% reduction in the area under the curve by the fifth trial. The most notable occurrence is the rapid habituation to the concentric electrode stimuli (Figure 6).

Figure 5: Area under the curve for blink reflex in response to 21 normal electrode stimuli presented at 1Hz.

Figure 6: Area under the curve for blink reflex in response to 21 concentric electrode stimuli presented at 1Hz.
Discussion

In our patient, pain rating data illustrate that pain perception to both types of stimuli presented to the left (affected) side was inhibited. However, the blink reflex response was greater to the normal electrode stimuli presented to the left side than the normal electrode stimuli presented to the right side. Interestingly, the blink reflex response to the nociceptive stimuli presented to the left side was inhibited when compared to the stimuli presented to the right side. Overall, these results suggest an abnormality of the nociceptive afferent system on the affected side. This is similar to Cruccu et al.’s findings (Cruccu, et al., 2001), in that trigeminal neuralgia patients have a dysfunctional nociceptive afferent system on the painful side. However, contrary to Cruccu et al.’s (Cruccu, et al., 1990) statement that patients with idiopathic trigeminal pain show abnormalities in trigeminal reflexes, we found an anomaly in the nociceptive blink reflex but not the normal blink reflex in our patient with idiopathic trigeminal pain.

According to Kaube et al (Kaube, et al., 2000), the higher intensities of the concentric electrode penetrate deeper into the skin and therefore stimulate the deeper located A-beta fibres. This is illustrated in this case study because the lack of response to the concentric electrode only happened at the lower intensities.

In a wider context, what this case study supports is the notion that two pathways exist for the two different types of stimuli. The data from this case study suggest that A-beta fibres are involved in the normal electrode blink reflex because the blink reflex in response to the normal electrode stimuli were not affected. However, the nociceptive blink reflex was inhibited in the blink reflex in response to the concentric electrode stimuli suggesting that only the A-delta fibres are involved in the nociceptive blink reflex at low intensities. If this patient has a dysfunctional trigeminal nociceptive afferent system, which we are suggesting, and if the normal electrode blink reflex also involves the A-delta fibres, then we would have expected some type of deficit in the normal electrode blink reflex. However, there could always be the possibility that this was masked by the A-beta component.

If Ellrich and Treede’s (Ellrich, et al., 1998) theory of common WDR neurons for both A-beta and A-delta pathways holds true, then our patient’s abnormality occurs prior to the subnuclci interpolaris and caudalis of the spinal trigeminal nucleus. If the common pathway of both fibres was damaged we would see a deficit in the normal electrode blink reflex in our patient. Alternatively, if the Ellrich and Treede theory is not correct and the A-delta fibres converge only onto the nociceptive fibres, then the dysfunction could be beyond the spinal trigeminal nucleus, but before the facial nucleus because blink reflexes in response to stimuli to the right side were normal in the patient. Because the blink reflex in response to a single pulse from the concentric electrode was not inhibited by DNIC (Giffin, et al., 2004) and the results of this case study illustrating a nociceptive specific pathway (both before and after the spinal trigeminal nucleus) it is suggested that in general, the A-delta fibres of the trigeminal system converge onto nociceptive specific neurons, not WDR neurons as suggested by Ellrich (Ellrich, 2000, 2002).

The suggestion that the patient has a dysfunctional nociceptive afferent system is supported in the pain ratings in response to the nociceptive specific concentric electrode in which the lower intensities (A-delta fibre activation) to the left side (affected side) were not rated as painful, but were rated as painful when presented to the right side. However, it is unclear why there was a difference in pain ratings for each side in response to the A-beta normal electrodes. Ellrich (Ellrich, 2002) suggests that C fibres aren’t involved in the generation of...
the blink reflex, but perhaps they are involved in pain perception of the A-beta stimulus and as part of the nociceptive trigeminal system are also dysfunctional in some way on the affected side.

Perhaps the patient’s constant tingling behind her nose or the episodes of severe trigeminal pain has de-sensitised her trigeminal nociceptive afferent system. However, what causes the pain in the first place remains a mystery. Perhaps the trigeminal nociceptive afferent system has bursts of nervous activity as part of the dysfunction. Based on this assertion, a GABA agonist (gabapentin) may help in the treatment of the patient’s severe attacks by inhibiting the bursts of neural activity in the trigeminal system. Alternatively, the continued use of pregabalin, which presumably has the same function as gabapentin, is suggested.

