Cervical Afferents and Primary Headache:
An investigation of the potential role of cervical nociceptors in sensitising the trigemino-cervical nucleus in primary headache

Dean H Watson
Master Applied Science in Manipulative Therapy

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School of Psychology and Exercise Science, Murdoch University Western Australia
DECLARATION

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

Dean H Watson.

May 2016
ABSTRACT

An underlying disorder in the migraine condition is an apparent subclinical sensitization of the trigemino cervical nucleus (TCN) indicated, for example, by an interictal deficient habituation of the nociceptive blink reflex (nBR). This has ramifications for tension-type headache (TTH), as there is considerable support for a pathogenesis of TTH which overlaps with that of migraine. The aim of this thesis was to investigate the upper cervical (C1-3) afferents as a potential sensitising source of the TCN in migraine and TTH, thereby addressing the hypothesis that upper cervical afferents evoke sensitisation of the TCN in migraine and TTH.

Firstly, manual examination of the upper cervical (atlanto-occipital and C2-3) joints was performed in 20 migraineurs, 14 TTH patients and 14 controls. The reproduction of customary head pain in 100 and 95 per cent of TTH patients and migraineurs, respectively, supports a role of the upper cervical spine in primary headache, perhaps involving sensitization of the TCN.

The second study employed the nociceptive blink reflex (nBR) to assess processing of trigeminal nociceptive information during reproduction and resolution of customary head pain (as the examination technique was sustained) in 15 migraineurs interictally. Reproduction and resolution of head pain was repeated over four 90 second trials; each trial was separated by 30 seconds. Migraineurs reported significant lessening of reproduction and increasing resolution of customary head pain over the four trials. In parallel was a significant increase in latency and decrease in amplitude of the nBR. The desensitizing effect of this examination technique on head pain implies
that modulation of cervical afferent information may benefit migraineurs during manual cervical reproduction of customary head pain.

Whiplash of the neck is considered a musculo skeletal event and subsequent headache implies involvement of upper cervical (C1-3) afferents. The symptomatic profile of chronic whiplash associated headache (CWAH) mirrors that of primary headache, inviting speculation that CWAH shares a pathophysiology similar to that of primary headache. This prompted us to assess trigeminal nociceptive processing in CWAH patients in the third study. The symptomatic profile of 22 CWAH patients confirmed previous studies demonstrating similar profiles to primary headache. Furthermore, when compared to controls (n=25), CWAH patients had significant photophobia and allodynia. In addition, analysis of the nBR revealed hyperexcitability in central nociceptive pathways in CWAH patients, thus reinforcing the hypothesis that CWAH could be driven by central sensitization from upper cervical afferents.

Together, these studies support the view that upper cervical (C1-3) nociceptive information may contribute to sensitising the TCN in primary headache. Thus, therapeutic strategies that aim to alleviate aberrant discharge of cervical afferents may play a role in the management of primary headache.
PUBLICATIONS

Refereed articles

Watson DH, Drummond PD. Head Pain Referral During Examination of the Neck in Migraine and Tension-Type Headache. Headache 2012;52:1226-1235


The following ‘STATEMENT OF AUTHORSHIP’ applies to the (3) abovementioned referred articles.

STATEMENT OF AUTHORSHIP

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(a) Conception and Design
    Peter D. Drummond; Dean H. Watson

(b) Acquisition of Data
    Dean H. Watson

(c) Analysis and Interpretation of Data
    Peter D. Drummond; Dean H. Watson

Category 2

(a) Drafting the Manuscript
    Dean H. Watson; Peter D. Drummond

(b) Revising It for Intellectual Content
Category 3

(a) Final Approval of the Completed Manuscript

Peter D. Drummond; Dean H. Watson

Dean H. Watson

Professor Peter D. Drummond
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CHAPTER 1

LITERATURE REVIEW AND INTRODUCTION

1.0 Literature Review and Introduction

Headache disorders are common: headache is one of the most frequent medical complaints with over 10% of adults experiencing disabling headache at some stage and three percent reporting more headache days than not. Whilst tension-type headache (TTH) is more common than migraine, (global prevalence 20.1% and 17.7% respectively), opinions differ as to which is more disabling. In a search of 107 epidemiological studies, TTH was considered more disabling than migraine whilst, conversely, in the more recent Global Burden of Disease Survey 2010, migraine was considered more disabling and considered globally as the seventh highest cause of disability. Notwithstanding this discrepancy, these statistics do little more than highlight that substantial numbers of people are disabled by headache and are not receiving effective management. Obviously headache is a common, disabling problem; what is required is a more comprehensive understanding of headache mechanisms so that those affected by headache receive appropriate care.

Currently, there is discord between the International Headache Society’s (IHS) classification of headache, which describes TTH and migraine as separate entities, with unknown pathophysiologies, and alternate models, which imply that TTH and migraine are only different presentations of a common underlying mechanism. Initially, therefore, this treatise will review the IHS classification and alternate models. (Chapter 2)
Whilst the principal cause of migraine and tension-type headache remains elusive, the trigeminal system appears to be intimately involved.\textsuperscript{10,11} The sensory trigeminal nerve nuclei are the largest of the cranial nerve nuclei, and extend through the whole of the midbrain, pons and medulla, and into the cervical spinal cord. That part extending into the upper cervical spinal cord - the spinal trigeminal nucleus - is subdivided into three parts from rostral to caudal: pars oralis, pars interpolaris, and the pars caudalis. A significant body of research has demonstrated that the par caudalis extends to include the C1 and C2 dorsal horns (DH).\textsuperscript{12-19} This group of cells could be regarded as the trigemino cervical nucleus (TCN).\textsuperscript{20}

Afferents of the trigeminal system\textsuperscript{21-23} and convergent synaptic input from cervical (C2) spinal afferents\textsuperscript{21,23-31} project to second order neurons in the TCN. The extensive convergence of trigeminal and C1 and C2 afferents demonstrated in the C1 and C2 DH\textsuperscript{23,31-33} as well as the pars caudalis\textsuperscript{34-36} supports the notion that the TCN complex may play a critical role in headache.\textsuperscript{32,37-39} The afferent convergence from the trigeminal and cervical afferent sources in the C1 and C2 DH and adjacent pars caudalis supports the view that the DH of the upper cervical spinal cord (C1 and C2 spinal segments) and pars caudalis form a functional continuum in processing sensory information.\textsuperscript{23,31,32} Strong noxious trigeminal stimulation evokes central sensitisation of nociceptive second order neurons.\textsuperscript{21-23,38} Similarly, stimulation of upper cervical afferents induces central sensitisation of nociceptive second order neurons in the TCN.\textsuperscript{19,23,24,26,28-31} Therefore, central sensitisation of the second order neurons in the TCN could result either from noxious trigeminal or upper cervical afferents; the clinical correlates comprising head pain referral, cephalic cutaneous allodynia and cervical tenderness.\textsuperscript{40-43}
Cervicogenic headache is defined as referred head and/or face pain from a validated cervical lesion. Reproduction of headache when examining the upper cervical spine is considered a key diagnostic criterion for a diagnosis of cervicogenic headache. This phenomenon then invites speculation as to the presence of a peripheral or cervical lesion. Occipital and suboccipital structures comprising deep paraspinal cervical muscles, the atlanto occipital, atlanto axial (C1-2) and C2-3 zygapophyseal joints are recognised as sources of head pain. Afferent nociceptive information from these structures is also conveyed by the C1 and C2 nerve roots terminating in the DH of the cervical spine extending from the C2 spinal segment cranially to the medullary DH.

However, reproduction of accustomed head pain does not necessarily involve a peripheral or cervical lesion. Stimulating cervical afferents (reproduction of accustomed head pain) may provide a neuromodulatory effect on the central mechanism of primary headache, increasing the excitability of trigeminal input. The reproduction and lessening of accustomed head pain in migraineurs when examining upper cervical joints potentially diminishes cervical input and increases the threshold for pain in the TCN. Cervical afferent involvement in primary headache therefore may not be reliant on an aberrant source residing in the upper cervical spine.

A straightforward interaction between converging cervical and dural afferents cannot explain the symptomatology of primary headache. However, a sensitised state of the TCN is considered central in initiating primary headache.

If the TCN is already sensitised then non noxious afferent cervical information could represent a form of pathology; i.e., ordinary (sub clinical) cervical input augments
pain. Potentially, increased normal input could be a source of pain in the presence of a sensitised TCN. Therefore, whilst cervical afferents may be involved, by definition, this sequence of events does not constitute cervicogenic headache.

Undoubtedly, the TCN plays a pivotal role in migraine pathogenesis; i.e., stimulation of nociceptive second order neurons in the TCN, by trigeminal and C2 spinal afferents, instigates central sensitisation. This has implications for tension-type headache, as there is significant support for a pathogenesis similar to that of migraine. Nevertheless, irrespective of whether migraine and TTH share a common pathogenesis, both migraine and TTH are disorders conveyed by a final common pathway; the TCN. Despite widespread acceptance of the role of the trigeminal system in the migraine process, controversy engulfs the primary driver of central sensitisation of nociceptive second order neurons in the TCN.

Chapter 3 is a review of the literature investigating a potential sensitising role of upper cervical (C1-3) afferents in primary headache. In this chapter the relationship between cervical signs and symptoms and primary headache will be explored. Because the profile of chronic whiplash associated headache (CWAH) mirrors that of primary headache and is, by definition, a consequence of a musculoskeletal event, a review of the source of pain in CWAH follows. As contemporary literature implicates the upper cervical joints (primarily the C2-3 zygapophyseal joint) as a source of pain in CWAH, research investigating the role of the zygapophyseal joints will be considered from the perspective of pathology, dysfunction and treatment will be presented.

In studies on trigeminal activity in primary headache syndromes, it is essential that the accent be on nociceptive processing. Nociceptive specific (NS) and wide
dynamic range (WDR) neurons respond to noxious stimuli and are present in the interstitial nucleus of the spinal trigeminal nucleus (STN). Animal and human studies has demonstrated that nociceptive processing occurs within the STN, and as NS and WDR neurons are involved in conveyance of the blink reflex (BR), the BR and more specifically the nociceptive BR (R2 nBR), provides a vehicle to assess trigeminal nociceptive processing. Chapter 4 comprises a review of studies analyzing the BR and employing the nBR in migraineurs.

The primary aim of this dissertation was to investigate the C1-3 afferents as a sensitising source of the TCN in migraine, TTH and CWAH. Any affirmation of a causal role of C1-3 afferents may substantiate the use of treatments that target these afferents as an alternative form of care that supplements or replaces other forms of treatment (e.g., medication).
References


CHAPTER 2
CLASSIFICATION OF HEADACHE

2.1 Introduction

The contemporary presiding authority for the classification of primary headache disorders is the International Headache Society’s (IHS) Classification system which was first published in 1988\(^1\) with revisions in 2004\(^2\) and 2013.\(^3\)

Classifications of medical conditions discriminate between clinical-symptomatic presentation and etiological approaches. The clinical-symptomatic approach considers symptom clustering and ostensible characteristics, whilst the etiological system relies on a recognised biological cause.\(^4\) The IHS system currently provides a classification based not on biology but on clinical features and symptoms and the exclusion of other disorders,\(^5\) and, whilst pathophysiological mechanisms remain unclear, views the primary headache conditions, migraine, episodic tension-type headache (ETTH) and the trigeminal autonomic cephalalgias, as separate entities.\(^3\,6\,7\,8\) However, the IHS classification continues to be revisited and challenged by alternative perspectives.

2.2 Models of Headache Classification

According to the IHS classification, migraine is characterized by unilateral, throbbing head pain of moderate to severe intensity, accompanied by nausea, vomiting, photo- and phono- phobia.\(^3\) (Table 1) (Fig. 1) In contrast, bilateral, mild to moderate dull aching, pressure or tightening, and no more than either photo- or phono phobia typifies ETTH.\(^3\) (Table 1)
Table International Headache Society Diagnostic Criteria for Migraine and Episodic Tension-type Headache

<table>
<thead>
<tr>
<th></th>
<th>Migraine Without Aura</th>
<th>Episodic Tension-type Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration:</strong></td>
<td>4 to 72 hours</td>
<td>30 minutes to 7 days</td>
</tr>
<tr>
<td><strong>Pain (2 of 4):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area</td>
<td>Unilateral</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Intensity</td>
<td>Moderate to severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Quality</td>
<td>Pulsating</td>
<td>Pressure / ache / heaviness</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Aggravates</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Associated symptoms (1 or 2):</td>
<td>Nausea or</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>Photophobia and</td>
<td>Photophobia *</td>
</tr>
<tr>
<td></td>
<td>Phonophobia</td>
<td>Phonophobia*</td>
</tr>
</tbody>
</table>

No evidence of organic disease

* Either photo- or phono-phobia allowed.

Those contending that migraine and ETTH are separate disorders assert that migraine is underpinned by neuro vascular mechanisms and ETTH arises from other sources (e.g., emotional distress or abnormal muscle activity). However, whether the primary headache conditions constitute heterogeneous entities with distinct pathophysiological processes or different clinical expressions of a common pathophysiology has been the subject of vigorous debate. At the centre of this dissension is ETTH and migraine, the most common primary headache disorders, and the most difficult to distinguish from each other.
In the mid 1800s Willis proposed that migraine and TTH existed on a ‘continuum’.\textsuperscript{8,15} The fundamental ideology of the ‘continuum theory’ is that variable presentations experienced by migraineurs are different manifestations of a common pathophysiological foundation.\textsuperscript{5-45} Thus, the ‘continuum theory’ provides an alternative perspective to the current medical model, which views migraine and episodic tension-type headache (ETTH) presentations as distinct pathophysiological entities.\textsuperscript{3,5-8}

The continuum theory remained essentially unchallenged until the mid 1950s,\textsuperscript{19} when Wolff’s clinical and experimental investigations\textsuperscript{46,47} elaborated on the potential role of the intracranial vasculature in migraine. The consequence of this research effectively partitioned migraine from TTH and weakened the ‘continuum theory’.\textsuperscript{7}

The endorsement of migraine and ETTH as separate entities was strengthened in the 1990s by studies demonstrating a limited effect of sumatriptan on ETTH when compared with migraine.\textsuperscript{48,49} However, the IHS classification relies on symptom presentation.\textsuperscript{3} Complexity then arises when there is either the concomitant presence of more than one headache type, or one or more associated features of one specific headache type are present in the other.\textsuperscript{5-45,50,51} For example, migraineurs experience a range of headache including migraine without aura (IHS 1.1), migraine with aura (IHS 1.2), probable migraine (previously ‘migrainous disorder’) (IHS 1.5) and ETTH (IHS 2.1; 2.2).\textsuperscript{3,5,7} In the early studies investigating the effectiveness of sumatriptan,\textsuperscript{52,53} migraine and ETTH patients with precise diagnoses of migraine and ETTH were included. However, some studies since then have included patients who, whilst not meeting the IHS criteria for migraine, experienced \textit{clinically} defined migraine and ETTH episodes.\textsuperscript{5,21} In these studies, sumatriptan was found to be equally effective for
migraine, migrainous and ETTH episodes,\textsuperscript{5,21} which supports the hypothesis of the existence of a common underlying pathophysiological process.\textsuperscript{5-45}

Furthermore, numerous studies have demonstrated that not only do ETTH patients and migraineurs share many symptoms, but also an absence of unique, differentiating clinical features,\textsuperscript{5,6,48,49} supporting the concept that ETTH and migraine are opposite extremes of a continuum.\textsuperscript{7,8} Another consistent, attendant finding was an incremental increase in associated symptoms with increasing severity of pain.\textsuperscript{5-18,22-24,27-34,42-45,54} Consequently, proponents of the ‘continuum theory’ based their perspective on the ‘severity model’, i.e., pain intensity increases with accumulation of other symptoms, rather than qualitative differences.\textsuperscript{9-11,13,15,23,30} That is, at one end of the continuum is severe headache, which is more likely to be unilateral, throbbing in nature and accompanied by nausea, vomiting, photo- and or phono- phobia and aggravated by routine physical activity. At the opposite end is the ETTH presentation, i.e., mild to moderate bilateral ache or dull pain, with perhaps some photo- or phonophobia. Between these extremes lies a wide range of clinical presentations, including combinations of one feature or another. (Fig. 1)

An alternative model to explain the variable and overlapping headache presentations was based upon the convergence of vascular, supraspinal and myofascial (e.g. temporalis muscle) factors upon the trigemino cervical nucleus (TCN); the vascular-supraspinal-myofascial (‘VSM’) model.\textsuperscript{55} In this model, headache presentation was hypothesized to depend on the magnitude of contribution from each of these three sources. For example, if the vascular component was predominant, a headache of migrainous quality results; conversely ETTH, if the major input was myofascial. (Fig. 2) Potentially, these three factors are likely to vary between patients,
and within patients, over time, accounting for the overlap and variable severity of symptoms and different types of headache. Whilst uncertainty surrounded the extent of supraspinal influences, the ‘VSM’ model considered the supraspinal input to play a prominent, facilitatory role.\(^5\)

**Figure 1.** A diagrammatic representation of the ‘severity’ perspective of the ‘continuum theory’ demonstrating the relationship between severity, associated symptoms, and area and quality of pain. Note the ‘grey’ area representing the variable, inconsistent clinical presentations, including combinations of one feature or another.

Another hypothesis, the ‘Tension Headache, Migraine continuum’,\(^28\) also considers the convergence and integration of several factors on the TCN. Like the ‘VSM’ model, these factors include vascular and somatic influences, but this model differs in that the somatic sources of pain are postulated to reside in the upper cervical spine (e.g. muscles, ligaments, disc of the upper cervical spine), instead of ‘supraspinally’, in the serotonergic system.\(^28\) (Fig. 3)
An important distinction, therefore, is that this model incorporates the spinal C1-3 (cervical) afferents, whilst the ‘VSM’ model is essentially confined to the trigeminal system.

Accordingly, if a patient had a significant vascular component their headache would present with migrainous characteristics, whereas if the somatic component prevailed an ETTH results. Advocates of this theory consider that both cervicogenic headache and ETTH are part of the somatic end of the continuum and use ‘cervicogenic headache’ as a descriptor and not a diagnosis. Whilst ETTH, migraine and cervicogenic headache are considered separate entities, there is evidence that cervical factors are involved in the pathogenesis of TTH and migraine.
Figure 3. A diagrammatic representation of the ‘Tension Headache, Migraine Continuum’ according to Nelson.\textsuperscript{31} Note: the somatic contribution comprises the C1-3 spinal afferents; also the variability in serotonin levels. Those headaches without a predominance of either vascular or somatic contributions in the ‘grey’ area are likely to be diagnosed as IHS Probable Migraine.

Incorporating and building on converging influences on the TCN is the ‘convergence hypothesis’.\textsuperscript{7,8} Instrumental in the development of this hypothesis were studies demonstrating uniform effectiveness of sumatriptan, not only in patients with IHS criteria for migraine with and without aura, but also non-IHS migraine i.e., IHS criteria for probable migraine (previously ‘migrainous’ headache) and ETTH.\textsuperscript{5,21} This hypothesis, as in the ‘continuum model’, postulates that a single, escalating, pathophysiological process is responsible for the vacillating presentations evident in migraine. (Fig.4)

Subsumed in this process is the merging and integration of afferent information from ophthalmic, maxillary and mandibular branches of the trigeminal nerve and upper
cervical dermatomes in the TCN. Equally significant is that the TCN is influenced by a range of supraspinal inhibitory and excitatory effects.\textsuperscript{7} In the event of continuing central disinhibition or sensitisation extending to second order neurons in the TCN, trigeminal and C1-3 spinal afferent information is amplified. If the process ceases soon after commencing, the resultant headache would resemble ETTH headache, whilst if it continues uninterrupted, IHS migraine results replete with associated symptoms. If the process terminates in the mid range then IHS probable migraine eventuates.\textsuperscript{7} (Fig 4) This process embodies the increasing severity and associated symptoms elucidated in earlier studies suggesting a ‘severity’ continuum.\textsuperscript{5-18,22-24,27-34,42-49,52-54,71,72}

Figure 4. A diagrammatic representation of the ‘convergence hypothesis’ demonstrating a single, escalating process of sensitisation. Note the symptom overlap between migraine and ETTH in the ‘probable migraine’ group.

Because afferent information from visceral, trigeminal and spinal fields converges on the nucleus tractus solitarius, an escalating process of sensitisation could
explain nausea and vomiting associated with migraine. This has been supported by a study in which recurring head pain (induced by an ice block applied to the temple) provoked nausea in migraineurs, but not in controls. Furthermore, this effect was magnified during and after provocation of motion sickness. Potentially this finding represents hyper excitability within the emetic or trigeminal nociceptive pathways.

The ‘convergence hypothesis’ also describes ETTH assuming a unilateral presentation - a feature of migraine. This could suggest an asymmetric activation of the TCN. This possibility has been supported by a study demonstrating ipsilateral activation of the dorsolateral pons in unilateral headache episodes induced by glyceryl trinitrate. Ipsilateral activation also occurred in bilateral headache with a unilateral predominance.

Furthermore, as in the aforementioned ‘VSM’ model and ‘Tension Headache, Migraine continuum’, the variability of symptoms could be a manifestation of the magnitude of the various afferent inputs. For instance, if disinhibition affects primarily the ophthalmic contribution, IHS migraine results; conversely if disinhibition of the mandibular and/or upper cervical afferents prevail, ETTH develops. Another common headache presentation, erroneously interpreted as ‘sinus headache’ could occur, should disinhibition of maxillary afferents be more profound.

