Understanding Migraine

Maria Eliza Ruiz Aguila

A thesis submitted in fulfilment of the

requirements for the degree of

Doctor of Philosophy

Faculty of Health Sciences

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Candidate's statement

I, **Maria Eliza Ruiz Aguila**, hereby declare that this submission is my own work and that it contains no material previously published or written by another person except where acknowledged in the text. Nor does it contain material which has been accepted for the award of another degree.

I, **Maria Eliza Ruiz Aguila,** understand that if I am awarded a higher degree for mythesis entitled "Understanding Migraine" being lodged herewith for examination, the thesis will be lodged in The University of Sydney library and be available immediately for use. I agree that the University Librarian (or in the case of a department, the Head of the Department) may supply a photocopy or microform of the thesis to an individual for research or study or to a library.

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Maria Eliza Ruiz Aguila

31 March 2017

Supervisor's statement

As primary supervisor of **Maria Eliza Ruiz Aguila**'s doctoral work, I certify that Iconsider her thesis "Understanding Migraine" in fulfilment of the requirements for the degree of Doctor of Philosophy (Health Sciences) is in a form ready for examination.

Primary Supervisor:

(Signed)

Dr Trudy Rebbeck

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31 March 2017

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I dedicate this thesis to my family. They have been my inspiration to always strive to be a better person for others. Their confidence in me and emotional and spiritual support strengthened my determination through the last four years.

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Abstract

The aim of this thesis was to better characterise migraine through more detailed investigation of selected headache-related factors and to compare these factors with those seen in other commonly occurring recurrent headaches. The factors investigated in this thesis were neurochemical profile; cervical musculoskeletal impairments; and patient experience, represented by pain and disability characteristics, emotional state and other personal factors.

This thesis had six objectives: first, to describe how headaches are defined in clinical trials; second, to compare levels of brain neurochemicals in migraine to controls; third, to explore the relationship between brain neurochemicals and relevant disease characteristics of migraine; fourth, to characterise cervical musculoskeletal impairments and patient experience in migraine compared to non-migraine headaches and controls; fifth, to characterise the six-month clinical course of migraine and non-migraine headaches and the factors associated with the clinical course; and lastly, to examine changes in disability over six months in migraine and non-migraine headaches.

To set the stage for characterising migraine and comparing it with non-migraine headaches including tension-type headache (TTH) and cervicogenic headache (CGH), it was first necessary to determine how these headaches were defined in clinical trials. Whilstthe International Classification of Headache Disorders (ICHD) has been widely considered the reference standard for classification and diagnosis of headaches, the extent of its application in research wasunknown.In Chapter Two, a systematic review was conducted with the aim of exploringand describingthe definitions of study populations in clinical trials of frequent recurrent headaches including TTH, CGH and cluster headache. Data extracted from each

study which defined the study population included the ICHD diagnostic criteria as reported in theeligibility criteria and baseline characteristics of participants. This review demonstratedthat there was general adherence (205 out of 229 studies, 89.5%) to the ICHD criteria in defining study populations. However, whilst study populations were diagnosed mostly through interview, clinical examination and diary entry, over half of all studies (127/229, 55.5%) did not specify the method used to define the study population. Furthermore, reporting of inclusion criteria differed between headache types: pain intensity was most commonly reported for migraine and tension-type headache studies (n = 123, 66.1% and n = 21, 67.7%, respectively), episode frequency for cluster headache studies (n = 5, 71.4%), and neck-related pain for cervicogenic headache studies (n = 3, 60%). Few studies described the extent to which study populations demonstrated ICHD features at baseline. The findings of Chapter Two provide insight into applicability of results of clinical trials to clinical populations and highlight the need for detailed reporting of participant selection in research.

The levels of brain neurochemicals in migraine and the relationship between neurochemicals and clinicalcharacteristics were explored ina case-control study (Chapters Three and Four). Twenty individuals withmigraine and 20 age- and gender-matched controls were recruited. In Chapter Three, the levels of neurochemicals, particularly gamma-aminobutyric acid (GABA), were comparedbetween individuals with migraine and controls using proton magnetic resonance spectroscopy (^{1}H-MRS). Usingaspecialised technique called Mescher-Garwood point resolved spectroscopy, two significantfindings were demonstrated. First, individuals with migrainehad higher GABA levels[median (IQR)1.41 (1.31–1.50)institutional units] compared to age- and gender-matched controls [1.18 (1.12–1.35)institutional units, p = 0.002]. Second, brain GABA levels hadgood diagnostic accuracy in classifying individuals as

having migraine [area under the curve = 0.84 (95% confidence interval, CI, 0.71 to0.96), $p<$ 0.001]. Specifically, brain GABA levels of 1.30 institutional units or higher had a positive likelihood ratio of +2.67 to indicate migraine, with a sensitivity of 84.2% and specificity of 68.4%. These findings imply a putative role of GABA in the pathophysiology of migraine and suggest the potential of GABA as a biomarker for migraine.

In Chapter Four, the process of validating GABA as a migraine biomarker was continued.In this chapter,the association between brain GABA levels and clinical characteristics,including pain, central sensitisation symptoms, emotional state, and headache-related disability, in individuals with migraine were explored in a case-control design.Fair positive associations were found between GABA levels and pain scores ($\rho = .47$, $p = 0.04$) and between GABA levels and symptoms of central sensitisation ($\rho = .48$, $p = 0.03$). GABA levels were not associated with headache history, frequency, duration or intensity, with symptoms of emotional state, nor with levels of disability ($p> 0.05$).These findings corroborate the role of GABA in migraine pathophysiology and its potential as a biomarker. These findings also provide preliminary evidence for the usefulness of measuring pain and central sensitisation in characterising migraine.

To characterise cervical musculoskeletal impairments and patient experience in different headache types, we conducted a cross-sectional study in Chapter Five. The aim of this study was to compare the prevalence and severity of these factors between migraine and non-migraine headaches. Forty people with migraine, 45 people with non-migraine headaches (TTH and CGH), and 40 controls participated. Fewer participants in the migraine group [n=4 (10%)] had cervical articular impairment compared to the non-migraine group [n=26 (58%); $p < 0.001$].Further, migraine and non-migraine groups did not differ on cervical muscle

impairment measures. Participants in the migraine group[median (IQR) 7.0 (6.0–7.0)]had more intense pain (numerical rating scale 0–10)than non-migraine[5.0 (4.0–7.0)p = 0.009]. Similarly,the migraine group [43(31–53) out of 90]had higher disability scoreson Headache Disability Questionnairethan the non-migraine group [27 (20–42); p = 0.006].Additionally, a combination of the following variableshad 80.0% sensitivity and 75.6% specificity in identifying migraine: no pain on manual examination of the cervical spine, less change in deep cervical extensors thickness during contraction measured using real-time ultrasound imaging, less frequent headaches, and higher disability scores. Thus Chapter Five presents new evidence that a combination of tests can differentiate migraine from non-migraine headaches.

In Chapter Six, we followed the same participants from the cross-sectional studyover 6 months in a longitudinal cohort design.The aim of this study was to characterisemigraine, based on its clinical courseover 6 months. A secondary aim was to examine the extent to which the clinical course was associated with demographic and headache characteristics, cervical musculoskeletal impairments, and other personal factors.Participants underwent physical examination of cervical musculoskeletal impairments at baseline, completed an online diary daily for 6 months, and self-report questionnaires at baseline, 1, 3 and 6 months after enrolment. Headache frequency, intensity and activity interference varied from month-to-month for all headache types.However, day-to-day variability in headache intensity and activity interference differed between migraine and non-migraine headaches, with greater volatility demonstrated in migraine. A multifactorial model comprising migraine headache group, receiving physical treatment, pain on manual examination of the upper cervical joints, higher scores on disability questionnaires, and lower level of physical activity explained 27.7% of the variation in disability at 3 months (p = 0.040). Likewise, a multifactorial model

comprising headache group, age, headache intensity, activity interference, pain on manual examination of the upper cervical joints, disability scores and level of physical activity explained 32.3 % of the variation in disability at 6 months (p = 0.031). Of these factors, pain on manual examination of the upper cervical joints increased the odds of non-improvement in disability by nearly 6 times [odds ratio (95% CI) = 5.58 (1.14 to 27.42); p = 0.034]. These results therefore suggest that the clinical course of migraine is more volatile than non-migraine headaches and that factorsinfluencing this clinical course include headache features, cervical joint dysfunction, disability and physical activity.

The final objective of examining short- to medium-term changes in disability in different headachetypes was investigated inChapter Seven.The internal responsiveness of four commonlyused questionnaires was evaluated by calculating effect size, and external responsiveness was calculated using receiver operating characteristic curve analysis.The Headache Impact Test-6 and Headache Disability Questionnaire were the most responsive questionnaires for individuals with both migraine and non-migraine headaches. At short-term (3 months), effect sizes (84% CI) ranged from 0.31 (0.07 to 0.56) to 0.47 (0.11 to 0.82), while at medium-term (6 months), effect sizes ranged from 0.40 (0.06 to 0.74) to 0.60 (0.26 to 0.94). Headache Disability Questionnaire generally had the greatest external responsiveness to change in headache frequency at both short- and medium-term [areas under the curve (95% CI) 0.52 (0.32 to0.72) to 0.69 (0.49 to 0.89). These findings add to the evidence presented in Chapter Four by demonstrating that the HIT 6 and the HDQ are usefulquestionnaires to use in clinical practice.

Collectively, this thesis provides deeperinformation regardingthe nature and characteristics of migraine compared with non-migraine headaches, including TTH and CGH.This thesis has

established the potential of GABA as a biomarker for migraine, and thus implies the possible role of GABA in the disease process. In addition to exploring the neurochemical profile, this thesis has also characterised migraine according to cervical musculoskeletal impairments and patient experience embodying disability, pain, central sensitisation, and other personal factors. The implications for clinical practice are to assess cervical musculoskeletal impairments and patient experience to facilitate diagnosis and prognostication, and to educate patients on the nature of their headaches. Findings from the thesis may also be used by guideline developers, providing stimulus for further discussions regarding the definition of migraine and the reporting of participant selection criteria, with reference to this definition, in clinical trials. Future research directions are identified in validating GABA as a biomarker for migraine and elucidating its pathophysiology. By characterising migraine more fully, findings from this thesis will inform the development of effective treatments that possibly could be targeted at GABA or at the clinical characteristics found to be present in migraine. Ultimately this should achieve better health outcomes for people with migraine and other headaches.

Table of contents

Thesis structure

This thesis is structured as a thesis by publication, comprising chapters that can be read independently. The University of Sydney accepts papers that have been published, accepted for publication or submitted for publication written during the candidature to be included in the thesis. Thus Chapters Two, Three and Four are presented in their versions accepted for publication in refereed journals. Links to the publisher's versions are provided on the title pages of these chapters. Chapter Six is presented in its peer reviewed version accepted for publication with revisions. Chapters Five and Seven are presented in the format following guidelines of the refereed journals to which they were submitted for publication. Because Chapters Two to Seven appear in journal publication format, each of these chapters contains its own abstract, introduction, methods, results, discussion, conclusion, and reference list. Similarly, Chapters One and Eight each has its own reference list. Appendices for specific chapters appear at the end of the thesis.

The aims of this thesis can be found in the abstract, Chapter One and Chapter Eight. Chapter One serves as the introductory chapter for the thesis and therefore presents concepts related to Chapters Two to Seven. Chapter Eight serves as the concluding chapter and summarises the findings and their implications to headache definitions, clinical practice and future research.

The studies presented in Chapters Two to Seven were granted ethics approval by The University of Sydney Human Research Ethics Committee.

Please note that the table of contents is interactive. Click on either words or the page number to jump to a particular section.

Publications, research dissemination and awards

Parts of the work presented in this thesis have been published and /or presented.

Published peer-reviewed papers

Aguila ME, Rebbeck T, Mendoza KG, De La Peña MG, Leaver AM. Definitions and participant characteristics of frequent recurrent headache types in clinical trials: A systematic review. *Cephalalgia*. Epub 2017 Apr 25. doi: 10.1177/0333102417706974

Aguila ME, Rebbeck T, Leaver AM, Lagopoulos J, Brennan PC, Hübscher M, ,Refshauge KM. The association between clinical characteristics of migraine and brain GABA levels: An exploratory study. *J Pain*. 2016; 17:1058–67. doi:10.1016/j.jpain.2016.06.008

Aguila ME, Lagopoulos J, Leaver AM, Rebbeck T, Hübscher M, Brennan PC, Refshauge KM. Elevated levels of GABA+ in migraine detected using ^{1}H-MRS. *NMR Biomed*. 2015; 28:890–7. doi: 10.1002/nbm.3321

Paper accepted for publication

Aguila ME, Rebbeck T, Hau SA, Ali K, Pope A, Ng K, Leaver AM. Six-month clinical course and factors associated with non-improvement in migraine and non-migraine headaches. *Cephalalgia* (accepted with revision).

Papers submitted for publication

Aguila ME, Leaver AM, Hau SA, Ali K, Ng K, Rebbeck T. Characterizing cervical musculoskeletal impairments and patient experience in migraine as distinguished from non-migraine headaches. *J Headache Pain* (submitted).

Aguila ME, Leaver AM, Ng K, Rebbeck T. Responsiveness of disability questionnaires in migraine and non-migraine headaches. *Qual Life Res* (submitted).

Published abstracts / Conference proceedings

Aguila ME, Rebbeck T, Leaver AM, Lagopoulos J, Brennan PC, Hübscher M, Refshauge KM. Pain and self-reported central sensitisation symptoms are associated with brain gamma-aminobutyric levels in migraine: Insights for physiotherapy assessment. Conference abstract e-book of Connect Physiotherapy Conference 2015: Australian Physiotherapy Association Conference 2015; 2015 Oct 3–6; Gold Coast, QLD (Australia). p. 3.

Aguila ME, Leaver A, Rebbeck T, Lagopoulos J, Brennan P, Hübscher M, Refshauge K. Clinical characteristics associated with perceived disability and GABA level in adults with migraine: Insights for physiotherapy assessment [abstract]. *Physiotherapy*.(Special Issue for World Confederation for Physical Therapy Congress 2015) 2015;101:e37–8.

Aguila ME, Lagopoulos J, Leaver AM, Rebbeck T, Hübscher M, Brennan PC, Refshauge KM. Elevated GABA level in occipital region in migraine detected using proton magnetic resonance spectroscopy. Conference handbook of the Australian Pain Society 34th Annual Scientific Meeting; 2014 Apr 13–16; Hobart, TAS (Australia). p. 77.

Conference presentations: Podium

Distinguishing migraine from non-migraine headaches based on pain, disability and neck impairments. 2017 Australian Pain Society 37th Annual Scientific Meeting. 9–12 April 2017, Adelaide, SA, Australia.

Pain and self-reported central sensitisation symptoms are associated with brain gamma-aminobutyric levels in migraine: Insights for physiotherapy assessment. Australian Physiotherapy Association Conference 2015. 3–6 October 2015, Gold Coast, QLD, Australia.

Clinical characteristics associated with GABA level in adults with migraine: What's next? Masterclass Symposium 2015 (organised by the Australian Specialist Physiotherapy Education). 1 August 2015, Sydney, NSW, Australia.

Clinical characteristics associated with perceived disability and GABA level in adults with migraine: Insights for physiotherapy assessment. WCPT Congress. 1–4 May 2015, Singapore.

Exploratory study of the association between clinical characteristics of migraine and levels of gamma-aminobutyric acid. FHS Biennial HDR Conference (Imag!ne.U – Creating the Future). 3–5 November 2014, Sydney, NSW, Australia.

Understanding migraine using proton magnetic resonance spectroscopy. APA Symposium ACT 2014 Research Symposium. 23 August 2014, Canberra, ACT, Australia.

Elevated GABA level in occipital region in migraine detected using proton magnetic resonance spectroscopy. Australian Pain Society's 34th Annual Scientific Meeting. 13–16 April 2014, Hobart, TAS, Australia.

Can neurochemicals distinguish headache types? Masterclass Symposium 2013 organised by the Australian Specialist Physiotherapy Education. 29 June, 2013, Sydney, NSW, Australia.

Conference presentations: Poster

Levels of GABA in the brain have good diagnostic accuracy for migraine. SPR:ING (Sydney Pain Researchers: Introducing the Next Generation) 2015 Symposium, 15 December 2015, Sydney, NSW, Australia.

Occipital concentration of GABA has good diagnostic accuracy for migraine. 15th World Congress on Pain. 6–11 October 2014, Buenos Aires, Argentina.

Other forms of research dissemination

- Media spokesperson for the study on GABA levels in migraine (Chapter Three in this thesis). The study was released to the media in October 2015, gaining an estimated audience reach of more than 2 million people, with the biggest audience share from television. A summary from The University of Sydney media office can be found in Appendix 6.

- Cover art for The Journal of Pain Volume 17, Issue 10 (October 2016) (http://www.jpain.org/issue/S1526-5900(16)X0011-9). The cover illustration. The cover illustration was a stylised image from an output of the editing process of GABA from the study in Chapter Four published in the same issue: [Aguila ME, Rebbeck T, Leaver AM, Lagopoulos J, Brennan PC, Hübscher M,Refshauge KM. The association between clinical characteristics of migraine and brain GABA levels: An exploratory study. *J Pain.* 2016; 17:1058–67.doi:10.1016/j.jpain.2016.06.008]. A copy of the cover art can be found in Appendix 7.

Invited presentations

The role of GABA in primary headaches. Primary headache in our hands: A bottom up perspective (a symposium organised by the Watson Headache Institute), 30–31 July 2016, Sydney, NSW, Australia.

How to create an online survey using Research Electronic Data Capture (REDCap). Workshop facilitated at The University of Sydney Faculty of Health Sciences, 17 March 2016, Sydney, NSW, Australia.

How to create an online survey using Research Electronic Data Capture (REDCap). Workshop facilitated during the HDR Bazaar at The University of Sydney Faculty of Health Sciences, 2 November 2015. Sydney, NSW, Australia.

What is a clinically worthwhile treatment effect? Workshop facilitated during the Philippine Physical Therapy Association-University of Sydney Collaboration Continuing Professional Development Activity. 29 August 2015, Manila, Philippines.

Role of physical therapy in headache management. Philippine Physical Therapy Association-University of Sydney Collaboration Continuing Professional Development Activity. 29 August 2015, Manila, Philippines.

Using Research Electronic Data Capture (REDCap) as a data management tool: What, why, how. Workshop at The University of Sydney Faculty of Health Sciences, 22 July 2015. Sydney, NSW, Australia.

Awards and grants

The candidate received the following awards and grants during her candidature:

- University of Sydney International Scholarship
- UP Research Dissemination Grant awarded by the University of the Philippines to present at the Australian Physiotherapy Association Conference 2015 in Gold Coast, QLD, Australia, 3–6 October 2015
- IASP Financial Aid Award conferred by the International Association for the Study of Pain to attend the 15th World Congress on Pain in Buenos Aires, Argentina, 6–11 October 2014

- Finalist, University of Sydney 3-Minute Thesis Competition, Sydney, Australia, 20 August 2014
- Winner, Three-Minute Thesis Competition, Faculty of Health Sciences, (Faculty of Health Sciences Dean's Research Scholar Award) The University of Sydney, Sydney, Australia, 26 June 2014
- PhD Student Travel Grant awarded by the Australian Pain Society to attend its 34th Annual Scientific Meeting held in Hobart, TAS from 13–16 April 2014

Other grants received

- Member of HDR Student Executive Group awarded a Healthy Sydney University student scholarship for 2017 to implement HDR Student Stepathon, aimed to support student-led initiatives, such as the, to promote wellbeing
- Member of HDR Student Executive Group awarded an HDR+ Students Grant for 2015 to implement the HDR Bazaar, aimed to enhance the academic experience and outcomes of higher degree by research programs
- Member of the team awarded a Sydney Southeast Asia Centre Research Capacity Building Grant in 2015 aimed to improve productivity in clinical rehabilitation research through partnerships between Australia and the Philippines

Additional work by the author not forming part of this thesis

Trott, CA, Aguila, MER, Leaver, AM. The clinical significance of immediate symptom responses to manual therapy treatment for neck pain: Observational secondary data analysis of a randomized trial. *Man Ther*. 2014;19:549–54.doi: 10.1016/j.math.2014.05.011

CHAPTER ONE

Current Understanding of Migraine and

Recurrent Non-Migraine Neck-Related Headaches

This is Meg. She's that girl who makes plans with friends then cancels at the last minute, giving the migraine excuse. "Migraine Meggy", she'd be teased, but then her friends realised it really wasn't funny!