Further investigation via neuroimaging methods of the trigeminal system to investigate the original source of the pain is warranted.
Appendix D Data Tables
Table D-0-1: Ch. 3 Migraine Symptom Means (SD)

<table>
<thead>
<tr>
<th></th>
<th>Headache</th>
<th>Nausea</th>
<th>Body Temp</th>
<th>Dizziness</th>
<th>Drowsiness</th>
<th>Unpleasantness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After Drink</td>
<td>Baseline</td>
<td>After Drink</td>
<td>Baseline</td>
<td>After Drink</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>0.11</td>
<td>0.3</td>
<td>0.37</td>
<td>3.02</td>
<td>0.61</td>
<td>-0.54</td>
</tr>
<tr>
<td>(n=18)</td>
<td>(0.32)</td>
<td>(0.58)</td>
<td>(0.77)</td>
<td>(2.36)</td>
<td>(1.59)</td>
<td>(2.36)</td>
</tr>
<tr>
<td>Migraine Sufferers</td>
<td>0.96</td>
<td>(1.1)</td>
<td>0.94</td>
<td>4.28</td>
<td>1.41</td>
<td>0.29</td>
</tr>
<tr>
<td>(n=17)</td>
<td>(0.72)</td>
<td>(0.71)</td>
<td>(0.62)</td>
<td>(2.87)</td>
<td>(2.28)</td>
<td>(2.86)</td>
</tr>
<tr>
<td>Not Nauseated</td>
<td>0.61</td>
<td>1.7</td>
<td>0.86</td>
<td>5.04</td>
<td>0.88</td>
<td>-0.19</td>
</tr>
<tr>
<td>(n=12)</td>
<td>(0.99)</td>
<td>(1.84)</td>
<td>(1.18)</td>
<td>(2.14)</td>
<td>(1.98)</td>
<td>(2.76)</td>
</tr>
<tr>
<td>Nauseated</td>
<td>1.31</td>
<td>(2.36)</td>
<td>1.41</td>
<td>2.32</td>
<td>1.73</td>
<td>3.95</td>
</tr>
<tr>
<td>(n=22)</td>
<td>(1.16)</td>
<td>(2.24)</td>
<td>(2.36)</td>
<td>(2.3)</td>
<td>(3.09)</td>
<td>(2.48)</td>
</tr>
</tbody>
</table>

Table D-0-2: Ch. 3 Scalp and Fingertip Tenderness Ratings Means (SD)

<table>
<thead>
<tr>
<th>Pressure (grms)</th>
<th>60</th>
<th>140</th>
<th>220</th>
<th>60</th>
<th>140</th>
<th>220</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After Drink</td>
<td>Baseline</td>
<td>After Drink</td>
<td>Baseline</td>
<td>After Drink</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>0.35</td>
<td>0.71</td>
<td>1.59</td>
<td>1.59</td>
<td>1.88</td>
<td>2.41</td>
</tr>
<tr>
<td>(n=17)</td>
<td>(0.7)</td>
<td>(1.16)</td>
<td>(1.58)</td>
<td>(1.5)</td>
<td>(1.9)</td>
<td>(1.84)</td>
</tr>
<tr>
<td>Migraine Sufferers (n=16)</td>
<td>1.31</td>
<td>1.44</td>
<td>2.31</td>
<td>2.75</td>
<td>3.5</td>
<td>4</td>
</tr>
<tr>
<td>(n=16)</td>
<td>(2.36)</td>
<td>(2.48)</td>
<td>(2.47)</td>
<td>(2.46)</td>
<td>(2.71)</td>
<td>(2.68)</td>
</tr>
<tr>
<td>Not Nauseated</td>
<td>0.36</td>
<td>0.36</td>
<td>1.18</td>
<td>1.09</td>
<td>1.73</td>
<td>1.64</td>
</tr>
<tr>
<td>(n=11)</td>
<td>(0.5)</td>
<td>(0.67)</td>
<td>(0.98)</td>
<td>(0.94)</td>
<td>(1.56)</td>
<td>(1.21)</td>
</tr>
<tr>
<td>Nauseated</td>
<td>1.05</td>
<td>1.41</td>
<td>2.32</td>
<td>2.68</td>
<td>3.14</td>
<td>3.95</td>
</tr>
<tr>
<td>(n=22)</td>
<td>(2.1)</td>
<td>(2.24)</td>
<td>(2.36)</td>
<td>(2.3)</td>
<td>(3.69)</td>
<td>(2.48)</td>
</tr>
</tbody>
</table>
Table D-0-3: Ch. 3 Electrical Stimuli Pain Ratings Means (SD)