An additional feature reinforcing the concept that migraine and TTH are intimately related is the morphing of migraine into daily or near daily headache. Many of these patients have a history of migraine, intimating a consequential relationship between migraine and near daily headache. In this transformation, episodic migraine often assumes a similar presentation to chronic tension-type headache (CTTH) (IHS
2.3), i.e., increased duration of episodes, with decreased severity and diminution of associated features.\textsuperscript{35,36} (Fig 5) This metamorphosis (chronification) of episodic migraine to CTTH presentation accentuates progression of a common underlying pathophysiological process.\textsuperscript{9}

![IHS Migraine vs IHS Chronic migraine / CTTH Diagram](image)

Figure 5. A diagrammatic representation of the morphing of migraine to daily or almost daily headache over time. Note decreasing severity and associated symptoms and increased frequency and duration of episodes.

Initially the only classification describing frequent daily headache was chronic tension-type headache (CTTH).\textsuperscript{1} However this was considered inappropriate as most patients classifiable as CTTH also experience migraine or migrainous symptoms. Furthermore, these daily headaches often evolved from episodic migraine; thus, to consider them as an embodiment of TTH was deemed to be incongruous.\textsuperscript{9} Currently, after various terminologies were proposed, notably, ‘transformed’ or ‘evolutive migraine’,\textsuperscript{35} this ‘chronic daily headache’ group is classified as ‘chronic migraine’ (IHS
1.3). Notably, in the description of chronic migraine, headache resembling ‘tension-type’ is allowed.

2.3 Summary

Substantial research has demonstrated significant symptomatic overlap between migraine and ETTH, the existence of modified forms, the dual experience of migraine and ETTH, and transformation of migraine to headache resembling CTTH. Thus, migraine and TTH, based on a set of signs and symptoms, represent different points on a continuum rather than being discrete entities. This is recognized by the IHS, as evidenced by subsequent revisions of the classification system. However, the conundrum of whether a single common mechanism underlies this headache spectrum, or whether two or more mechanisms interact to produce head pain, can only be determined by further studies of the pathophysiology of headache. The aim of this thesis was to examine the potential role of C1-3 afferents in TTH, migraine and chronic whiplash associated headache, to determine whether cervical input might be a source of pain in all three clinical conditions.
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CHAPTER 3
ROLE OF THE UPPER CERVICAL (C1-3) AFFERENTS IN PRIMARY
(MIGRAINE AND TENSION-TYPE) HEADACHE AND CHRONIC WHIPLASH
ASSOCIATED HEADACHE

3.1 Introduction

The Primary Headache syndromes are characterised by hyperalgesia, allodynia and referral of pain into trigeminal and cervical sclerotomes.\textsuperscript{1-6} This constellation of symptoms is thought to be underpinned by anatomical convergence of afferents from the trigeminal \textsuperscript{7-9} and cervical fields,\textsuperscript{10,11} and sensitisation of second order neurons in the trigemino cervical nucleus (TCN).\textsuperscript{12-15}

Corroborating earlier observations,\textsuperscript{7,8} anatomical convergence of trigeminal and cervical afferents was confirmed when neurons in the C2 dorsal horn were shown to have characteristics common to the ophthalmic division of the trigeminal nerve, the C2-3 dermatome and cervical musculature innervated by the greater occipital nerve (GON).\textsuperscript{9} Animal studies \textsuperscript{16-18} have established that convergence in the TCN extends distally to the second and third cervical spinal (C2-3) segment.

Therefore, whilst stimulation of the supratentorial dura refers sensations to the ophthalmic division of the trigeminal nerve,\textsuperscript{19} the convergence phenomenon accounts for referral to the upper cervical sclerotomes.\textsuperscript{20} Conversely, stimulation of the upper cervical nerve roots,\textsuperscript{8,21} subcutaneous tissue innervated by the GON\textsuperscript{22,23} and the atlanto-occipital-axial (O-C1-C2)\textsuperscript{24} and C2-3\textsuperscript{25} spinal segments results in head pain.
These studies confirm anatomic and functional coupling between nociceptive dural afferents and cervical afferents onto neurons in the TCN. Therefore, neurons in the TCN may be considered the principal conduit for nociceptive input from the trigeminal and cervical fields. Consequently, the TCN is likely to govern head pain in primary headache conditions.\textsuperscript{12,26,27}

The presence of hyperalgesia, allodynia and referral of pain into trigeminal and cervical sclerotomes in primary headache conditions implies facilitation or sensitisation of neurons in the TCN.\textsuperscript{14,15} This process could account for pain referral from trigeminal to cervical structures and vice versa without necessarily involving pathology in the cervical or trigeminal innervation territories respectively.\textsuperscript{5}

The notion of central sensitisation considers an increased barrage of afferent information from nociceptive C-fibers onto second-order neurons as pivotal in the development of this hyper excitability, effectively increasing their response to afferent information.\textsuperscript{28-30} In addition, it is recognised that pain modulating circuits in the brainstem also influence the degree of second-order neuron excitability.\textsuperscript{13}

Accordingly, sensitisation of nociceptive second-order neurons in the TCN could result from two pathophysiological mechanisms: facilitatory (noxious) neurotransmission from the trigeminal\textsuperscript{12,31-33} or cervical regions;\textsuperscript{33-41} or dysfunctional central pain-modulatory controls that disinhibit\textsuperscript{42-44} or facilitate\textsuperscript{45-47} afferent neurotransmission into the TCN. This review focuses on the potential sensitizing role of converging cervical afferent discharge\textsuperscript{41} in primary headache.\textsuperscript{26,48,49}
Hence, the relationship between cervical signs and symptoms and primary headache will be explored. Because the profile of chronic whiplash associated headache (CWAH) mirrors that of primary headache and is, by definition, a consequence of a musculoskeletal event, a review of the source of pain in CWAH follows. As contemporary literature implicates the upper cervical joints (primarily C2-3 zygapophyseal) as the primary source of pain in CWAH, research investigating the role of the zygapophyseal joints will be considered. The effect of various interventions (including manual cervical treatments) that potentially mitigate noxious afferent cervical discharge will also be reviewed.

3.2 Cervical Signs and Symptoms in Primary Headache

As early as 1917 a causal relationship between headache and neck symptoms was inferred. However, despite the common occurrence of concomitant neck pain in the primary headache syndromes, cervical symptoms are often considered to be an epiphenomenon of activation of the TCN.

Although neck pain is highly prevalent in the general population it is even more prevalent in individuals with primary headaches and, whilst the extent of reported associated cervical symptoms in primary headache varies, their presence is nevertheless significant. For example, in an extensive population survey, self reported migraineurs were 2.3 times more likely to experience neck pain than participants without headache whilst, in a similar survey, 38 per cent of migraineurs reported neck pain compared to 11 per cent of controls.
This compares to studies\textsuperscript{56,60,65} in tertiary settings which established that 40 to 64\% of migraine patients reported accompanying neck and occipital symptoms. Furthermore, in a cross sectional study in which participants were assigned to migraine, TTH and combined migraine and TTH groups, neck pain was reported by 76, 88 and 89\% of those with migraine, TTH and coexistent migraine and TTH respectively.\textsuperscript{49}

Aside from the prevalence of neck pain, a causal role is strengthened by reports that when compared to controls, the intensity of neck pain in a cohort of headache patients increased appreciably during headache.\textsuperscript{72} The authors suggested that rather than concomitant cervical symptoms being an epiphenomenon,\textsuperscript{13,26,77,78} they were likely to be instrumental in headache pathogenesis.\textsuperscript{53} This is supported by another study in which 69.4\% of migraineurs (n=487) reported neck pain during the migraine phase.\textsuperscript{80} In addition, the significance of concomitant neck pain has been underscored by its preeminence above nausea, which is considered to be a key feature of migraine.\textsuperscript{72}

Reinforcing the relevance of cervical symptoms, not only in migraine but also TTH, are studies of neck function in migraineurs inferring a comorbid relationship; perhaps facilitating the chronification of migraine.\textsuperscript{72} Utilising the CROM (Performance Attainment Associates, St Paul, MN) device, a validated device providing a 3-dimensional measure of cervical range of movement, a tertiary based study demonstrated comparable decreased cervical movement in women with episodic and transformed migraine when compared to controls.\textsuperscript{71}

Self-reported headache frequency, severity, and symptomatic days significantly predict disability independent of headache characteristics.\textsuperscript{69} The Neck Disability Index (NDI) is a validated questionnaire assessing functional impairment related to neck
This instrument was used to assess neck disability in 91 patients with episodic migraine and 34 with chronic migraine. Cervical range of motion was measured using a CROM. Not only was the prevalence of cervical symptoms in migraineurs confirmed, but neck pain disability also increased with increased frequency of migrainous episodes and correlated with the probability of migraine chronification. This was more pronounced in individuals with chronic migraine and in those with symptoms during neck movements, when compared to those with episodic migraine. These findings were confirmed in another NDI study in which disability due to neck pain was apparent in 69 and 92% of individuals with episodic and chronic migraine respectively.

Clearly, concomitant cervical symptoms and dysfunction are common in primary headache. However, speculation surrounds the source of symptoms and their role; are they epiphenomena, i.e., trigeminal referral (a result of the bidirectional TCN pathway), or instrumental in primary headache conditions?

There is a dearth of literature investigating the source of neck symptoms and signs in primary headache (as indicated by a search in CINHAL, Cochrane, Medline, Ovid, Pubmed (≤ 2015), using the terms, cervical symptoms, cervical pain, neck symptoms, neck pain, migraine, tension headache, tension-type headache pain). This is not surprising, because it is the absence of demonstrable cervical lesions in primary headache which primarily is responsible for the assumption that cervical dysfunction plays no role in primary headache conditions. However, given that the symptomatic profile of chronic whiplash associated headache (CWAH) mirrors the profiles of primary headache and that, by definition, whiplash headache involves cervical trauma, extrapolation to primary headache may be drawn from an appreciation of the source of symptoms in whiplash-associated headache.
3.3 Whiplash Headache and Primary Headache

The term ‘Whiplash’ describes a musculoskeletal mechanical event\(^5\) with pathophysiological considerations including micro trauma to the musculoskeletal systems of the neck.\(^6\) Thus, it is not surprising that concomitant cervical symptoms are characteristic of chronic whiplash associated headache (CWAH).\(^7\)-\(^9\) Furthermore, acute\(^9\) and CWAH patients,\(^6,9,1\) like migraineurs,\(^8,2\) exhibit comparable neck disability on the NDI. In addition, surveys\(^9,2,10,\) have shown that the profile of CWAH mirrors that of primary headache. This feature, coupled with the high prevalence of concomitant cervical symptoms and comparable neck disability, raises the possibility that CWAH may share a common mechanism with primary headache.\(^9,7\)

Clinical\(^8,6,9,10,1-3\) and biomechanical\(^10,4-11,5\) studies have identified the cervical zygapophyseal joints as the most common source of injury and accompanying neck and head pain in CWAH. However, other sub occipital structures at risk during the whiplash mechanism include the deep cervical paravertebral muscles and intervertebral discs.\(^11,6,11,7\) Human subject and biomechanical modeling has predicted that potentially injurious\(^11,8,11,9\) muscle fascicle strains in cervical paravertebral muscles could occur as a result of forced lengthening during reflex neck muscle activation during trauma.\(^12,0,12,1\) Furthermore, MRI based studies have demonstrated the extensive presence of fatty infiltrates in neck muscles of chronic whiplash patients.\(^12,2,12,5\) However, these were not evident in patients with chronic spontaneous onset neck pain,\(^12,4\) and whilst it is acknowledged that muscles reside within areas of pain,\(^12,6\) no research has produced clinical evidence for compromised muscles as determinants of CWAH.\(^12,6,12,7\)
Similarly, whilst lesions of the anterior longitudinal ligament and anterior aspect of the annulus fibrosis (of the intervertebral disc) have been demonstrated in cadavers and post mortem studies of patients with CWAH, their nociceptive role has not been ascertained. Furthermore, determining the incidence of disc injury in the whiplash mechanism is problematic because of the high prevalence of asymptomatic intervertebral disc disease. Therefore, conceivably the primary nociceptive focus lies with other vulnerable structures in the neck.

It has been hypothesised that neuromuscular abnormalities observed in CWAH, for example, altered range of cervical movement, originate from muscle spasm triggered by abnormal afferents from compromised zygapophyseal joint capsules and associated ligaments. This is supported by evidence of increased laxity of zygapophyseal joint capsules after exposure to the whiplash mechanism. The capsular innervation by nerve fibres, particularly nociceptors, and the mechanical vulnerability of the zygapophyseal joints support the joint’s nociceptive role.

Further incriminating the zygapophyseal joints and associated capsules are biomechanical studies demonstrating that movements of the upper cervical segments can exceed physiological limits during motor vehicle trauma. Indeed, of the purported structures responsible for neck pain and headache, the C2-3 zygapophyseal joint and capsule is the only validated source. Whilst atlanto axial (C1-2) and atlanto occipital joints have been shown to refer head pain, C1-2 involvement is relatively uncommon and a dearth of studies investigating the atlanto occipital joints precludes any consequential discussion.
The C2-3 zygapophyseal joint is innervated by the third occipital nerve. Accordingly, stimulation to the C2-C3 zygapophyseal joint provokes head pain; conversely, cervical medial branch blocks anaesthetize afferents from the zygapophyseal joints, and ameliorate headache not only in CWAH patients but in atraumatic headache patients. Consequently, because this form of headache is alleviated by anaesthetizing the third occipital nerve, it became known as ‘third occipital headache’.

To determine the prevalence of C2-3 zygapophyseal joint involvement in CWAH, a search of CINHAL, Cochrane, Medline, Ovid, Pubmed (≤ 2015), using the terms, whiplash headache, C2-3 zygapophyseal joint, C2-3 facet joint, C2-3 z-joint, third occipital headache, was undertaken. As different methodologies and outcome variables were employed in the studies identified, each study is reviewed separately below.

A cohort of 100 patients with chronic neck pain post whiplash underwent diagnostic anaesthetic blocks of the third occipital nerve (medial branch of C3 nerve). Seventy-one patients reported headache; of those, headache was the predominant symptom in 41. Anaesthetic blockade of the C2-3 zygapophyseal joint was successful in 27% of all patients and 53% in which headache was the dominant feature. In a similar study, the C2-3 zygapophyseal joint was incriminated in 50% of post whiplash patients in whom headache was the predominant symptom.

Both the presence of cervical pain and response to anaesthetic blocks of the third occipital nerve in whiplash patients is paralleled in patients with neck pain who had not been subject to overt trauma. In a study of mild to moderate neck pain, whiplash
patients (n=133) and atraumatic neck pain patients (n=691) were assessed.\textsuperscript{152} After considering perceived neck pain, functional limitation (NDI) and prognosis, there were no relevant differences between the two groups.\textsuperscript{152} Fifty-four and 48.4\% of the whiplash and atraumatic neck pain patients respectively reported associated headache. There was no attempt to classify headache type. Similarly, studies in which the third occipital nerve was anaesthetized in patients with atraumatic neck pain reflect the results in whiplash patients; anaesthetic blockade afforded complete relief in 36\% to 67\% of atraumatic neck pain patients.\textsuperscript{153,155,156} The authors of the study\textsuperscript{153} in which prevalence of pain relief was relatively low (36\%) accept that their result was conservative because many patients declined a second confirmatory anaesthetic block.

Furthermore, denervation of the zygapophyseal joint utilising percutaneous radiofrequency medial branch neurotomy of the third occipital nerve has been shown to produce complete and long-lasting relief from cervical (below C2-3) zygapophyseal joint (neck) pain.\textsuperscript{157-161} In a consummate study,\textsuperscript{161} radio frequency neurotomy of the C2-3 zygapophyseal joints provided complete relief from headache for around 297 days in 43 of 49 patients. In addition, neurotomies were repeated in 14 patients, 12 of whom achieved further relief for a median duration of 217 days. It was not clear how many patients had symptoms that were attributable to trauma, but 33 were involved in litigation.

Moreover, reflecting the effect of anaesthetic blockade of the third occipital nerve in whiplash patients is the amelioration of headache following this procedure in seven or 10 atraumatic headache patients.\textsuperscript{149} Furthermore, the characteristics of headache resembled TTH, implying that other forms of (primary) headache may be masquerading as ‘third occipital headache’.\textsuperscript{149,162}
In addition to the positive effect of medial branch blocks of the third occipital nerve on headache and neck pain, further evidence of zygapophyseal joint involvement is furnished by reduction of sensory hypersensitivity (pressure pain and cold pain thresholds) in patients with chronic whiplash associated disorders (WAD) following anaesthetic blockade of the joint. As with pressure pain thresholds, cold hyperalgesia is usually related to altered sensory processing, and has been associated with poor prognosis in patients with chronic WAD.

In another study, increased pressure pain thresholds in patients with chronic WAD resulted from anaesthetic blockade of myofascial trigger points in the upper fibres of the trapezius. Furthermore, symptoms of photophobia resolved in all but two of the 11 subjects for the duration of the anaesthetic block. This result suggests a central mechanism as the mediator between the myofascial trigger points and sensitivity to light. However, the increase in pressure pain thresholds in this study conflicts with an earlier study, leading to speculation that other cervical structures were responsible for central sensitisation. This contrary result was considered to be due to the difference in technique used to identify trigger points, for in the earlier study anaesthetic infiltration of ‘tender’ as opposed to ‘trigger’ points was administered. Nevertheless, the reduction in pain, reduced sensory hypersensitivity and photophobia following modulation of cervical afferents reflects decreased nociceptive input into the central nervous system with probable decreased excitability of central nociceptive pathways and/or facilitation of inhibitory pathways.

In favour of the former possibility (i.e., decreased nociceptive input into the central nervous system) were the results of a recent study in which sensory processing
in the head in chronic neck pain patients was investigated.\textsuperscript{168} The organisation of sensory processing is considered to be a result of functional transmission via the functional interaction between trigeminal and upper cervical afferents.\textsuperscript{169-172} This allows bidirectional transmission and processing of nociceptive afferents between the cervical and trigeminal sensory receptive fields of the face and head.\textsuperscript{7,8,25,26,147,169-172} Using a multi modal quantitative sensory testing protocol (incorporating pressure pain, thermal and electrical threshold testing), along with assessment of descending inhibitory controls using the conditioned pain modulation (CPM) paradigm, the sensory organisation in cervicogenic headache patients with associated chronic zygapophyseal joint pain was compared to patients with chronic zygapophyseal joint pain without headache.\textsuperscript{168} Pressure hyperalgesia and accompanying cold and warm hyperaesthesia on the headache side in cervicogenic headache patients compared to the non headache group implied ongoing sensitisation of the TCN driven by cervical afferents.\textsuperscript{168}

Alternatively, generalized hyperalgesia could be due to dysfunctional supraspinal, descending inhibitory controls.\textsuperscript{165,167,173} However, the finding that CPM was unimpaired in both the cervicogenic headache and non headache groups implies that descending inhibitory controls were fully operational and therefore unlikely to be responsible for central sensitisation in the cervicogenic headache patients.\textsuperscript{168}

This conclusion is strengthened by a review of 16 studies investigating the nociceptive flexion reflex (NFR) in subjects with chronic musculoskeletal pain.\textsuperscript{174} The NFR is considered to be a more diametrical measure of spinal cord excitability relying less on psychological factors\textsuperscript{175-177} when compared to quantitative sensory testing.\textsuperscript{178} The reviewers included studies of primary headache, fibromyalgia, knee pain and whiplash subjects. All groups demonstrated central hyperexcitability evidenced by
impairment of NFR. Notably, this review included studies of migraineurs and tension headache patients and supports the possibility of a sensitisation from noxious cervical afferents. This is mirrored by studies revealing impaired NFR in acute whiplash headache and chronic whiplash associated disorders.

Whilst not employing traditional joint blockades, a study of 229 occipital migraine patients undergoing ‘migraine surgery’ investigated the effect of third occipital nerve resection. Excision of the third occipital nerve (n=111), effectively blocking C2-3 zygapophyseal joint afferents, did not affect ‘migraine surgery’ outcomes. Given that the C2-3 zygapophyseal joint is innervated by the third occipital nerve, this suggests that afferents from the C2-3 zygapophyseal joint are not directly involved in the migraine process. However, the effect of zygapophyseal joint anaesthetic blockade on primary headache per se has not been investigated and a search of the subsequent literature (CINHAL, Cochrane, Medline, Ovid, Pubmed (2004 - 2015), using the terms, C2-3 zygapophyseal joint, anaesthetic blockade, migraine, tension headache, tension-type headache, chronic tension-type headache) failed to uncover any studies.

3.4 Modulation of Cervical Afferents in Primary Headache

Because primary headache often includes pain in the back of the head, anaesthetic blockade of the greater occipital nerve (GON) has become an increasingly common practice, despite denunciation of its value on the basis that it supplies only the skin, muscles and vessels of the scalp which are not established sources of pain. The predominant interventions include anaesthetic blockade of the GON (GON block) and occipital nerve stimulation (ONS).
Whilst some studies support the efficacy of anaesthetizing the GON in acute and chronic migraine, the great heterogeneity of published studies renders their evaluation difficult. In an extensive review of eleven studies, the authors highlight inconsistencies surrounding patient selection, timing of the procedure i.e. interictally, variability of technique (including bilateral / unilateral), inclusion of other nerves and/or the presence of trigger points, local anaesthetic agent alone or combined with different types and dosages of steroids, and variable outcome measures.