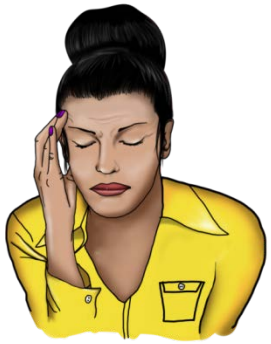

Illustration by David Val Christian B. Agoncillo, 2014
forpresentations related to studies in this thesis

Meg's friends thought that migraine was just a bad headache; but it's more than that. Sure, Meg gets headaches –severe, throbbing headaches that are unrelenting for a day or two each time. But aside from headaches, Meg's migraines make her vomit and intolerant to light, so much so that she had to install block out curtains. During her migraine attacks, Meg lies still in her dark room, debilitated and frustrated, waiting for her symptoms to pass or for science to find a cure.

[Excerpt from Three-Minute Thesis Presentation (3MT®) by Maria Eliza Ruiz Aguila; Winner,Faculty of Health Sciences 3MT® 2014]

The more we know about characteristics of frequently occurring headaches, the more Meg and her friends might understand these conditions. With better understanding, we might also move closer to effective targeted headache treatments. Thus the aim of this thesis was to further characterise migraine and other headaches that most frequently present in primary care namely tension type headache and cervicogenic headache. This was achieved by firstly exploring conventions in classification and diagnosis. The next step was an exploration of the neurochemical profile of migraine, which yielded new findings about migraine biochemistry. The final step was to investigate cervical musculoskeletal impairments, clinical characteristics and elements of a patient's experience that characterise migraine and distinguish it from other headache types.

This introductory chapter provides a background on the current understanding of migraine and other frequently presenting recurrent headaches. In the first section, headaches, in general, and migraine, tension-type headache and cervicogenic headache, in particular, are defined according to the most accepted classification system, the International Classification of Headache Disorders. These definitions directly influence prevalence estimates of these recurrent neck-related headaches. Therefore the next section discusses the prevalence and associated burden of these headaches. Next, an overview of the clinical features and course of these headaches is discussed, followed by a depiction of cervical musculoskeletal impairments which may be common to migraine, tension-type headache and cervicogenic headache. Pathophysiologic mechanisms which may relate with the clinical features and course of migraine, tension-type headache and cervicogenic headache are then briefly described. This section on pathophysiology also includes a summary of extant evidence on neurochemical profile in migraine. The current understanding of the clinical features and pathophysiology of these recurrent headaches directly influences their assessment. Therefore the previous sections set the stage for the subsequent section on assessment of these headaches. To broaden the perspective on the pain experience of patients with migraine, tension-type headache and cervicogenic headache, a section is provided describing factors that may influence patient experience, and the importance of measuring these factors and the impact of headache on patients' lives.

Current understanding of migraine and recurrent non-migraine neck-related headaches

1.1. Headache definition, classification and diagnosis

The term “headache” refers to a symptom of many disorders and is characterised as either a painful or nonpainful discomfort of the entire head, including the face and upper neck (1). “Headache” may also refer to an independent disorder characterised by headache and other associated symptoms. Because the term “headache” may be used inconsistently, a consensus on headache terminology is necessary to facilitate communication in research and clinical practice.

The first demonstration of a consensus in headache terminology was with the publication of a classification system for headache disorders in 1962 (1). This classification system was based on aetiology of headaches and comprised brief definitions of a limited number of headache types. Headaches were then classified as “vascular headache” or “muscle-contraction” headache, and so forth. This system eventually was perceived to be inadequate and confusing (2). Headache practitioners acknowledged the need for a better classification system that would operationally define headache types. Thus the International Classification of Headache Disorders (ICHD) emerged (3). ICHD was the first classification system to be accepted internationally as the uniform approach to the classification and diagnosis of headache disorders in clinical practice and research (4). The operational definitions in ICHD wereoriginally based on clinical descriptions of headache attacks and mostly based on expert opinion, in the absence of published evidence at that time. Increased evidence from clinical

trials and longitudinal and epidemiological studies of, genetics, neuroimaging, and pathophysiology from have since contributed to the evolution of ICHD.

The ICHD, now its third edition, beta version (ICHD-3 beta),is the reference standard for headache classification and diagnosis (5, 6). ICHD reflects research evidence on which headache types should be classified, which rules to apply to diagnose the headache types, and how to organise these headache types. The current ICHD divides headaches into three groups; primary headache, secondary headache and other headaches not better classified as primary or secondary headache. This third group includes painful cranial neuropathies and other facial pain. Across the three parts of ICHD are 14 main headache types, each defined operationally with key clinical criteria required for its diagnosis. Primary headaches are those whose aetiologies are unknown and which exist independent from any other medical condition (7), such as migraine, tension-type headache (TTH) and cluster headache. In contrast, secondary headaches are those whose aetiologies are known, attributed to another medical disorder, such as headaches due to trauma, vascular disorder, infection, and disorder of the neck (such as cervicogenic headache, CGH). Thus primary headaches, like migraine and TTH, are classified and diagnosed based on headache features whilst secondary headaches, such as CGH are classified and diagnosed based on headache features, the presence of the causative disorder and evidence for causation of the headache by the causative disorder (8).

Definitions for migraine and non-migraine headaches, such as TTH and CGH, have been refined over the three editions of the ICHD. Whilst the diagnostic criteria for these headaches have not fundamentally changed from the first to the third editions of ICHD, these criteria

have been revised to reflect current evidence and to improve applicability of the criteria (9). The current diagnostic criteria for migraine, TTH and CGH are presented in Table 1.

The diagnostic criteria in Table 1 specifying the minimum number of attacks or episodes for classification of migraine, TTH and CGH connote the recurrent nature of these headaches. The diagnostic criteria also illustrate how TTH and CGH are relatively "featureless" compared to migraine, as many of the diagnostic features of TTH and CGH refer to absence of symptoms (10).

Compared to the clear definitions of migraine and TTH since the first ICHD, it was only since the second ICHD that CGH has been recognised as a discrete headache. Prior to this, ICHD referred to "headache…associated with disorder of …neck…" (3). This was despite the introduction of the term "cervicogenic headache" by Sjaastad and colleagues in 1983 (11) to refer to headaches provoked by head or neck movements. The non-use of the term "cervicogenic headache" as a headache classification in the first ICHD reflected the view that CGH was not considered sufficiently proven in the absence of a neck disorder (12). Aside from the ICHD definition, an even more specific definition of CGH is provided by the Cervicogenic Headache International Study Group (CHISG) (13). A comparison between the ICHD and the CHISG definitions of CGH is presented in Table 2. The required criteria for diagnosis differ between the two classification systems. For example, ICHD required clinical evidence of cervical lesion whilst the CHISG required diagnostic blockade. The CHISG criteria also lists other characteristics of less importance for diagnosis which are not included in the ICHD criteria.

Table 1. Diagnostic criteria for migraine, tension-type headache and cervicogenic headache

The International Classification of Headache Disorders, 3rd edition (beta version)
Cephalalgia. 2013;33:629–-808.

Migraine without aura

Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
Headache has at least two of the following characteristics:

- Unilateral location
- Pulsating quality
- Moderate or severe pain intensity
- Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

During headache at least one of the following

- Nausea and/or vomiting
- Photophobia and phonophobia

At least 5 attacks fulfilling the above criteria

Migraine with aura

Aura consisting of at least one of the following fully reversible aura symptoms:

- Visual
- Speech and/or language
- Motor
- Brainstem
- Retinal

At least two of the following:

- At least one aura symptom spreads gradually over ≥ 5minutes, and/or two or more symptoms occur in succession
- Each aura symptom lasts 5–60 minutes
- The aura is accompanied, or followed within 60 minutes, by headache

At least 2 attacks fulfilling the above criteria

Infrequent episodic tension-type headache

Headache lasting from 30 minutes to 7 days
Headache has at least two of the following characteristics

- Bilateral location
- Pressing or tightening (non-pulsating) quality
- Mild or moderate intensity
- Not aggravated by routine physical activity such as walking or climbing stairs

Both of the following:

- No nausea or vomiting
- No more than one of photophobia or phonophobia

At least 10 episodes fulfilling the above criteria

Frequent episodic tension-type headache

Similar criteria as infrequent episodic tension-type headache except
At least 10 episodes of headache occurring on 1–14 days per month on average for >3 months (≥ 12 and <180 days per year)

Chronic tension-type headache

Similar criteria as episodic tension-type headache except
Headache occurring on ≥15 days per month on average for >3 months (≥180 days per year)

Cervicogenic headache

Clinical, laboratory and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck known to be able to cause of headache
Evidence of causation demonstrated by at least two of the following:

- Headache has developed in temporal relation to the onset of the cervical disorder or appearance of the lesion
- Headache has significantly improved or resolved in parallel with improvement in or resolution of the cervical disorder or lesion
- Cervical range of motion is reduced and headache is made significantly worse by provocative manoeuvres
- Headache is abolished following diagnostic blockade of cervical structure or its nerve supply

Table 2. Comparison of diagnostic criteria for cervicogenic headache

The International Classification of Headache Disorders, 3rd edition (beta version) *Cephalalgia*. 2013;33:629–808.	Diagnostic Criteria	Cervicogenic Headache International Study Group *Headache.* 1998;38(6):442–445.
Required criterion: Clinical, laboratory and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck known to be able to cause of headache	Clinical, laboratory and/or imaging evidence of a cervical lesion	
At least two of the following: • Headache has developed in temporal relation to the onset of the cervical disorder or appearance of the lesion • Headache has significantly improved or resolved in parallel with improvement in or resolution of the cervical disorder or lesion • Cervical range of motion is reduced and headache is made significantly worse by provocative manoeuvres • Headache is abolished following diagnostic blockade of cervical structure or its nerve supply	Evidence of causation of the headache by the cervical spine lesion	At least one of the following (in decreasing importance) : • Headache pain similar to the usually occurring one induced subjectively and/or iatrogenically (part of confirmatory combination of criteria) o by neck movement and/or sustained awkward head positioning,(may be the sole criterion for neck involvement), and/or o by external pressure over the upper cervical or occipital region on the symptomatic side • Restriction of cervical range of motion • Ipsilateral neck, shoulder, or arm pain of a rather vague non-radicular nature or, occasionally, arm pain of a radicular nature Evidence by diagnostic anaesthetic blockades (part of confirmatory combination of criteria)
	Unilaterality of the head pain, without sideshift	Part of confirmatory combination of criteria for scientific work
	Other characteristics that are not part of confirmatory combination of criteria	Moderate-severe, non-throbbing, and non-lancinating pain, usually starting in the neck Episodes of varying duration Fluctuation, continuous pain Only marginal effect or lack of effect of indomethacin Only marginal effect or lack of effect of ergotamine and sumatriptan Female sex Not infrequent occurrence of head or indirect neck trauma by history, usually of more than only medium severity Various attack-related phenomena, only occasionally present, and/or moderately expressed when present • Nausea • Phonophobia and photophobia • Dizziness • Ipsilateral “blurred vision” • Difficulties on swallowing • Ipsilateral oedema, mostly in the periocular area

For purposes of this thesis, study populations for migraine and non-migraine headaches (TTH and CGH) were defined using the ICHD diagnostic criteria. For CGH, ICHD was used instead of CHISG criteria for consistency with the other headache types, as ICHD lists criteria for migraine, TTH and CGH. We also could not fulfil CHISG criteria in our protocols because we did not include diagnostic blockade, which is required to confirm diagnosis using CHISG criteria.

Efforts continue toward further improving the ICHD to mirror the advancing state of evidence on headaches. Thus far, the ICHD has been a useful tool in understanding headaches and in developing and evaluating new headache treatments. The ICHD has been deemed useful to clinicians when a patient's diagnosis is uncertain, and to researchers, in selecting patients for clinical trials (4). Being internationally accepted, the ICHD represents agreement among headache practitioners in headache classification. As such, ICHD facilitates the conduct of epidemiological studies on the prevalence and disability rates of certain headache types. Consequently ICHD contributes to the appreciation of headaches as a public health concern.

Despite continuous efforts to improve the classification system, there remain challenges in its use related to the nature of the classification system itself and the nature of the headaches. First, diagnosis based on headache features as in ICHD may be challenging because symptoms may overlap between headache types (14). Further one headache type may coexist with one or more other headache types (15) which may influence the ability to detect a headache diagnosis (16). Symptom overlap or coexistence of other headaches may be the reason for at least 50% of migraine cases being misdiagnosed as other headache types, such as episodic tension-type headache (17), sinus headache or stress-related headache (18).

Second, the decision rules in the ICHD present diagnostic criteria for each headache types as a combination of clinical features. For example, diagnosis for migraine without aura requires that two criteria be met, at least two of four symptoms for one criterion be present, and at least one of two symptoms in another criterion be present (see Table 1) (8). These decision rules increase the sensitivity of the ICHD but also increases the heterogeneity of the possible clinical presentations of a particular headache diagnosis. Another criticism for such a system is its complexity may be confusing and consequently influence reliability of diagnosis (19).

Despite these challenges in headache diagnosis, the ICHD remains the most widely accepted classification system for headache diagnosis. In fact, guidelines for clinical trials of headaches recommend using the ICHD in selecting participants such that all participants fulfil the diagnostic criteria for the headache being studied (20-22). Such guidelines allow standardisation of study populations despite the complex presentations of headaches. In the clinics, however, the extent of use of ICHD for diagnosis is unknown. This may be interesting to know as the ICHD is not designed to be used for day-to-day clinical practice for obvious headache cases but only when the diagnosis is uncertain (8).Chapter Two presents the extent of application of ICHD in defining study populations in treatment efficacy trials.

Diagnosis could be improved by a better understanding of mechanisms, especially of the primary headaches. Elucidating pathophysiological mechanisms of migraine and TTH, for example, could add objective criteria to the classification system. These could include biological markers, presented in ChaptersThree and Four,for migraine. As well, other clinical features beyond those currently listed in the ICHD diagnostic criteria could be explored to improve diagnosis and improve understanding of headaches. Thus we compared clinical features between headache groups in Chapters Five and Six.

1.2. The prevalence of migraine and non-migraine headaches

Headaches are among the most prevalent disorders in the world. Prevalence studies estimate that half to three quarters of adults aged 18 to 65 years in the world have had a headache in the last year (23), with about half (47%) having an active headache disorder (24).Three of the most prevalent headaches are migraine and non-migraine headaches, namely TTH and CGH. Of these three, migraine and TTH are the most prevalent, affecting more than 10% of the world population (25). It is therefore not surprising that migraine, TTH and the combination of these are the top three headaches seen in primary and specialist clinics (23).

Migraine ranks seventh in global prevalence among all disorders according to the 2013 Global Burden of Disease Study, affecting nearly 850 million individuals (25). Among headaches, migraine ranks second, with a total prevalence of 10%, and 11% among adults (24). Females are two to three times as likely as males to have migraine (14). Thus the prevalence of migraine among adults is different between females (mean = 16.6%) and males (mean = 7.5%) (26). The most common age of onset of migraine is between 20 to 30 years (27). Its prevalence increases with age, peaks at around 40 years, after which the prevalence declines, especially for women (14).

TTH is more prevalent than migraine, ranking second among all disorders according to the 2013 Global Burden of Disease Study, affecting about 1.6 billion individuals (25). Unlike migraine, females are only slightly more affected by TTH than males, with a male:female ratio of 4:5 (14). Thus the prevalence of TTH among adults is also only slightly different between females (mean = 22.36%) and males (mean = 16.9%). (26) Compared to migraine,

TTH has a later age of onset between 25 and 30 years (14). Its prevalence peaks between 30 and 39, increases until 50 years, and slightly declines with age.

The third most prevalent headache seen in primary and specialist care is CGH (28). Compared to the epidemiological studies for migraine and TTH, only a few have investigated CGH. Of the few prevalence studies on CGH, most were clinic-based studies that calculated prevalence rates of CGH as defined by ICHD or the CHISG, resulting in varied prevalence estimates. In a small study using modified ICHD criteria, prevalence of CGH was estimated at 17.8% among adults with frequent headaches aged 20 to 59 years (29). Another clinic-based study among adults with idiopathic headaches (30) that used ICHD criteria (3) reported CGH prevalence to be 16.1%. Larger studies resulted in smaller prevalence estimates. For example, prevalence was estimated by Sjaastad and colleagues (31) to be 4.1% for adults aged 18 to 65 years old fulfilling the CHISG criteria (32). In the only population study of CGH prevalence to date [(33) cited in (34)], even lower prevalence estimates were reported: 0.4% using the ICHD criteria (3) and 1% applying five criteria of the CHISG (32). The varied prevalence estimates for CGH nevertheless indicates that CGH is among the most frequently seen headaches in the clinics.

1.3. The burden of migraine and non-migraine headaches

Headaches cause substantial burden on the individual and the society. On the individual level, burden arises from the pain and other symptoms associated with the headache (35). These symptoms may reduce functional ability, which may, in turn, reduce work productivity and pay. Work loss for individuals with headaches is estimated at 4.2 days per year, with 70% of

this time lost due to reduced effectiveness at work (36). This cost of headaches on work productivity and income is highlighted because headaches are more prevalent in the work productive years. For individuals with recurrent headaches, the burden caused by the headache is not only present when symptoms are active but also in between headache episodes. Individuals with headaches may need to modify their lifestyle and defer social activities in attempt to prevent another headache episode.

On the societal level, burden arises from direct treatment costs and the indirect costs of reduced work productivity. Between direct and indirect costs, direct costs are estimated to be lower because 50% of individuals with headaches worldwide do not consult health professionals (23), Therefore the burden of headaches is believed to be underestimated (14). Nevertheless, the burden due to the two most prevalent headaches, migraine and TTH, has been characterised in a number of population studies.

Migraine is the sixth most disabling condition in the world in 2013, making it the most disabling headache, based on years lived with disability (YLDs) (25). Disability calculated using YLDs considers prevalence and severity of health loss. Migraine is more disabling than TTH based on YLDs, causing more than 28 billion YLDs, compared to more than 2 million YLDs for TTH (25). A slightly different picture is presented when disability is calculated using frequency, duration of headache episode and intensity. Using this calculation, TTH was found to cause disability at least as much as, if not more than, as migraine (24). It is apparent then that migraine and TTH are the two most disabling headaches, migraine for its higher severity than TTH, and TTH, for its higher prevalence than migraine.

No epidemiologic study has focused on disability due to CGH. Yet evidence from clinic-based studies and randomised controlled trials indicates that individuals with CGH experience disability comparable with that in migraine and TTH. In a retrospective clinic-based study, 32–65% of patients with chronic and recurrent CGH perceived the impact of their headache on function and relationships to be considerable or debilitating (37). The area of function most affected in 87% of the patients was loss of productivity in paid work. The considerable disability associated with CGH was also demonstrated at baseline by participants of randomised controlled trials when measured using different patient-report questionnaires(38-41).

This thesis characterises disability in migraine (Chapter Four), how it differs from non-migraine headaches (Chapter Five), how it changes over time (Chapters Six) and its measurement using patient-report outcomes (Chapter Seven). Collectively, the studies in these chapters sought to broaden understanding of the burden of different headache types on the individual level.

1.4. Clinical presentation and course of migraine and non-migraine headaches

Headache disorders that affect most individuals at least at one point of their lives (23) are usually non-life threatening, mild or infrequent (42). In contrast, headaches that recur have varied clinical presentations that may not be fully captured in the ICHD criteria (Table 1).