<table>
<thead>
<tr>
<th></th>
<th>Pain Ratings</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Concentric Electrode</td>
<td>Low Intensity Standard Electrode</td>
<td>High Intensity Standard Electrode</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>After Drink</td>
<td>Baseline</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=18)</td>
<td></td>
<td>0.79 (0.88)</td>
<td>0.67 (0.78)</td>
<td>0.59 (1.06)</td>
</tr>
<tr>
<td>Migraine Sufferers</td>
<td></td>
<td>0.99 (1)</td>
<td>1.04 (1.2)</td>
<td>0.75 (0.96)</td>
</tr>
<tr>
<td>(n=17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Nauseated</td>
<td></td>
<td>1.01 (1)</td>
<td>0.92 (1.05)</td>
<td>0.51 (0.69)</td>
</tr>
<tr>
<td>(n=12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nauseated</td>
<td></td>
<td>0.82 (0.91)</td>
<td>0.81 (1.01)</td>
<td>0.74 (1.13)</td>
</tr>
<tr>
<td>(n=23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table D-0-4: Ch. 3 Blink Reflex Frequency Means (SD)

<table>
<thead>
<tr>
<th></th>
<th>Blink Reflex Frequency (/4)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Concentric Electrode</td>
<td>Low Intensity Standard Electrode</td>
<td>High Intensity Standard Electrode</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>After Drink</td>
<td>Baseline</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=18)</td>
<td></td>
<td>3.74 (0.63)</td>
<td>3.62 (0.82)</td>
<td>3.67 (0.63)</td>
</tr>
<tr>
<td>Migraine Sufferers</td>
<td></td>
<td>3.8 (0.57)</td>
<td>3.76 (0.45)</td>
<td>3.98 (0.08)</td>
</tr>
<tr>
<td>(n=17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Nauseated</td>
<td></td>
<td>3.86 (0.3)</td>
<td>3.69 (0.86)</td>
<td>3.83 (0.48)</td>
</tr>
<tr>
<td>(n=12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nauseated</td>
<td></td>
<td>3.72 (0.7)</td>
<td>3.69 (0.54)</td>
<td>3.81 (0.48)</td>
</tr>
<tr>
<td>(n=23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table D-0-5: Ch. 3 Blink Reflex Area Under the Curve Means (SD)

<table>
<thead>
<tr>
<th></th>
<th>Blink Reflex Area Under the Curve (mV·sec)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Concentric Electrode</td>
<td>Low Intensity Standard Electrode</td>
<td>High Intensity Standard Electrode</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>After Drink</td>
<td>Baseline</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=18)</td>
<td></td>
<td>1.96 (1.06)</td>
<td>1.94 (1.21)</td>
<td>2.4 (1.1)</td>
</tr>
<tr>
<td>Migraine Sufferers</td>
<td></td>
<td>2.45 (1.42)</td>
<td>2.41 (1.49)</td>
<td>2.82 (1.45)</td>
</tr>
<tr>
<td>(n=17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Nauseated</td>
<td></td>
<td>2.04 (0.98)</td>
<td>1.97 (1.27)</td>
<td>2.27 (1.01)</td>
</tr>
<tr>
<td>(n=12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nauseated</td>
<td></td>
<td>2.3 (1.4)</td>
<td>2.28 (1.43)</td>
<td>2.78 (1.39)</td>
</tr>
<tr>
<td>(n=23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table D-0-6: Ch. 3 Blink Reflex Frequency Latency Means (SD)