Unfortunately, randomized, double-blinded, placebo-controlled studies of GON block in migraine have produced conflicting results. Supporting the benefit of GON block outcomes in open-label studies or case series in addition to the perception of benefit among clinicians was the larger (n=73) of two studies, whilst the smaller (n=33) found no benefit of GON block in the management of migraine. Thus, the role of GON block in migraine remains uncertain.

Comparatively few studies have investigated the effect of anaesthetic blockade of the GON in TTH. Furthermore, these studies were plagued by similar (to migraine) inconsistencies with contrasting results. As with migraine, whether GON blocks are an effective treatment for TTH will require additional clinical trials.

Regardless of the ambivalence surrounding GON block in primary headache, GON block provides relief for some patients; however, the relief is mostly only temporary. This has led to increasing interest in occipital nerve stimulation (ONS). Subsequent to the first published (1999) ONS study for intractable occipital neuralgia, ensuing studies have reported promising results for chronic migraine.
which, in turn, encouraged randomised trials.\textsuperscript{207-209} Of these, only one study\textsuperscript{209} met its primary end point, demonstrating 39\% of 29 patients with chronic migraine at three months follow-up experienced a three point or more decrease in severity from baseline or greater than 50\% decrease in headache days per month.

Whilst these studies failed to meet expectations, results from subsequent studies\textsuperscript{210,211} have been more promising. Although investigating primarily the significance of paraesthesia and possible placebo effects, the first of the double-blinded trials (n=8)\textsuperscript{210} reported consistent stimulation dependent benefit. In the second and larger (n= 157) study,\textsuperscript{211} 59.5\% and 47.8\% of chronic migraine patients reported a corresponding 30\% and 50\% reduction in headache days and / or pain severity over 12 months. After completing the randomised, double blinded section of the study (three months), patients continued with open-label ONS for the remaining 40 weeks. Therefore, in both studies the effect appears to be stimulation dependent; further investigations are required to determine long-term efficacy in a non stimulation environment.\textsuperscript{210}

A search of the CINHAL, Cochrane, Medline, Ovid, and Pubmed databases (≤ 2015), using the terms, \textit{occipital nerve stimulation, ONS, tension headache, tension-type headache, chronic tension-type headache} failed to disclose any studies on the effect of ONS in TTH.

Debate continues as to whether the modulatory effect of the GON block or ONS on migraine is peripherally driven or activates central inhibitory mechanisms.\textsuperscript{145,210} However, GON afferent information arises from structures not considered as sources of pain in migraine and in itself the GON is not compromised. Therefore, modulation
cannot be interpreted as ‘anaesthetizing’ the source of pain. Conceivably the ongoing relief provided by neurotomy or (to a lesser extent) medial branch blocks, supports the assertion that targeting the GON as the primary source of pain in migraine is suboptimal. 

3.5 Zygaphophysial Joints and Animal Studies

As in humans, histological studies of zygaphophysial joints in rats and goats have identified nociceptive nerve fibres in the joint’s capsular ligament. Mechanical hyperalgesia or allodynia represents enhanced nociceptive processing and as such is commonly used as an indicator of pain outcomes in animal studies.

A substantial body of evidence from animal models has demonstrated the development of mechanical hyperalgesia from controlled, non-injurious loading of the zygaphophysial joint capsule. Conversely, after removal of the capsule, stressing the joint resulted in no pain, indicating that capsular tension is a requirement for pain from zygaphophysial joint loading. Furthermore, intra-articular injection of ketorolac, a non-steroidal anti-inflammatory drug, attenuated zygaphophysial joint pain. This was considered to be due to a concomitant reduction (which had increased in parallel with mechanical hyperalgesia) in astrocytic Protease-activated receptor -1. Protease-activated receptor -1 is considered instrumental in the maintenance of pain.

Substance P is a common nociceptive mediator, both locally and spinally, for joint pain. The potential for Substance P to influence nociceptive signalling has been demonstrated in a study in which lumbar zygaphophysial joint proprioceptive and
nociceptive afferents in rabbits were enhanced by application of substance P.\textsuperscript{229}

Similarly, in the rat, increased substance P expression in the dorsal root ganglia (associated with mechanical hyperalgesia) was detected after capsular loading of cervical joints.\textsuperscript{215} Furthermore, increased substance P was still evident seven days later.\textsuperscript{215} In addition to increased expression in the spinal cord of prostaglandin (E\textsubscript{2}) and interleukin-1\textalpha, other markers associated with joint inflammation and pain\textsuperscript{229-234} were observed within a day\textsuperscript{224} and persisted for seven days\textsuperscript{223} after loading of cervical zygapophyseal joints,\textsuperscript{223,224} implying that spinal inflammation not only initiates but also contributes to maintenance of pain after joint compromise.

In addition, extracellular recordings of spinal dorsal horn neuronal activity were taken seven days after capsular loading. The presence of increased neuronal firing was interpreted as direct evidence of neuronal modulation and in part likely to be responsible for central sensitisation underpinning chronic pain.\textsuperscript{221}

Furthermore, in a recent study, intra articular zygapophyseal joint injections of saline induced nociceptor activation (as measured by mechanical hyperalgesia), dorsal horn hyper excitability and up-regulation of excitatory signaling proteins.\textsuperscript{225} These changes were attenuated by intra articular bupivacaine only within (and not after spinal modifications develop) four hours, implying that initial afferent activity induces spinal sensitisation via spinal glutamatergic signaling.\textsuperscript{225}

Conspicuously, mechanical hyperalgesia and associated aforementioned neurophysiological changes result from relatively small loads;\textsuperscript{214-217,223,225} joint distractions ranging from 0.35 mm\textsuperscript{224} to 0.9 mm\textsuperscript{214} have been shown to elicit mechanical allodynia in rats. Reflecting the relatively low consequential distraction
loads, capsular loading was quantified in terms of strain, with mechanical hyperalgesia evident at as low as 11.1% of maximum capsular strain. This finding raises the possibility of pain-initiating events occurring before joint tensile strain threshold is reached.

This hypothesis is supported by evidence of capsular fibre realignment at 0.51 mm distraction, preceding the capsular yield (defined by a decrease in stiffness). Ligament yield is defined by any decrease in the maximum tangent stiffness of at least 10%. By definition, for any data point where failure is detected, yield will also be detected because the tangent stiffness during failure decreases enough to become negative. Therefore, it is possible that anomalous fibre realignment may occur at lower thresholds than detected in this study. Furthermore, because yield forces correspond with joint distractions producing mechanical hyperalgesia and associated cellular responses, yield may also provide a barometer for pain, and therefore may be a superior measure of injury thresholds more relevant to pathophysiological events.

These results imply that the aforementioned neurophysiological phenomena, notably zygapophyseal joint mediated spinal hyperexcitability, plasticity of dorsal horn neuronal activity and pain, occur in response to abnormal alterations in fibre patterns of the capsule’s collagen matrix during loading occurring at or preceding capsular yield.

Pathophysiologival effects identified in mechanistic studies of the zygapophyseal joint in animal studies may be important in human pain processes. In particular, animal studies indicate that nociceptive afferent information from
zygapophyseal joints contribute to central sensitisation; moreover, when considered with the ameliorating effect of anaesthetizing or neurotomy of the medial branch of the third occipital nerve, animal data provide a compelling argument for cervical zygapophyseal joints as a source of neck pain and/or headache.

Additional extrapolation from animal research suggests that symptomatic compromise of the zygapophyseal joint may occur in the absence of any macroscopic lesion. When considered with studies demonstrating parallel profiles of neck pain, functional limitation and prognosis and the effect of anaesthetic blockade of the third occipital nerve in CWAH and atraumatic patients, this implies that overt trauma is not a prerequisite for cervical zygapophyseal joint compromise.

This in part explains why whiplash remains one of the most debated and controversial painful musculoskeletal conditions, for whilst it is generally acknowledged that an initial cervical injury occurs during a whiplash event, specific patho anatomical lesions are, in the main, not evident.

Notwithstanding the absence of clinical evidence for compromised cervical muscles in the CWAH, and the focus on zygapophyseal joints, studies using animal models have demonstrated that algesic chemical stimulation of deep cervical paraspinal muscles evokes effects in the trigeminal field. These include prolonged increased activity of the ipsilateral jaw musculature and alterations in the jaw opening reflex, an established model for the investigation of sensorimotor processing of the trigeminal brainstem. These findings are supported by studies in which neuronal brainstem activity was recorded during cervical intervention. In one study, long-term increased neuronal excitability in the brainstem resulted from a single
intra muscular injection of low dose adenosine 5'-triphosphate (ATP) into murine neck musculature.\textsuperscript{36} (ATP is an algogenic molecule which is used widely for experimental induction of noxious input from muscles.)\textsuperscript{39,40} This finding was replicated by research in which inflammatory irritant mustard oil was injected into deep paraspinal structures adjacent to the C1-2 spinal segment - 70 per cent of neurons exhibited increased excitability.\textsuperscript{41} Another pertinent finding reflecting central sensitisation was the expansion post injection of the orofacial and cervical neuronal receptive fields.\textsuperscript{41} This body of research involving cervical musculature provides additional support for cervical afferent sensitisation of the TCN.

3.6 Primary Headache: are Cervical Lesions Necessary?

The fact that neurophysiological phenomena result from non injurious loading of the zygapophyseal joint capsule has significant implications. Not the least is that these findings are incongruent with the biomechanical premise that the degree of symptoms would be proportional to magnitude of soft tissue loading.\textsuperscript{125,243} Accordingly, there is general agreement that conventional medical imaging lacks sensitivity for capsular and intra-articular injuries of the spine.\textsuperscript{125,131,152,155-158,160,161} Consequently, computed tomography and magnetic resonance imaging are not appropriate tests to rule out pathology.\textsuperscript{125,131,152,157,160,161} Instead, identifying lesions is likely to require more sophisticated and specialised methods. For example, in a positron emission tomography study, tracer uptake in proximity to the second cervical vertebra was significantly greater in CWAH patients than controls, indicating local persistent peripheral tissue inflammation.\textsuperscript{244}
Secondly, and conspicuously in relation to whiplash disorders, the inability of customary medical imaging to identify pathology implies that the source of patients’ symptomatology is not always clinically detectable; \(^{126,155-158,160}\) that is, the absence of extensive, conspicuous zygapophyseal joint capsular damage does not rule out nociceptive relevance.\(^{125,152,155}\) However the exact pathophysiology of CWAH and associated neck pain remains an enigma for many.\(^{245-248}\)

This puts CWAH in the same category as cervicogenic headache and primary headache conditions. Cervicogenic headache, like CWAH, is considered a musculoskeletal condition but its purported existence continues to be debated.\(^{249,250}\) Underpinning this debate is the lack of identifiable pathology. In this respect diagnoses of migraine,\(^{83}\) and tension-type headache,\(^{84}\) suffer from the same limitations.

3.7 Upper Cervical Joint Dysfunction in Primary Headache

Notwithstanding the lack of identifiable spinal pathology, noxious afferent cervical information has been linked to TTH\(^{49,54,59,251-261}\) and migraine.\(^{49,54,56,72,261,262}\) In a recent observational, case-control study,\(^{262}\) significant hypomobility of the atlanto occipital and C1-2 segments in a cohort of 20 migraineurs was demonstrated. In an earlier larger study of 90 patients,\(^{261}\) comprising 39 migraine, 11 TTH and nine patients with combination headache (the remaining 31 patients were assigned cluster, post-traumatic or drug rebound headache diagnoses), manual palpation detected dysfunction of the C1-2, C2-3 and C3-4 segments in 86% of migraineurs, while in 78% of TTH patients dysfunction was demonstrated at atlanto occipital, C1-2, and C2-3 segments. Furthermore, there were no statistically significant differences in cervical dysfunction between groups. Similarly in another study,\(^{54}\) 84% of patients with either TTH or
migraine without aura exhibited hypomobility of the atlanto occipital and C1-2 segments.

Corroborating the manual findings was the radiological assessment which confirmed reduced segmental motion at the atlanto occipital segment in 90% and 70% of participants in flexion and extension, respectively. However, in stark contrast, another study found no evidence of palpable upper cervical segmental dysfunction in TTH patients or migraineurs. The dissimilarity in results is likely to be due to different examination approaches and underlines the importance of developing a standardized protocol for assessing the cervical spine; currently, reliable and valid testing methods have not been established.

A symptomatic (and potentially more relevant), non manual correlate is provided by studies demonstrating referral of head pain from symptomatic upper cervical facet and C2-3 zygapophyseal joints. This suggests that head pain referral is a pivotal characteristic of cervical afferent involvement in headache.

3.8 Cervical Treatment of Primary Headache

Randomized controlled trials (RCTs) are considered an optimal method with which to assess the efficacy of any intervention. Furthermore, it is now recognised that for unambiguous interpretation of the efficacy of RCTs in headache, assessment using a primary end-point (headache frequency) and secondary end-points (duration and intensity) are mandatory.
The first systematic and comprehensive review assessing the efficacy of manual therapy RCT for primary headache in which headache frequency and duration and intensity were used as primary and secondary endpoints respectively was conducted in 2014 and considering its currency provides the basis of this overview. In a search of the CINHAL, Cochrane, Medline, Ovid and PubMed databases using the terms *migraine, chronic migraine, chronic tension-type headache combined with spinal mobilisation, spinal manipulative therapy, manipulative therapy, physiotherapy, osteopathic treatment, chiropractic, massage therapy*, six RCTs were identified, all addressing CTTH; no available studies assessed migraine. Five studies applied physiotherapy and the other, massage therapy. The methodological quality of the RCTs was evaluated using the PEDro scale - four studies were considered of good quality.

Additionally, of particular relevance is the upper three cervical (C1-3) afferents from the apposite spinal joints. Furthermore, if additional interventions were involved, results were inconclusive; determining which intervention was effective is problematic. None of the studies identified focused exclusively on the atlanto occipital, C1-2 and C2-3 spinal segments and only two avoided co-intervention; headache and neck massage and biofeedback only. By way of example, in one study manual therapy intervention comprised mobilisation of the thoracic and cervical (segmental levels not specified) spines, craniocervical exercises and postural correction. At each treatment session the therapist, depending on the outcome from previous sessions, selected the intervention. Typically, mobilisation commenced with exercises and, if necessary, progressed to spinal mobilisation, complemented by muscle stretching and massage. Whilst this study demonstrated that manual therapy is more effective in the
management of chronic tension type headache than standard general medical practitioner care, the role of C1-3 afferents is uncertain.

However, a later double blind, randomised, placebo controlled trial addressed the atlanto occipital segment specifically and also avoided co-intervention. Patients with either chronic or episodic tension type headache were divided into four groups; atlanto occipital manipulation, sub occipital soft tissue massage, a combination of both and a placebo-control group. Those patients who had received manipulation only, and also combined with sub occipital massage, reported significant improvement in frequency and intensity of headache; the latter group showing greater improvement. Whilst patients completed headache diaries, it is unclear whether the interventions also impacted on duration. Possibly the inclusion of both (and not discriminating between) episodic and chronic tension type headache patients precluded any meaningful analysis of duration.

While the underlying pathophysiology of tension type headache is uncertain, the most accepted theory is that tension type headache is underpinned by central sensitisation due to prolonged afferent nociceptive inputs from peripheral tissues. Moreover, peripheral factors are implicated in episodic tension-type headache, whereas central factors are considered to be instrumental in chronic tension-type headache. Therefore, in patients with episodic tension type headache where the peripheral input is probably dominant, manual therapy is likely to be more effective than in those with chronic tension type headache. Conceivably, then, the amalgamation of episodic and chronic tension-type headache patients could have blurred interpretation of results.
Whilst the results of this study\textsuperscript{278} are promising, the four week follow-up period, as the authors conceded, could be considered to be a limitation; longer periods of observation after treatment are necessary to adequately judge the value of atlantooccipital, C1-2 and C2-3 mobilisation/manipulation as a potential first line of therapy for tension-type headache\textsuperscript{278}.

In relation to TTH, the available RCTs\textsuperscript{260,273-277} suggest that massage and physiotherapy are effective treatment options in the management of CTTH\textsuperscript{272} without specifically identifying, with the exception of one study\textsuperscript{278}, a potential causative role of the upper cervical afferents.

Building on the 2014 review\textsuperscript{272}, another comprehensive 2015 systematic review and meta-analysis of physiotherapy clinical trials in primary headache\textsuperscript{282} identified trials for TTH\textsuperscript{277,283,284} and migraine\textsuperscript{285-289} (for search terms and strategy, the reader is referred Luedtke et al\textsuperscript{282}). However all trials used aerobic exercise or a multidisciplinary approach and as such provide no meaningful information as to the role of upper cervical afferents in primary headache. The authors of the latter review concluded that whilst there was low level evidence for appreciable reduction in the severity of TTH and duration of migrainous episodes\textsuperscript{282}, unequivocal evidence for a beneficial effect of physiotherapy/cervical intervention on primary headache conditions can only be provided by future RCTs of incontrovertible methodological rigor and adequate sample sizes\textsuperscript{272,282}.
3.9 Summary

The significant presence of neck pain and cervical dysfunction in TTH and migraine suggests that cervical afferents are instrumental in primary headache pathophysiology. This relationship is reinforced by impairment of the nociceptive flexion reflex in migraineurs and TTH patients. Additional support is afforded by the similar profile of CWAH to that of primary headache (including the incidence of neck pain) and that the C2-3 zygapophyseal joint has been validated as a source of neck pain and headache in CWAH. Furthermore, minor stress on zygapophyseal joints can lead to zygapophyseal joint mediated spinal hyperexcitability, plasticity of dorsal horn neuronal activity and pain. That the C2-3 zygapophyseal joint could play a causal role in primary headache conditions is strengthened by the significant relief following neurotomy of the C2-3 zygapophyseal joint.

Conversely, modulating cervical afferents by anaesthetizing or influencing the GON in primary headache has produced inconsistent results, reinforcing the notion that targeting the GON is suboptimal. Similarly, manual cervical treatment of primary headache conditions suffers the same fate, perhaps because rigorously designed clinical trials have not focused specifically on the C2-3 zygapophysial and adjacent joints.


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CHAPTER 4
BLINK REFLEX

4.1 Introduction

In studies on trigeminal activity in primary headache syndromes, it is mandatory that the emphasis be on nociceptive processing. Wide dynamic range (WDR) and nociceptive specific (NS) neurons respond to noxious stimuli and are present in the interstitial nucleus of the spinal trigeminal tract and the spinal trigeminal nucleus (STN). The STN comprises 3 sub-nuclei; the nucleus oralis (SNo), interpolaris (SNi) and caudalis (SNc).

Data from animal and human studies have demonstrated that nociceptive processing occurs predominantly within the medullary SNi and SNc of the STN.1,2 Furthermore WDR and NS neurons are involved in mediation of the blink reflex (BR), and therefore the BR provides a model by which to assess trigeminal pain processing.3

4.2 Anatomy and Measurement of the Blink Reflex

The BR can be evoked by electrical stimulation of the supra orbital nerve and is measured from responses of the obicularis oculi muscle. The BR response comprises 3 components: an early ipsilateral component (R1); a bilateral late component (R2) and a bilateral ultra late component (R3).4

Innocuous electrical and mechanical stimuli elicit R1 and R2, implying mediation by Aβ afferents,4 whereas R3 is evoked by strong electrical stimuli. The ultra
late R3 response is not always present and because it cannot be elicited unconditionally is considered to be part of the ‘startle’ response.\textsuperscript{5,6}

Whilst initially R2 and R3 were considered nociceptive components of the BR,\textsuperscript{7} it has been demonstrated that R3 is not a suitable measure of trigeminal nociceptive processing.\textsuperscript{8} The electrical threshold of R3 is mainly determined by activation of Aβ fibres (and to a lesser extent nociceptive Aδ fibres). However, application of local anaesthetic in the supra orbital region failed to alter R3,\textsuperscript{8} implying that nociceptive Aδ fibres were probably not involved in R3 and therefore R3 is an inappropriate measure of nociception.

Because both nociceptive and non-nociceptive afferents can elicit R2, two reflex paths are possible.\textsuperscript{3} The first involves Aβ afferents converging onto low threshold mechano receptive (LMT) neurons and Aδ onto nociceptive specific neurons. The second reflex path involves both Aβ and Aδ afferents projecting onto common WDR neurons. That is, both reflex paths share the same interneurons.\textsuperscript{3} Activation of the DNIC system (WDR neurons) involves nociceptive specific neurons in the sub nucleus reticularis dorsalis inhibiting WDR in the trigeminal system and spinal cord.\textsuperscript{9} R2 was inhibited, demonstrating that Aβ and Aδ afferents converge onto WDR neurons in the medullary spinal trigeminal nucleus.\textsuperscript{9} Furthermore, noxious stimulation to the forehead facilitated R2, consistent with convergence of low-threshold mechanoreceptive and nociceptive afferents onto medullary WDR neurons.\textsuperscript{10}

Another assessment technique developed to measure trigeminal brainstem nociception is the corneal reflex (CR). This reflex involves applying noxious heat or air puff stimulation of the cornea to evoke selective stimulation of trigeminal nociceptive
fibers, thus increasing the nociceptive sensitivity of the blink reflex response.\textsuperscript{11,12} The CR consists of two late bilateral symmetrical components, analogous to the R2 component.\textsuperscript{13} That is, the BR comprises R1, 2 and 3; the CR R2 only. Further, the BR is essentially a cutaneous reflex elicited by mechanoreceptors from afferent A\textbeta and nociceptive A\textalpha fibres, whilst the CR results from stimulation of nociceptive A\textalpha afferent fibres in the corneal epithelium. In addition, the CR nociceptive afferents project onto the second order neurons of laminae I and II, and V, and VI of the SNc, whereas the A\textbeta afferents of the BR terminate on laminae III and VI of the SNc with tactile and nociceptive information converging on WDR neurons at more rostral levels of the trigeminal system.\textsuperscript{14} These characteristics of the BR, along with findings demonstrating fewer fibres and inter neurons in the CR, have led to the thesis that the BR affords greater stability than the CR.\textsuperscript{15,16}

Because approximately 90\% of the R2 reflex response of a BR to standard electrical stimuli depends on non-nociceptive A\textbeta fibre input,\textsuperscript{17} the possibility of selective stimulation of superficial nociceptive fibres in the area of the supra orbital nerve to elicit a ‘nociception specific’ blink reflex (R2 nBR) was explored.\textsuperscript{18} Blink reflex responses elicited by the standard parallel electrode were compared to those elicited by a custom built concentric electrode (R2) before and after local anaesthetic cream was applied to the supra orbital area. Importantly, the R2 component was reduced by 12 and 90\% respectively. The authors concluded that the almost total inhibition of R2 nBR after local anaesthetic using the novel electrode demonstrated selective stimulation of nociceptive fibres at a low current intensity in the region of the supraorbital nerve that was more tolerable than stimulation of the cornea.\textsuperscript{18} A subsequent study investigating the optimal parameters of the R2 nBR confirmed the R2 nBR to be a reliable, non invasive electrophysiological technique to assess activity of
the trigeminal system in primary headache conditions.\textsuperscript{19} Therefore, those studies investigating migraine utilising the R2 nBR are reviewed below.