1.4.1. Clinical presentation of migraine and non-migraine headaches (TTH and CGH)

1.4.1.1. Clinical presentation of migraine

Migraine presents as two main subtypes: migraine without aura and migraine with aura (8). Both subtypes may occur a few episodes in a month (i.e., episodic migraine) or as many as 15 or more days in a month (i.e., chronic migraine) (8). Migraine with aura differs from migraine without aura in that the headache in migraine with aura is preceded, accompanied or, in rare cases, followed by transient neurologic symptoms. For both migraine subtypes, the headache phases, and aura phase in the case of migraine with aura, are preceded by prodrome (or premonitory) symptoms (8, 43). The prodrome symptoms may be general, such as anorexia, neck pain or stiffness, or food cravings, or psychogenic, such as mood change, fatigue, irritability, or neurogenic, such as difficulty concentrating, repetitive yawning (44-47). Prodrome symptoms may also include those also associated with the headache phase such as nausea, photophobia, or phonophobia (46). It is estimated that as much as 86.9% of people with migraine experience these prodrome symptoms (45, 46). These symptoms may again appear after the headache phase, as postdrome (or resolution) symptoms. Other typical postdrome symptoms include weakness, lightheadedness and mild residual head discomfort (43, 48). Postdrome symptoms appear to be as prevalent as prodrome symptoms, with as much as 80% of people with migraine experiencing at least one postdrome symptom (46). Further, nausea and/or vomiting during the headache phase and aggravation of the headache by routine physical activity are considered the most characteristic symptoms of migraine without aura, distinguishing it from other headache types (49, 50).

1.4.1.2. Clinical presentation of TTH

TTH may also occur a few episodes in a month (i.e., episodic TTH) or as many as 15 or more days in a month (i.e., chronic TTH). (8). Of those features of TTH listed in Table 1, the feature 'not aggravating the headache by routine physical activity' is considered its most characteristic symptom, and that which most distinguishes it from migraine (49, 51, 52). Unlike migraine, prodrome and postdrome symptoms are believed to be not typical of TTH (53). The absence of prodrome and postdrome symptoms is consistent with the characterization of TTH as a "featureless" headache (51). However, a clinical study reported prodrome symptoms similar to those in migraine in as many as 87% of patients with episodic TTH(44). In the same study, significantly fewer patients with TTH reported general prodrome symptoms such as food craving, feeling cold, and diarrhoea than patients with migraine. The similarity in prodrome symptoms between migraine and TTH led some authors tohypothesise that these two headache types are not distinct entities and instead are the same headache from the opposite severity spectrum (54, 55). This hypothesis is discussed later in section 1.6.5. Still, similar features between migraine and TTH necessitate in-depth characterisation of these headaches to arrive at a correct diagnosis and effective treatment. Such characterisation is the focus of Chapter Five of this thesis.

Aside from TTH features listed in Table 1, another feature common to patients with TTH is increased pericranial tissue tenderness that is present during the headache phase and even between headache episodes (8). Among patients with TTH, increased tenderness [mean tenderness score 25.6 (SD 5.8) out of 48] was demonstrated in cephalic and neck muscles and the coronoid and mastoid processes (56). Pericranial tenderness is thought to increase with

headache frequency (57), although this was not replicated when data on headache frequency were prospectively collected (56).

1.4.1.3. Clinical presentation of CGH

Whilst the scientific community is in general agreement as regards the clinical presentation of migraine and TTH, the same cannot be said for CGH. Table 2 demonstrates this, with the ICHD criteria differing from the CHISG criteria on clinical features that are considered diagnostic for CGH (8, 13). Although the unilaterality of the headache that does not shift sides is a confirmatory diagnostic criterion for CGH according to the CHISG criteria but not for ICHD, this feature is recognised by ICHD as a typical presentation of CGH (8). Similarly, ICHD recognises CGH as being typically reproduced by external pressure on the cervical spine (8). Alternatively, pain radiating to the shoulder and arm, moderate, non-throbbing pain, and history of neck trauma have also been suggested as being the most characteristic associated symptoms of CGH (58).

It is therefore relevant to determine the extent to which patients demonstrate the above-named features that are believed to be characteristic of migraine non-migraine headaches, specifically TTH and CGH. Doing so would characterise these headaches better and possibly clarify their distinction. With this in mind, we determined the extent to which study populations in treatment efficacy trials demonstrated these characteristics, and other ICHD criteria, in a systematic review presented in Chapter Two. To date, no study has investigated how study populations are defined and therefore to whom evidence from the trials should apply. Chapter Two fully explores this question.

1.4.2. Overlaps and variability in clinical presentation of migraine and non-migraine headaches (TTH and CGH)

Despite the characteristic features of each headache type, migraine and common non-migraine headaches, such as TTH and CGH, may have overlapping symptoms (14). For example, characteristic features of migraine such as photophobia and aggravation of the headache by physical activity are also present in 65% and 53%, respectively, in patients with TTH (52). Other diagnostic criteria for migraine, namely headache episodes lasting 4 to72 hours, unilaterality, pulsating quality, and aggravation of headache by physical activity, were also demonstrated by patients with TTH (33%, 11%, 23%, and 17%, respectively) (59). Additionally, photophobia and phonophobia were also demonstrated in patients with TTH (18% for both symptoms) (59) and CGH (19% and 28%, respectively) (60); and nausea and vomiting were also present in CGH (up to 45.5% and 21.2%, respectively) (28). Conversely, muscle tenderness, which is typically associated with TTH, was present to a notable degree in patients with migraine (tenderness scores of 10–18 out of 24) (57). Headache provoked during passive accessory intervertebral movement examination of the cervical spine, considered diagnostic for CGH, was also present in 95% of patients with migraine and 100% of patients with TTH (61). Moreover, all three headaches may present as unilateral headache that does not shift sides (62). Despite the presence of features diagnostic for other headache types, it must be noted that patients examined in the studies cited above still fulfilled the ICHD diagnostic criteria for their respective headache types. Still, the overlapping symptoms may make diagnosis challenging in some cases.

An individual with one headache type may also present with features characteristic of one or more other headaches if these headaches coexist (63). It is estimated that 94% of individuals

with migraine have coexisting TTH (64). The coexistence between migraine and TTH has been well recognised, that it has been included in the list of chronic overlapping pain conditions by the National Institutes of Health and the United States of America Congress (65). A population study, for example, demonstrated overlap of TTH with migraine without aura in 83% of the sample and with migraine with aura in 75% of the sample (59). Similarly, CGH has been shown to coexist with migraine and/or TTH in 1.8% of a population (31).

Aside from possible overlap in features between headache types, clinical presentation of migraine, TTH and CGH may also be variable within the individual and between individuals with the same headache type (49). Individuals with the same headache type may have different clinical features considering the nature of the ICHD criteria where a combination of features is used as basis for diagnosis. Therefore, not all diagnostic features are expected to be present in individuals with a particular headache type. As well clinical presentations may vary within the same individual and still fulfil the ICHD criteria for that particular headache type. Of the three headache types, it is apparent from the classification rules in Table 1 that clinical presentations that migraine has more variable symptoms than the non-migraine headaches.

The apparent overlap of headache classifications and variability of headache features provides another important reason to improve characterisation of migraine as distinct from non-migraine headachessuch as TTH and CGH. Such characterisation of migraine was explored in Chapters Five and Six.

1.4.3. Clinical course of migraine and non-migraine headaches

1.4.3.1. Clinical course of migraine

Aside from understanding the typical clinical features of migraine and non-migraine headaches, understanding their clinical courses may also aid in characterising them better. Evidence suggests that migraine does not progress. A 12-year retrospective study showed that migraine episodes ceased in 29% of patients experiencing episodic migraine, and of those who continued to experience migraine episodes 80% reported reduced frequency and. more than 50% reported milder intensities, 1.6% developed chronic migraine (66). Similarly, a prospective study showed that headache frequency decreased by more than 25% in almost 50% of patients whilst 16% reported an increase in headache frequency by more than 25% (67).

1.4.3.2. Clinical course of TTH

Similar to migraine, evidence suggests that TTH generally does not progress (68). Population studies showed that 45 to 48% remitted into less frequent or no headaches, 16 to 75% had an unchanged frequency and 25 % progressed from episodic to chronic TTH (69, 70). Whilst TTH does not seem to progress, TTH persists throughout young adulthood(71) or possibly throughout life (72). Larger population studies are needed to know if TTH remits at some point.

Whether migraine and TTH remit or progress is predicted by non-modifiable and modifiable factors. For migraine, the most commonly cited factor in literature for progression of

migraine is high frequency, with headaches occurring 10–14 days per month having 20 times the risk for progression compared to a frequency 4 days per month (73).Persistence of chronic tension-type headache is associated with coexistence of other headaches (74), medication overuse (74, 75), older age at baseline, duration longer than 6 years (75).

Other factors associated with progression of migraine or TTH to chronic daily headaches in population studies are low level of education, arthritis, female, diabetes, previously married, obese, and white people (76). Odds ratios for these factors for headache progression were highest for low level of education [odds ratio (95% confidence interval) 3.35 (2.1 to 5.3)] and lowest for white people [0.77 (0.6 to 1.0) for non-white people compared to white people]. Of these factors, obesity was the most notable as it was also associated with five times higher risk of developing new chronic daily headache, suggesting its importance as a potential target of intervention to modify outcome in headaches (77). Conversely, remission after one year from chronic to episodic headache was associated with higher education, diabetes, non-white people, being married,and increasing age for females (78). Odds ratios for these factors for remission was highest for higher education [odds ratio (95% confidence interval) 0.21 (0.1 to 0.5) for low education level] and lowest for increasing age for females [1.04 (1.01 to 1.06)]. It is difficult to explain how diabetes could be associated with remission. Nonetheless, diabetes being a factor for both remission from and progression to chronic daily headache suggests its potential as another target of intervention in headaches. For migraine, other factors associated with remission are lower headache frequency [0.29 (0.11 to 0.75) for headaches occurring 25–31 days per month compared to 15–19 headache days per month], absence of allodynia [0.29 (0.11 to 0.75)] and non-use of preventive medications [0.41 (0.23 to 0.75) for preventive medication use] (78).

1.4.3.3. Clinical course of CGH

In contrast to the studies done on clinical course of migraine and TTH, only one study to date exclusively investigated the course of cervicogenic headache, observed in a cohort who had whiplash injury. In this study by Drottning and colleagues (79), recovery from CGH was shown to be slow, with 35% of patients still having CGH and further restrictions in cervical range of motion six years after the whiplash injury. The authors hypothesised that it may take as long as 10 years for the patients to be fully symptom-free. The trajectory of this slow recovery showed a steep drop in the initial months followed by a slow decline, without reaching full freedom from symptoms at six years. Results of this study suggest non-recovery from CGH to be associated with younger age (mean age 44 years old versus 62 in those who recovered from CGH); being female (82 % versus 71% in those who recovered). More longitudinal studies with larger sample size of participants without associated whiplash injury are needed to clarify the course of CGH. Given the trajectory of recovery shown in this study, it would be interesting to validate the short-term course in individuals with CGH. In this thesis, we investigated the six-month course of CGH and TTH compared with migraine in Chapter Six.

Less is known too about short-term clinical course of migraine. One longitudinal observational study has shown that clinical characteristics of migraine remain stable over 3 months, with a general trend toward improvement in disability (80). Additionally, improved disability had a moderate positive association with headache frequency in 3 months. Further evidence is required to build on these findings by identifying the short-term variations in headaches. Thus Chapter Six of this thesis characterises how migraine changes over 6 months.

1.5. Cervical musculoskeletal impairments in migraine and non-migraine headaches

1.5.1. Rationale for considering cervical musculoskeletal impairments in migraine and non-migraine headaches such as TTH and CGH

An understanding of impairments that are associated with particular headache types may help further elucidate their pathophysiologic mechanisms. Among impairments that can be present in both migraine and non-migraine headaches are those that affect the cervical musculoskeletal system. This is due to the bidirectional relationship between nociceptive input from the upper cervical spine and the brainstem, resulting from the convergence of trigeminal and cervical afferents on to common neurons in the TCC. Cervical musculoskeletal impairments may include neck pain and tenderness, deviations from normal cervical articular movement and function and deviation from normal cervical muscle structure and function.

The proposed role of cervical musculoskeletal impairments in TTH is illustrated by its former descriptor ‘muscle contraction headache’. This term reflects the hypothesised origin of TTH and the involvement of the muscles in the head and neck (8).Similarly, CGH is recognised as a neck-related headache and its classification requires association of neck-related symptoms and signs of impairments (8). Further studies characterising the nature of cervical musculoskeletal impairments in migraine and non-migraine headaches are needed to determine any similarity and difference between these headaches.

1.5.2. Neck pain

Understanding the nature of neck pain in headaches is particularly important because of the widespread global prevalence of and disability due to neck pain itself (25).Neck pain has been shown in population and clinical studies to be prevalent in individuals with migraine or non-migraine headaches. Prevalence rates for coexisting neck pain with migraine ranged from 16.7 % to as high as 72.6% (81-85).The association between migraine and chronic neck pain ranged from odds ratio (95% confidence interval) 4.25 (3.84 to 4.70) (81) to 5.4 (5.2 to 5.6) (83). Whether neck pain is a comorbidity or is part of the migraine picture is still contentious. One study supporting the notion that neck pain is part of the migraine episode reported neck pain during the headache phase of the migraine in 69.4% of the patients (86). Neck pain was also present among 36.1% of individuals with non-migraine headaches (82). The frequent coexistence of neck pain in migraine and non-migraine headaches suggest the relevance of specifying other impairments of the cervical spine that may be associated with the headaches.

1.5.3. Cervical articular impairments

Cervical articular impairment, as used in this thesis, comprises restricted cervical range of motion along the cardinal planes of movement and painful or restricted joint dysfunction demonstrated during manual examination of the upper cervical spine or on rotation in flexion at C1-C2 segment. There is strong evidence for the presence of cervical articular impairment in headaches, especially for CGH. Their presence in CGH is expected and is among the diagnostic criteria for CGH (8, 13). Cohort studies have demonstrated worse cervical articular impairments in patients with pure CGH (87, 88) or CGH coexisting with one or more other

headaches (89) compared to individuals with migraine, TTH and controls. These impairments included less cervical spine range of flexion (87), extension (87, 88) and rotation (88), and pain on manual examination of the upper three cervical spine(87, 88). Individuals with CGH also had significantly reduced range of motion at C1-C2 segment compared to individuals with migraine and those with mixed headaches (90). These results from cohort studies were consistent with a meta-analysis of studies, which further showed medium to large effect sizes for differences in these impairments between individuals with CGH and controls (91). Cervical rotation with cervical flexion showed the largest effect size [standardised mean difference = 22.23 (95% confidence interval 22.73 to 21.73)] in favour of decreased range in individuals with CGH compared to controls (91).

Evidence of cervical articular impairment is scant for TTH but suggests restrictions in cervical range of motion in both episodic and chronic TTH. Specifically, restrictions in cervical flexion, and right lateral flexion and rotation were demonstrated in episodic TTH compared to controls (92) whilst restrictions in cervical rotation were demonstrated in chronic TTH compared to episodic TTH and controls (93). In both studies, the groups which demonstrated restrictions in cervical mobility also had reduced flexor head posture. This may explain the difference in findings for episodic TTH and cervical mobility between the two studies. One study also reported referred head pain on manual examination of the upper cervical spine in 14 out of 14 participants with TTH (61). More studies are required to validate these results.

Evidence of cervical articular impairment in migraine has been inconsistent. There is evidence for restricted cervical rotation and upper cervical rotation in flexion in women with episodic or chronic migraine compared to controls (94) and the presence of symptomatic

upper cervical joints in 80–100% of participants with migraine (61, 94). However, these findings conflict with those indicating no cervical articular impairment in migraine compared to controls (87, 88).

1.5.4. Cervical muscle impairments

Cervical muscle impairments in migraine and non-migraine headaches are also relevant to characterise in relation to cervical articular impairment due to the role of the cervical muscles, especially the deep muscles, in supporting the cervical joints. Cervical muscle impairments may be deviations from normal physical structure, muscle behaviour (comprising motor control aspects of contraction), and muscle function (including strength and endurance).

1.5.4.1. Impairments in cervical muscle physical structure

Impairments in the structure of the cervical muscles have been observed in individuals with TTH and CGH. In individuals with chronic TTH, atrophy of the rectus capitis posterior muscleswas detected using magnetic resonance imaging(95). In individuals with CGH, atrophy of the semispinalis capitis was also observed as reduced cross sectional area measured using real-time ultrasound at C2 level on the symptomatic side in CGH(88). This atrophy was not observed for other cervical extensors, namely,the longissimus capitisand trapezius muscles of the cervical extensors, nor in migraine, TTH or controls. Muscle atrophy in CGH was hypothesised to be associated with nerve supply coming from the dorsal rami of the upper cervical nerves.

1.5.4.2. Impairments in cervical muscle behaviour

Impairments in muscle behaviour during contraction have strong evidence for CGH although these have also been demonstrated in TTH and migraine. In CGH, large effect sizes [standardised mean difference = -1.86 (95% confidence interval -2.74 to 0.99) were reported for CGH compared to controls in terms of timing and activation of the deep cervical flexors tested using the cranio-cervical flexion test (91). These findings were confirmed in more recent studies that showed increased activity in the sternocleidomastoid in CGH, not observed in migraine, TTH and controls (88). Similar impairments in muscle behaviour were demonstrated in chronic TTH, where significantly lower pressure scores were achieved during the cranio-cervical flexion test compared to controls (96).

Whilst cranio-cervical flexion test did not reveal impairments in muscles in migraine, one impairment in muscle behaviour observed in episodic and chronic migraine was significantly higher coactivation of cervical extensors during maximal cervical flexion compared to controls(97, 98).Similarly, higher coactivation of antagonistic muscles was demonstrated in chronic TTH during cervical flexion, and also during cervical extension (99).Whether or not the increased muscle activity observed in these headache types is associated with any comorbid cervical musculoskeletal disorder remains to be investigated.

1.5.4.3. Impairments in cervical muscle function

Impairments in cervical flexor function have been consistently demonstrated in CGH compared to controls. These have been characterised as significantly worse than controls, with large effect sizes indicating weaker cervical flexors [standardised mean difference =

-0.93 (95% confidence interval -1.33.to 0.54)] and lower cervical flexor endurance [standardised mean difference = -1.56 (95% confidence interval -2.83 to 0.29)] in CGH (91). These findings were confirmed in a more recent, larger cohort study (88).

One study (100) demonstrated similar findings for cervical extensors in CGH with large effect sizes, indicating weaker cervical extensors [standardised mean difference = -1.01 (95% confidence interval -1.59to -0.42)](91). Cervical extensor endurance in traumatic CGH was also lower than controls (100). Aside from impaired strength and endurance, less extensibility of the upper trapezius, scalenes and suboccipital extensors was also demonstrated in CGH, not present in migraine with aura and controls (87).

Whilst some studies did not find impairments in cervical muscle function in TTH and migraine compared to CGH, there is evidence for weakness of cervical extensors in TTH compared to controls (101). Moreover, there is also evidence for weaker cervical extensorsand of slower peak force generation for cervical flexion and left lateral flexion in episodic migraine compared to controls (97).

Other cervical musculoskeletal impairments have been shown to be present in migraine, TTH and/or CGH, including forward head posture (87, 93, 102), active trigger points (92, 93, 103), and pressure pain threshold on sites relevant to cervical symptoms (87) but these are beyond the scope of this thesis. Nevertheless, the cervical musculoskeletal impairments described previously for migraine, CGH and TTH remain to be elucidated as to their role in headache pathophysiology. Future studies may investigate whether these impairments are a prodrome, comorbidity, cause, result, or feature of the headache phase. A step toward understanding the nature of these impairments is exploring other cervical musculoskeletal impairments that may

be present in migraine and non-migraine headaches. This gap is particularly true for migraine, where evidence of cervical musculoskeletal impairments is not as conclusive as for TTH and CGH. The need to investigate cervical musculoskeletal impairments and their assessment further is also suggested by an expert panel of physiotherapists which nevertheless recommended a comprehensive examination of musculoskeletal impairments in headaches (104). These findings point to the need for more evidence comparing cervical musculoskeletal impairments in migraine and non-migraine headaches, especially for impairment in cervical extensor function. Thus Chapters Five and Six describe cervical musculoskeletal impairments in migraine and compare these with non-migraine headaches.