<table>
<thead>
<tr>
<th></th>
<th>Blink Reflex Latency</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concentric Electrode</td>
<td>Low Intensity Standard</td>
<td>High Intensity Standard</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>After Drink</td>
<td>Baseline</td>
<td>After Drink</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>44.33 (6.61)</td>
<td>43.33 (6.35)</td>
<td>40.89 (5.13)</td>
<td>38.43 (4.9)</td>
</tr>
<tr>
<td>(n=18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine Sufferers</td>
<td>44.13 (5.11)</td>
<td>43.38 (4.83)</td>
<td>42.29 (5.45)</td>
<td>41.79 (5.4)</td>
</tr>
<tr>
<td>(n=17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Nauseated</td>
<td>43.72 (6.44)</td>
<td>42.25 (5.56)</td>
<td>41.78 (4.6)</td>
<td>39.4 (6.06)</td>
</tr>
<tr>
<td>(n=12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nauseated</td>
<td>44.51 (5.59)</td>
<td>43.96 (5.59)</td>
<td>41.49 (5.69)</td>
<td>40.5 (5.04)</td>
</tr>
<tr>
<td>(n=23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Table D-7: Ch. 5-8 Migraine Symptom Means (SD)

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls</th>
<th>Between Migraine</th>
<th>During Migraine</th>
<th>Healthy Controls</th>
<th>Between Migraine</th>
<th>During Migraine</th>
<th>Healthy Controls</th>
<th>Between Migraine</th>
<th>During Migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Headache</td>
<td>Nausea</td>
<td>Perceived Body Temperature</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>0.38 (0.53)</td>
<td>0.14 (0.35)</td>
<td>5.15 (1.8)</td>
<td>0 (0)</td>
<td>0.05 (0.21)</td>
<td>2.15 (2.56)</td>
<td>0 (0.73)</td>
<td>-0.32 (0.72)</td>
<td>-0.05 (2.54)</td>
</tr>
<tr>
<td>Baseline Stimuli</td>
<td>1 (1.37)</td>
<td>0.36 (0.66)</td>
<td>5.3 (2.75)</td>
<td>0.15 (0.37)</td>
<td>0.09 (0.43)</td>
<td>2.25 (2.42)</td>
<td>0.2 (0.89)</td>
<td>0.05 (1)</td>
<td>0.2 (2.24)</td>
</tr>
<tr>
<td>Finger in ice</td>
<td>0.55 (0.83)</td>
<td>0.43 (0.73)</td>
<td>5.05 (2.19)</td>
<td>0.15 (0.49)</td>
<td>0.05 (0.21)</td>
<td>2.5 (2.64)</td>
<td>-0.35 (1.26)</td>
<td>-0.27 (0.98)</td>
<td>-0.65 (2.81)</td>
</tr>
<tr>
<td>Ice on Temple</td>
<td>1.33 (2.39)</td>
<td>1.18 (1.89)</td>
<td>4.85 (2.77)</td>
<td>0.3 (0.73)</td>
<td>0.05 (0.21)</td>
<td>2.2 (2.82)</td>
<td>-0.1 (0.91)</td>
<td>0 (1.27)</td>
<td>0 (1.7)</td>
</tr>
<tr>
<td>During Darkness</td>
<td>1.05 (1.28)</td>
<td>0.39 (1.09)</td>
<td>5.11 (2.15)</td>
<td>0.37 (0.83)</td>
<td>0.09 (0.29)</td>
<td>2.17 (2.18)</td>
<td>0.5 (1.24)</td>
<td>0.39 (1.13)</td>
<td>0.89 (2.09)</td>
</tr>
<tr>
<td>During Bright Light</td>
<td>0.55 (0.89)</td>
<td>1.39 (1.63)</td>
<td>6.65 (1.8)</td>
<td>0.35 (0.93)</td>
<td>0.55 (1.22)</td>
<td>3.5 (3.37)</td>
<td>0.7 (1.17)</td>
<td>0.36 (1.65)</td>
<td>1.2 (2.1)</td>
</tr>
<tr>
<td>After Intense Sound</td>
<td>0.7 (1.03)</td>
<td>1.41 (1.65)</td>
<td>6.5 (1.96)</td>
<td>0.2 (0.52)</td>
<td>0.18 (0.39)</td>
<td>3 (3.06)</td>
<td>0.25 (1.12)</td>
<td>0.55 (1.71)</td>
<td>0.4 (2.01)</td>
</tr>
<tr>
<td>Final Stimuli</td>
<td>0.85 (1.63)</td>
<td>1.24 (1.64)</td>
<td>6.5 (1.96)</td>
<td>0.35 (0.93)</td>
<td>0.33 (1.06)</td>
<td>3.1 (3.25)</td>
<td>0.45 (1.23)</td>
<td>0.26 (1.48)</td>
<td>0 (2.36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>Drowsiness</td>
<td>Unpleasantness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>0.1 (0.31)</td>
<td>0.05 (0.21)</td>