4.3 Migraine and the ‘nociceptive specific’ blink reflex

A search of the literature comprising the search terms ‘R2, migraine, nBR’ from 2000 to 2015 identified seven studies employing the nBR.\textsuperscript{17,19-24} (Table 3.1) Researchers have assessed various properties of the nBR, namely habituation, onset latencies, area under the curve (AUC) and, to a lesser degree, the recovery cycle (RC).

Habituation is a complex, multi factorial phenomenon. The dual process theory considers two separate divergent processes that influence the response profile to repetitive stimuli.\textsuperscript{25} Habituation, considered to be a rudimentary and omnipresent form of behavioural plasticity, has been defined as “a response decrement as a result of repeated stimulation”\textsuperscript{26} (cited by \textsuperscript{27}) and therefore is a measure of decreased responsiveness. The opposing process comprises facilitation or sensitisation i.e., increased responsiveness.\textsuperscript{25}

Sensitisation, when present, occurs during the initial stages of exposure to repeated stimuli, accounting for an increase in response amplitude; conversely, habituation prevails subsequently. As with habituation, sensitisation is considered an elementary form of behavioural plasticity, and as such is regarded with equal importance.\textsuperscript{28} Therefore, habituation and sensitisation are considered to reflect activity in neuronal substrates of information processing in the CNS.\textsuperscript{28}
Table 1 Nociceptive blink reflex studies and migraine.

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Experimental Groups (n)</th>
<th>Modus operandi</th>
<th>Results</th>
<th>Conclusions</th>
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<tr>
<td>Kaube et al 2002&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Migraineurs=17 (Ictal &amp; interictal)</td>
<td>R2 latencies &amp; AUC ictally &amp; post treatment (lysine acetylsalicylate (ACA) or zolmitriptan) i.e. interictally</td>
<td>↓ latencies &amp; ↑ AUC R2 nBR  680% ictally; ↑ latencies &amp; ↓ AUC post treatment</td>
<td>Temporary central trigeminal sensitisation during migraine</td>
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<td>Katsavara et al 2002&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Migraine=14 (Ictal &amp; interictal); Controls with sinusitis headache=14</td>
<td>R2 nBR during migraine &amp; sinusitis headache</td>
<td>R2 nBR facilitated ipsilaterally during migraine</td>
<td>Facilitation in migraine not peripherally mediated</td>
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<tr>
<td>Katsavara et al 2003&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Migraineurs=17 (Ictal &amp; interictal); Controls=15</td>
<td>AUC R2 nBR ictally &amp; interictally to repeated stimulation</td>
<td>↑ AUC in migraineurs but not controls interictally</td>
<td>Interictal deficit of habituation in migraineurs</td>
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<tr>
<td>Katsavara et al 2004&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Migraineurs=28 (Ictal &amp; interictal) Controls=30</td>
<td>R2 nBR ictally and post treatment (ACA or zolmitriptan) i.e. interictally</td>
<td>↑ latencies R2 nBR and suppression of AUC post treatments ictally but not interictally</td>
<td>Medication inhibited R2 nBR ictally but not interictally</td>
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Table. Nociceptive blink reflex studies and migraine. (cont.)

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<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Findings</th>
<th>Conclusion</th>
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<tr>
<td>Di Clemente et al 2005²²</td>
<td>Migraineurs=15</td>
<td>AUC R² nBR interictally to</td>
<td>↑ AUC R² nBR in migraineurs but not controls interictally</td>
<td>Interictal deficit of habituation in migraineurs not due to trigeminal sensitisation</td>
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<td>Controls=15</td>
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<td>Di Clemente et al 2007²³</td>
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<td>AUC R² nBR interictally to</td>
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<td>Coppola et al 2007²⁴</td>
<td>Migraineurs=14</td>
<td>R² nBR recovery curve (paired</td>
<td>No difference in onset latencies and AUC R² nBR between migraine &amp; controls; R² nBR</td>
<td>Interictal sensitisation of trigeminal system non existent; descending brainstem pathways are</td>
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<td>recovery curves normal</td>
<td>controls. R² nBR recovery curves normal</td>
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<td>Controls=15</td>
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4.3.1 Central sensitisation

Central sensitisation refers to plastic changes in neural structures belonging to the “pain matrix” that result in decreased nociceptive thresholds and increased responsiveness to noxious and innocuous peripheral stimuli, and expansion of the receptive fields of CNS nociceptive neurons.29

In an early ictal study utilising both BR and R2 nBR responses in migraineurs,17 sensitisation of the trigemino cervical nucleus (TCN) was demonstrated. Seventeen patients were assessed within 6 hours of migraine onset, and after treatment with either acetylsalicylic acid (ASA) or oral zolmitriptan, i.e., interictally. No differences were evident for onset latencies or AUC at any time on the non headache side. However, on the headache side, R2 nBR demonstrated significant shortening of latencies ictally, which lengthened following either drug treatment. The AUC increased significantly, and similarly was attenuated by either ASA or zolmitriptan.17 (Table 1)

In a similar drug intervention study,21 the effects of ASA and zolmitriptan were found to be different ictally versus interictally. The R2 nBR was used to investigate 28 migraine patients ictally and interictally in a double blind crossover study. Patients were assessed before, 0 and 90 minutes after treatment comprising either ASA or oral zolmitriptan. Thirty non migrainous participants (controls) received either ASA, zolmitriptan or placebo. Neither of the drug treatments inhibited R2 nBR in the control
group, whereas both ASA and zolmitriptan inhibited nBR response ictally, but not interictally.\textsuperscript{21} (Table 1)

These findings demonstrate corresponding effects of ASA and zolmitriptan on both headache resolution and inhibition of amplified AUC of R2 nBR. It has been shown that both the triptans\textsuperscript{30-32} and ASA\textsuperscript{33,34} arrest transmission of nociceptive impulses in the TNC.

Furthermore, in a study contrasting migraineurs and patients with sinusitis headache, an interictal habituation deficit was demonstrated in migraineurs only.\textsuperscript{20} Thus, the facilitation of trigeminal nociception was considered to be specific for the migraine process rather than a product of peripheral (sinusitis) pain.\textsuperscript{20}

The R2 nBR can be inhibited by preceding stimulations of the supraorbital nerve.\textsuperscript{35} Increasing the intervals between the first (conditioning or inhibitory) stimulus and second stimulus (i.e., paired stimuli) enables determination of a ‘recovery curve’ (RC) i.e., a representation of recovery of the second (inhibited) R2 response with increasing interstimulus intervals. Therefore, the RC of R2 nBR after paired supra orbital stimuli is considered to be a reflection of the excitability of the R2 nBR at a segmental level.\textsuperscript{4}

Only one study investigating the RC of R2 nBR in migraine was identified.\textsuperscript{24} This interictal study, employing paired supra orbital stimuli, did not demonstrate any
difference in the R2 AUC between 14 migraineurs and 15 controls. This result does not support interictal sensitisation of the TCN. Additionally, participants were also subjected to (pre conditioning) electrical stimulation of the index finger. Similarly, changes in R2 AUC were similar in migraineurs and controls, implying normal interictal control of nociceptive neurotransmission by descending brainstem pathways in migraineurs.24

Two other studies investigating RC have been identified, but because one used the BR36 and the other R2 nBR in cluster headache, direct extrapolation is not possible. In the BR study, the effects of attention and habituation on the BR in (interictal) migraineurs were investigated. Perhaps surprisingly (given evidence that facilitation occurs ictally), an increase (areas of averaged R2 responses generated by the conditioning stimulus expressed as a percentage of that of the averaged test responses) in R2 RC after the conditioning stimulus was demonstrated.36 The authors postulated that this finding reflected ongoing hyperexcitability of the TCN after the last migrainous episode.36 The other study investigated RCs in ten cluster headache patients ictally,37 and revealed increased ipsilateral (to headache) RCs after paired supra orbital stimuli. The authors concluded that the unilateral decrease of R2 nBR inhibition was a manifestation of TCN sensitisation.37

The paucity of studies investigating RC behaviour of R2 nBR in migraineurs prevents any meaningful discussion. However, deficient habituation is considered the most consistent and prevalent interictal abnormality of the migraine condition.27
4.3.2 Habituation

The expected effect of habituation on the AUC of the R2 nBR is decreasing amplitude during repetitive electrical stimulation.\textsuperscript{36,38,39} In migraine, R2 nBR has demonstrated an interictal habituation deficit during short\textsuperscript{19,20} as well as long time courses.\textsuperscript{22,23} (Table 1)

Habituation of R2 nBR was investigated interictally in a group of 15 migraineurs.\textsuperscript{22} The findings included a tendency for shorter (sensitised) mean R2 latencies in migraineurs in the first stimulation block compared to (15) controls. Habituation in this study was defined as the percentage difference of the R2 AUC between the first and tenth block of five averaged responses. The difference in R2 AUC habituation between migraineurs and controls was not only significant in most blocks, but also increased progressively with the number of blocks. In addition, the frequency of migrainous episodes correlated with R2 AUC responses. This revealed increasing R2 nBR habituation with increased frequency of episodes, implying that the interictal habituation deficit was unlikely to be the result of trigeminal sensitisation.\textsuperscript{22}

This finding was confirmed in a later study from the same group. Using similar methodology, in which habituation was measured as percentage AUC decrease in 10 consecutive blocks of five averaged rectified responses, 16 migraineurs were found to have an interictal deficit of habituation of R2 nBR.\textsuperscript{23}
However, uncertainty surrounding the neural mechanisms underlying the interictal habituation deficit in migraine means agreement has not been reached as to the interpretation of this characteristic.\textsuperscript{40,41}

4.4 Summary

It appears that migraine can influence R2 nBR. The R2 nBR has reliably demonstrated an interictal habituation deficit\textsuperscript{19,22,23,27,28} and facilitation (sensitisation)\textsuperscript{17,20,21,42} during migrainous episodes.
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blink reflex after supraorbital or index finger stimulation is normal in migraine


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CHAPTER 5

CERVICAL REPRODUCTION OF CUSTOMARY HEAD PAIN IN PRIMARY HEADACHE

5.1 Introduction

The symptomatic profile of CWAH mirrors that of primary headache,\textsuperscript{1-9} and cervical symptoms and neck disability are similar in CWAH and primary headache syndromes.\textsuperscript{6} Furthermore, the C2-3 zygapophyseal joint appears to play a primary role in neck pain and associated headache both in CWAH\textsuperscript{10-31} and in patients with atraumatic headache.\textsuperscript{32} In addition to the C2-3 zygapophyseal joint, the AO and C1-2 joints are also capable of referring head pain.\textsuperscript{33-35}

Whilst the IHS classification system of headache questions the significance of customary head pain referral during examination of the neck in primary headache patients,\textsuperscript{36} others consider this to be a cornerstone of cervical relevance.\textsuperscript{36-39} Therefore, we sought to investigate the incidence of head pain referral during examination of the AO and C2-3 joints in primary headache patients and non headache volunteers.
References


5.2 Study 1.

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Head Pain Referral During Examination of the Neck in Migraine and Tension-Type Headache

Dean H. Watson, MAppSc; Peter D. Drummond, PhD

Objective.—To investigate if and to what extent typical head pain can be reproduced in tension-type headache (TTH), migraine without aura sufferers, and controls when sustained pressure was applied to the lateral posterior arch of C1 and the articular pillar of C2, stressing the atlanto occipital and C2-3 segments respectively.

Background.—Occipital and neck symptoms often accompany primary headache, suggesting involvement of cervical afferents in central pain processing mechanisms in these disorders. Referral of head pain from upper cervical structures is made possible by convergence of cervical and trigeminal nociceptive afferent information in the trigemino-cervical nucleus. Upper cervical segmental and C2-3 zygapophysial joint dysfunction is recognized as a potential source of noxious afferent information and is present in primary headache sufferers. Furthermore, referral of head pain has been demonstrated from symptomatic
upper cervical segments and the C2-3 zygapophysial joints, suggesting that head pain referral may be a characteristic of cervical afferent involvement in headache.

Methods.—Thirty-four headache sufferers and 14 controls were examined interictally. Headache patients were diagnosed according the criteria of the International Headache Society and comprised 20 migraine without aura (females n = 18; males n = 2; average age 35.3 years) and 14 TTH sufferers (females n = 11; males n = 3; average age 30.7 years). Two techniques were used specifically to stress the atlantooccipital segments (Technique 1 – C1) and C2-3 zygapophysial joints (Technique 2 – C2). Two techniques were also applied to the arm – the common extensor origin and the mid belly of the biceps brachii. Participants reported reproduction of head pain with “yes” or “no” and rated the intensity of head pain and local pressure of application on a scale of 0 -10, where 0 = no pain and 10 = intolerable pain.

Results.—None of the subjects reported head pain during application of techniques on the arm. Head pain referral during the cervical examination was reported by 8 of 14 (57%) control participants, all TTH patients and all but 1 migraineur (P < .002). In each case, participants reported that the referred head pain was similar to the pain they usually experienced during TTH or migraine. The frequency of head pain referral was identical for Techniques 1 and 2. The intensity of referral did not differ between Technique 1 and Technique 2 or between groups. Tenderness ratings to thumb pressure were comparable between the Techniques 1 and 2 when pressure was applied to C1 and C2 respectively and across groups. Similarly, there were no significant differences for tenderness.
ratings to thumb pressure between Technique 1 and Technique 2 on the arm or between groups. While tenderness ratings to thumb pressure for Technique 2 were similar for both referral (n = 41) and non-referral (n = 7) groups, tenderness ratings for Technique 1 in the referral group were significantly greater when compared with the non-referral group (P = .01).

Conclusions.—Our data support the continuum concept of headache, one in which noxious cervical afferent information may well be significantly underestimated. The high incidence of reproduction of headache supports the evaluation of musculoskeletal features in patients presenting with migrainous and TTH symptoms. This, in turn, may have important implications for understanding the pathophysiology of headache and developing alternative treatment options.

From the School of Psychology, Murdoch University, Perth, WA, Australia.

Address all correspondence to D.H. Watson, School of Psychology, Murdoch University, South Street Campus, 90 South Street, Perth, WA 6150, Australia, email: dean@watsonheadache.com

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Conflict of Interest: Dean H. Watson presents training programs to manual therapists in the assessment of the upper cervical spine in primary headache conditions; Peter D. Drummond has nothing to disclose.
Occipital and neck symptoms often accompany headache. Furthermore, occipital nerve injections are effective in tension-type headache (TTH) and migraine, and occipital nerve stimulation is also effective in migraine. Together, these observations suggest the involvement of afferent cervical nociceptive inputs in these primary headache disorders.

Cervical musculoskeletal abnormalities recognized as potential sources of noxious afferent cervical information have been linked to TTH and migraine. Mercer et al investigated the presence of cervical dysfunction in 90 consecutive patients with chronic headache. The sample comprised 39 migraineurs, 11 patients with TTH and 9 with combination headache. Other diagnoses (eg, cluster, posttraumatic, or drug rebound headache) were assigned to the remaining 31 patients. Eighty-six percent of migraineurs had dysfunction at C1-2, C2-3, and C3-4 segments, while 78% of TTH patients had dysfunction of the atlantooccipital (AO), C1-2, and C2-3 segments. There were no statistically significant differences in cervical dysfunction between groups. Similarly, in another study, 84% of patients with TTH or migraine without aura had hypomobility of the upper 2 spinal segments, while radiological assessment...
demonstrated reduced segmental motion at the AO segment in 90% and 70% of participants in flexion and extension, respectively. Hypomobility was most pronounced at the AO segment. Interestingly, these findings mirror those of Pfaffenrath et al who, using functional roentgenograms, demonstrated significantly reduced sagittal mobility of the AO and C1-2 segments in 15 cervicogenic headache sufferers when compared with 18 controls.

Referral of head pain from upper cervical structures is made possible by convergence of cervical and trigeminal nociceptive afferent information in the trigemino-cervical nucleus where second-order neurons receive nociceptive information from the C1, C2, and C3 spinal nerves and from the first division of the trigeminal nerve. The anatomical and functional nature of this convergence has been demonstrated in laboratory animal experiments and also in humans. Furthermore, in studies involving asymptomatic participants, pain referral to the head was demonstrated during noxious stimulation of the basal-occipital area (corresponding to the AO segment), C1-2, and C2-3 interspinous spaces; the AO joints; and C2-3 zygapophysial joints. These studies, along with a substantive body of research demonstrating referral of head pain from symptomatic upper cervical facet and C2-3 zygapophysial joints, suggest that head pain referral is a pivotal characteristic of cervical afferent involvement in headache.

What has not been determined is if, and to what extent, head pain can be reproduced in TTH sufferers and migraine without aura patients during manual
examination of the upper cervical spine. Therefore, we sought to investigate the incidence of reproduction of typical head pain in these patients when sustained pressure was applied to the lateral posterior arch of C1 and the articular pillar of C2, stressing the AO and C2-3 segments respectively. We hypothesized that manual examination of the upper cervical spine would precipitate greater referral of head pain in these patients than in controls without a history of migraine or frequent TTH.

MATERIALS AND METHODS

Participants.—Thirty-four headache sufferers and 14 controls were examined. Participants in the non-headache group experienced mild non-migrainous headache no more than 6 times per year – 4 could not recall ever having experienced headache. Participants were recruited from the general population and from patients attending a headache clinic. Headache sufferers were diagnosed according to the criteria of the International Headache Society.42 Eleven females and 3 males (average age 30.7 years) fulfilled the diagnostic criteria of TTH, and 20 patients met the criteria for migraine without aura (average age 35.3 years; 18 females and 2 males). All 14 patients in the TTH group had bilateral headache in various areas including frontal, temporal, and occipital. Nineteen migraineurs experienced unilateral headache with side-shift, and while headache was bilateral in the remaining patient, the other features fulfilled the criteria for migraine without aura. Nine females and 5 males, with an average age of 32.8 years, represented the control group. All participants signed an informed consent form. Ethical approval was obtained from the Ethics Committee of Murdoch University.
**Passive Accessory Intervertebral Movement Examination.**—The data examination was performed by a single clinician (D.H.W. – musculoskeletal physiotherapist) with 20 years experience, whose practice is limited to examination and treatment of the upper cervical spine in primary headache conditions. Intra-examiner reliability was analyzed using Cohen’s Kappa in a previous study in which 11 passive accessory intervertebral movement techniques were employed. Intervertebral mobility was graded on a 5-point scale, ranging from hypomobile to very hypermobile. Grade 3 was considered normal, while grade 4 was classified as hypomobile; very hypomobile was graded as 5. Conversely, grade 2 indicated hypermobility and 1 considerably hypermobile. A symptomatic response was also recorded – no discomfort, local pain, local pain and headache, and headache only. There was perfect agreement in 17 of 22 passive accessory intervertebral movement tests (k = 1.0). Of the 5 remaining tests, the lowest Kappa score was $k = 0.667, P = .01$, which indicated good agreement.

Two techniques were used with the intention of passively stressing a specific intervertebral segment either on the side of headache (in the case of unilateral headache), the side of greatest frequency of headache (in the case of alternating headache), and in the case of bilateral headache, on the side that the spinous process of axis (C2) was deviated toward. In those participants who had never experienced headache, the side of technique was randomly assigned. Technique 1 comprised applying pressure on the posterior arch of the atlas (C1) with the participant’s head in approximately 20 degrees of contralateral rotation, with the other hand rotating the participant’s head ipsilaterally, thereby stressing the AO segment. The second technique
involved applying pressure to the articular pillar of the axis (C2) with the participant’s head in approximately 30 degrees of contralateral rotation, in this instance stressing the C2-3 segment.

On a separate occasion, thumb pressure was applied at 2 sites on the ipsilateral arm. Technique 1 comprised pressure on the common extensor origin (lateral epicondyle of the humerus); Technique 2 involved pressure over the mid belly of the biceps brachii.