1.6. Overview of pathophysiology of migraine and non-migraine headaches

1.6.1. Common anatomy and physiology of headaches

Despite the different possible presentations and causes of headaches, it is believed that all headaches involve the activation of the trigeminocervical complex (TCC) in the brainstem (105, 106). Within the TCC, trigeminocervical neurons receive input from the periphery through the trigeminal nerve, the upper three cervical nerves (Figure 1) and other cranial nerves such as the facial, glossopharyngeal and vagus nerves (105, 106). The TCC makes direct ascending connections with different areas in the brainstem, including the superior salivatory nucleus and the ventrolateral periacqueductal grey (PAG), the rostral ventromedial medulla (RVM), the nucleus cuneiformis, and with higher structures including several hypothalamic and thalamic nuclei, which in turn make ascending connections with the cortex (Figure 2). Thus activation of the second order neurons in the trigeminocervical neurons

results in transmission of nociceptive information to higher-order neurons in the thalamus. This in turn, leads to activation of other higher-order pain centres in the cortex, such as the frontal cortex, sensory cortex, insula, and cingulate cortex, resulting in headache (107).

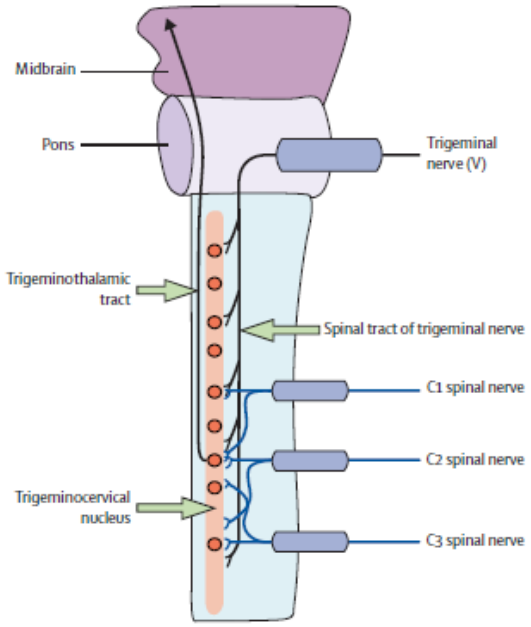

*Figure 1.*The trigeminocervical nucleus, spanning the brainstem and spinal cord. It receives afferents from the spinal tract of the trigeminal nerve and from the upper cervical spinal nerves. It sends input to supraspinal centres through the trigeminothalamic tract. Reprinted from The Lancet Neurology, Vol. 8, Bogduk N &Govind J, Cervicogenic headache: an assessment of the evidence on clinical diagnosis, invasive tests, and treatment, pp 959–968, 2009, with permission from Elsevier.

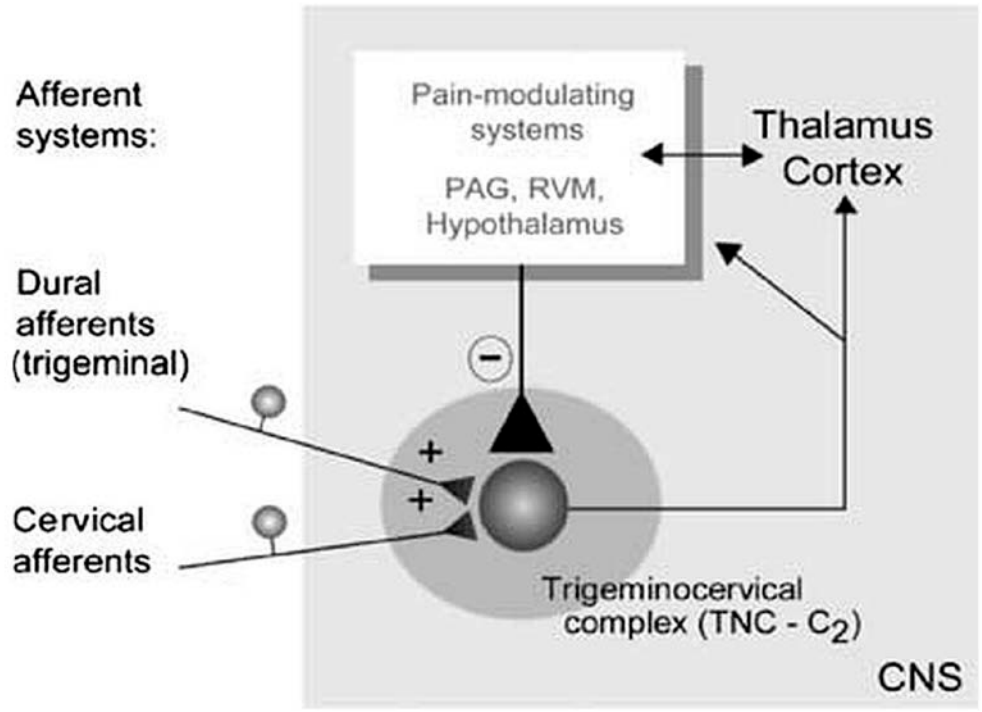

Figure 2. Overview of the peripheral and central nociceptive system involved in the transmission and modulation of headache. Reprinted from Headache Currents, Vol. 2, Bartsch T, Goadsby PJ, Anatomy and physiology of pain referral patterns in primary and cervicogenic headache disorders, pp 42–48, 2005, with permission from SAGE Publications.

For chronic headaches, regardless of the headache type, there is also a common nociceptive processing system that involves the peripheral and central nociceptive pathways. Peripheral mechanisms involve the activation and sensitisation of peripheral nociceptors and A and C fibres (108, 109). The activation may be due to ischaemia, mechanical stimuli or chemical mediators (110)whilst the peripheral sensitisation may be due to dysfunctional nociceptive processing. The exact nature of the peripheral sensitisation remains unknown but may involve increased nociceptive input from the periphery (for example the pericranial muscles, as depicted in Figure 3), resulting in plastic changes in the trigeminal nucleus. As a

consequence, the normally inhibitory effect of low-threshold A fibres on nociceptive transmission in the spinal dorsal horn is altered to a pain stimulatory effect, and the response to nociceptive A and C fibres is potentiated. The amplified nociceptive stimulation of supraspinal structures, such as the TCC and in the thalamus, results in central sensitisation (111). It appears that this central sensitisation also involves the activation of descending modulating pathways in the RVM and in the PAG such that nociceptive input is amplified and the anti-nociceptive input that would normally inhibit pain in a healthy nociceptive system is inhibited. Together, these mechanisms may induce and maintain the chronic headache. Central sensitisation due to amplified nociceptive input and disinhibition from the descending modulating systems may result in clinical features such as hyperalgesia, increased sensitivity to typically noxious stimuli. Additionally, when the TCC is sensitised, stimulus that are normally noxious such as movement or touch may trigger a headache. This increased sensitivity to typically non-noxious stimuli, allodynia, is manifested, for example, as hypersensitivity during shaving or when wearing glasses (110, 112).

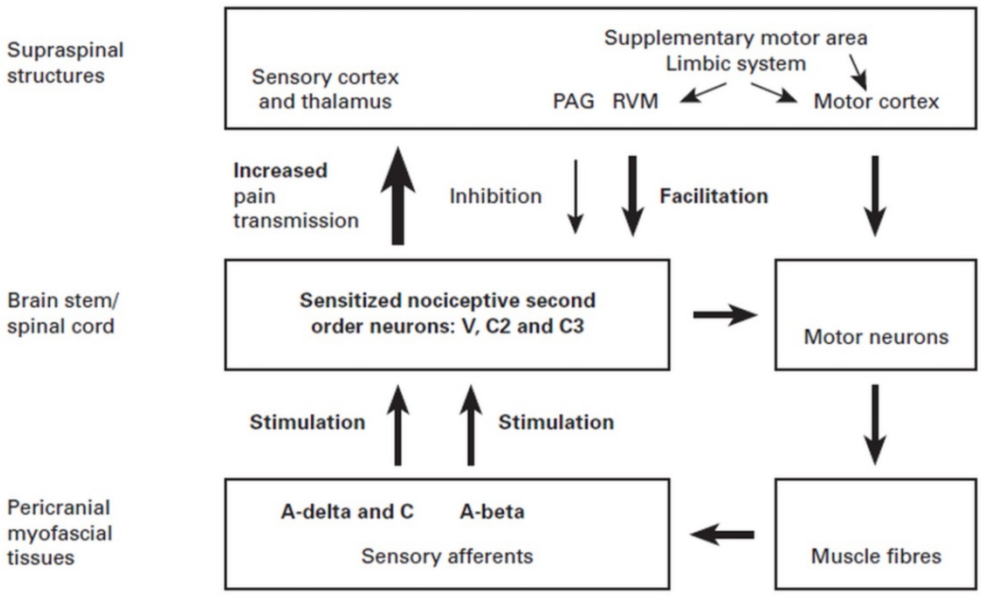

Figure 3.Dysfunctional nociceptive processing in chronic headaches. Important alterations from the normal nociceptive state are presented in bold. V, Trigeminal nerve; C2 and C3, second and third cervical segment of the spinal cord; PAG, periaqueductal grey; RVM, rostral ventromedial medulla. Reprinted from Cephalalgia, Vol. 20, Bendtsen L, Central sensitization in tension-type headache — Possible pathophysiological mechanisms, pp 486–508, 2000, with permission from SAGE Publications.

Beyond the TCC, there are other anatomic structures and functional interactions involved in the pathophysiology of the different headache types. Mechanisms that are specific for each headache type are believed to be manifested as differences in clinical features. Different theories have been proposed for the pathophysiology of specific headache types but so far these are still inadequate in clarifying the entire range of possible features of a headache within and between individuals or the definite mechanisms that initiate, propagate and terminate the headache. Until these features and mechanisms are conclusively elucidated,

headache assessment, diagnosis and treatment may remain nonspecific and inadequate. Thus pathophysiology of headaches remains a dynamic research area. The current widely known pathophysiologic theories for migraine, TTH and CGH are briefly discussed in sections 1.6.2–1.6.4 below.

1.6.2. Overview of pathophysiology of migraine

1.6.2.1. Role of the trigeminovascular system

The currently accepted theory on the pathophysiology of migraine implicates the activation and sensitisation of the trigeminovascular system. (TGVS) (Figure 4) (111, 113). The TGVS consists of the trigeminal ganglion (TG) projecting peripherally to cerebral blood vessels and dura mater innervated by the trigeminal nerve and centrally to the TCC in the brainstem and spinal cord. Peripheral nociceptive input in migraine comes from nociceptors and nociceptive A-δ and C fibres innervating the intracerebral blood vessels and dura mater (113). Nociceptive input is then transmitted to the trigeminal nerve, the trigeminal ganglion, and synapses on second-order neurons in the TCC (53).

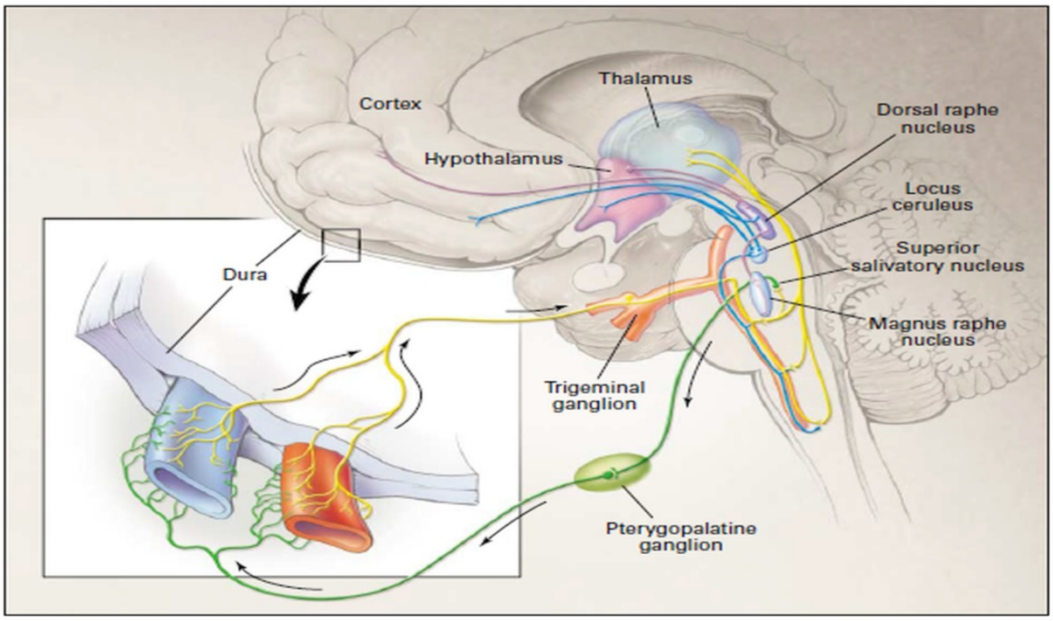

Figure 4.Pathophysiology of migraine.The key pathways for the pain are the trigeminovascular input from the meningeal vessels, which passes through the trigeminal ganglion and synapses on second-order neurons in the trigeminocervical complex in the brainstem. These neurons, in turn, decussates in the brainstem and form synapses with neurons in the thalamus. Reproduced with permission from Goadsby PJ, Lipton RB, Ferrari MD. Migraine — Current understanding and treatment.*N Engl J Med*. 2002;346:257–270. Copyright Massachusetts Medical Society.

1.6.2.2. Mechanisms responsible for headaches phases

The exact mechanisms responsible for the premonitory, aura, headache, and postdrome phases of headaches, and transitioning between these phases, remain unclear. Current evidence suggests that mechanisms for these phases overlap (43). During the premonitory phase, it is generally believed that the central nervous system mediates the release of dopamine and activity of and therefore blood flow in the hypothalamus increase (114). This increased activity in the hypothalamus is part of a bigger picture of brain excitability before the headache phase. Just before or during the aura phase, regional cortical cerebral blood flow decreases, usually starting posteriorly and progressing anteriorly (8). This decrease in blood flow is above the threshold for ischaemic injury. The decrease in blood flow gradually progresses into increased blood flow over a period of hours. This change in regional cortical cerebral blood flow is believed to be due to cortical spreading depression (CSD). In CSD, a slow short-lasting depolarization wave propagates across the cortex that is followed by a period of inactivity. In migraine forms that do not have auras, a similar mechanism is postulated to be present but inactive. Animal studies suggest that CSD could be the mechanism activating the TGVS. This probable link provides an explanation for the headache that follows aura in migraine. As previously described, the headache phase of migraine involves activation and sensitisation of meningeal nociceptors and afferents say by mechanical stimuli. The sensitisation of meningeal afferents provides a mechanism that may explain the throbbing nature of the migraine headache as well as the exacerbation of the headache during events (e.g., coughing or sudden head movements) that increase intracranial pressure (111). Experiments showed that activation of the meningeal nociceptors may initiate a cascade of events leading to the release of inflammatory mediators. This neurogenic inflammation then results in the sustained activation and sensitisation of the meningeal

afferents, which then activates and sensitises second-order and third-order trigeminocervical neurons. Activation of the trigeminocervical neurons then activates different areas of the brain, resulting in headache. After the headache phase, symptoms occur comprising the postdrome phase. The few studies about postdrome phase suggest that this phase is linked with persistent changes in brain activity past the headache phase (115). These changes include bilateral posterior cortical hypoperfusion, midbrain and hypothalamic activation, and increased blood flow in the visual cortex. The overlap of postdromal symptoms with premonitory symptoms sets the scene for further investigation of the nature of postdromal symptoms.Therefore it is thought that migraine is fundamentally due to an abnormality in central processing of not necessarily abnormal input. Yet in some cases, as described earlier, meningeal nociceptors may also be involved (Figure 2). The exact mechanisms of sensitisation in migraine remain unknown.

1.6.2.3. Role of neurochemicals in migraine pathophysiology

Another area in migraine pathophysiology that remains inadequately understood is the relationship between migraine and alterations in neurochemicals in the central nervous system, particularly the possible imbalance between excitatory and inhibitory neurotransmission (116, 117). The activation of the TGVS is thought to release calcitonin gene-related peptide (CGRP) and substance P which, in turn, cause further vasodilation and neurogenic inflammation through the secretion of inflammatory mediators such as serotonin, adenosine diphosphate, platelet-activating factor, nitric oxide, and interleukins. The vasodilation and neurogenic inflammation further sensitise the neurons in the TG, followed by the neurons in the TNC in the brainstem (116). It is through this mechanism that CGRP, in particular, is postulated to transmit nociceptive information.

As regards excitatory-inhibitory neurotransmitter imbalance, there is evidence of a number of anomalies in metabolism of excitatory neurotransmitters in migraine compared with controls. These include higher glutamate-to-glutamine ratios in the occipital cortex (118) and altered levels of N-acetyl-aspartylglutamate in the anterior cingulate cortex as well as the insula (119). In contrast to evidence for excitatory neurotransmitters in migraine, the role of the principal inhibitory neurotransmitter gamma aminobutyric acid (GABA) has only been indirectly demonstrated, at best. For example, increased salivary GABA levels have been reported in people with migraine without aura during attacks, compared to interictal periods and to people with non-migraine headaches (120). These results suggested that increased GABA metabolism may somehow be a protective mechanism to limit symptomatic episodes. Increased levels of GABA in the cerebrospinal fluid (CSF) have also been demonstrated in people with migraine compared to controls (121). The increased CSF GABA was purported to be indicative of increased GABA concentration in the brain due to ischemia.

Despite these findings, the role of GABA in migraine has not yet been fully established because of the lack of studies directly measuring GABA levels in the brain (122). Thus the possible role of GABA in pathophysiology was investigated in a study presented in Chapter Three in this thesis, where GABA levels in the brain were compared between migraine and controls.

1.6.3. Overview of pathophysiology of a non-migraine headache: TTH

Details of mechanisms of TTH, especially of its initiation, are still under debate. The prevailing theory is that both peripheral and central nociceptive mechanisms contribute to

TTH, with peripheral nociceptive mechanisms being most likely responsible for episodic TTH whereas central nociceptive mechanisms being most likely responsible for chronic TTH (8, 93). An example of activation of the peripheral system in TTH is a slightly increased muscle activity, which may result in microtrauma of muscle fibres and tendon, causing accumulation of chemical mediators. Such events may then activate and sensitise the A and C fibres (123) and eventually cause increased myofascial tenderness, a feature of a specific subtype of TTH (8). Prolonged nociceptive impulses from the myofascial tissues result in summation of such impulses leads to sensitisation of the second-order neurons of the trigeminal nerve and second and third cervical segment of the spinal cord. This, in turn, results in increase nociceptive transmission to the supraspinal structures such as the thalamus and sensory cortex, and decreased supraspinal nociceptive modulation (108) resulting in headache.

The role of central sensitisation in TTH is only recently recognised. As such, central sensitisation represents additional shared anatomic and physiologic substrates between TTH and migraine and fuels the debate on whether migraine and TTH are distinct headache types or belong to the same headache type with opposing severities. The arguments for and against this view of migraine and TTH being indistinct headache types are presented later in section 1.6.5.

1.6.4. Overview of pathophysiology of a non-migraine headache: CGH

Compared to migraine and TTH, pathophysiologic mechanisms for CGH are better understood. The most important differentiator of CGH from migraine and TTH is the perception of pain in the head referred from a disorder in the cervical spine (34). The

mechanism for referral of pain from the cervical spine to the head involves the convergence between afferents from the upper cervical nerve roots and trigeminal afferents on common neurons in the TCCin the brain stem (Figure 1) (58, 106). Information received in the TCC from the upper cervical spine may relate to changes in muscle (spasm or tension), head and neck posture, neck strain, or nerve irritation. Such information on dysfunction in the upper cervical spine can cause sensitisation of the TCC.