<td>0.85 (1.53)</td>
<td>0.4 (0.75)</td>
<td>0.27 (0.55)</td>
<td>1.9 (1.81)</td>
<td>0.45 (1.1)</td>
<td>0.32 (0.72)</td>
<td>4.6 (3.17)</td>
</tr>
<tr>
<td>Baseline Stimuli</td>
<td>0.18 (0.37)</td>
<td>0.14 (0.47)</td>
<td>1.2 (1.83)</td>
<td>0.75 (0.8)</td>
<td>0.36 (0.79)</td>
<td>2.55 (2.75)</td>
<td>1.33 (1.38)</td>
<td>1.61 (1.27)</td>
<td>5.15 (3.2)</td>
</tr>
<tr>
<td>Finger in ice</td>
<td>0.15 (0.49)</td>
<td>0.14 (0.64)</td>
<td>1.05 (1.67)</td>
<td>0.6 (0.99)</td>
<td>0.36 (0.9)</td>
<td>1.9 (1.6)</td>
<td>3.93 (2.26)</td>
<td>4.18 (2.54)</td>
<td>6.06 (2.63)</td>
</tr>
<tr>
<td>Ice on Temple</td>
<td>0.25 (0.64)</td>
<td>0.41 (1.05)</td>
<td>1.5 (2.76)</td>
<td>0.35 (0.67)</td>
<td>0.27 (1.08)</td>
<td>2.25 (2.4)</td>
<td>5.23 (2.64)</td>
<td>5.32 (2.73)</td>
<td>7.6 (2.22)</td>
</tr>
<tr>
<td>During Darkness</td>
<td>0.26 (0.56)</td>
<td>0.41 (1.1)</td>
<td>1 (1.41)</td>
<td>1.05 (1.08)</td>
<td>0.86 (1.36)</td>
<td>1.56 (1.42)</td>
<td>1.5 (1.77)</td>
<td>1.39 (2.05)</td>
<td>2.61 (2.52)</td>
</tr>
<tr>
<td>During Bright Light</td>
<td>0.45 (1.1)</td>
<td>0.57 (1.12)</td>
<td>1.55 (2.81)</td>
<td>0.85 (1.31)</td>
<td>1.64 (1.81)</td>
<td>2.9 (2.56)</td>
<td>2.9 (2.38)</td>
<td>3.3 (2.26)</td>
<td>6.3 (3.02)</td>
</tr>
<tr>
<td>After Intense Sound</td>
<td>0.4 (1.19)</td>
<td>0.59 (1.05)</td>
<td>1.6 (2.63)</td>
<td>0.6 (1.47)</td>
<td>1.02 (1.28)</td>
<td>2.2 (2.49)</td>
<td>2.4 (2.5)</td>
<td>3.52 (2.28)</td>
<td>6.25 (2.8)</td>
</tr>
<tr>
<td>Final Stimuli</td>
<td>0.4 (1.35)</td>
<td>0.62 (1.24)</td>
<td>1.85 (2.63)</td>
<td>0.65 (1.76)</td>
<td>1.19 (1.66)</td>
<td>3.1 (2.51)</td>
<td>1.63 (2.04)</td>
<td>1.79 (1.33)</td>
<td>4.7 (2.75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Light Sensitivity</td>
<td>Sound Sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>0.1 (0.31)</td>
<td>0 (0)</td>
<td>3.85 (2.75)</td>
<td>0.05 (0.22)</td>
<td>0 (0)</td>
<td>2.3 (2.54)</td>
<td></td>
<td></td>
<td>Healthy Controls (n=20)</td>
</tr>
<tr>
<td>Baseline Stimuli</td>
<td>0.3 (0.59)</td>
<td>0.14 (0.47)</td>
<td>3.7 (2.95)</td>
<td>0.05 (0.22)</td>
<td>0.27 (0.88)</td>
<td>1.8 (2.49)</td>
<td></td>
<td></td>
<td>Between Migraine (n=22)</td>
</tr>
<tr>
<td>Finger in ice</td>
<td>0.23 (0.53)</td>
<td>0.23 (0.53)</td>
<td>3.3 (3.27)</td>
<td>0.1 (0.31)</td>
<td>0.23 (1.07)</td>
<td>2 (2.83)</td>
<td></td>
<td></td>
<td>During Migraine (n=10)</td>
</tr>
<tr>
<td>Ice on Temple</td>
<td>0.2 (0.52)</td>
<td>0.32 (0.89)</td>
<td>3.2 (2.97)</td>
<td>0.18 (0.56)</td>
<td>0.23 (1.07)</td>
<td>1.75 (2.35)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During Darkness</td>
<td>0.21 (0.54)</td>
<td>0 (0)</td>
<td>1.06 (1.33)</td>
<td>0.32 (0.58)</td>
<td>0.27 (0.94)</td>
<td>1.5 (2.47)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During Bright Light</td>
<td>1.38 (2.18)</td>
<td>2.41 (1.94)</td>
<td>5.1 (3.39)</td>
<td>0.45 (1.61)</td>
<td>0.43 (0.82)</td>
<td>1.85 (2.38)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After Intense Sound</td>
<td>0.43 (1.37)</td>
<td>0.75 (1.07)</td>
<td>3.2 (2.97)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final Stimuli</td>
<td>0.45 (1.61)</td>
<td>0.79 (1.19)</td>
<td>3.3 (2.95)</td>
<td>0.55 (1.61)</td>
<td>0.69 (1.17)</td>
<td>2.35 (2.33)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table D-8: Ch. 5-8 Scalp and Fingertip Tenderness Ratings Means (SD)