All participants were examined interictally and in the supine position. The order of the examination (ie, arm vs cervical) alternated from 1 participant to the next within each group. Technique 1 was always performed first. In each technique, the pressure was applied and sustained for 5 seconds. The interval between each technique exceeded 3 minutes. Participants reported reproduction of head pain with “yes” or “no” and rated the intensity of head pain and local tenderness to thumb pressure on a scale of 0-10, where 0 = no pain and 10 = intolerable pain.

**Statistical Approach.**—Data were analyzed using SPSS Version 16 software (SPSS Inc., Chicago, IL, USA). Ratings for arm tenderness were investigated in a 2 X 3 (Technique [Technique 1, Technique 2] X Group [Migraine, TTH, Control]) analysis of variance. Values for tenderness over C1 and C2 and referred head pain intensity were investigated in similar analyses. The incidence of head pain referral was compared across the 3 groups using chi-square analysis. Participants without head pain referral were excluded from analyses of referred head pain intensity. Tenderness ratings for the referral and non-referral participants were investigated in a 2 X 2 (Technique X Referral vs Non-referral) analysis of variance.
$P < .05$ was considered to be statistically significant in all analyses, and tests of statistical significance were 2-tailed.

**RESULTS**

None of the participants reported head pain during application of techniques on the arm. In all participants who experienced referral of head pain when pressure was applied to the neck, the pain eased immediately on cessation of the technique. Preliminary inspection of the data revealed that the frequency of head pain referral was identical for Techniques 1 and 2.

Table 1.—Tenderness Ratings Stratified by Headache Groups and Site

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 14)</th>
<th>TTH (n = 14)</th>
<th>Migraine (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tenderness ratings (arm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common extensor origin</td>
<td>5.500 ± 0.419</td>
<td>5.400 ± 0.351</td>
<td>6.214 ± 0.419</td>
</tr>
<tr>
<td>Biceps brachii</td>
<td>5.357 ± 0.440</td>
<td>5.350 ± 0.368</td>
<td>5.786 ± 0.440</td>
</tr>
<tr>
<td><strong>Tenderness ratings (cervical)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AO segment (C0-1)</td>
<td>6.071 ± 0.479</td>
<td>6.429 ± 0.479</td>
<td>6.700 ± 0.401</td>
</tr>
<tr>
<td>C2-3 zygapophysial joint</td>
<td>6.143 ± 0.457</td>
<td>6.786 ± 0.457</td>
<td>7.250 ± 0.383</td>
</tr>
</tbody>
</table>

AO = atlantooccipital; TTH = tension-type headache.

There were no significant differences for tenderness ratings to thumb pressure between sites on the arm ($F[2,45] = 0.403; P = .67$) or between groups ($F[2,45] = 0.822; P = .45$) (Table 1). Similarly, values for tenderness ratings to thumb pressure were comparable when pressure was applied to C1 and C2 respectively ($F[2,45] = 3.43; P = .07$) and across groups ($F[2,45] = 1.145; P = .33$) (Table 1). These results suggest that
thumb pressure was applied consistently across groups and also that there was no evidence of primary hyperalgesia in either of the headache groups.

In each case, participants reported that the referred head pain was similar to the pain they usually experienced during TTH or migraine. Head pain referral was reported by 8 of 14 (57%) control participants, 100% of TTH participants (n = 14), and 19 of 20 (95%) migraineurs (c2 = 12.85; P < .002). The intensity of referral did not differ between sites (F[1,38] = 0.178; P = .675) or groups (F[2,38] = 0.480; P = .622) (Table 2).

Table 2.—The Intensity of Head Pain Referral

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 8)</th>
<th>TTH (n = 14)</th>
<th>Migraine (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head pain referral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AO segment (C0-1)</td>
<td>5.875 ± 0.863</td>
<td>4.500 ± 0.645</td>
<td>5.474 ± 0.553</td>
</tr>
<tr>
<td>C2-3 zygapophysial joint</td>
<td>5.500 ± 0.815</td>
<td>5.000 ± 0.616</td>
<td>5.000 ± 0.529</td>
</tr>
</tbody>
</table>

AO = atlanto occipital; TTH = tension-type headache.

Tenderness ratings to thumb pressure were significantly greater in the referral group (n = 41) than the non-referral group (n = 7) for both techniques (F[1,46] = 6.597; P = .014), and ratings were greater when pressure was applied to C2 than C1 (F[1,46] = 4.231; P = .045 (Table 3).
DISCUSSION

The aim of this study was to investigate the incidence of reproduction of typical head pain in TTH, migraine without aura, and controls when stressing the AO segments and C2-3 zygapophysial joints.

The reproduction of usual head pain in 85% of participants in our study provides a manual, clinical parallel with previous research supporting convergence of cervical afferents on trigeminal nuclei.\textsuperscript{22-25,44}

Table 3.—Tenderness Ratings for Referral and Non-Referral Groups

<table>
<thead>
<tr>
<th></th>
<th>Referral (n = 41)</th>
<th>Non-Referral (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenderness ratings (cervical)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AO segment (C0-1)</td>
<td>6.707 ( \pm ) 0.260</td>
<td>4.857 ( \pm ) 0.629</td>
</tr>
<tr>
<td>C2-3 zygapophysial joint</td>
<td>7.000 ( \pm ) 0.262</td>
<td>5.571 ( \pm ) 0.635</td>
</tr>
</tbody>
</table>

AO = atlanto occipital.

More specifically, the findings indicate that head pain can be referred by stimulating the AO joints\textsuperscript{32,34} and the C2-3 zygapophysial joints.\textsuperscript{35,36,38,39} Furthermore, it is interesting to consider that referral occurred only in headache sufferers; ie, every TTH participant, all but 1 migraineur and 8 of the 10 control participants who experienced infrequent headache (6 or less/year, resembling TTH). In the non-referral participants (n = 7), 4 had never experienced headache, 2 had infrequent headache, and 1 had migraine.
The high incidence of headache reproduction in both symptomatic groups is in stark contrast to the findings of earlier studies in which passive accessory intervertebral movement examinations were used and which did not demonstrate significant abnormalities in TTH or migraine.\textsuperscript{8,19} However, both passive accessory intervertebral movement assessment techniques used in this study not only involved movement of C2 in relation to C3 and of the occiput relative to C1, but also sustaining thumb pressure at the end of a segment’s range of movement for 5 seconds. This contrasts with the traditional, standard movement examination generally employed by manual therapists,\textsuperscript{8,19} in which thumb pressure is applied in an oscillatory manner. Variation in application pressure across studies may also account for differing rates of headache reproduction. The dissimilarity in results is likely to be due to the different examination approaches and underlines the importance of developing a standardized protocol for assessing the cervical spine.

The pressure was applied for 5 seconds, and the referred pain on all occasions ceased immediately or within seconds of release of thumb pressure. Predictably, therefore, the symptoms usually associated with typical migraine were not reported. Nevertheless, the pain generally referred to the usual site of headache; sometimes of greater intensity than usual “attacks.”

The relatively high incidence of production of head pain in the control group is perhaps surprising. This group comprised 4 participants who had not experienced headache, and 10 who experienced non-migrainous headache no more than 6 times per year. Not only was head pain produced in 8 of the 10 participants who experienced headache infrequently, but also the intensity of referral in these 8 controls did not
differ from the migraine or TTH groups. This suggests that a “primary headache” mechanism may lie dormant in infrequent headache sufferers. Because of difficulties recruiting participants who had never experienced headache, past practice has allowed the inclusion of participants experiencing mild non-migrainous headache (resembling TTH) up to 6 times per year. However, our findings suggest that these participants had more in common with the TTH group than the other controls and imply the existence of an “infrequent” headache group. This raises concerns over the composition of “control” groups in headache studies.

Mechanical precipitation of head pain with neck movements or manual pressure over the upper cervical area is a pivotal diagnostic criterion for cervicogenic headache. Furthermore, side-locked unilaterality is also considered a cornerstone of the cervicogenic headache diagnostic criteria, and therefore, participants were meticulously selected to rule out this symptom. Nineteen of the 20 migraine experienced alternating headache, whereas the other had bilateral headache. All 14 TTH sufferers presented with bilateral headache. Assuming therefore that misdiagnosis is unlikely, this could suggest that mechanical precipitation of usual head pain as a diagnostic criterion is not specific to cervicogenic headache, but rather is a non-specific, homogeneous pain reaction pattern in headache sufferers.

The results of our study not only are consistent with convergence of cervical afferents onto neurons in the trigeminal nuclei, but also imply that this mechanism might contribute both to migraine and TTH. The significant reproduction of head pain in the TTH and migraine groups concurs with the relatively high incidence of segmental dysfunction found previously. Furthermore, while TTH is considered to be a
separate entity of unknown pathophysiology, cervical dysfunction is becoming increasingly implicated in the TTH mechanism, thus blurring the distinction between TTH and cervicogenic headache. Recent research, in which rehabilitation of cranio-cervical flexors significantly reduced symptoms of TTH, supports the notion that cervical dysfunction may play a role in the TTH mechanism. The existence of a “shared” mechanism supports the “Convergence Theory” postulated by Cady et al, which places TTH and migraine on the same etiological spectrum, perhaps with an underlying cervicogenic basis for central sensitization of nociceptive second-order neurons in the trigemino-cervical nucleus and subsequent hyperexcitability to afferent stimulation.

The notion of central sensitization considers an increased barrage of afferent noxious information from C-fibers onto second-order neurons as crucial in the development of this hyperexcitability. Moreover, it has been demonstrated that stimulation of afferents from deep somatic tissues such as joints and muscles is more effective than cutaneous input in generating central hyperexcitability. Given the nature of examination techniques used in this study, it is reasonable to assume that, among other structures, the deep articular restraining anatomy (eg, joint capsules and ligaments of the AO articulation and the C2-3 zygapophysial joint) was stressed. These structures are innervated by the upper cervical roots and are recognized as sources of head pain. Accordingly, our findings suggest that hyperexcitability of nociceptive second-order neurons in the trigemino-cervical nucleus could result from noxious afferent information from dysfunctional spinal segments, thereby increasing the sensitivity to subclinical afferent information from the trigeminal field. The ensuing
exaggerated information is perceived as a noxious event that results in pain. This possibility has been demonstrated by increased excitability to dural input after central sensitization evoked by stimulation of the greater occipital nerve\textsuperscript{23} and is supported by modulation of the nociceptive blink reflex following blockade of the greater occipital nerve.\textsuperscript{30,31} Conceivably, this represents the cervicogenic equivalent to application of an “inflammatory soup” onto the dura which has been shown to induce central sensitization and ensuing increased sensitivity to trigeminal inputs.\textsuperscript{24} Alternatively, the incidence of reproduction of head pain in migraine and TTH participants could reflect a state of primary hyperalgesia.\textsuperscript{51,56-58} However, we believe that this is unlikely as tenderness ratings to thumb pressure were similar across the groups.

Another interesting finding was that in every participant with head pain referral, both of the cervical techniques precipitated their usual head pain. If the assumption is that reproduction of usual head pain is indicative of cervical involvement in headache, this result supports the prominence of the C2-3 zygapophysial joint in headache reported by others.\textsuperscript{36,38,59,60} However, what is surprising is the frequency with which referral occurred when the AO joint was stressed. This mirrors the high incidence of dysfunction at the AO segment in earlier studies\textsuperscript{7,14,15,17} and provides a manual parallel of referral from intra-articular injections of the AO joint demonstrated by Dreyfuss and colleagues.\textsuperscript{32,34} Multi-joint involvement in headache has important implications, because this indicates that when the C2-3 zygapophysial joint is symptomatic, the AO joint will also be involved. Speculation then arises as to a course of action if blocking the third occipital nerve (innervating the C2-3 zygapophysial joint)\textsuperscript{36,59-61} only partially relieves headache. According to guidelines established by Bogduk, anesthetizing a
neighboring joint should alleviate all of the pain. Our result suggests that the AO joint should be investigated as a potential source of pain.

If the assumption that local tenderness is a reflection of relevant pathology or dysfunction, our finding that tenderness ratings to thumb pressure were greater for both techniques in the referral group is not surprising. While this result challenges a recent study which demonstrated that local tenderness is not diagnostic of cervical zygapophysial joint pain, it does confirm the findings of Lord et al, who reported that patients with “third occipital nerve headache” were more likely to be tender over the ipsilateral C2-3 zygapophysial joint. Direct (thumb) access to the deeply situated AO joint is not possible, while the C2-3 zygapophysial joint is more readily palpable and would explain the increased local tenderness ratings for stimulation of this site.

Limitations.—The examiner was not blinded when assessing controls. However, the lack of significant difference between tenderness ratings to thumb pressure between the controls and symptomatic groups lessens this potential influence. In addition, there was no prior expectation that head pain referral would differ between those in the control group with infrequent headache and those without a history of headache; thus, this difference is unlikely to be due to examiner bias. Although standardization of pressure clearly is important, for it to be achieved during application of techniques used in this study and in a passive accessory intervertebral movement examination, pressure algometers would need to be devised which not only attach to the thumb but are sufficiently fine to allow for skilled palpation and perception of mobility. The absence of such a device in our study could be regarded as a shortcoming. Sample sizes could also be considered a limitation. However, the very high incidence of
reproduction of headache questions whether the result would differ in a larger group.

We followed standard clinical protocol by examining the AO joint before examining C2-3. Although this might have facilitated referral of head pain during the examination of C2-3, this seems unlikely because each technique was applied for no more than 5 seconds. In addition, the referred head pain eased within a few seconds of cessation of the examination in all cases, and the interval between techniques exceeded 3 minutes. Furthermore, if the initial examination had facilitated subsequent responses, the frequency or intensity of head pain referral should have increased during the second examination. Neither was the case.

CONCLUSIONS

According to Antonaci and Sjaastad, a common misunderstanding is that one can provoke head pain by exerting external pressure (eg, over identified tendon insertions in the occipital area) in individuals who have never experienced headache to the same degree as in some headache conditions. This was borne out in the current study – referral of usual head pain occurred only in the symptomatic groups including those in the control group with a history of infrequent headache.

Our data support the continuum concept of headache, one in which noxious cervical afferent information may well be significantly underestimated. The high incidence of reproduction of headache during cervical examination supports the evaluation of musculoskeletal features in patients presenting with migrainous and TTH symptoms. This, in turn, may have important implications for understanding the pathophysiology of headache and developing alternative treatment options.
STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Peter Drummond, Dean Watson

(b) Acquisition of Data
Dean Watson

(c) Analysis and Interpretation of Data
Peter Drummond, Dean Watson

Category 2

(a) Drafting the Article
Dean Watson, Peter Drummond

(b) Revising It for Intellectual Content
Dean Watson, Peter Drummond

Category 3

(a) Final Approval of the Completed Article
Peter Drummond, Dean Watson

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6.1 Introduction

Previously we demonstrated a high incidence of customary head pain referral in migraineurs and TTH patients. (Section 5.2) Whilst our findings support the role of cervical afferent nociceptors in primary headache, confirmation of cervical involvement in the pathophysiological mechanisms of primary headache is uncertain. The author’s clinical observation is that as the examination technique, which reproduces accustomed head pain, is sustained, head pain resolves within a varied but relatively short timeframe, e.g., 30 - 90 seconds. Furthermore, some patients also report that longstanding ‘tenderness’ in the trigeminal field resolves.

Allodynia is a common accompaniment of migraine, and is thought to be the consequence of sensitisation of central second-order neurons, which receive dual input from the trigeminal and cervical fields. Clinical deduction, therefore, could suggest that reproduction and resolution of customary head pain has a positive effect on the status of the trigemino cervical nucleus (TCN).

Referral of head pain when examining upper cervical structures is mediated by convergence of cervical and trigeminal afferents in the TCN of the brainstem. Convergence, when coupled with sensitisation of central trigeminal neurons, accounts for perception of pain distant from the site of origin. The nociceptive blink reflex (R2 nBR) has been used extensively to assess the status of the TCN. This body of
research has demonstrated an interictal habituation deficit\textsuperscript{15,17,18,20,21} and facilitation (sensitisation) during migrainous episodes\textsuperscript{12,14,16,22}.

Therefore, to elucidate further the potential role of cervical afferent nociceptors in the pathophysiology of migraine, R2 nBR was used to assess activity in the TCN during cervical reproduction and resolution of customary head pain in migraineurs.
References


Cervical Referral of Head Pain in Migraineurs: Effects on the Nociceptive Blink Reflex

Dean H. Watson, MAppSc; Peter D. Drummond, PhD

Objective.—To investigate cervical, interictal reproduction of usual head pain and its effect on the nociceptive blink reflex in migraineurs.

Background.—Anatomical and neurophysiological studies in animals and humans have confirmed functional convergence of trigeminal and cervical afferent pathways. Migraineurs often present with occipital and neck symptoms, and cervical pain is referred to the head in most cases, suggesting that cervical afferent information may contribute to headache. Furthermore, the effectiveness of greater occipital nerve blockade in migraine and demonstrable modulation of trigeminal transmission following greater occipital nerve blockade suggest an important role for cervical afferents in migraine. However, to what extent cervical afferents contribute actively to migraine is still unknown.

Methods.—The passive accessory intervertebral movements of the atlanto-occipital and C2-3 spinal segments of 15 participants (14 females, 1 male; age 24-44 years, mean age 33.3 years) with migraine were examined interictally. During 1 session, either the atlanto-occipital or C2-3 segment was examined, resulting in referred usual head pain, while in another session, pressure was applied over the
common extensor origin (lateral epicondyle of the humerus) of the ipsilateral arm. Each intervention was repeated 4 times. The nociceptive blink reflex to a supraorbital electrical stimulus was elicited ipsilaterally during both sessions before and during each intervention. The main outcome variables were the number of recorded blinks, area under the curve and latencies of the R2 components of the nociceptive blink reflex. Participants also rated the intensity of referred head pain and the supraorbital stimulus on a scale of 0-10, where 0 = “no pain” and 10 = “intolerable pain,” and rated the intensity of applied pressure where 0 = “pressure but no pain” and 10 = “intolerable pain.”

Results.—Participants reported a significant reduction in local tenderness ratings across the 4 trials for the cervical intervention but not for the arm (P = .005). The cervical intervention evoked head pain in all participants. As the cervical intervention was sustained, head pain decreased significantly from the beginning to the end of each trial (P = .000) and from the beginning of the first trial to the end of the last (P = .000). Pain evoked by the supraorbital stimulus was consistent from baseline to across the 4 trials (P = .635) and was similar for the cervical and arm interventions (P = .072). The number of blinks decreased significantly across the experiment (P = .000) and was comparable in the cervical and arm interventions (P = .624). While the R2 area under the curve decreased irrespective of intervention (P = .000), this reduction was significantly greater for the cervical intervention than when pressure was applied to the arm (P = .037). Analysis of the R2 latencies revealed a notable increase across the experiment (P = .037). However, this increase was significantly greater following the cervical than arm intervention (P = .012).

Conclusions.—Our findings corroborate previous results related to anatomical and functional convergence of trigeminal and cervical afferent
pathways in animals and humans, and suggest that manual cervical modulation of this pathway is of potential benefit in migraine.

Key words: migraine, nociceptive blink reflex, central sensitization, cervical headache

Abbreviations: AO atlanto-occipital, AUC area under the curve, DNIC diffuse noxious inhibitory control, GON greater occipital nerve, nBR nociceptive blink reflex, PAIVM passive accessory intervertebral movement, TCN trigemino cervical nucleus

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From the School of Psychology, Murdoch University, Perth, WA, Australia

Address all correspondence to D.H. Watson, South Street, Murdoch, WA 6150, Australia, email: dean@watsonheadache.com

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Temporary reproduction of usual head pain when examining structures of the cervical spine is considered to be one of the key diagnostic criteria for cervicogenic headache,1,2 but this might also be important in other forms of headache. For example, we recently demonstrated reproduction of usual head pain in 95% of migraineurs3 fulfilling the International Headache Society’s Classification criteria for migraine2 when examining the passive accessory intervertebral movements (PAIVMs) of the atlanto-
occipital (AO) and C2-3 spinal segments.

The extremely high incidence of reproduction of headache in migraineurs could suggest an underlying cervicogenic basis for central sensitization of nociceptive second-order neurons in the trigeminocephalic nucleus (TCN) with subsequent hyperexcitability to afferent stimulation.④ The notion of central sensitization considers an increased barrage of afferent noxious information from C-fibers onto second-order neurons as crucial in the development of this hyperexcitability.⑤,⑥ Moreover, it has been demonstrated that stimulation of afferents from deep somatic tissues such as joints and muscles is more effective than cutaneous input in generating central hyperexcitability.⑦,⑧ More specifically, provocation of the deep paraspinal tissues at the level of the atlantoaxial (C1-2) spinal segment was shown to induce central sensitization in medullary and C1-C2 dorsal horns.⑨ Together, these findings suggest that hyperexcitability of nociceptive second-order neurons in the TCN could result from noxious afferent information from dysfunctional spinal segments, thereby increasing sensitivity to subclinical afferent information from the trigeminal field. The ensuing exaggerated information is perceived as noxious and results in pain. In support of this possibility, central sensitization evoked by stimulation of the greater occipital nerve (GON) resulted in occipital afferent activation of second-order neurons in the TCN⑩,⑪ and increased excitability to dural input.⑫ Further support was provided by modulation of the nociceptive blink reflex (nBR) following blockade of the GON.⑬,⑭ The nBR is a trigeminofacial brainstem reflex and has been established as a valid technique for assessing central trigeminal transmission.⑮-⑰ Recently, the R2 component of the nBR was examined before and after unilateral GON blocks where it was found that the R2 latency increased and area under the curve (AUC) decreased after GON blockade.⑬,⑭ This result provides empirical evidence for a functional influence on
trigeminal nociceptive inputs from cervical afferents. Conceivably, occipital activation of the TCN represents the cervicogenic equivalent to application of an “inflammatory soup” onto the dura that has been shown to induce central sensitization and ensuing increased sensitivity to trigeminal inputs.19

Notwithstanding the effectiveness of GON blockades for migrainuers,20-22 the mechanism(s) for the successful outcome remain uncertain.23 It has been postulated that GON blockade influences central pain processing mechanisms by modulating responses to convergent synaptic input from cervical and trigeminal nociceptive afferents.23

In our clinical experience, patients often report lessening of their referred, usual pain as the examination of the cervicospinal segment is sustained. The pain usually lessens (to a variable degree, but often with complete resolution) within 90 seconds. Moreover, sustaining the examination repeatedly results not only in decreasing intensity of head pain referral but also in more expeditious resolution. Furthermore, patients presenting with allodynia frequently report that after lessening of their referred pain, the allodynia has decreased or resolved,24-26 perhaps indicating that a pre-existing central sensitization state had diminished.