However, the role of the cervical spine as a generator of the headache in CGH and its diagnosis still lacks consensus (124, 125). One argument against the cervical spine as a headache generator is the shared cervical musculoskeletal impairments between CGH and other headache types(29, 88, 126), as described earlier in section 1.5. Another argument is that not all patients with upper cervical spine impairments complain of headache (125). For these reasons, it is possible that the cervical spine and a central mechanism are required to produce CGH (125, 127). Correspondingly, central sensitisation has been demonstrated in chronic forms of CGH, as previously described. Central sensitisation was evidenced by bilateral and generalised hyposensitivity, manifested as higher thermal detection thresholds (128). These results need to be validated in larger studies to hopefully clarify the exact mechanisms of central sensitisation in CGH.

1.6.5. Alternative hypothesis on shared pathophysiology of migraine and TTH: Continuum theory

Migraine and TTH are classified as two distinct headache types in the ICHD. However, many have challenged this notion that migraine and TTH are two distinct entities and instead have proposed that they are the same disorder in opposite ends of the severity spectrum, with

migraine in the more severe end of the spectrum, and TTH in the less severe end (55). This alternative view has been referred to as the *convergence hypothesis*(54) or *continuum severity model* (129).

1.6.5.1. Arguments for the continuum severity model

A review of the diagnostic features of migraine and TTH (Table 1) may be interpreted by proponents of the convergence hypothesis as supporting their position. The diagnostic features of TTH are mostly absence or milder expressions of the diagnostic features of migraine (8, 51). Other overlaps between migraine and TTH have been noted, which to some, provide evidence for the convergence hypothesis. These overlaps include similarities in clinical features where features considered diagnostic for migraine are present in TTH and features typically associated with TTH are present in migraine [e.g. (63)]. One study revealed that the convergence hypothesis is demonstrated more in young adults with chronic headaches (129). Some prodrome symptoms are also similar between migraine and TTH (44). Having similar clinical features also challenge the notion of distinct pathophysiologic mechanisms for these two headache types, and therefore their being distinct headache types. Cady and colleagues propose that episodic TTH may evolve to migraine with increasing severity and central sensitisation(54). Response to treatment has also been cited as a similarity between the two with both being responsive to sumatriptan especially for migraine with neck pain (130). Another argument for the convergence hypothesis is the coexistence of migraine and TTH (e.g. 94% of individuals in a population study (64).

1.6.5.2. Arguments against the continuum theory

Despite these similarities between migraine and TTH supporting the convergence hypothesis, there is evidence that migraine and TTH differ in their epidemiologic profile, specifically in terms of age and sex distribution. Notwithstanding the difference in epidemiologic profile, the strongest evidence for migraine and TTH being distinct lies on their genetic heritability. Migraine has been shown to have as high as 50% heritability, with identified genetic markers for familial hemiplegic migraine (117). Similarly, a genetic population study showed concordance for ETTH and having no TTH among monozygotic twins (131).

1.6.6. Gaps in evidence on pathophysiology addressed in this thesis

The debate on whether migraine and TTH are distinct entities or not is still ongoing. Further genetic profiling of these two headache types is critical in resolving the question on their being distinct. Until genetic biomarkers are fully elucidated, an enhanced clinical characterisation of the migraine and TTH may help in understanding how similar or distinct they are. Moreover, characterisation of the natural course of these two headaches, especially in cases which have coexisting diagnostic features for both, would help identify their distinction. To contribute to this debate, this thesis presents a characterisation of cervical musculoskeletal impairments and pain and disability in migraine versus non-migraine headaches (including TTH) in Chapter Five and a comparison of their clinical course over 6 months in Chapter Six.

Further evidence on the pathophysiology of migraine, TTH and CGH is required toward a full understanding of the exact mechanisms causing the headache. For migraine, the

propagation and termination of each attack also remains to be fully elucidated. The need to fully understand the pathophysiology of headaches also highlights the need to identify biomarkers for these headaches(111). Therefore the potential of one neurochemical, GABA, as a biomarker is explored in Chapters Three and Four. Further, hypotheses regarding pathophysiologic mechanisms might be generated by comparing clinical characteristics in these headaches. Thus the clinical characteristics of migraine are compared with non-migraine headaches in Chapters Five and Six.Among the characteristics examined to better understand pathophysiology was the extent of central sensitisation symptoms measured using patient-report outcomes.

1.7. Assessment to characterise migraine and non-migraine headaches

1.7.1. Interview

Because diagnosis using the ICHD involves differentiating one headache type from others primarily based on headache features, the most essential element of assessment is therefore patient history, through interview (132). For example, the clinician asks about headache frequency, location, quality and accompanying symptoms. The clinician then integrates and evaluates information from patient history to determine whether the headache is most likely primary or secondary. History is particularly critical for primary headaches like migraine and TTH which are not associated with objective clinical features that would allow objective basis for diagnosis. Based on patient history, the clinician determines if the headache is primary or secondary. This step in the diagnosis may require physical and neurological examination (133). Once the clinician has determined whether the patient has primary or

secondary headache, the clinician then determines the most likely headache diagnosis. The ICHD lists “Not better accounted for by another ICHD-3 diagnosis” as the final criterion for all headache types to remind clinicians to always consider other possible diagnoses (8).

1.7.2. Headache diary

Information on headache features from an interview may be supplemented through headache diaries (17). The advantage of the headache diary is that it prospectively collects headache symptoms and responses to the headache. The prospective collection of information reduces the recall bias which may be present during interview. The headache diary is also useful in closely following the behaviour of symptoms over time. (133). Doing so may help scrutinisevariability in patient symptoms.

1.7.3. Physical examination tests for cervical musculoskeletal impairments

An international panel of clinical and research physiotherapy experts has recommended a number of physical examination tests that may be useful in assessing patients with headaches, regardless of headache type (104). This recommendation is presumably related to evidence of the prevalence of cervical musculoskeletal impairments in headaches, as discussed earlier in section 1.5. The physical examination tests deemed useful or extremely useful by the expert panelwere manual joint palpation, cervical flexion-rotation test,active range of cervical movement,passive physiological intervertebral movements, reproduction and resolution of headache symptoms, cranio-cervical flexion test,combined movement tests, head forward position, trigger point palpation, muscles tests of the shoulder girdle, and screening of the

thoracic spine. It was not specified whether these tests are useful for diagnosis or for assessing treatment outcomes.

Of these tests, manual examination at C1/C2 segment of cervical spine and measurement of muscle length of the pectoralis minor muscle demonstrated discriminative ability for CGH versus migraine with aura and controls with a sensitivity of 80% (87). This finding was corroborated by another cohort study showing discriminative ability of a combination of manual examination of C0/C1 to C3/C4 segments, cranio-cervical flexion test and cervical extension range of motion measurement for CGH compared to migraine, TTH and controls with a sensitivity of 100% and specificity of 94% (88). In addition, flexion rotation test was also found to have good diagnostic accuracy for CGH versus migraine and mixed headache forms when used by an experienced examiner (area under the curve = 0.85 (95% confidence interval 0.75 to 0.95); $p< 0.001$). (90). Aside from tests found discriminatory for cervicogenic headache, tests for cervical muscle behaviour and function, especially of the cervical extensors, require further investigation.

1.7.4. Self-report questionnaires

Self-report questionnaires may be used to elicit information directly from the patient about the nature of his or her headache experience. The outcomes that can be assessed in headaches using self-report questionnaires may include quality of life, satisfaction about the treatment, pain beliefs, to name a few (133). The use of self-report questionnaires is consistent with recognising that headache is a subjective experience.

1.7.5. Assessment of migraine and non-migraine headaches used in this thesis

Participants of studies presented in Chapters Six and Seven of this thesis completed a headache diary to provide information about their headache symptoms and disability of participants over 6 months. Information from the diary supplemented information obtained from the participants during the interview and using a self-report questionnaire. Self-report questionnaires were used in this thesis to assess personal factors that possibly influence the patient experience. These self-report questionnaires are presented in Appendices 4 and 5. The outcomes collected from the self-report questionnaires are presented in Chapters Four through Seven of this thesis. Of the tests found discriminatory for CGH and recommended by the expert panel for headaches, we employed manual joint palpation, the cranio-cervical flexion test, the cervical flexion-rotation test and active range of cervical movement to characterise migraine and their distinction from non-migraine headaches. These tests are briefly described in Appendix 5. Findings from these assessments of cervical musculoskeletal impairments in migraine and non-migraine headaches are reported in Chapters Five and Six. In an attempt to fill the gap in evidence about cervical muscle behaviour and function, especially of the extensors, we also included such tests in the physical examination of participants in the studies presented in Chapters Five and Six.

1.8. Recognising factors that influence the patient experience in headaches

1.8.1. The importance of assessing more than the diagnostic criteria

Existing headache classification systems were designed to focus on describing headache features and associated symptoms of each headache episode. Whilst such information is generally considered adequate for diagnosis, it is arguably inadequate for understanding the impact of the symptoms on the person (133). In headaches that persist and recur like migraine, TTH and CGH, the impact of the headache may extend to all domains of life and factors other than the headache symptoms may influence the patient experience of the pain (133). Therefore other factors influencing the headache experience and the response to the headache must be assessed to enhance the understanding of the patient experience.

1.8.2. Factors influencing the patient experience

1.8.2.1. Disability

Disability pertains to how a health condition affects the person on the ability to function at home, at work or socially and how the person responds to the condition (133). The World Health Organisation defines disability in the *International Classification of Functioning, Disability and Health* (ICF) as an umbrella term for a person's functioning in society that encompasses impairments, activity limitation and participation restriction (134). Impairments are deviations from typical body structure or function, activity limitations are restrictions in the ability to perform daily activities in a manner that is considered efficient and competent, and participation restriction is the inability to perform roles expected by society according to

a person's context (134). Defining disability in this manner recognises that a health condition affects a person according to biomedical factors that are present and personal and environmental factors that may influence the person's response to these biomedical factors(133). Disability must therefore be assessed because it cannot be fully explained by headache frequency, intensity and symptoms (135). The headache research community seems to agree with the recommendation of measuring disability and functioning as a secondary outcome measure in headache trials (20, 21). Some even argue that disability is the most important indicator of severity of the disorder (136) as disability may differ even among individuals with the same type and severity of headache.

1.8.2.2. Pain

When assessing pain in patients with headaches, we recognise that the person is living through an unpleasant and complex experience (137). The complexity of the pain experience rests on its subjective nature and the involvement of different dimensions contributing to the pain experience. The sensory-discriminative dimension contributes the sensation of the nociception. This in, turn, is modified by the cognitive-evaluative dimension contributes the meanings attached to the pain from past experiences or knowledge, and the motivation-affective dimension contributes to emotions associated with the pain which relates with the escape or attack response to the pain.

1.8.2.3. Central sensitisation symptoms

A construct related to pain is central sensitisation. The occurrence of central sensitisation was presented in an earlier section. Briefly, central sensitisation involves the hypersensitivity of the central nervous system to stimuli which may or may not be known to cause pain (138). Examples of manifestations of central sensitisation in patients with headaches are hyperalgesia (139) such as headaches associated with increased tenderness to palpation, and cutaneous allodynia (112) such as experiencing pain or any unpleasant sensation on the skin during a headache episode attack when tying the hair in a ponytail or being exposed to heat in the kitchen.

1.8.2.4. Personal factors contributing to the headache experience

The broad view of disability, as defined above, has implications on assessing a diverse range of information from patients with headaches. A comprehensive assessment may take into account factors including biomedical factors such as head pain characteristics and associated symptoms, and personal and environmental factors including but not limited to the extent of comorbidities, sleep quality, level of physical activity, and emotional state and response to pain such as depression, anxiety and stress, Such comprehensive assessment would allow better understanding of the patient's experience of the headache and therefore contribute to managing that experience. In keeping with a patient-focused management approach, the assessment of these factors should also include information that are coming directly from the patient and that are meaningful to the patient.

1.8.3. Biomedical and personal factors assessed in this thesis

A comprehensive assessment of the patient experience, incorporating biomedical and personal factors, was done in this thesis. For cross-sectional and cohort studies presented in this thesis (Chapters Four through Seven), headache characteristics were assessed through an interview and through a self-report questionnaire. Additional biomedical factors assessed using self-report questionnaires were pain and central sensitisation. Other biomedical factors assessed in studies presented in Chapters Five andSix were cervical musculoskeletal impairments using physical examination tests. These tests were previously shown to be discriminatory for CGH (87, 88, 90) and recommended by an international panel of experts as appropriate for people with headaches (104). Personal factors were assessed using self-report questionnaires in studies presented in Chapters Four, Five and Six. These personal factors were comorbidities, sleep quality, level of physical activity, and emotional state. Lastly, disability was assessed using headache-specific and generic questionnaires in studies presented in Chapters Four through Six. The meaningfulness of assessing disability was further investigated in Chapter Seven by looking at how disability changes over six months and the ability of the questionnaire to detect clinically relevant change. Such multidimensional assessment may improve characterisation of each headache type, particularly if there are notable differences between headaches types. Whether such differences exist between migraine and non-migraine headaches, namely TTH and CGH, was explored in this thesis.

1.9. Summary

In summary, migraine and non-migraine headaches,specifically TTH and CGH, are the most prevalent headaches which have in common some pathophysiologic mechanisms and clinical features related to cervical musculoskeletal impairments. Migraine, TTH and CGH cause significant disability partly due to a lack of full understanding of their pathophysiological mechanisms, their clinical characteristics that may help distinguish them, and other factors that may influence the impact of the headache. As such, headache classification and diagnosis of these headaches may be difficult for some cases. A comprehensive snapshot of the state of the art in the application of the headache classification system in defining migraine, TTH and CGH populations in headache trials is reviewed in Chapter Two. Results of this review guided the definition of our study populations in studies presented in this thesis. A candidate biomarker for migraine was investigated in Chapter Three. The good diagnostic accuracy of the candidate biomarker for migraine stimulated the continuation of its validation as a biomarker in Chapter Four by determining its association with clinical characteristics of migraine. The clinical characteristics that correlated with the candidate biomarker in Chapter Four were included as outcome measures in the cohort study characterising migraine and non-migraine headaches in Chapter Five. The findings in Chapter Five that disability differed between migraine and non-migraine headaches and changed over 6 months in Chapter Six led to investigating the meaningfulness of measuring disability over time in migraine and non-migraine headaches in Chapter Seven. Therefore this thesis substantiates the current standard in classifying headaches, adds new evidence on the pathophysiologic mechanisms of migraine and the clinical course of migraine and non-migraine headaches, and confirms and augments what is known about the extent of cervical musculoskeletal impairments and disability in migraine and non-migraine headaches.

1.10. Aims of the thesis

The broad aim of this thesis was to characterise migraine on the basis of its neurochemical profile, cervical musculoskeletal impairments and patient experience as distinguished from non-migraine headaches.

The objectives were to:

1. Describe how headaches are defined in clinical trials (Chapter Two)
2. Compare levels of brain neurochemicals in migraine to controls (Chapter Three)
3. Explore the relationship between brain neurochemicals and relevant disease characteristics of migraine (Chapter Four)
4. Characterise cervical neck impairments and patient experience in migraine compared to non-migraine headaches and controls (Chapter Five)
5. Characterise the six-month clinical course of migraine and non-migraine headaches and the factors associated with the clinical course (Chapter Six)
6. Examine changes in disability over six months in migraine and non-migraine headaches (Chapter Seven)

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CHAPTER TWO

Definitions and Participant Characteristics of Frequent Recurrent Headache Types in Clinical Trials: A Systematic Review

Chapter Two is the peer reviewed version of the following article: Aguila ME, Rebbeck T, Mendoza KG, De La Peña MG, Leaver AM. Definitions and participant characteristics of frequent recurrent headache types in clinical trials: A systematic review. *Cephalalgia*.Epub2017 Apr 25. doi: 10.1177/0333102417706974, which has been published in online form ahead of print at http://journals.sagepub.com/doi/pdf/10.1177/0333102417706974

Authorship Statement

As co-authors ofthe paper “Definitions and participant characteristics of frequent recurrent headache types in clinical trials: A systematic review”, we confirm that Maria Eliza Ruiz Aguila has madethe following contributions:

- Conception and design of the research
- Acquisition of data
- Analysis and interpretation of data
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Abstract

Background: Clear definitions of study populations in clinical trials may facilitate application of evidence to clinical populations. This review aimed to explore definitions of study populations in clinical trials on migraine, tension-type headache, cluster headache, and cervicogenic headache.

Methods: We performed a systematic review of clinical trials investigating treatment efficacy for migraine, tension-type headache, cluster headache, and cervicogenic headache. We extracted data on diagnosis, inclusion criteria and baseline headache characteristics.

Results: Of the 229 studies reviewed, 205 studies (89.5%) defined their populations in adherence to the International Classification of Headache Disorders (ICHD) criteria. Some studies (n = 127, 55.5%) specified diagnosing through interview, clinical examination and diary entry. The most commonly reported inclusion criteria were pain intensity for migraine and tension-type headache studies (n = 123, 66.1% and n = 21, 67.7%, respectively), episode frequency for cluster headache studies (n = 5, 71.4%), and neck-related pain for cervicogenic headache studies (n = 3, 60%). Few studies reported details on the extent to which diagnostic criteria were present at baseline.

Conclusions: ICHD is routinely used in defining populations in headache studies. Details of baseline headache characteristics were not as consistently reported.

Key words*:* Patient selection, International Classification of Headache Disorders, migraine, tension-type headache, cluster headache, cervicogenic headache

Introduction

Migraine, tension-type headache, cluster headache (1) and cervicogenic headache (2) are among the most commonly seen headaches in primary care and specialist clinics. Effective treatment of these headaches relies on correct diagnostic classification. Increased headache research over the past two decades (3) has contributed to improving the classification system for headaches such as the International Classification of Headache Disorders (ICHD). The ICHD, now on its third edition (beta version), provides a framework to standardize headache classification (4,5) and addresses the challenge of distinguishing headache types. A classification framework such as ICHD is important to ensure homogeneity of participants in clinical studies investigating treatment efficacy.

Despite this improvement, classification of headaches using ICHD may be challenging for certain cases given that the classification system is based on clinical features (6). For one, a headache type may coexist with one or more other headache types (7). Further, symptoms vary within and between individuals with the same headache type (8). Additionally, some headache features may overlap, especially for frequent recurrent and disabling headaches such as migraine, tension-type headache, cluster headache and cervicogenic headache (6,9). It is therefore important to examine how study populations are defined in clinical trials. Details on definitions of study populations may confer better understanding of current criteria used to classify headaches. This understanding, in turn, would potentially increase awareness on the nature of headaches between study populations and guide to whom the inferences from the trials could be applied.

The primary objective of this systematic review, therefore, was to explore and describe the definitions of study populations in clinical trials. In particular, this review aimed to explore the eligibility criteria for study populations of frequent recurrent headaches, namely migraine, tension-type headache, cluster headache, and cervicogenic headache. The

secondary objective of this review was to describe baseline characteristics of participants enrolled in clinical trials in terms of headache features listed as ICHD diagnostic criteria.

Methods

Protocol registration

The protocol for this systematic review was registered with PROSPERO (registration number CRD42014009167).

Eligibility criteria

We included research articles that were intervention studies (controlled studies or prospective cohort studies) that described participants as having 'primary headache', 'migraine', 'tension-type headache', 'cluster headache' or 'cervicogenic headache'. Inclusion was limited to studies published in English in peer-reviewed journals from the time of introduction of ICHD-II in 2004. When this second edition of classification was released, it was recommended for use as standard definitions of headaches for clinics and research (4).

We excluded articles that had cohorts other than the diagnoses of interest for this review and articles that presented data for the same cohort as an earlier publication already included in the review.

Information sources

Relevant articles were identified by searching the following electronic databases from 2005 to April 2015: Cochrane Library, Medical Literature Analysis and Retrieval System Online (MEDLINE), Cumulative Index to Nursing and Allied Health Literature (CINAHL). The Allied and Complementary Medicine Database (AMED), Embase, Physiotherapy Evidence Database (PEDro), and Web of Science. In addition, researchers scanned the "related articles" link of databases and SCOPUS to identify reports citing the included studies.