<table>
<thead>
<tr>
<th>Pressure (grms)</th>
<th>50</th>
<th>100</th>
<th>150</th>
<th>50</th>
<th>100</th>
<th>150</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End of Session</td>
<td>Baseline</td>
<td>End of Session</td>
<td>Baseline</td>
<td>End of Session</td>
</tr>
<tr>
<td>Healthy Controls (n=20)</td>
<td>1.1</td>
<td>0.65</td>
<td>1.85</td>
<td>1.4</td>
<td>2.38</td>
<td>2.4</td>
</tr>
<tr>
<td>Between Migraine (n=22)</td>
<td>0.57</td>
<td>1.05</td>
<td>1.05</td>
<td>1.34</td>
<td>1.7</td>
<td>2.52</td>
</tr>
<tr>
<td>During Migraine (n=10)</td>
<td>1.8</td>
<td>1.8</td>
<td>2.45</td>
<td>3.1</td>
<td>3.3</td>
<td>4.75</td>
</tr>
</tbody>
</table>

### Table D-7: Ch. 5-8 Electrical Stimuli Responses Means (SD)

<table>
<thead>
<tr>
<th>Ipsilateral Baseline Stimuli</th>
<th>Pain Rating</th>
<th>Blink Reflex Frequency (/6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral Baseline Stimuli</td>
<td>Blink Reflex AUC (mV·sec)</td>
<td>Blink Reflex Latency (ms)</td>
</tr>
<tr>
<td>Ipsilateral Baseline Stimuli</td>
<td>1.14 (0.65)</td>
<td>1.13 (0.61)</td>
</tr>
<tr>
<td>Ipsilateral Baseline Stimuli</td>
<td>0.71 (0.34)</td>
<td>1.03 (0.64)</td>
</tr>
<tr>
<td>Ipsilateral Baseline Stimuli</td>
<td>0.81 (0.42)</td>
<td>0.92 (0.59)</td>
</tr>
<tr>
<td>Ipsilateral Baseline Stimuli</td>
<td>1.01 (0.75)</td>
<td>0.96 (0.67)</td>
</tr>
<tr>
<td>Ipsilateral Baseline Stimuli</td>
<td>1.09 (0.81)</td>
<td>1.01 (0.64)</td>
</tr>
</tbody>
</table>
References


Bartsch, T., & Goadsby, P. J. (2002). Stimulation of the greater occipital nerve induces increased central excitability of dural afferent input. *Brain, 125*(Pt 7), 1496-1509.


sagittal sinus during electrical stimulation of the trigeminal ganglion. 
*Neuropharmacology, 30*(11), 1193-1200.