The purpose of the present study was to investigate cervical, interictal referral of usual head pain and its effect on the nBR in migrainuers. In particular, effects of PAIVMs of the AO and C2-3 spinal segments on referred head pain and trigeminal nociceptive activity were examined interictally. It was hypothesized that as referred head pain decreased, there would be a corresponding increase in latency and decrease in the AUC of R2, reflecting a decrease in excitability of the TCN.

MATERIALS AND METHODS

Participants.—Fifteen volunteers participated in the study (14 females, 1 male; age 24-44 years, mean age 33.3 years). All participants met the International
Headache Society’s diagnostic classification criteria for migraine with or without aura, experiencing 2-8 attacks of migraine within the previous 3 months. Each participant had been free from migraine for at least 24 hours. Informed consent was obtained from all participants, and the study was approved by the Ethics Committee of Murdoch University.

**PAIVM Examination.**—The PAIVM examination was performed by a single clinician (D.H.W. – Musculoskeletal Physiotherapist) with 22 years of experience, whose practice is limited to examination and treatment of the upper cervical spine in primary headache conditions. Intra-examiner reliability was analyzed using Cohen’s Kappa in a previous study that demonstrated perfect agreement in 17 of 22 PAIVM techniques. Of the 5 remaining tests, the lowest Kappa score was $k = 0.667$, $P = .01$, which indicated good agreement.

Critical to our study was that usual head pain could be reproduced during the cervical examination. Therefore, to exclude participants who did not develop head pain during this procedure, an “inclusion/exclusion” examination was performed prior to commencing the study. This examination also established which of the AO or C2-3 spinal segments referred usual head pain most clearly and therefore which segment would be examined further. The PAIVM techniques have been described previously. In brief, this involves applying thumb pressure to the AO or C2-3 spinal segments.

All participants were examined in the supine position in 2 sessions. Each session comprised 5 trials that were 90 seconds long and separated by 30 seconds. The nBR was recorded during the first trial of each session, but no manual pressure was applied. Thereafter, manual pressure was applied to either the ipsilateral common extensor origin (lateral epicondyle of the humerus) of the arm or the AO or C2-3 segments and was sustained for the length of each trial. The order of the examination (ie, cervical vs arm) alternated from 1 participant to the next. Participants reported reproduction of head
pain with “yes” or “no” and rated the intensity of head pain on a scale of 0-10, where 0 = “no pain” and 10 = “intolerable pain.” Participants also rated the intensity of applied pressure where 0 = “pressure but no pain” and 10 = “intolerable pain.”

**Trigeminal Nociception and Transmission.**—To study trigeminal brainstem nociception and transmission, the nBR was elicited ipsilaterally using a custom-made planar concentric electrode. The electrode comprised a central wire cathode (diameter 0.5 mm), an isolation insert and an external anode ring, both 5 mm in diameter providing a stimulation area of 235.5 mm². The electrode was placed on the forehead 10 mm above the supraorbital groove, and the nBR was recorded by 2 surface electrodes attached below the lower eyelid and 2-3 cm laterally. Current intensity (monopolar square wave pulses, 0.3 ms duration) was 2.3 mA. Main outcome variables were the number of recorded blinks, and AUC and latencies of the R2 component of the nBR.

The nBR was recorded during both sessions, which were separated by 30 minutes. Each session comprised 5 trials of 8 stimuli; the interstimulus interval varied between 12 and 18 seconds. The intertrial interval was 30 seconds.

After subtracting background noise from raw blink reflex data, latencies were established for each blink. Blinks were identified individually by inspecting each blink in the raw data files and were defined as present if the AUC was greater than background noise. Areas under the curve were assessed in the time window 27-87 ms after the stimulus.²⁸,²⁹

**Statistical Approach.**—Data were analyzed using SPSS Version 16 software (SPSS, Inc., Chicago, IL, USA). Local tenderness ratings were investigated in a 2 × 4 × 2 (site [arm, neck]) × trial [trials 1-4] × time [start, end of each trial]) analysis of variance. Similar analyses were computed for supraorbital pain ratings, head pain referral, number of blinks, and R2 latency and AUC. P < .05 was considered to be statistically
significant in all analyses, and tests of statistical significance were 2-tailed. Where appropriate, the Huynh–Feldt correction was used to correct for violation of the sphericity assumption.

**RESULTS**

In each case, headache was reproduced during preliminary assessment of the AO and C2-3 segments, and this referred pain ceased immediately after release of cervical pressure. None of the participants reported head pain during application of pressure to the arm.

$F$ values for all main effects of interactions for all of the independent variables are included in the Table.

**Table.—$F$ Ratios for the Main Effects and Interactions of the Dependent Variables**

<table>
<thead>
<tr>
<th></th>
<th>Tenderness Ratings</th>
<th>Referred Head pain</th>
<th>Supraorbital Ratings</th>
<th>No. of Blinks</th>
<th>Latency</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site (cervical/arm)</td>
<td>0.00</td>
<td>–</td>
<td>0.80</td>
<td>0.59</td>
<td>1.31</td>
<td>0.78</td>
</tr>
<tr>
<td>Trials</td>
<td>2.32†</td>
<td>31.01***</td>
<td>0.64†</td>
<td>25.23***</td>
<td>3.02‡</td>
<td>13.41***</td>
</tr>
<tr>
<td>Time (start/end of each intervention trial)</td>
<td>–</td>
<td>40.46***</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Trials x time</td>
<td>–</td>
<td>3.11*</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Site x trials</td>
<td>4.92**</td>
<td>–</td>
<td>2.49</td>
<td>0.66</td>
<td>4.07*</td>
<td>2.91*</td>
</tr>
</tbody>
</table>

*P < .05; **P < .01; ***P < .001.
†4 intervention trials.
‡Baseline + 4 intervention trials.
AUC = area under the curve.

During the cervical session, each participant reported referred head pain. As the examination technique was sustained, head pain lessened in all participants, decreasing significantly from the beginning to the end of each trial (main effect for time, $F[1,42] = 40.46; P = .000$) and from the beginning of the first trial to the end of the last (main effect for trials, $F[2.27,31.71] = 31.01; P = .000$) (Fig. 1). Also notable is that referred
head pain at the end of each trial decreased progressively across the 4 trials when compared with ratings at the beginning of each trial (trial × time interaction, $F[2.49,34.91] = 3.11, P = .047$). The referred head pain eased immediately on cessation of the technique at the end of each trial in all participants.

![Head pain referral](image)

**Fig 1.—** Referral ratings stratified by trials. Note that not only did referral ratings decrease, but the values at the end of each trial decreased progressively across the 4 trials when compared with the values at the start of each trial.

When averaged across the 4 trials, mean ratings of tenderness to thumb pressure were identical across the 4 trials for both interventions ($F[3,42] = 0.00; P = 1.0$). However, participants reported a significant reduction in tenderness across trials during the cervical but not the arm intervention (site X trial interaction, $F[3,42] = 4.92; P = .005$) (Fig. 2).

Mean ratings of the supraorbital stimulus were similar across the 5 trials ($F[4,56] = 0.64; P = .635$) and were comparable for cervical and arm interventions (site X trial interaction, $F[3.07,42.92] = 2.49; P = .072$) (Fig. 3).
Fig 2.—Tenderness ratings stratified by trials. Note that cervical tenderness ratings decreased progressively, while those for the arm remained unchanged.

Fig 3.—Supraorbital ratings stratified by trials (trials 1 = base-line, ie, no intervention). Note that the ratings remained unchanged across the trials for both sites.

To establish a baseline for R2, blinks were elicited in the absence of either the cervical or arm intervention during the first trial. Cervical and arm interventions were then applied in the ensuing 4 trials. The number of blinks decreased significantly across the 5 trials (main effect for trials, $F[4,56] = 25.23; P = .000$) and was comparable for the cervical and arm interventions (site × trial interaction, $F[4,56] = 0.66; P = .624$) (Fig. 4).
Fig 4.—Number of nociceptive blink reflex stratified by trials. Note the decreasing number of blinks across the trials for both sites.

While the R2 AUC decreased irrespective of intervention (main effect for trial, $F[4,32] = 13.41; P = .000$), this reduction was significantly greater for the cervical than arm intervention (site × trial interaction, $F[4,32] = 2.91; P = .037$) (Fig. 5).

Fig 5.—R2 areas under the curve (AUC) stratified by trials (trial 1 = baseline, ie, no intervention). Of note is the significant decrease of AUC during the cervical but not the arm intervention.
Analysis of the R2 latencies revealed a notable increase across the 5 trials (main effect for trials, $F[4,24] = 3.02; P = .037$). However, this increase was significantly greater for the cervical than arm intervention (site X trial interaction, $F[4,24] = 4.07; P = .012$) (Fig. 6).

No participant experienced a migraine attack for at least 48 hours following the study.

![Fig 6.—R2 latencies stratified by trials (trial 1 = baseline, ie, no intervention). Of note is the significant increase of latencies during the cervical but not the arm intervention.](image)

**DISCUSSION**

In our previous study, local and referred head pain was reproduced during manual pressure over the atlas or C2 in 95% of migraineurs. Similarly, in the present study, head pain was reproduced during this procedure in all 15 participants. Thus, referral of head pain from upper cervical structures could be an important but underrecognized characteristic of migraine. Furthermore, after repeated application of manual pressure, local and referred head pain decreased in parallel with decreases in the trigeminal nBR (ie, a decrease in the AUC and increase in latency of the ipsilateral R2 waveform). To our knowledge, this is the first time a manual cervical examination
technique has been shown to influence trigeminal nociceptive neurotransmission.

Spinal mobilization is typically applied when dysfunctional areas of the vertebral column are found. Clinicians utilizing manual therapy identify spinal dysfunction based on various features; among these are the ability to reproduce local and referred pain, and restrictions in spinal joint motion. The clinician’s objective in applying manual techniques is to restore normal motion and normalize afferent input from the neuromusculoskeletal system. Despite clinical evidence for the benefits of spinal mobilization, the biological mechanisms underlying the effects of spinal mobilization are not known. One of the principal rationales for manual therapy intervention is that an ongoing barrage of noxious sensory input from biomechanical spinal dysfunction increases the excitability of neurons or circuits in the spinal cord. Mechanoreceptors including proprioceptors (muscle spindles, both primary and secondary endings and Golgi tendon organs), low- and high-threshold mechanoreceptors, high-threshold mechano-nociceptors, and high-threshold polymodal nociceptors within deep paraspinal tissues react to mechanical deformation of these tissues. A significant effect of this “biomechanical remodeling” could be restoration of zygapophyseal joint mobility and joint “play,” precisely the intention of the techniques used in this study. Thus, biomechanical remodeling resulting from mobilization may have physiological ramifications, ultimately reducing nociceptive input from receptive nerve endings in innervated paraspinal tissues.

Our findings of decreased AUC and increased latency of R2 during the cervical intervention are supported by a functional magnetic resonance imaging study in which manual therapy was administered to the ankle joints of rats following capsaicin injection. Subsequent to mobilization, there was decreased activation of the dorsal horn. By analogy, upper cervical afferents may have an excitatory influence on
trigeminal circuits in migraine sufferers that can be reduced by reproduction and lessening of usual head pain.

The reduction in the nBR during spinal mobilization is consistent with previous studies demonstrating a functional connectivity between the cervical and the trigeminal system in the trigeminocervical complex of the brainstem.\textsuperscript{9-12,42-44} This inhibitory effect may be due to a general reduction of afferent cervical nociceptive/excitatory input in the trigeminocervical complex as result of biomechanical remodeling, perhaps restoring joint mobility and joint play,\textsuperscript{40} as inhibition of R2 was more significant than during the arm intervention. Therefore, the highly significant reduction in head pain referral during the cervical intervention could be a clinical correlate of lessening central sensitization of the TCN. In particular, it is conceivable that palpation and stretch of dysfunctional cervical paraspinal tissues elicits tenderness that lessens as remodeling occurs.\textsuperscript{35,36,39} This could explain why tenderness ratings decreased during the cervical intervention and not the arm for, presumably, participants’ arm tissues were not dysfunctional and subject to remodeling.

However, the perception of pain is not only determined by the intensity of the afferent pain signal (nociception).\textsuperscript{45} Nociceptive inputs to the dorsal horn of the spinal cord are also influenced by potent endogenous descending inhibitory and facilitatory processes from supraspinal regions. This bidirectional, central control incorporates a frontal, limbic, brainstem, and spinal cord neuronexus\textsuperscript{46-49} that is driven primarily by noxious inputs and associated emotional responses. Importantly, this includes spinal cord activity because the spinally mediated nociceptive flexion reflex is influenced by central pain modulation processes.\textsuperscript{50} While the exact mechanisms responsible for emotional modulation of pain are not fully understood, heightened anxiety appears to increase sensitivity to pain (hyperalgesia),\textsuperscript{51-68} while moderate fear inhibits pain (hypoalgesia).\textsuperscript{51,69-77} This suggests that anticipation of an unpredictable, threatening
intervention could result in enhanced pain, while hypoalgesia results from exposure to a predictable, threatening event (fear).\textsuperscript{51}

As we did not assess the participants’ psychological state, we are unsure whether this changed over the course of the experiment. Nevertheless, it seems unlikely that psychological factors had a major influence on our findings for the following reasons. First, participants were included only if usual head pain could be produced when stressing either the AO or C2-3 segments – the “inclusion/exclusion” session. In the case of head pain referral, both segments were examined (prior to the experimental sessions) to ascertain which segment reproduced usual head pain most clearly. Thus, participants experienced reproduction of their usual head pain, which ceased immediately on cessation of the technique (ie, essentially, participants were “cued” to believe that the procedures were not threatening). Second, participants, armed with the knowledge that they could terminate the experimental session at any time, were in control, further lessening the role of psychological factors.\textsuperscript{78-83} Third, pain ratings to the supraorbital stimuli were comparable for the cervical and arm interventions, and remained unchanged across the trials. This dissociation between pain perception and R2 activity supports the possibility that the reductions in referred head pain, cervical tenderness, and inhibition of R2 were due to a specific “cervical,” neurophysiological effect, rather than psychological influences.

Another possible mechanism for the inhibitory effect on pain demonstrated in our study is that of placebo. Previous work has shown that the prospect of reduced pain can reduce the pain reported in response to a noxious stimulus.\textsuperscript{84-88} The “inclusion/exclusion” session provided an expectation that head pain would increase during the interventions and cease immediately after cessation of the technique. However, participants had no prior expectation of the likely course of referred head pain as the technique was sustained. Accordingly, we considered that any placebo effect was
An additional potential inhibitory mechanism is diffuse noxious inhibitory controls (DNICs). The DNIC process involves inhibition of neurons in the dorsal horn of the spinal cord in response to nociceptive stimuli applied to any part of the body, unconnected to their facilitatory fields. However, if DNICs were operational, we would have expected identical effects on the nBR during the arm and cervical interventions as mean ratings of local tenderness were the same.

**Limitations.**—Although standardization of pressure clearly is important, for it to be achieved during application of techniques used in this study and in a PAIVM examination, pressure algometers would need to be devised, which are not only attach to the thumb but are sufficiently fine to allow for skilled palpation and perception of mobility. The absence of such a device in our study could be regarded as a shortcoming. The sample size could also be considered a limitation; nevertheless, effects of the cervical intervention were strong enough to be detected even in our small sample. Perception and self-reporting of pain clearly involve psychological influences such as anxiety and fear. These influences need to be investigated in future studies.

**CONCLUSIONS**

To our knowledge, this is the first time cervical manual examination techniques have been shown to influence trigeminal nociceptive neurotransmission. Our results suggest that cervical spinal input contributed to lessening of referred head pain and cervical tenderness, and inhibition of R2. These findings support the concept that noxious cervical afferent inputs contribute to headache in migraine sufferers. They corroborate previous results related to anatomical and functional convergence of trigeminal and cervical afferent pathways in animals and humans, and suggest that manual modulation of the cervical pathway is of potential benefit in migraine.
STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design

    Peter D. Drummond; Dean H. Watson

(b) Acquisition of Data

    Dean H. Watson

(c) Analysis and Interpretation of Data

    Peter D. Drummond; Dean H. Watson

Category 2

(a) Drafting the Manuscript

    Dean H. Watson; Peter D. Drummond

(b) Revising It for Intellectual Content

    Dean H. Watson; Peter D. Drummond

Category 3

(a) Final Approval of the Completed Manuscript

    Peter D. Drummond; Dean H. Watson

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CHAPTER 7
THE TRIGEMINO CERVICAL COMPLEX AND CHRONIC WHIPLASH
ASSOCIATED HEADACHE: A CROSS-SECTIONAL STUDY

7.1 Introduction

It has been established that the symptomatic profile of chronic whiplash
associated headache (CWAH) mirrors that of primary headache.\(^1\)\(^-\)\(^9\) A substantial body
of evidence suggests that cervical afferent nociceptors (C2-3 zygapophyseal joint) play
a pivotal role in the genesis of CWAH.\(^10\)\(^-\)\(^31\)

Studies utilising R2 (the nociceptive blink reflex) have demonstrated deficient
habituation\(^32\)\(^-\)\(^36\) and facilitation (sensitisation)\(^37\)\(^-\)\(^40\) in migraine. These features are
recognised to be genuine traits of the migraine condition. Therefore, we sought to
investigate whether, along with similar symptomatic profiles, migraine and CWAH
share these characteristics, thereby supporting cervical afferent nociceptors as a
potential sensitising source of the TCN in migraineurs.
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7.2 Study 3.

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**The Trigemino Cervical Complex And Chronic Whiplash Associated Headache: A Cross-Sectional Study.**

Dean H. Watson, MAppSc; Peter D. Drummond, PhD

**Objective.—** To investigate signs of central sensitization in a cohort of patients with chronic whiplash associated headache (CWAH).

**Background.—** Central sensitization is one of the mechanisms leading to chronicity of primary headache, and thus might contribute to CWAH. However, the pathophysiological mechanism of CWAH is poorly understood and whether it is simply an expression of the primary headache or has a distinct pathogenesis remains unclear. Thus, the factors involved in the genesis of CWAH require further investigation.

**Methods.—** Twenty-two patients with CWAH (20 females, 2 males; age 25-50 years, mean age 36.3 years) and 25 asymptomatic participants (13 females, 12 males; age 18-50 years, mean age 35.6 years) rated glare and light-induced discomfort in response to light from an ophthalmoscope. Hyperalgesia evoked by a pressure algometer was assessed bilaterally on the forehead, temples, occipital base and the middle phalanx of the third finger. The number, latency, area under the curve and recovery cycle of nociceptive blink reflexes elicited by a supraorbital electrical stimulus were also recorded.
Results.—Eight and 6 CWAH patients had migrainous and tension-type headache (TTH) profiles respectively; the remainder had features attributable to both migraine and TTH. Patients in the whiplash group reported significantly greater light-induced pain than controls (8.48 ± .35 versus 6.66 ± .43 on a 0-10 scale; p=0.001). The CWAH patients reported significantly lower pressure pain thresholds at all sites. For stimuli delivered at 20 second intervals, whiplash patients were more responsive than controls (4.8 ± .6 blinks versus 3.0 ± .6 blinks in a block of 10 stimuli; p=0.036). Whilst R2 latencies and the AUC for the 20 second interval trials were comparable in both groups, there was a significant reduction of the area under the curve from the first to the second of the 2-second interval trials only in controls (99 ± 8 percent of baseline in whiplash patients versus 68 ± 7 percent in controls; p=.009). The recovery cycle was comparable for both groups.

Conclusions.— Our results corroborate previous findings of mechanical hypersensitivity and photophobia in CWAH patients. The neurophysiological data provide further evidence for hyperexcitability in central nociceptive pathways, and endorse the hypothesis that CWAH may be driven by central sensitization.

Key words: Whiplash, Chronic whiplash associated headache, migraine, Tension-type headache, nociceptive blink reflex, central sensitization, sensory hyperalgesia, photophobia, recovery cycle

Abbreviations: CWAH chronic whiplash associated headache, TTH tension-type headache, CTTH chronic tension-type headache, AUC area under the curve
Chronic whiplash associated headache (CWAH) is a relatively new diagnostic entity in the ICHD-2 (5.4). To fulfill the criteria for this diagnosis, headache and neck pain must develop within 7 days of a whiplash trauma (i.e., an extension of the neck followed by flexion), which persists for at least 3 months. Whiplash associated disorders are controversial concepts, primarily because a lack of objective biomarkers prevents a precise diagnosis.3,7,42-44

Whiplash trauma may generate CWAH. It would seem plausible, therefore, to assume that the trauma produces a permanent disorder that preserves the pain.7 Chronic whiplash associated headache resembles various forms of primary headache, for example chronic tension-type headache (CTTH), chronic migraine, or cluster headache,1-6,45 and neck pain often accompanies the most prevalent primary headaches.1

Therefore, as CWAH and primary headache share similar symptomatic profiles, potentially CWAH could share a common mechanism with primary headache syndromes.9 Central sensitization is one of the mechanisms leading to chronicity of headache,5,46-49 and thus might contribute to CWAH. However, the pathophysiological mechanism of CWAH is poorly understood and whether it is simply an expression of
the primary headache or has a distinct pathogenesis remains unclear.\textsuperscript{5} Thus, the factors involved in the genesis of CWAH require further investigation.