Search strategy

We used a sensitive search strategy using a combination of Medical Subject Headings (MeSH) and words “primary headache” OR “migraine” OR “tension-type headache” OR “cluster headache” OR “cervicogenic headache” and related terms. The search was limited to ‘peer-reviewed publication, 2005 to 2015’ and ‘humans’ (Appendix A) and conducted by a single investigator (MA).

Study selection

Two reviewers (MA and GD) removed duplicate citations and independently determined eligibility of retrieved articles by applying the inclusion criteria through title and abstract screening in EndNote™ X7.3 (Thomson Reuters. Endnote. New York: Thomson Reuters; 2015). Two other reviewers (TR and AL) were consulted for articles that did not clearly meet the inclusion criteria. The full text of the remaining citations was retrieved and independently assessed by two reviewers (MA and AL or TR or KM or MD). Disagreement between the reviewers on study selection was resolved by a third researcher (TR or AL).

Data extraction

A data extraction spreadsheet was designed and pilot tested by all reviewers. Data were extracted independently by two reviewers (MA and AL or TR or KM or MD). Disagreement between the reviewers on extracted data was resolved by a third researcher (TR or AL).

Data extracted included study and participant characteristics (Appendix B). Study characteristics included research design, sample size, intervention and control, method of headache diagnosis, and inclusion and exclusion criteria for the study. Participant characteristics comprised demographic information and headache features of the participants at baseline. Headache features included the diagnostic criteria for the each headache type according to ICHD-II (4). Studies were grouped by diagnosis for descriptive analysis. Data

on the process of diagnosis and inclusion criteria used in the clinical studies were analyzed to define the patient populations. Frequency distribution of studies that reported the ICHD clinical features as baseline characteristics of participants, and the means and standard deviations of these features or percentage of participants demonstrating these reported baseline characteristics were also described.

Results

Two hundred twenty nine studies met the selection criteria for this review (Figure 1). The list of studies included in this review appears as Appendix C. Of these studies, 222 (96.9%) were randomized controlled trials and 7 (3.1 %) were controlled clinical trials. Sample sizes ranged from 11 to 1935 [mean (SD) 243.31 (336.30)] (Table 1), with a total of 48661 participants across all studies. Migraine was the most studied headache type while cervicogenic headache was the least studied. Most investigated pharmacologic interventions (*n* = 158, 69.0%). Non-pharmacologic interventions (*n* = 71, 31.0%) included complementary and alternative medicine (*n* = 29, 12.7%), psychotherapeutic intervention (*n* = 15, 6.6%), neurostimulation and nerve blockade (*n* = 16, 7.0%).

Definition of study population and selection of participants in clinical trials

Two hundred ten studies (91.7%) used a classification system to define their study populations, with 205 studies (89.5%) reporting adhering to the ICHD. One hundred twenty seven studies (55.5%) diagnosed participants through interview, clinical examination and diary entry (Table 2). It is unclear how diagnoses were arrived at or how the classification system was used in the other 102 studies as these details were not provided.

Not all clinical features listed as ICHD diagnostic criteria for the headache types were routinely specified among the inclusion criteria (Figure 2). For migraine studies, the most

commonly reported inclusion criteria was pain intensity (*n* = 123, 66.1%) and the least common was pulsating quality of headache (*n* = 22, 11.8%). For tension-type headache studies, the most commonly reported inclusion criteria were pain intensity (*n* = 21, 67.7%) and frequency of attacks (*n* = 17, 54.8%) while the least common were bilateral location, non-pulsating quality of headache and not affected by physical activity (all *n* = 7, 22.6%). For cluster headache studies, the most commonly reported inclusion criteria were frequency of attacks (*n* = 5, 71.4%) and severity, location and duration of headache (*n* = 4, 57.1%). For cervicogenic headache studies, the most commonly reported inclusion criteria were pain referred from the neck (*n* = 4, 80% of cervicogenic headache studies) and evidence of cervical spine or muscle disorder (*n* = 3, 60% of cervicogenic headache studies). No cervicogenic headache study specified improvement or resolution of pain in parallel with the resolution of the neck disorder or lesion as an inclusion criterion.

Other inclusion criteria unrelated to the ICHD criteria but necessary to control for potential confounders were frequently used in the headache studies. In general, participants were included in studies if they belonged to a specific age group (mostly 18 to 65 years old), were younger than 50 years old on their first headache attack, were experiencing a single headache type or able to differentiate attacks according to headache types, were experiencing headaches for at least 1 year, and had no comorbidities such as malignancy or depression. Other selection criteria for study populations were related to the intervention investigated. For example, many studies excluded participants who were pregnant or lactating, had taken or were responsive to certain medications, or were taking other medications considered to be prophylactic or contraindicated to the intervention.

Description of participants at baseline in terms of ICHD criteria

Not all clinical features listed as ICHD criteria for the headache types were routinely reported

as baseline characteristics of participants in the studies (Table 3). Nevertheless, among the migraine studies that reported the baseline clinical features, the most reported characteristics were severity of the headache (*n* = 64, 34.4%) and presence of photophobia and/or photophobia (*n* = 44, 23.7%). Where reported, most participants demonstrated moderate to severe pain intensity (92.5% of participants) and photophobia and/or phonophobia (79.4% of participants) at baseline. For tension-type headache studies, the baseline headache characteristic most reported was severity of the headache (*n* = 15, 46.9%). It was not possible to pool severity data because different headache intensity scales were used. For cluster headache studies, only two ICHD clinical features were reported as baseline characteristic of participants: duration and frequency of attacks. Participants in the cluster headache studies had about 3 attacks per day lasting for about an hour. For cervicogenic headache, the only clinical feature reported as baseline characteristic of participants was abolition of headache following nerve blockade (*n* = 1, 20%).

On further examination of the reported baseline characteristics of participants, there was little to no information describing the extent to which participants demonstrated the clinical features that were thought to least overlap with other headache types. For migraine studies, nausea and/or vomiting, photophobia and phonophobia, and aggravation of the attack by routine physical activity (8, 10) were reported in less than a quarter of the studies. Similarly, the following features were not reported as baseline characteristics: headaches not aggravated by routine physical activity for tension-type headache (8, 11, 12); presence of autonomic symptoms for cluster headache (13); and pain, referred from the neck and evidence of a cervical spine lesion for cervicogenic headache (2).

Discussion

This review reveals that the ICHD is routinely used to define study populations in headache

studies, suggesting consensus and endorsement among researchers of ICHD in providing a framework for selecting participants. The use of a common framework such as the ICHD in defining study populations, in turn, allows for better comparison and synthesis of data across clinical trials. The methods of applying the ICHD criteria varied between studies, with most conforming to the "gold standard" for diagnosing headaches of using the ICHD through interview and physical examination (14).

Study populations across studies were homogenous beyond their headache features because participants were also selected based on other criteria. These selection criteria, such as being of a certain age at first headache episode and enrolment in the study, gender, health status, medication use, and frequency of attacks, were apparently used to fit outcomes of interest and to control for potential confounders. Whereas these selection criteria do not reflect the validity of the diagnostic criteria used in the studies, they conform to guidelines for clinical trials (15,16). The use of these guidelines in conjunction with the ICHD reflects how well these tools complement each other in defining study populations. While study populations were generally selected based on headache features listed in the ICHD, results of this review did not make it possible to describe the extent to which these features were demonstrated by participants at baseline. Few studies have provided this level of detail. Of the ICHD features reported at baseline, the most reported were intensity, severity and frequency of headaches. These headache features were consistent with some of the recommended outcome measures for headache trials (15-18).

It is reasonable to think that not all headache features were reported as baseline characteristics because the researchers of the studies already mentioned adhering to the ICHD criteria in selecting the participants. Although selection criteria provide some information on participant characteristics, further details on baseline headache characteristics may be helpful. Because diagnosing using the ICHD is based on combinations of headache features, details

on which and to what extent headache features were demonstrated at baseline would clarify participant features and potentially improve understanding and confidence in headache classification in studies. Ultimately, such details may aid translation of research findings to clinical populations.

Nevertheless, this large review presents a comprehensive snapshot of the landscape of definitions of study populations in headache trials. The limitations of this review were that we could not pool data for meta-analysis due to lack of standardization of outcome measures used and we did not assess risk of bias within studies. However, these were redundant because this review did not aim to evaluate treatment efficacy nor report pooled effect sizes for treatment outcome. A step forward may be to explore the importance and impact of reporting baseline headache characteristics of participants in headache trials.

In summary, study populations of treatment efficacy studies investigating migraine, tension-type headache, cluster headache, and cervicogenic headache were generally defined based on the ICHD criteria. It is unclear to what extent participants demonstrated the ICHD criteria at baseline. This review provides a comprehensive snapshot of how study populations are defined in headache trials. Results of this review also provide a starting point for discussing the level of detail in reporting diagnostic headache features at baseline in clinical trials.

Conflict of Interest Statement: All authors declare no conflicts of interest.

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Article Highlights:

- Definitions of study populations in most treatment efficacy studies of frequent recurrent headaches, namely, migraine, tension-type headache, cluster headache, and cervicogenic headache strictly adhered to the International Classification of Headache Disorders.
- It is unclear to what extent participants demonstrated the diagnostic criteria at baseline as few studies provided this level of detail.
- Results of this review provide a starting point for discussing the level of detail in reporting diagnostic headache features at baseline in clinical trials.

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Figure Legends

Figure 1. Flow diagram of study selection

Figure 2. ICHD diagnostic criteria reported as inclusion criteria for study populations

Table Legends

Table 1. Characteristics of studies and participants in the review

Table 2. Process of diagnosing headaches used in clinical studies

Table 3. ICHD diagnostic criteria described among baseline characteristics of participants with recurrent headache

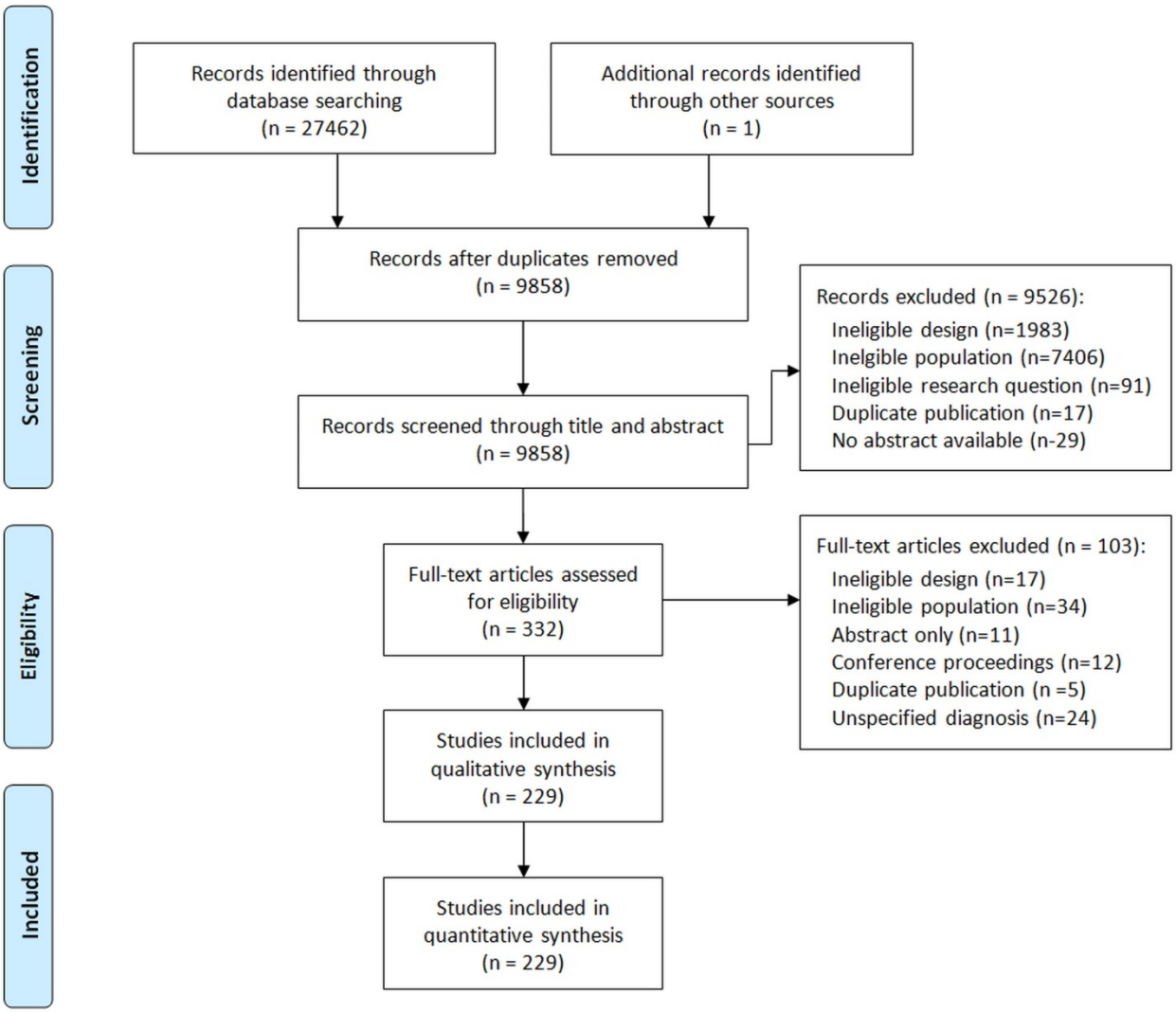

Figure 1. Flow diagram of study selection

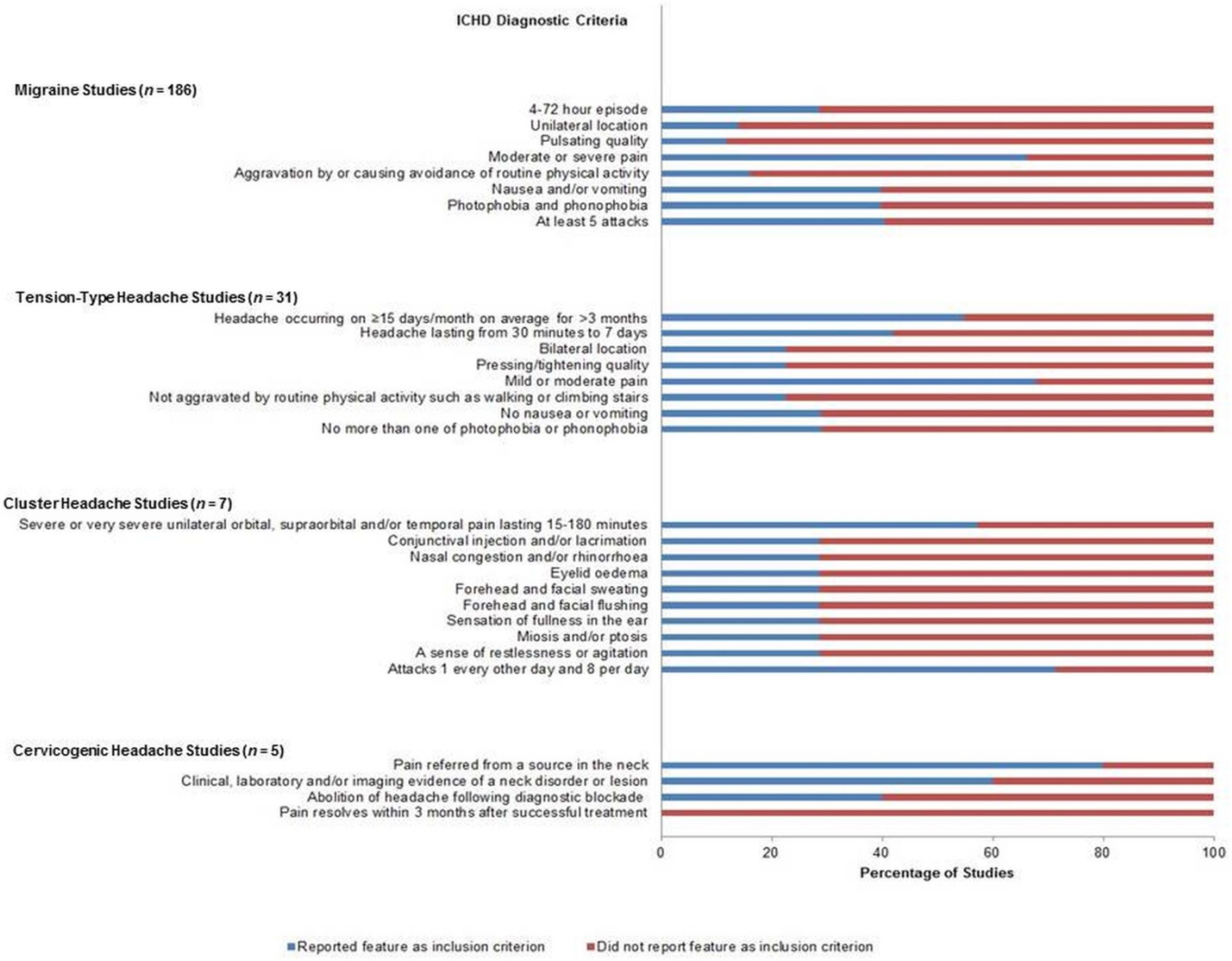

Figure 2. ICHD diagnostic criteria reported as inclusion criteria for study populations

Table 1. Characteristics of studies and participants in the review

Study characteristics	
Design	
RCT (*n*, %)	222 (96.9)
CCT (*n*, %)	7 (3.1)
Number of participants (mean, SD)	243.31 (336.30)
Headache classification studied [*n* (%) of total studies reviewed]	
Migraine	186 (81.2)
Tension-type headache	31 (13.5)
Cluster headache	7 (3.1)
Cervicogenic headache	5 (2.2)
Participant characteristics	
% Female (mean, SD)	78.74 (17.88)
Age, *years* (mean, SD)	39.43 (0.48)
History of headaches, *years* (mean, SD)	11.2 (12.85)

Table 2. Process of diagnosing headaches used in clinical studies

Process of Diagnosis	*n* (%) Studies
Use of classification system	
Used a classification system	210 (91.7)
ICHD	205 (89.5)
Guidelines for controlled studies of drugs in migraine by the International Headache Society Clinical Trial Subcommittee	3 (1.3)
Silberstein-Lipton criteria for chronic migraine	2 (0.9)
Sjaastad criteria for cervicogenic headache	2 (0.9)
Did not report	19 (8.3)
Method of Diagnosis	
Interview	81 (35.4)
Clinical examination	55 (24.0)
Diary	40 (17.5)
Diagnosed by health professional/s	26 (11.4)
Questionnaire	15 (6.6)
Diagnostic and laboratory tests	13 (5.7)
Self-identified	2 (0.9)
“Screening”	12 (5.2)
Did not report	102 (44.5)

Table 3. ICHD diagnostic criteria described among baseline characteristics of participants with recurrent headache

ICHD Clinical Features	*n* (%) Studies that Measured and Reported the Feature as Baseline Characteristic	Mean (SD) of the Reported Headache Feature or % of Participants Demonstrating the Feature at Baseline
A. MIGRAINE		
Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)	29 (15.6)	21.31 (18.14) hours
Unilateral location	11 (5.9)	59.8%
Pulsating quality	8 (4.3)	85.9%
Moderate or severe pain intensity	64 (34.4)	92.5%
Aggravation by or causing avoidance of routine physical activity	6 (3.2)	76.91
Nausea and/or vomiting	36 (19.4)	52.4%
Photophobia and phonophobia	44 (23.7)	79.4%
At least 5 attacks		
B. TENSION-TYPE HEADACHE		
Headache occurring on ≥15 days/month on average for >3 months (≥180 days/year)	1 (3.1)	21 days
Headache lasting from 30 minutes to 7 days	5 (15.6)	11.46 (4.89) hours
Bilateral location	0 (0)	
Pressing/tightening (non-pulsating) quality	1 (3.1)	67%
Mild or moderate intensity	14 (45.2)	5.81 (1.70) (out of 10)
Not aggravated by routine physical activity such as walking or climbing stairs	0 (0)	
No nausea or vomiting (anorexia may occur)	1 (3.1)	100%
No more than one of photophobia or phonophobia	1 (3.1)	100%

ICHD Clinical Features	*n* (%) Studies that Measured and Reported the Feature as Baseline Characteristic	Mean (SD) of the Reported Headache Feature or % of Participants Demonstrating the Feature at Baseline
C. CLUSTER HEADACHE		
Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes if untreated	3 (50)	82.75 (37.89) minutes
Conjunctival injection and/or lacrimation	0 (0)	
Nasal congestion and/or rhinorrhoea	0 (0)	
Eyelid oedema	0 (0)	
Forehead and facial sweating	0 (0)	
Forehead and facial flushing	0 (0)	
Sensation of fullness in the ear	0 (0)	
Miosis and/or ptosis	0 (0)	
A sense of restlessness or agitation	0 (0)	
Attacks have a frequency between one every other day and 8 per day for more than half the time when the disorder is active	1 (16.67)	3.33 (0.77) per day
D. CERVICOGENIC HEADACHE		
Pain, referred from a source in the neck and perceived in one or more regions of the head and/or face	0 (0)	
Clinical, laboratory and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck known to be, or generally accepted as, a valid cause of headache	0 (0)	
Abolition of headache following diagnostic blockade of a cervical structure or its nerve supply using placebo- or other adequate controls	1 (20)	61.0 (5.4%)
Pain resolves within 3 months after successful treatment of the causative disorder or lesion	0 (0)	

CHAPTER THREE

Elevated Levels of GABA+ in Migraine Detected Using ^{1}H-MRS

Chapter Three is the peer reviewed version of the following article: Aguila ME, Lagopoulos J, Leaver AM, Rebbeck T, Hübscher M, Brennan PC, Refshauge KM. Elevated levels of GABA+ in migraine detected using ^{1}H-MRS. *NMR Biomed*. 2015; 28:890–7. doi: 10.1002/nbm.3321, which has been published in final form at http://onlinelibrary.wiley.com/doi/10.1002/nbm.3321/full. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

Supplementary methods and results on levels of excitatory and other brain chemicals in migraine detected using proton magnetic resonance spectroscopy are presented in Appendix 3.