Cutaneous allodynia is a notable feature of migraine and other primary headaches,\textsuperscript{48,50-55} and is thought to be caused by sensitization of central second-order neurons, which receive dual input from the trigeminal and cervical fields.\textsuperscript{53,56} Cutaneous allodynia is considered a manifestation of central sensitization and a risk factor for the chronification of migraine\textsuperscript{48,49} and tension-type headache.\textsuperscript{54} Chronic pain following injury is often associated with centrally mediated hyperalgesia or allodynia.\textsuperscript{57} Not surprisingly, therefore, allodynia and hyperalgesia have been demonstrated in patients with chronic whiplash associated disorders and, as in migraine and CTTH, occurs not only in the cervical region but also at distant sites.\textsuperscript{58-65} This characteristic of chronic whiplash associated disorders is attributed to hyperexcitability of nociceptive circuits within the central nervous system.\textsuperscript{66-68}

Photophobia is also a feature of primary headache,\textsuperscript{69,70} and is a fundamental aspect of the diagnostic criteria for migraine.\textsuperscript{1} Photophobia can be evaluated in two ways – the perception of ‘brightness’ or ‘glare’, and the level of discomfort evoked by light.\textsuperscript{71} Photophobia may result from a lack of sub cortical inhibitory influences which ordinarily modulate sensations of glare and light induced pain.\textsuperscript{72} This is supported by a recent study which demonstrated activation of neurons in the trigemino cervical nucleus in response to a bright light stimulus.\textsuperscript{73} Studies eliciting the nociception specific R2 component of the nociceptive blink reflex have demonstrated a lack of habituation in the interictal phase of migraine, which implies abnormal trigeminal nociceptive processing in migraine patients.\textsuperscript{34,74} This deficient habituation seems to reflect a consistent interictal trait of migraine patients.\textsuperscript{75,76} The R2 response can be inhibited by a
preceding conditioning stimulus, and its recovery-curve after paired stimuli is thought to reflect the excitability of the trigemino-brainstem-facial circuit.\textsuperscript{77,78} In a study of the classical R2 blink reflex\textsuperscript{79} faster recovery for migraineurs than controls was thought to demonstrate trigeminal hyperexcitability.

The aim of the present study was to investigate signs of central sensitization of the trigemino cervical nucleus in CWAH patients. It was hypothesised that CWAH patients would manifest photophobia, sensory hyperalgesia and alterations of R2 concomitant with hyperexcitability of the trigemino cervical nucleus.

**MATERIALS AND METHODS**

**Participants.** – Patients fulfilling the International Headache Society’s classification diagnostic criteria of chronic post whiplash headache\textsuperscript{41} were invited to participate in the study. Furthermore, in accordance with the diagnostic criteria of chronicity of TTH\textsuperscript{1} and migraine,\textsuperscript{1} patients experienced headache on at least 15 days per month. Twenty-two headache patients (20 females; age range 25-50 years, mean age = 36.3 years) who had experienced whiplash trauma in a motor vehicle accident, were recruited from various physiotherapy clinics. Friends, family and associates of patients attending the first author’s clinic were invited to participate as non headache controls. Participants in the non-headache group (N=25; 13 females; age range 18-50 years, mean age = 35.6 years), were either headache-free or experienced mild non-migrainous headache no more than six times per year. Sample sizes were based on similar previous studies investigating allodynia in chronic whiplash patients,\textsuperscript{58,61,62,80} photophobia (chronic whiplash patients),\textsuperscript{80} glare and light induced pain (migraineurs),\textsuperscript{71} and the nociceptive blink reflex (migraineurs).\textsuperscript{34-36,38,39,81}
Participants were enrolled independently of the experimenter (DW) to ensure that he remained blind to the participant’s diagnostic category. Data collection commenced in March 2009 and was completed in September 2009. Every endeavour was made to examine patients interictally. All participants signed an informed consent form. Ethics approval was obtained from the Ethics Committee of Murdoch University.

**Photophobia.** – In the first part of the experiment, an ophthalmoscope light (WelchAllyn PocketScope) was shone directly into participants’ eyes for 10 seconds from a distance of 10 cm. Each eye was tested separately, with ~60s between tests. Initially the ophthalmoscope was adjusted to 50% intensity and subjects rated the glare on a scale of 0-10 where 0 corresponded to “not glary”, 1 to ‘glary’ and 10 to ‘the most dazzling light they had ever seen’. Then the ophthalmoscope was adjusted to maximum intensity and participants rated light induced pain on a 0-10 scale where 0 corresponded to ‘not at all painful’ and 10 to ‘extremely painful’. 71

**Sensory hyperalgesia.** – Next, a pressure algometer (Wagner Force Gage FPX 50; (flat) surface area = .5 inch) was applied bilaterally to the forehead, temples, base of the occiput and the posterior aspect of the middle phalanx of the third finger. Pressure was increased at one pound force per second. Participants were asked to report immediately when the sensation of pressure became uncomfortable. Sites were tested in random order, with a recovery period of at least 3 minutes between each application. The reliability of pressure algometry has been found to be high [intraclass correlation coefficient (ICC) 0.91, 95% confidence interval 0.82, 0.97]. 82

**Trigeminal nociception.** – In the final part of the study, the nociceptive blink reflex was elicited with a custom-built planar concentric electrode, placed on the forehead, ipsilateral to the side of headache or worst side of headache, 10 mm above the supraorbital groove. Blink reflexes were recorded from surface electrodes placed below
the lower eyelids and 2-3 cm laterally. Current intensity was 2.3 mA (mono polar square wave pulses, 0.3 ms duration). This current intensity elicits R2, but not R1, consistent with excitation of superficial nociceptors but not of the deeper A-beta non nociceptive fibres. Outcome variables were the number of recorded blinks, the recovery curve, the response area under the rectified curve (AUC), and latency of the R2 component of the nociceptive blink reflex.

After subtracting background noise from raw blink reflex data, latencies were established for each blink. Blinks were identified individually by inspecting each waveform in the raw data files and were defined as present if the R2 component of the AUC was greater than background noise. Areas under the curve were assessed in the time window 27-87 ms after the stimulus.

The recovery curve was examined by delivering paired shocks at different inter stimulus intervals. The initial component of the recovery curve was established using eight pairs of stimuli; inter stimulus interval 100 ms; each pair separated by two seconds. Five minutes later this was repeated except that the inter stimulus interval was 500 ms. The recovery curve was calculated as a percentage of the second of the paired stimuli to the conditioning stimulus.

This was followed 10 minutes later by four blocks of 10 stimuli; each block was separated by 40 seconds. The inter stimulus interval in the first two blocks was two seconds and 20 seconds in the remaining two blocks.

**Statistical Approach.**— Data were analyzed using SPSS Version 16 software (SPSS, Inc., Chicago, IL, USA). Pressure pain thresholds were investigated in a 4 x 2 x 2 (site [forehead, temples, occiput, fingers] x (group [whiplash, control] x side [left, right]) analysis of variance (ANOVA). Tests of statistical significance were based on
Pillai’s trace ($V_{\text{Pillai}}$), and significant effects were investigated further in ANOVAs for each site. Differences between female patients and female controls, between male and female controls, and between phenotypic subgroups (chronic migraine, CTTH, or a combination of both) were investigated in exploratory analyses. Sensitivity to light (glare, and light induced discomfort ratings) was examined in a multivariate ANOVA using a similar approach. The number of blinks to nociceptive stimuli (defined as an R2 component greater than background noise) was investigated in a group [whiplash, control] x block [number of blinks in the first ten trials versus the number of blinks in the next ten trials] x inter-stimulus interval [2 s, 20 s] repeated measures ANOVA. As some patients did not blink in response to the nociceptive stimuli, R2 AUC and R2 latency were each investigated separately for stimuli presented at 2 s and 20 s intervals to allow most use of the available data. R2 latency was investigated in 2 x 2 (group [whiplash, control] x block [first 10 stimuli, second 10 stimuli]) ANOVAs for stimuli presented at 2 s and 20 s intervals. As R2 AUC was expressed as the percent change from baseline (the first block of stimuli or the first of two paired stimuli), differences between patients and controls were investigated at each inter-stimulus interval with Student’s t-test. To limit type 1 errors in analyses of R2 latency and R2 AUC for stimuli presented at 2 s and 20 s intervals, the criterion of statistical significance was adjusted using Bonferroni’s correction (i.e., $p<0.025$ was considered to be statistically significant). For all other tests, $p < 0.05$ was considered to be statistically significant; tests of statistical significance were 2-tailed. Results are reported as the mean ± standard error (SE).

RESULTS

**Group characteristics.**— Eight patients fulfilled the requirements for chronic migraine; alternating head pain was a feature in five. Six patients met the criteria for
CTTH, whilst the remainder (n = 8) presented with features attributable to both TTH and migraine. The number of headache days per month ranged from 15 to 30 (M=22.1, SD=6.0). Two of the migraine patients, one in the TTH group and another with symptoms common to TTH and migraine, had suffered direct head trauma. The mean history was 6.16 years.

Two patients reported a previous history of migraine. Both reported significantly increased frequency after the whiplash injury; one also reported that her previously side-locked migraine now alternated and that she had also developed daily lesser headache resembling TTH. Similarly, two patients with features of TTH reported substantial increases in frequency of pre-existing infrequent episodic TTH. Of the remaining 18 patients, 10 experienced mild non-migrainous headache no more than six times per year before the whiplash injury and eight could not recall ever having experienced headache.

Three patients from each of the TTH cohort and the group comprising patients presenting with a combination of TTH and migrainous symptoms presented with headache at the time of assessment. The intensity of headache on a visual analogue scale (0 = no pain; 10 = intolerable pain) ranged from 2 to 4.

Eighty-six percent of patients reported associated neck symptoms (pain and/or stiffness) (Table 1). Bilateral headache was described by 63.6% of patients, and 54.5% reported unilateral headache; 66.6% of these alternated. Head pain occurred most commonly frontally (63.6%). Aching/pressure was reported by 63.6% of patients, pulsating (45.5%) and sharp/stabbing in 9.1%. Sixty-eight percent and 45.5% of patients reported nausea and vomiting respectively; photo and/or phonophobia occurred in 54.5% of patients.
Table 1. Clinical characteristics of whiplash subjects (n=22)

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Tension-type headache (n = 6)</th>
<th>Migraine (n = 8)</th>
<th>Mixed (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical symptoms</td>
<td>4</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Bilateral</td>
<td>6</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Unilateral</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Alternating</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Frontal</td>
<td>6</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Retro orbital</td>
<td>4</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Occipital</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Ache/Pressure</td>
<td>6</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Pulsating</td>
<td>8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Sharp/stabbing</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Photo/phonophobia</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

**Sensory hyperalgesia.** – Pressure pain thresholds differed across sites \[V_{\text{Pillai}} = 0.91, \text{multivariate } F(3,43) = 150.4, p<0.001\] (Figure 1). Follow-up tests with Bonferroni’s adjustment indicated that pressure pain thresholds were lower in the temples than at all other sites, and higher in the fingers than at all other sites. However, pressure pain thresholds were similar in the forehead and occipital region.
At all sites, pressure pain thresholds were significantly lower in CWAH patients than controls [main effect for group F(1,45) = 17.3, p<0.001; forehead (3.93 ± .29 versus F(1,45)=30.5; p=0.001); occiput (4.2 ± .41 versus 5.41 ± .51 lbf; F(1,45)=13.31; 4.84 ± .33 lbf; F(1,45)=14.61; p=0.001)] temples (2.15 ± .19 versus 3.10 ± .24 lbf; p=0.001); finger (11.77 ± .94 versus 14.34 ± 1.17 lbf; F(1,45)=9.40; p=0.004] (Figures 1a, b, c, and d respectively). In exploratory analyses, pressure pain thresholds were similar at all sites in patients with chronic migraine, CTTH or a combination of both.

![Pressure pain threshold ratings](image)

Figure 1. — Pressure pain thresholds (PPT) ± S.E. at the different sites. Note that at all sites pressure pain thresholds were lower in the whiplash group.

Pressure pain thresholds were lower for the left temple than the right (2.5 ± .14 versus 2.75 ± .20 lbf; F(1,45)=8.52; p=0.005) (Figure 1b) but there were no other significant differences between sides [site x side interaction $V_{\text{Pillai}} = 0.33$, multivariate F(3,43) = 6.95, p=0.001].
By-and-large, pressure pain thresholds were lower in female patients than female controls [main effect for group F(1,31) = 4.65, p=0.039] (Table 2). Within the control group, pressure pain thresholds were significantly lower at all sites in females than males [main effect for gender F(1,23) = 8.73, p=0.007] (Table 3).

**Photophobia.** – Overall, sensitivity to light was greater in patients than controls [VPillai = 0.34, multivariate F(2,44) = 11.1, p<0.001]. Univariate analyses indicated that

Table 2. Photophobia and Pressure pain thresholds in female patients and female controls.

<table>
<thead>
<tr>
<th></th>
<th>Patients (N = 20)</th>
<th>Controls (N = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photophobia (0-10)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glare</td>
<td>4.79 ± 0.4</td>
<td>4.5 ± 0.5</td>
</tr>
<tr>
<td>Discomfort</td>
<td>8.48 ± 0.35</td>
<td>6.66 ± 0.43*</td>
</tr>
<tr>
<td>Pressure pain thresholds (lbf)***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forehead</td>
<td>3.93 ± 0.29</td>
<td>4.84 ± 0.36</td>
</tr>
<tr>
<td>Temples</td>
<td>2.15 ± 0.19</td>
<td>3.1 ± 0.24*</td>
</tr>
<tr>
<td>Occipital</td>
<td>4.2 ± 0.41</td>
<td>5.41 ± 0.51</td>
</tr>
<tr>
<td>Finger</td>
<td>11.77 ± 0.94</td>
<td>14.34 ± 1.17</td>
</tr>
</tbody>
</table>

* p<0.01 between patients and controls
** rated on a 0-10 scale
*** units of force measured in pounds force (lbf)

glare ratings were similar in patients and controls (4.79 ± .4 versus 4.5 ± .5 on a 0-10 scale; F(1,45)=1.68; p=0.202) (Figure 2a). However, the CWAH group reported significantly greater light-induced pain than controls (8.48 ± .35 versus 6.66 ± .43 on a
0-10 scale; F(1,45)=22.61; p=0.001) (Figure 2b). In exploratory analyses, ratings of glare and light-induced pain were similar in patients with chronic migraine, CTTH or a combination of both.

Glare (4.95 ± .33 versus 4.34 ± .33 on a 0-10 scale; F(1,45)=5.85; p=0.020) and light-induced pain (7.0 ± .29 versus 7.43 ± .33 on a 0-10 scale; F(1,45)=6.02; p=0.018) were greater on the right than left side in both groups [V_{Pillai} = 0.17, multivariate F(2,44) = 4.61, p=0.015].

Table 3. Photophobia and Pressure pain thresholds in female and male controls.

<table>
<thead>
<tr>
<th>Mean ± S.E.</th>
<th>Females (N=13)</th>
<th>Males (N=12)</th>
<th>F values</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Photophobia (0-10)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glare</td>
<td>4.50 ± 0.42</td>
<td>4.20 ± 0.44</td>
<td>F(1,23) = 0.17</td>
<td>P = 0.69</td>
</tr>
<tr>
<td>Discomfort</td>
<td>6.65 ± 0.48</td>
<td>6.30 ± 0.50</td>
<td>F(1,23) = 0.57</td>
<td>P = 0.57</td>
</tr>
<tr>
<td><strong>Pressure pain thresholds (lbf)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forehead</td>
<td>4.48 ± 0.38</td>
<td>6.24 ± 0.40</td>
<td>F(1,23) = 6.45</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>Temples</td>
<td>3.10 ± 0.24</td>
<td>4.28 ± 0.25</td>
<td>F(1,23) = 11.88</td>
<td>P &lt; 0.002</td>
</tr>
<tr>
<td>Occiput</td>
<td>5.41 ± 0.56</td>
<td>7.47 ± 0.58</td>
<td>F(1,23) = 6.49</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>Finger</td>
<td>14.34 ± 1.26</td>
<td>18.14 ± 1.31</td>
<td>F(1,23) = 4.42</td>
<td>P = 0.05</td>
</tr>
</tbody>
</table>

* rated on a 0-10 scale

** units of force measured in pounds force (lbf)

In general, female patients were more sensitive to light than female controls [V_{Pillai} = 0.27, multivariate F(2,30) = 5.42, p=0.010]. Specifically, ratings of light-
induced discomfort were greater in female patients than in female controls (8.5 ± 0.35 versus 6.7 ± 0.43 on a 0-10 scale; F(1,31)=10.8; p=0.003) (Table 2). Glare and light-induced discomfort were comparable in female and male controls (Table 3).

**Nociceptive Blink Reflex.** — The number of blinks decreased significantly across the two 10-trial blocks of stimuli when stimuli were delivered at two-second intervals (4.19 ± .46 versus 2.78 ± .4; F(1,38)=33.26; p=0.001) but remained stable when stimuli were delivered at 20-second intervals [main effect for block, F(1,38) = 17.7, p<0.001; block x interval interaction, F(1,38) = 6.94, p = 0.012]. By-and-large, the number of blinks was greater for patients than controls [main effect for group, F(1,38) = 4.75, p = 0.036]. (Figure 3). This may have been due, in part, to gender differences between groups because the number of blinks was similar in female patients and controls [main effect for group, F(1,26) = 0.43, p = 0.519]. Nevertheless, any gender effect appeared to be small because the number of blinks was similar in male and female controls [main effect for gender, F(1,19) = 3.73, p = 0.069]. In an exploratory analysis, the number of blinks was similar in patients with chronic migraine, CTTH or a combination of both.

![Photophobia](image)

*Figure 2.* — ‘Glare’ and ‘Pain’ ratings ± S.E.. Note the significantly higher ratings for ‘Pain’ in the Whiplash group but not for ‘Glare’.
R2 latencies were similar in both groups (Figure 4). Similarly, the change in R2 AUC from the first to the second block of trials was comparable in both groups for the 20-second inter stimulus interval trials.

However, in the two-second inter stimulus interval trials, R2 AUC decreased from the first to the second block of stimuli only in controls [99 ± 8 percent of baseline in whiplash patients vs 68 ± 7 percent in controls; t(28)= 2.804; p=0.009] (Figure 5).

**Figure 3.** — Number of blinks (No. nBR) ± S.E. stratified by trials. The number of blinks was greater in the whiplash group. (ISI: inter stimulus interval)

**Figure 4.** — R2 latencies ± S.E. stratified by trials. (ISI: inter stimulus interval)
The RC of R2 was comparable for the CWAH and control groups across both the 100 ms (Figure 6a) and 500 ms trials (Figure 6b).

As some of the females did not respond to the nociceptive stimuli, numbers were insufficient to compare R2 latency or AUC in female patients and controls. Similarly, numbers were insufficient to compare R2 latency or AUC across groups with chronic migraine, CTTH or their combination.

Figure 5. — R2 area under the curve (AUC) ± S.E. stratified by trials. Note the significant increase in AUC for the whiplash group in the 2 second ISI (inter stimulus interval) trial compared with the control group.

Figure 6. — Recovery curve (RC) stratified by trials. Note the recovery curves were comparable for both groups. (ISI: inter stimulus interval)
DISCUSSION

We identified sensory hyperalgesia, photophobia, and modifications of R2 in the CWAH group. These features are consistent with central sensitization and are comparable to primary headache conditions. In addition, there were no differences between the separate headache phenotypes when pressure pain threshold, glare, light induced pain ratings and number of blinks were considered. This supports a common pathogenesis to migraine, TTH \(^{85-87}\) and CWAH. Indeed, the shared clinical features of patients in our study (Table 1) and primary headache is in accordance with previous studies,\(^{1,2,4-7,42,45,46}\) and reinforces the possibility that CWAH shares a common mechanism with primary headache.\(^4\) In contrast to previous studies, in which the majority of patients presented with profiles similar to TTH,\(^{3,7}\) our patients favoured a migrainous presentation (Table 1).

Eighty-six percent of patients reported accompanying cervical pain, which is a common feature of primary headache.\(^3,88\) The term ‘Whiplash’ describes a mechanical event.\(^89\) Accordingly, clinical and biomechanical studies have identified the cervical zygapophyseal joints as the most common source of injury and accompanying neck and head pain,\(^{10,14-16,18,20,21}\) and have demonstrated that movements of the upper cervical segments during motor vehicle accidents can exceed physiological limits.\(^{25-27}\) Indeed, the location of symptomatic joints is consistent with the location predicted by biomechanical studies: joints at C5-6 or C6-7 and at C2-3 are most commonly affected.\(^11,24,27,28\)

Furthermore, in a positron emission tomography study, tracer uptake in proximity to the second cervical vertebra was significantly greater in CWAH patients than controls, indicating local persistent peripheral tissue inflammation.\(^90\) In-vivo animal models indicate that tissue injury leads to modifications in nociceptor activation, immediate and sustained dysfunction in afferents and spinal neurons, neuroplastic
changes and pain. Together, these findings provide a compelling case for cervical afferents being a peripheral driver of CWAH.

Sensitivity to mechanical stimulation and light are considered intrinsic characteristics of the primary headaches. In accordance with previous studies, pressure-pain thresholds were lower in CWAH patients than in controls, including sites remote from the cervical and trigeminal fields. Our finding of decreased pressure pain thresholds in female patients is consistent with previous findings of mechanical hypersensitivity in female migraineurs. Whilst in our cohort of participants females outnumbered males significantly (i.e. 33:14), only two (CWAH females) reported a prior history of migraine. Therefore, although we cannot exclude the possibility of sensory hyperalgesia (and photophobia) being present pre injury, the absence of significant previous histories lessens potential gender bias of our findings.

The mechanism for asymmetrical perception is unknown, but perhaps indicates asymmetry of pain modulation processes and could explain our finding of lower pressure-pain thresholds on the left at the temples (Figure 1). The significant presence of cephalic, cervical and remote sensory hyperalgesia in patients with CWAH mirrors the presentation of primary headache and is considered a clinical manifestation of central sensitization.

Given this centrally-sensitized environment, the augmentation of light-induced pain in our CWAH group is not surprising. This combination of sensory hyperalgesia and light-induced pain suggests that, in those with CWAH, light may have a relevant role in trigeminal and cervical pain perception thresholds for, whilst the mechanism of photophobia remains unclear, involvement of converging visual and trigeminal nociceptive activity is likely. Because of converging trigeminal and retinal afferents
on thalamic neurons, these neurons interpret light as a nociceptive signal. This is supported by an animal study in which increased activity of neurons in the trigemino cervical nucleus was noted when exposed to light, a finding that was interpreted as a nociceptive (photophobic) response. Glare and light-induced pain were greater on the right side than the left, possibly because headaches had a right-sided bias in most of our patients. This is in accordance with an early study in which light-induced pain was greater on the symptomatic side in 19 of 25 patients with unilateral headache. Symptoms of trigeminal excitability, such as ice cream headache and icepick-like pains, are often most intense at the habitual site of headache, suggesting that trigeminal hyperexcitability persists between headache episodes. Thus, it is intriguing that sensitivity to blunt pressure was greater in the left temple than the right, despite the opposite trend for visual discomfort.

That central sensitization could be responsible for the sensory hypersensitivity and photophobia demonstrated in our CWAH patients is supported by our neurophysiological findings of a significant delay in habituation in area under the curve in the two-second inter stimulus interval trial, and more blinks to trigeminal nociceptive stimuli in CWAH patients. These findings reinforce those of an earlier study demonstrating altered central pain control in CWAH patients. Furthermore, the larger number of blinks in the CWAH patients parallels migraine, as deficient habituation of R2 interictally is considered a trait of the migraine condition. However, these findings should be interpreted cautiously as latencies were similar in CWAH patients and controls, as was AUC in the 20 second inter stimulus interval and recovery curve trials.
Whilst the mechanisms underlying sensory hypersensitivity and photophobia remain unclear, peripheral, spinal, and supraspinal involvement has been proposed.\textsuperscript{67,80,116} However, consistent with cervical musculoskeletal involvement in the ‘whiplash’ mechanism and the considerable evidence incriminating the cervical zygapophyseal joints,\textsuperscript{10,14-21} it seems plausible that a peripheral mechanism drives central hyperexcitability.\textsuperscript{57,117} This is reinforced by demonstrable alterations in neuronal excitability in the spinal cord secondary to ongoing peripheral nociception.\textsuperscript{92,95,96,118} Furthermore, a recent study has demonstrated significant concomitant diminution of recognised central sensitization measures in association with improved cervical movement.\textsuperscript{119} This finding strengthens the notion that chronic pain in cervical whiplash patients could be maintained by peripheral nociceptive input.\textsuperscript{57,119} In addition, amelioration of widespread sensory hyperalgesia has occurred following medial branch blocks of cervical zygapophyseal joints\textsuperscript{61} and anesthetic injections of cervical myofascial trigger points.\textsuperscript{80} Moreover, anesthetic injections of cervical myofascial trigger points also resolved photophobia.\textsuperscript{80}

Psychological distress is considered a feature of chronic whiplash.\textsuperscript{120} As we did not assess participants’ psychological state, we cannot be certain of the influence of psychological factors on our data. However, some evidence suggests that whilst psychological distress may be present it is not solely responsible for central sensitization.\textsuperscript{61,80,119-121}

Nine of our CWAH patients were involved in litigation. It has been suggested that litigation or monetary issues may amplify chronic symptoms of whiplash,\textsuperscript{122} and whilst we cannot exclude litigation factors we think this was unlikely to have had a major influence on our findings given our neurophysiological data.
Limitations.— The sample size could be considered a limitation; nevertheless, significant differences between groups in the pressure-pain threshold and light induced pain suggest that the complexion of our data would be unaffected by a larger sample. Whilst we surmise that augmentation of light induced pain suggests central sensitisation, we acknowledge that there have been no formal studies validating this. Perception and self-reporting of pain clearly involve psychological influences, and these need to be investigated in future studies. Controls and patients were not matched for gender and therefore we investigated (i) photophobia and pressure pain thresholds in men and women in the control group and also (ii) ran separate analyses for female patients versus female controls. Despite women being more sensitive to pressure-pain than men, nevertheless tenderness was greater in female patients than female controls. We inferred central sensitization by the presence of photophobia and hyperalgesia to pressure-pain in the forehead, temples, neck and fingers, and of delayed habituation to trigeminal nociceptive stimuli. However, this could be investigated further using additional tests (e.g., of temporal summation to punctate or thermal stimuli, and the integrity of conditioned pain modulation). Furthermore, additional support for central sensitisation in CWAH may be furnished by future studies comparing CWAH patients with a group of patients with acute whiplash associated headache. Phenotyping our cohort of CWAH patients using dependent variables employed in this study failed to differentiate between patients with features of chronic migraine, CTTH or their combination. Whilst this could suggest a common mechanism across chronic migraine, CTTH and CWAH, larger samples would be needed to corroborate this finding.

CONCLUSIONS

Our data confirm previous findings of sensory hypersensitivity and photophobia in CWAH patients, providing further evidence for hyperexcitability in central
nociceptive pathways. To our knowledge, this the first study to investigate R2 in CWAH patients. Our neurophysiological data provide additional endorsement for the hypothesis that CWAH may be driven by central sensitization. Furthermore, whilst additional mechanisms are probably involved in CWAH, considerable evidence supports the role of spinal afferents as the primary driver of CWAH.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design

Peter D. Drummond; Dean H. Watson

(b) Acquisition of Data

Dean H. Watson

(c) Analysis and Interpretation of Data

Peter D. Drummond; Dean H. Watson

Category 2

(a) Drafting the Manuscript

Dean H. Watson; Peter D. Drummond

(b) Revising It for Intellectual Content

Dean H. Watson; Peter D. Drummond

Category 3

(a) Final Approval of the Completed Manuscript

Peter D. Drummond; Dean H. Watson

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CHAPTER 8
CONCLUSION

8.1 Summary of the three studies

The aim of the three studies (sections 5.2, 6.2, 7.2) was to investigate a potential sensitizing role of the upper cervical (C1-3) afferents on the trigemino cervical nucleus (TCN) in primary headache.

In the study presented in Chapter 5 (section 5.2), the incidence of manual cervical referral of accustomed head pain was investigated in migraine and tension-type headache (TTH) patients. Referral of accustomed head pain was reported by 95 and 100 percent of 20 migraineurs and 14 TTH patients respectively. In addition, reproduction of accustomed head pain occurred from both the (cervical) C2-3 and atlanto occipital segments in all subjects who experienced head pain referral.

The second study (section 6.2) investigated the clinical phenomenon of manual cervical reproduction and resolution (while the examination technique was sustained) of accustomed head pain in 15 migraineurs and its effect on a TCN reflex, the nociceptive blink reflex. Sustaining the examination technique over four 90 second trials resulted in significant lessening of referred accustomed head pain and local tenderness. In parallel, a significant increase and decrease of nociceptive blink reflex (R2 nBR) latencies and area under the curve (AUC) respectively, was demonstrated.

The symptomatic profiles of chronic whiplash associated headache (CWAH) mimic those of primary headache, implying a shared pathophysiological mechanism. If
this were the case, then given ‘whiplash’ is considered a musculoskeletal event, a sensitizing role of cervical afferents in primary headache becomes a possibility. This was the subject of the third study (section 7.2). The symptomatic profiles of 22 CWAH patients confirmed previous studies, mimicking profiles of primary headache. Patients with CWAH reported significant photophobia and hyperalgesia when compared to controls (n=25). Analysis of R2 nBR was consistent with hyperexcitability in central nociceptive pathways in CWAH patients.

8.2  Limitations

The sample sizes in all three studies (sections 5.2, 6.2, 7.2) could be considered a limitation. However the very high incidence of head pain referral in study one suggests that the result would be replicated in a larger cohort. Similarly, in study two (section 6.2) the effects of the cervical intervention were convincing, and in study three (section 7.2), highly significant differences between the CWAH and control group in the pressure pain thresholds and light induced pain were demonstrated regardless of small sample sizes.

In study one (section 5.2), the examiner was not blinded when assessing head pain referral in patients and controls, which could be considered a limitation. However, tenderness ratings for thumb pressure between controls and symptomatic groups were comparable, lessening this possibility. Furthermore, there was no prior assumption that head pain referral would be different between those in the control group with infrequent headache and those without a history of headache. Accordingly, this difference is unlikely to be due to examiner bias.
Examination of the atlanto occipital and C2-3 segments in succession in study one (section 5.2) could suggest facilitation of head pain during examination of the subsequent segment (C2-3), potentially distorting our result. This appears unlikely because each technique was applied for no longer than five seconds, referred head pain eased within seconds of ceasing the examination technique, and the interval between each technique was greater than three minutes. In addition, if the initial technique had facilitated succeeding responses, the frequency and severity of head pain referral should have increased during the second (C2-3) examination. This was not the case.

The standardisation of thumb pressure during cervical intervention in studies one and two (sections 5.2 and 6.2) is clearly desirable. Examination of passive accessory intervertebral movement requires skilled palpation, which includes perception of mobility. Therefore, pressure algometers would need to be developed which not only attach to the thumb but are sufficiently fine to allow for perception of mobility. An absence of such a device in both studies could be considered a shortcoming.

In study three (section 7.2), controls and patients were not matched for gender, and as a result female participants outnumbered males. This might have influenced our result. Recognising that females are more sensitive to pressure-pain than males, we investigated photophobia and pressure pain thresholds in men and women in the control group and also compared findings in female patients and controls. Our finding that tenderness was greater in female patients than female controls lessens a potential gender bias in our results. Furthermore, only two (CWAH females) reported a prior history of migraine. Therefore, whilst it is not possible to exclude the possibility of sensory hyperalgesia (and photophobia) being present before injury, the absence of previous histories further diminishes the likelihood of gender influence on our data.
Other limitations in these studies included reliance on perception and self-report of pain. Clearly, these involve psychological influences such as anxiety and fear, and as we did not assess participants’ psychological state, we cannot be certain of the effect of psychological factors on our findings.

8.3 Future research

Pivotal to this thesis has been the investigation of cervical nociceptors in sensitization of the brainstem in primary headache utilising manual cervical reproduction of customary head pain when examining the atlanto occipital and C2-3 segments (sections 5.2 and 6.2). Perception and self-reporting of pain clearly involve psychological influences such as anxiety and fear. Moderate fear inhibits pain (hypoalgesia),\textsuperscript{1-10} while heightened anxiety appears to increase sensitivity to pain (hyperalgesia).\textsuperscript{1,11-27} This implies that anticipation of an unpredictable, threatening intervention could result in enhanced pain, while diminished pain results from exposure to a predictable, threatening event (fear).\textsuperscript{1} An additional potential inhibitory mechanism is diffuse noxious inhibitory controls (DNICs), expressed as ‘conditioned pain modulation’ in humans. The DNIC process involves inhibition of neurons in the dorsal horn of the spinal cord in response to nociceptive stimuli applied to any part of the body.\textsuperscript{28-30} Whilst is has been shown that DNICs are impaired in tension headache\textsuperscript{31,32} and migraine,\textsuperscript{32,33} it remains to be determined whether DNIC impairment is responsible for the development of central sensitisation in nociceptive pathways or is a nonspecific neuro physiological manifestation of chronic pain. A recent study investigating menstrual migraineurs found no impairment of DNICs,\textsuperscript{34} prompting the authors to speculate as to whether the DNICs play a patho physiological role in migraine or
whether migraine compromises DNIC.\textsuperscript{34} Furthermore, an animal study\textsuperscript{35} demonstrated concomitant DNIC impairment and sensitisation of the TCN. Perhaps then, another explanation needs to be explored; could it be that the magnitude of central sensitization during a severe migraine attack defeats the inhibitory capacity DNICs, thereby reducing their effectiveness?\textsuperscript{36} Studies investigating potential influences of these processes (fear, anxiety, DNICs) on sensitization of the TCN in primary headache, utilising R2 nBR, are warranted.

A further study to supplement the findings of study 1 (section 5.2) in which migraineurs and TTH patients were examined could include a cohort of patients from the third primary headache group i.e., the trigeminal autonomic cephalalgias (TACs), comprising cluster headache, chronic paroxysmal hemicrania and short lasting unilateral neuralgiform headache attacks with conjunctival injection. In both the first and second studies (sections 5.2 and 6.2), the clinical experience of the author directed examination of the atlanto occipital and C2-3 segments. However, referral of head pain from the atlanto axial (C1-2) segment is also possible. Whilst not a specific aim of this thesis, a future study comparing the incidence of head pain referral from each of the atlanto occipital, C1-2 and C2-3 segments could benefit clinicians.

The results of study 2 (section 6.2), could be supplemented by replicating studies in cohorts of TTH and TAC patients. If similar effects on the nBR were demonstrated, this would support the role of cervical nociception across the primary headache spectrum.

In the third study (section 7.2) the presence of widespread hyperalgesia to pressure-pain, photophobia and delayed habituation of nBR in chronic whiplash
associated headache (CWAH) patients suggests a state of central sensitisation. However, future studies using additional tests (e.g., of temporal summation to punctate or thermal stimuli and the integrity of conditioned pain modulation) would provide further information about sensitization of the TCN in CWAH. Also, additional support for central sensitisation in CWAH may be furnished by studies comparing a cohort of patients with acute whiplash associated headache to others with CWAH. In addition, assessing the incidence of reproduction of customary head pain (study 1) and the effect of reproduction and resolution of head pain on the nBR (study 2; section 6.2) in CWAH patients could provide further support for the relevance of cervical nociception in CWAH. Also replicating study 3 (section 7.2) in which participants were matched for age and gender would help to clarify whether these characteristics moderate vulnerability to sensitization of the TCN in CWAH.

8.4 Theoretical and clinical implications

Differentiating migraine without aura, TTH and cervicogenic headache patients on the basis of symptoms alone is problematic.\(^{37-39}\) Whilst abolition of head pain following anaesthetic blocks of a cervical structure or its nerve supply (notably the C2-3 zygapophyseal joint / third occipital nerve) is considered the ‘gold standard’ for a diagnosis of cervicogenic headache,\(^{40-43}\) these blocks are invasive, placebo responses also need to be considered, and many practitioners do not have facilities for such procedures.\(^{43,44}\) However, manual cervical reproduction of accustomed head pain is also considered an important diagnostic criterion of cervicogenic headache.\(^{40-42}\)

The high incidence of temporary reproduction of accustomed head pain in migraineurs and TTH patients during palpation of the upper cervical spine (section 5.2)
reinforces the importance of assessing musculoskeletal features of the upper cervical spine\(^4^5\) - notably the C2-3 zygapophyseal and atlanto occipital segments - in patients presenting with TTH and migrainous symptoms. This, in turn, potentially provides an alternative treatment option for those primary headache patients in whom headache referral occurs during examination of the upper cervical spinal segments.

However, controversy surrounds the interpretation of temporary reproduction of head pain as a diagnostic criterion of cervicogenic headache, for this also occurs in primary headache i.e., reproduction in this manner is not unique to cervicogenic headache.

Although the pathophysiology of primary headache remains unclear,\(^4^6\) the assumption that C1-3 afferents are merely a bystander in primary headache\(^4^7-4^9\) must now be seriously questioned. It seems reasonable that the opposite perspective be considered i.e., manual cervical reproduction of accustomed head pain in primary headache could suggest that C1-3 afferents play a pivotal role in the pathophysiology of primary headache. In our second study (section 6.2) we sought to investigate this phenomenon further by exploring the relationship between manual cervical referral and lessening of accustomed head pain in migraine, and its effect on trigeminal nociceptive processing. Migraine is characterised by an interictal habituation deficit of R2 nBR.\(^5^0-5^4\) Our finding of concomitant lessening of referred pain and cervical tenderness with increased latencies and decreased AUC of R2 nBR, mirrors earlier findings of the effects of drug interventions on R2 nBR in migraineurs. These ictal studies\(^5^5,5^6\) demonstrated increased R2 nBR latencies and decreased R2 nBR AUC in migraine patients following successful administration of acetylsalicylic acid or oral zolmitriptan.
To our knowledge, this is the first time that manual cervical intervention has been shown to influence trigeminal nociceptive neurotransmission.

Taken together, these results support the hypothesis that C1-3 afferent inputs contribute to headache in migraine; and that manual cervical referral and resolution in migraineurs is more than a reflection of convergence of C1-3 afferents on trigeminal nuclei. That is, hyperexcitability of nociceptive second-order neurons in the TCN could result from noxious afferent information from dysfunctional spinal segments, thereby increasing sensitivity to subclinical afferent information from the trigeminal field.

Therefore, whilst interpretation of temporary reproduction of customary head pain remains contentious, perhaps a more convincing (than temporary reproduction) diagnostic criterion of cervical relevance could be ‘reproduction and resolution’ of customary head pain. Furthermore, study 2 (section 6.2) demonstrates that manual modulation of C1-3 afferents may be of potential benefit in migraine patients in whom manual cervical referral and resolution of accustomed head pain occurs.

Another interesting finding in study 1 (section 5.2) with potential clinical implications was that in every participant with head pain referral, examination of both the atlanto occipital and C2-3 segments reproduced their usual head pain. This has important ramifications, because this indicates that when the C2-3 zygapophyseal joint is symptomatic, the atlanto occipital joint will also be involved. Confirmation of cervical afferent involvement in headache requires at least 90 percent resolution of head pain subsequent to anaesthetic blocks of a cervical structure or its nerve supply.\textsuperscript{41,57} According to established guidelines, in the event of partial resolution, anaethetising spinal segments adjacent to C2-3 should alleviate all of the pain.\textsuperscript{57} Whilst the C1-2
segment has been implicated in head pain referral\textsuperscript{58,59} and headache,\textsuperscript{60} another study\textsuperscript{61} in symptomatic subjects suggests minimal involvement of C1-2. The result of the second study (section 5.2) suggests that the atlanto occipital segment should be investigated as a potential source of pain.

‘Whiplash’ is defined as a (traumatic cervical) musculoskeletal event.\textsuperscript{62} All studies incriminating the C2-3 zygapophyseal joint as a source of headache have involved patients with a history of trauma.\textsuperscript{61,63-65} Therefore, it seems plausible that C1-3 (notably the third occipital nerve) afferents are instrumental in the development of CWAH. Furthermore, the symptomatic profile of CWAH resembles various forms of primary headache, for example chronic tension-type headache, chronic or transformed migraine, or cluster headache,\textsuperscript{66-72} and neck pain often accompanies the most prevalent primary headaches.\textsuperscript{68} Therefore, CWAH may share a common pathophysiology with primary headache syndromes.\textsuperscript{69-71} As central sensitization is one of the mechanisms leading to chronicity of headache,\textsuperscript{67,73-76} we investigated this possibility in our third study (section 7.2).

The results of our study not only confirmed previous studies demonstrating common symptomatic profiles, but also identified sensory hyperalgesia, photophobia, and delayed habituation of R2 nBR in the CWAH group. These features are consistent with central sensitization and are comparable to primary headache conditions.

Whilst the mechanisms underlying sensory hypersensitivity, photophobia and altered trigeminal nociception remain unclear, peripheral, spinal, and supraspinal involvement has been proposed.\textsuperscript{77-79} However, consistent with upper cervical musculoskeletal involvement in the ‘whiplash’ mechanism and the substantial evidence
implicating the cervical zygapophyseal joints, it seems logical that a peripheral (C1-3) mechanism is responsible for central hyperexcitability. This is reinforced by concomitant modifications of neuronal excitability in the spinal cord with ongoing peripheral nociception. Furthermore, a recent study has demonstrated significant moderation of recognised signs of central sensitization in association with improved cervical movement.

Our findings strengthen the hypothesis that CWAH - headache that resembles primary headache - could be maintained by peripheral nociceptive input. In turn, shared symptomatic profiles, clinical and neurophysiological (R2) modifications support the role of C1-3 afferents in primary headache.

Taken together, the findings of this thesis reinforce a sensitising role of the upper cervical afferents on the TCN in primary headache. In addition, from a clinical perspective, the findings also imply that in those primary headache patients in whom manual cervical examination refers accustomed head pain, cervical intervention comprising sustained reproduction and resolution of head pain, is of potential benefit.
References