The study protocol for the study presented in this chapter appears as Appendix 4.

Authorship Statement

As co-authors ofthe paper “Elevated levels of GABA+ in migraine detected using ^{1}H-MRS”, we confirm that Maria Eliza Ruiz Aguila has madethe following contributions:

- Conception and design of the research
- Acquisition of data
- Analysis and interpretation of data
- Drafting and revising of the manuscript and critical appraisal of its content

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ELEVATED LEVELS OF GABA+ IN MIGRAINE DETECTED USING PROTON MAGNETIC RESONANCE SPECTROSCOPY

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Abstract Summary

Gamma-aminobutyric acid (GABA) has been implicated in several pain conditions yet no study has systematically evaluated GABA levels in migraine using ^{1}H-MRS. Accurate detection, separation and quantification of GABA in people with migraine could elucidate the role of this neurotransmitter in migraine pathophysiology. Such information may eventually be useful in diagnosis and development of more effective treatment for migraine. The aims of this study were therefore to compare the concentration of GABA+ in people with migraine with asymptomatic individuals and to determine the diagnostic potential of GABA+ in classifying people as having migraine or not.

In this case-control study, GABA+ levels in the brain were determined in 19 participants with migraine and 19 matched controls by ^{1}H-MRS using MEGA-PRESS sequence. The diagnostic accuracy of GABA+ for detecting migraine and the optimal cut-off value were determined by receiver operating characteristic analysis.

GABA+ levels were significantly higher (P=0.002) in people with migraine [median 1.41 (interquartile range 1.31-1.50) institutional units] compared with controls [median 1.18 (interquartile range 1.12-1.35) institutional units]. GABA+ concentration appears to have good accuracy in classifying individuals as having migraine or not [area under the curve (95% CI) = 0.837 (0.71 – 0.96), P< 0.0001)]. The optimal GABA+ cut-off value for migraine was 1.30 institutional units, with a sensitivity of 84.2%, specificity of 68.4% and positive likelihood ratio of +2.67.

Outcomes of this study suggest altered GABA metabolism in migraine. These results add to the scarce evidence on the putative role of GABA in migraine and provide basis to further explore the causal relationship between GABA+ and the pathophysiology of migraine. This study also demonstrates that GABA+ concentration has good diagnostic accuracy for migraine. These findings offer new research and practice directions for migraine diagnosis.

Keywords

GABA, MRS, migraine disorders, ROC curve, sensitivity and specificity

Abbreviations

^{1}H-MRS = proton magnetic resonance spectroscopy

AUC = area under the curve

Cr = creatine

CSD = cortical spreading depression

CSF = cerebrospinal fluid

FWHM = full-width at half maximum

GABA = gamma-aminobutyric acid

GAD = glutamic acid decarboxylase

Glx = glutamate + glutamine

GM = grey matter

ICHD = International Classification of Headache Disorders

IQR = interquartile range

IU = institutional units

MEGA-PRESS = Mescher-Garwood point resolved spectroscopy

MP-RAGE = magnetization prepared – rapid acquisition gradient echo

ROC = receiver operating characteristic

TGVS = trigeminovascular system

WM = white matter

INTRODUCTION

Migraine is the third most prevalent disorder in the world and causes more than 22 million years of healthy life lost due to disability according to the 2010 Global Burden of Disease Study (1). Despite its high prevalence, chronicity and consequent disability, diagnosis of migraine is based on a set of signs and symptoms (2) that are not specific to migraine (3), but overlap with other headache classifications. The lack of specificity in migraine diagnosis is, in part, because diagnostic markers (4) related to neurobiological mechanisms (5) are lacking. These uncertainties in diagnosis impact on treatment of migraine, which many consider to be inadequate (6). It follows that identification of specific diagnostic markers may improve understanding of the neurobiological mechanisms of migraine and open new avenues for development of effective therapeutics.

The pathophysiological events that are widely accepted as contributory to the symptoms of migraine include cortical spreading depression (CSD)as well as activation and sensitisation of the trigeminovascular system (TGVS) (5). CSD is described as a wave of a brief, intense excitation of neurons and glial cells in the central nervous system followed by a long, slowly propagating wave of inhibition (7, 8). The development of CSD triggers changes in cortical blood flow, featuring an initial increase in cortical blood flow, followed by a period of reduced cortical blood flow (9). CSD activates and sensitises the TGVS pain pathway, resulting in headache (5).

Despite recent evidence supporting these pathophysiological bases for migraine, the mechanisms of activation, propagation and termination of these events remain unclear. One way to gain insight about the neurobiological mechanisms of migraine is to investigate the role of excitatory and inhibitory neurotransmitters. It has

been hypothesised that an imbalance between excitatory and inhibitory mechanisms results in the pathophysiological events leading to migraine (5, 10). Whilst the role of excitatory neurotransmitters in migraine has been explored (11, 12), inhibitory neurotransmission has received less attention. To date, only one other study has reported *in vivo* concentrations of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), in people with migraine (13). Thus the role that GABA assumes in the pathophysiology of migraine remains poorly understood.

GABA is widely distributed and is the most abundant inhibitory neurotransmitter in the brain (14). Consequently, GABA has been implicated in neuronal excitability and cortical functions such as modulation of pain (15). Understanding the role of GABA in migraine is therefore important because alterations in both neuronal excitability and pain processing constitute CSD and TGVS activation and sensitisation in migraine (5).

Earlier investigations of GABA in migraine using indirect methods that sampled saliva, cerebrospinal fluid (CSF) and blood have consistently reported increased GABA levels. Increased salivary GABA has been reported during the ictal period in people with migraine without aura, compared with headache-free periods, and compared with non-migraine controls (16). Similar results were reported as early as 1975 where elevated GABA levels were measured in the CSF during migraine attacks and not present when the participants were free of migraine headaches (17). Platelet GABA levels were found to be similar in people with migraine during headache free periods and controls, but were not measured during migraine attacks (18). Taken together, these studies suggest that GABA concentrations could be increased in the brain in people with migraine.

Direct measures of GABA are now possible using proton magnetic resonance spectroscopy (^{1}H-MRS). Until recently, detecting GABA using ^{1}H-MRS was difficult due to spectral overlap between GABA and other neurometabolites (19), resulting in large estimation errors. Recent technological advances now allow resolution of such spectral overlaps using specialised sequences such as Mescher-Garwood point resolved spectroscopy (MEGA-PRESS) (20). However, GABA resolved using such editing techniques contain substantial macromolecule contamination and as such is denoted as GABA+ and referred to as such in this study. The aims of this study were to determine and compare GABA+ concentration detected by ^{1}H-MRS using MEGA-PRESS sequence in people with migraine and asymptomatic individuals and to determine the diagnostic potential of GABA+ in classifying people as having migraine or not.

MATERIALS AND METHODS

Design and outcome measure

In this cross-sectional case-control study, we compared GABA+ levels in the brainin people with migraine with asymptomatic controls using ^{1}H-MRS. To eliminate possible confounding, the migraine and control groups were matched for age and gender. Area under the receiver operating characteristic (ROC) curve, optimal cut-off value, sensitivity, specificity, and positive likelihood ratio of concentration of GABA+ for migraine were also determined. This research was granted ethics approval by the Human Research Ethics Committee of the University of Sydney (Protocol Number 15048).

Participant inclusion

Twenty participants with migraine were matched for age and gender with asymptomatic controls. Participants were recruited through advertisements posted at university, consumer support groups and primary care sites from 27 May to 15 August 2013. Participants were aged between 19 and 64 years.

Participants in the migraine group were included if they were diagnosed with migraine by their attending neurologist/physician, fulfilled the International Classification of Headache Disorders (ICHD)-II criteria for migraine (21), and had at least one migraine attack per month. Participants in the control group were included if they did not experience regular headaches and had no headache in the last three months.

Participants in both groups were excluded if they: had non-migrainous headaches according to ICHD-II criteria; had a history of neck injury, claustrophobia, or severe depression (i.e., Depression Anxiety Stress Scales-21 score >21); were pregnant; had conditions that would compromise spectroscopy data (e.g. implants, tattoo, dental braces); or used medications known to alter GABA levels.

We conducted initial telephone screening of study volunteers to determine eligibility. We then interviewed and physically examined all potential participants to confirm classification according to ICHD-II criteria and to exclude those with non-migrainous or mixed classification headache. Participants with migraine provided information on history of migraine, frequency of episodes, typical location of headache, and headache intensity in the last month and in the last 24 hours. All participants provided written informed consent prior to participation.

Magnetic resonance spectroscopy data acquisition

Imaging was conducted at the Brain and Mind Research Institute imaging centre on a 3-Tesla GE Discovery MR750 scanner (GE Medical Systems, Milwaukee, Wisconsin) using an 8-channel phased array head coil. The following images were acquired in order: (a) three-dimensional sagittal whole-brain scout for orientation and positioning of the subsequent ^{1}H-MRS scans. To aid in the anatomical localisation of sampled voxels, (b) a T1-weighted magnetization prepared – rapid acquisition gradient echo (MP-RAGE) sequence producing 196 sagittal slices was acquired (TR=7.2ms; TE=2.8ms; flip angle = 10°; matrix 256x256; 0.9mm isotropic voxels) and (c) single voxel ^{1}H-MRS using MEGA-PRESS acquisition (20)(TR=1800ms; TE=68ms; NEX (phase cycling)=8; number of acquisitions=256; number of points=4096; spectral width=5000; voxel size=3x3x3 cm^3;total scan time=8:24)with two chemical shift-selective imaging pulses for water suppression. Spectra were shimmed to achieve full-width at half maximum (FWHM) of <13Hz. Anatomical localisation of the voxel placement was based on the Talairach and Tournoux brain atlas (22)and positioning was guided by the T1-weighted image.The centre of the voxel was defined on the T1-weighted image on the midline sagittal plane andpositioned at the posterior cingulate cortex in a location that encompassed Brodmannareas 23 and 3. The superior-posterior most edge of the voxel extended into the precuneus (Brodmannarea 7) and inferiorly into the retrosplenial cortex (Brodmannarea 29 and 30). To cover asmuch grey matter (GM) as possible and ensure the voxel did not encroach within the lateral ventricles or the splenium of the corpus callosum, it was then rotated (in the sagittal plane) and translated to the left (in the axial plane). The final position of the rotated voxel was lateral to the midline

posterior cingulate and posterior andsuperior to the splenium of the corpus callosum (see Figure 1).

Following ^{1}H-MRS acquisition, data were transferred offline for post processing of GABA+ using the Gannet software toolkit (23) In brief the data were first processed using the GannetLoad module which parses variables from the data headers and applies a line broadening of 3 Hz. Next, individual spectra were frequency- and phase-corrected using Spectral Registration (24). The data were then processed by the GannetFit module, which employs a single Gaussian model to fit the edited GABA+ signal and evaluates GABA+ concentration in institutional units (IU) relative to water. The quality of the data was determined by the overall "Fit Error" index of each subject. This index represents the standard deviation of the fitting residual divided by the amplitude of the fitted peaks, and thus a measure of the signal-to-noise ratio. Only spectra with a relative Fit Error of GABA+ below 10% were used for the subsequent statistical analyses. There was no statistical difference between the Fit Error, FWHM or the number of rejected shots between the two groups. Next, the Tarquin software package was used to estimate glutamate + glutamine (Glx) from the MEGA-edited spectra from edited on and off shots using the following parameters: sampling frequency=5000; transmitter frequency=127MHz; data points=4096; water cut off=45Hz; reference signal=H2O. Unsuppressed water data served as the internal reference for all water scaling. Next, the coordinates of the acquisition voxels for each participant were determined using the SAGE (Spectroscopy Analysis GE) software package and the reconstructed acquisition voxels for all participants were corrected for grey matter. GM correction was achieved by segmenting each participant's structural image into GM, white matter (WM) and CSF using the FAST4 algorithm as implemented in FSL (25) and volume fractions were calculated. All statistical

analyses were conducted on GM-corrected GABA+. Finally, the radiographers, neuroimaging expert who read the spectroscopy data and the neuroradiologist were blinded to group allocation.

Statistical analyses

The calculated sample size (n=17 per group) was based on a hypothesised true mean difference of 0.2 IU between groups and an estimated within group standard deviation of 0.2 IU with a significance level of 0.05 with 80% power. Allowing for about 15% attrition, we determined sample size to be 20 per group.

Descriptive statistics (median and interquartile range, IQR) were used to report participant demographics and headache characteristics given the nonparametric distribution of the data. GABA+ and Glx levels were compared between participants with migraine and their matched asymptomatic controls using Wilcoxon Signed Ranks Test. Pairs were excluded from analyses if either case or control data were missing.

The ROC curve was drawn and the sensitivity, specificity and area under the curve (AUC) were calculated to determine the diagnostic potential of GABA+ in discriminating between people with migraine and controls. An AUC of 1 would indicate that GABA+ correctly classifies all participants as having migraine or not, and an AUC of 0.5 or less would indicate that GABA+ has no discriminatory value (26). Interpretation of AUC varies and we used the following scale in interpreting the discriminative ability of GABA+ for migraine: AUC greater than or equal to 0.90 as excellent; AUC greater than or equal to 0.80 and less than 0.90 as good; AUC greater than or equal to 0.70 and less than 0.80 as fair; and AUC of less than 0.70 as poor. The optimal cut-off value for GABA+ was calculated by finding the minimum

distance on the ROC curve to the top of the y-axis, representing the point on the curve closest to an ideal point where sensitivity and specificity are equal to one (27). Positive likelihood ratio for the optimal cut-off value was calculated using the formula sensitivity divided by one minus specificity.

Statistical analyses were conducted using Statistical Package for Social Sciences® statistical software, version 21 (SPSS Inc., Chicago, Illinois, USA) for Windows.

RESULTS

Participants

Twenty people with migraine and 20 age- and gender-matched controls participated in this study. Figure 2 describes the flow of participants through the study and reasons for exclusion of volunteers. Spectroscopy data were of sufficient quality to allow analysis from 19 participants each from migraine and control groups.

Twenty eight (70%) participants were female. The median age and IQR were 31.5 and 28-47.2 years, respectively (Table 1). Participants with migraine reported, on average, symptoms for more than 15 years and experienced approximately three episodes in a month. Average headache intensity in the preceding month was rated moderate to severe, and in the preceding 24 hours, rated none to moderate. No participant in the migraine group had migraine-related symptoms on the day of spectroscopy and none were taking GABAergic drugs for at least a month prior to participation in the study (Table 1).

Outcomes

The concentration of GABA+ in participants with migraine was significantly higher [median (IQR)] 1.41 (1.31-1.50) IU] than their age-matched controls [median (IQR)] 1.18 (1.12-1.35) IU]; *P*=0.002) (Figure 3). There was no difference in Glx between migraine and control groups (*P*=0.313).

GABA+ concentration appears to have good accuracy for classifying individuals as having migraine or not [AUC (95% confidence interval) = 0.837 (0.71 – 0.96), *P*<0.0001)] (Figure 4).

The optimal GABA+ cut-off value for the detection of migraine was 1.30 IU, with sensitivity of 84·2%, specificity of 68·4% and positive likelihood ratio of +2.67 (Table 2).

Post-hoc analyses demonstrate no statistically significant correlation between GABA+ concentration and age (correlation coefficient = -0.007, *P* = .950) and headache severity (correlation coefficient = .313, *P* = 192), thus excluding these variables as potential confounders.

DISCUSSION

This study is the first to provide direct evidence for the postulated role of GABA+ in migraine pathophysiology. Utilising the MEGA-PRESS sequence specific for resolving GABA+, we obtained accurate *in vivo* levels of GABA+ not previously possible (20).In so doing, our results demonstrated higher concentration of GABA+ in participants with migraine compared with their matched controls.

Our findings are consistent with previous work showing increased GABA concentration in the human cerebral cortex during painful stimulation (15), and corroborate earlier biochemical studies that suggested GABA levels may be increased in the brain, based on indirect methods of measurement (16, 17). Further, our results

show that GABA+ levels are elevated during the interictal period. Our results differ from those of an earlier study that reported no significant differences in GABA concentration between people with migraine and controls (13). This difference in findings is potentially because the spectroscopy technique we used was specific for GABA+.

Results of *post hoc analyses* showing no statistically significant correlation between GABA+ concentration and headache severity differ from an earlier report of lower GABA levels in people with migraine with severe headaches(13). We think this difference in findings may be explained by the lack of variability in headache intensities of our participants (Table 1). Whether similar results would be obtained from people with migraine with characteristics different from the participants of this study remains to be investigated.

There are several methodological limitations associated with our study that warrant further discussion. Firstly, the MEGA-PRESS technique, which we employed to detect GABA, is not able to separate pure GABA from the macromolecule component that arises from spins coupled at 3 and 1.7ppm. As such, the GABA+ signal we report needs to be interpreted with caution, as it is likely to have macromolecule contamination. Next, the GABA+ signal in our study represents total GABA within the acquired voxel and is derived from both intra- and extracellular pools. This limits conclusions that can be made as to the relationship between the GABA ^{1}H-MRS signal and direct inhibitory processes. Further, we cannot explain the cause or mechanism of increased GABA+ levels because of the cross-sectional design of our study. However, the possibilities are that the increased GABA+ concentration could be the result of a previous migraine attack, a characteristic brain state prior to an attack or a feature of the “migraine brain” that initiates an attack. Of these, we

speculate that the increased GABA+ level in migraine contributes to the initiation or propagation of symptoms of migraine. This supposition is based on recent evidence that GABA causes vasodilation during the interaction between neurons, blood vessels and astrocytes during CSD and TGVS activation (9, 28, 29). We further propose that the increased GABA+ level is linked with the hypothesised altered excitability of cortical neurons during the interictal period (30). This is consistent with suggestions of increased GABA resulting from neurogenic inflammation (31), as is believed to occur in migraine. Finally, data on the consumption of substances that may affect GABA concentrations such as nicotine (cigarette), alcohol and caffeine were not collected.

Potential explanations for the increased GABA+ concentration could be an increase in the number of GABAergic neurons, changes in intracellular (e.g. increased pre-synaptic GABA due to changes in GABA synthesis or receptor expression, degradation or reuptake) or extracellular GABA levels (15, 32). Of these possibilities, we propose that the increased GABA+ level is due to an increase in intracellular GABA synthesis resulting from an altered function of its synthesising enzyme, glutamic acid decarboxylase (GAD) (33). This enzyme appears to be expressed only in GABAergic neurons and therefore is a good marker for neurons that use GABA as a neurotransmitter.

Results of ROC curve analysis demonstrate that GABA+ has good predictive ability for migraine, identifying people with GABA+ concentrations equal to or greater than 1.30IU as having migraine. These findings indicate the utility of GABA+ as a potential biomarker for migraine and are likely to contribute to more specific migraine diagnosis and possibly even targeted and individualised treatment. At present, no biomarker for migraine has been systematically validated (4). Further

research could determine the validity of GABA+ in discriminating between people with migraine, other headache types and controls. The cut-off value calculated from this study may be used in further investigations aimed at identifying objective diagnostic biomarkers for migraine.

This study provides new information on altered GABA+ in migraine and contributes to clarifying the neurobiological mechanisms of migraine. GABA has been previously shown to cause vasodilation during neurovascular coupling (29), as in that which occurs during CSD and TGVS activation (9).Given the link between GABA and the generally accepted theories of migraine pathophysiology, evidence from this study indicates that GABA+ could be a candidate diagnostic marker for migraine. Future research could also include investigations on the mechanisms causing the increased GABA+ in migraine through randomised controlled trials of drugs targeting GAD and on the nociceptive function of the increased GABA through longitudinal studies.

CONCLUSIONS

Our results demonstrate altered GABA+ metabolism in migraine when measured using magnetic resonance sequences specifically tailored to resolve GABA+. Our study thus adds to the scarce evidence on the putative role of GABA in migraine and provides basis to further explore the causal relationship between GABA+ and the pathophysiology of migraine. Results of this study also suggest good diagnostic accuracy for GABA+ for migraine and offer new research directions for migraine diagnosis.

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Conflict of interest statements

All authors report no disclosures.

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Table 1.Characteristics of participants (*n* =40)

PARTICIPANT CHARACTERISTICS	**GROUP**	
	MIGRAINE	**CONTROL**
	(*n*=20)	(*n*=20)
Demographic characteristics		
Age [median (IQR)] *(years)*	33 (28.25-47.25)	30 (26.5 – 47.5)
Gender (female) *[n(%)}*	14 (70)	14 (70)
Headache Characteristics		
History of migraine [median (IQR[a])] *(months since first episode)*	180 (60-288)	
Frequency of headache in a month [median (IQR)] *(n)*	2.75 (1.5-8.5)	
Episode duration [median (IQR)] *(hours)*	48 (24-48)	
Average headache intensity last month [median (IQR)] (0-10)[b]	6 (6-8)	
Average headache intensity last 24 hours [median (IQR)] (0-10)[b]	1.5 (0-6)	
Migraine Medications		
Non-steroidal anti-inflammatory drugs (number of participants) (*n*)	6	
Triptans (number of participants) (*n)*	4	
Paracetamol (number of participants) (*n)*	4	
Beta blockers (number of participants) (*n)*	2	
Selective serotonin reuptake inhibitor (number of participants) (*n)*	1	

[a]IQR = interquartile range
[b]Headache intensity: Numerical rating scale 0-10; 0=no pain, 10 = worst possible pain

Table 2. Distribution of GABA+ values in migraine (*n*=20) and control groups (*n* =20)

	Migraine group	Control group
GABA+ > 1.3IU[a]	16	6
GABA+ < 1.3IU	3	13
Missing data	1	1

[a]IU = institutional units

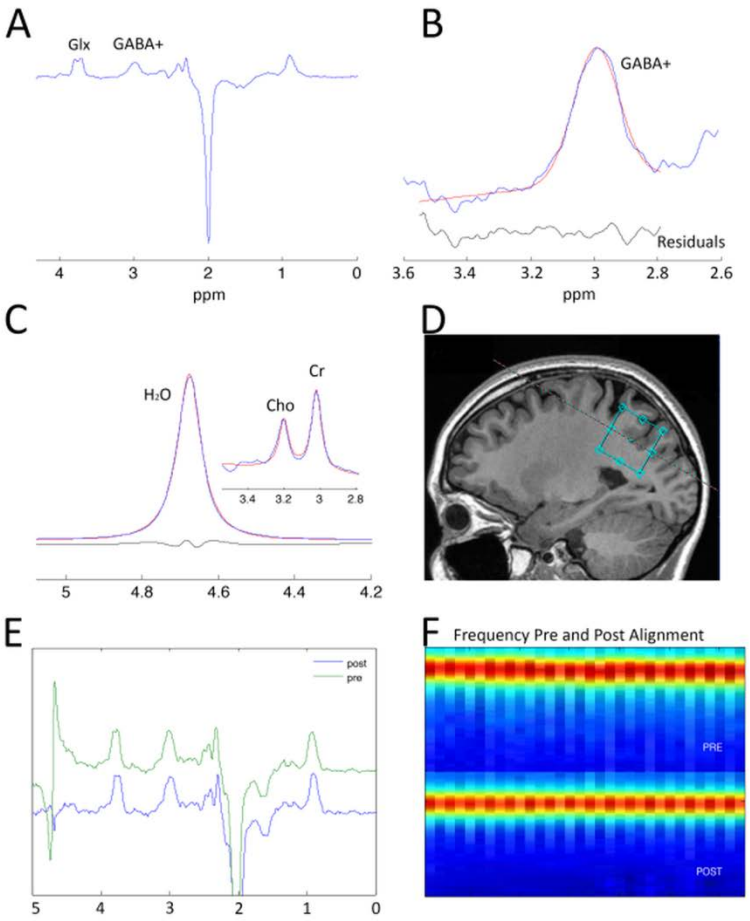
Figure Legends

Figure 1. Fitted GABA+ resolved data using MEGA-PRESS. (A) Raw GABA edited spectrum highlighting GABA+, Glx signals. (B) Modelled data (red), raw GABA+ signal (blue) and residuals (black) exemplifying the accuracy of the data fit. (C) Representative water data [inset: unedited raw data at 3.0ppm highlighting creatine (Cr) and choline peaks]. (D) T1-weighted structural image showing the anatomical localisation of 3x3x3 cm^3acquisition voxel. (E) Processed GABA+-edited difference spectrum before (green) and after (blue) frequency and phase correction. (F) Cr signal over the duration of the experiment. The y-axis represents the frequency (in ppm) of the Cr signal and shows that there is negligible drift over this period.

Figure 2. Flow of participants through the study.

Figure 3. Concentration of GABA+ in participants with migraine and asymptomatic controls. Data are presented as box plots, where the boxes represent values between the 25th and 75th percentiles (interquartile range, IQR), the line within the box, the median, and the bars outside the box (whiskers), the range of data. Outliers are plotted as circles (1.5×IQR or more below the 25th or above the 75th percentile) and stars (3×IQR or more below the 25th or above the 75th percentile).

Figure 4. Receiver operating characteristic curve evaluating GABA+ in people with migraine and controls. Area under the curve = 0.837 (95% confidence interval 0.71-0.96), $P < 0.0001$



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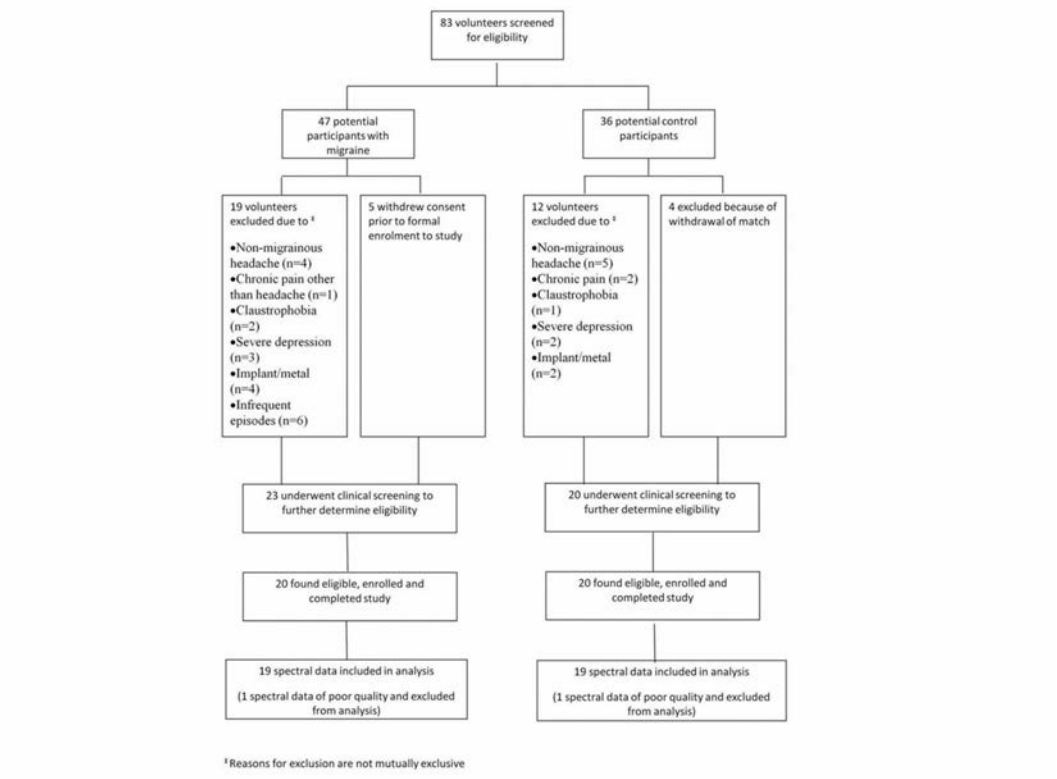

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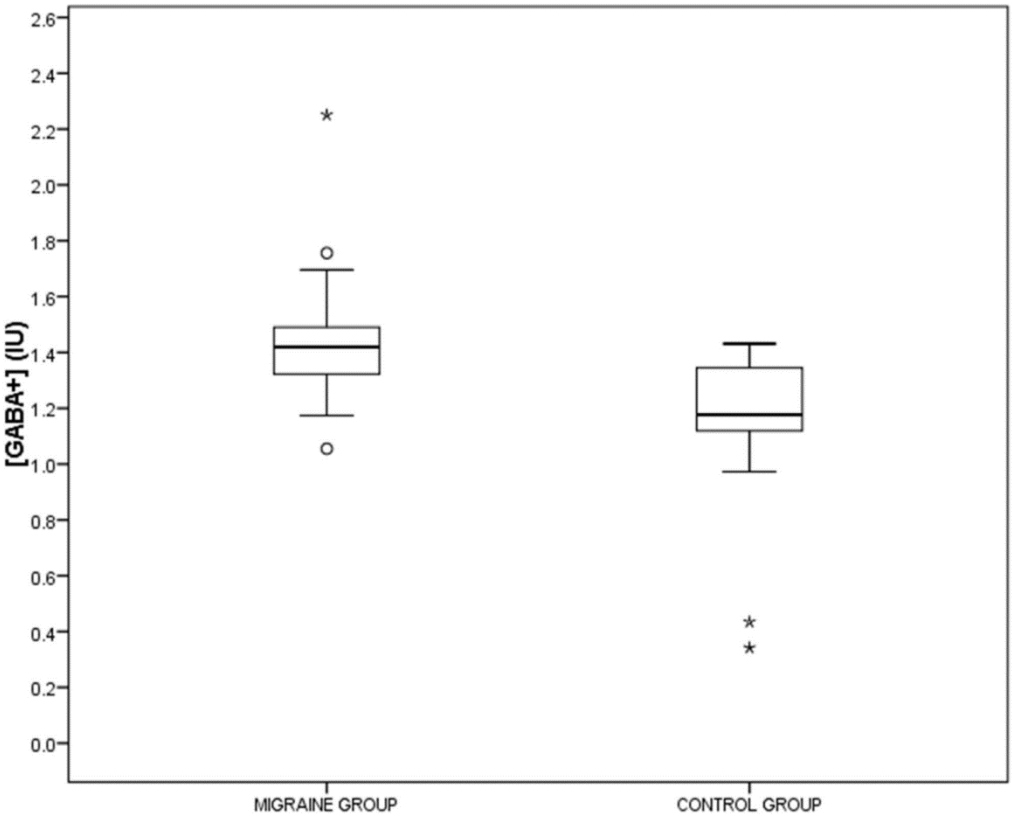

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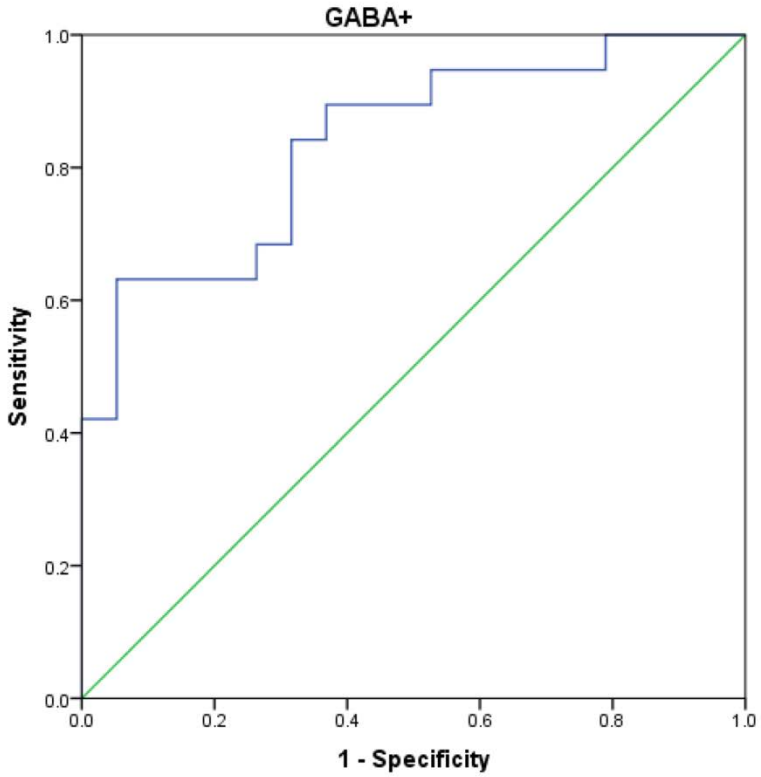

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CHAPTER FOUR

The Association Between Clinical Characteristics of Migraine and Brain GABA Levels: An Exploratory Study

Chapter Four is the peer reviewed version of the following article: Aguila ME, Rebbeck T, Leaver AM, Lagopoulos J, Brennan PC, Hübscher M, ,Refshauge KM. The association between clinical characteristics of migraine and brain GABA levels: An exploratory study.*JPain*.2016; 17:1058–67.doi:10.1016/j.jpain.2016.06.008, which has been published in final form at http://www.jpain.org/article/S1526-5900(16)30109-2/fulltext; with permission from the American Pain Society.

Authorship Statement

As co-authors ofthe paper “The association between clinical characteristics of migraine and brain GABA levels: An exploratory study”, we confirm that Maria Eliza Ruiz Aguila has madethe following contributions:

- Conception and design of the research
- Acquisition of data
- Analysis and interpretation of data
- Drafting and revising of the manuscript and critical appraisal of its content

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Signed:	Jim Lagopoulos	Date:	31 March 2017
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Signed:	Kathryn M Refshauge	Date:	31 March 2017

THE ASSOCIATION BETWEEN CLINICAL CHARACTERISTICS OF MIGRAINE AND BRAIN GABA LEVELS: AN EXPLORATORY STUDY

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Disclosures

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THE ASSOCIATION BETWEEN CLINICAL CHARACTERISTICS OF MIGRAINE AND BRAIN GABA LEVELS: AN EXPLORATORY STUDY

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Abstract

Migraine is prevalent and disabling yet is poorly understood. One way to better understand migraine is to examine its clinical characteristics and potential biomarkers such as gamma-aminobutyric acid (GABA). The primary objective of this study was to explore whether relevant disease characteristics of migraine are associated with brain GABA levels. Twenty adults fulfilling the established diagnostic criteria for migraine and 20 age- and gender-matched controls completed this cross-sectional study. Pain, central sensitization, negative emotional state, and perceived disability were measured using Short-form McGill Pain Questionnaire-2, Central Sensitization Inventory, Depression Anxiety Stress Scales-21, and Headache Impact Test-6, respectively. Secondary analysis of brain GABA levels of the same

cohort measured using proton magnetic resonance spectroscopy was conducted. The migraine group had significantly higher scores on pain, central sensitization and disability than the control group. Correlation analyses showed fair positive association between GABA levels and pain and central sensitization scores. No association was found between GABA levels and emotional state and disability. These findings are preliminary evidence supporting the use of questionnaires and GABA levels in characterizing migraine better and broadening the diagnostic process. These findings also strengthen the rationale for the role of GABA in migraine pathophysiology and corroborate the potential of GABA as a migraine biomarker.

Perspective

Higher pain and central sensitization scores were associated with increased brain GABA levels in individuals with migraine. These findings offer preliminary evidence for the usefulness of measuring pain and central sensitization in migraine and provide some support for the possible role of GABA in migraine pathophysiology and its potential as a diagnostic marker.

Key Words

GABA, migraine disorders, headache, central sensitization, disability, questionnaires

Introduction

Migraine is among the most prevalent and disabling chronic conditions globally [43]. Despite the burden that migraine imposes on the individual and society [26,27], its underlying mechanisms remain poorly understood. Consequently, migraine diagnosis is nonspecific [44] and its treatment may be inadequate [41]. A better understanding of migraine, and ultimately its diagnosis and treatment, may be gained by deeper investigation of characteristic clinical features and their relationship with potential biomarkers.

One possible biomarker for migraine is gamma-aminobutyric acid (GABA). GABA is the predominant inhibitory neurotransmitter in the central nervous system [13] and is an important regulator of the balance between excitation and inhibition in the brain [30]. As such, GABA has been implicated in clinical conditions thought to involve an imbalance between excitatory and inhibitory processes. Interestingly, recent studies have also implied that GABA mediates excitatory actions as well, for example in the development of epilepsy [45]. We have recently published findings that brain GABA levels are significantly higher in people with migraine compared to age- and gender-matched controls and have demonstrated that GABA has good diagnostic potential for migraine [1]. These findings were the first direct evidence for the putative role of GABA in migraine and its potential as a migraine biomarker. Following the three-stage model suggested by Hlatky and colleagues [22] to validate biomarkers, it is then necessary to establish migraine characteristics associated with GABA and finally to determine that screening using the biomarker leads to targeted treatment and eventually reduces disease burden. The second stage of validation might be furthered by exploring associations of GABA levels with important clinical characteristics.

Four important clinical characteristics of migraine are pain, central sensitization, negative emotional state and disability. Pain is important in migraine diagnosis to an extent that pain characteristics help distinguish migraine from other headache types [19,20].

Headache pain that is moderate to severe, throbbing and unilateral is characteristic of migraine [20]. Central nervous system sensitization involves decreased pain thresholds and exaggerated responses to noxious and nonnoxious stimuli [9]. Sensitization is commonly manifested in migraine as hyperalgesia [10] and cutaneous allodynia [9] such as pain when combing the hair, exposed to heat or cold, or wearing eyeglasses [28]. Symptoms of negative emotional states such as depression, stress and anxiety have been reported to be more frequent in people with migraine compared to controls [8,46] and associated with the tendency to perceive normal bodily sensations as disturbing [46]. Level of disability based on scores on self-report questionnaires has been consistently reported to be higher in people with migraine than people with other headache types [e.g. 33,40] and those without headaches [24]. An example of disability which differentiates migraine from other headache types is the avoidance of physical activity or reported aggravation of symptoms by routine physical activity during a migraine episode [19,20].

It is possible that pain, central nervous sensitization, emotional state, and disability are associated with GABA levels in migraine. First, pain has been shown to be modulated by GABA [13] and therefore any change in pain may be associated with changes in GABA levels. Second, central nervous system sensitization in migraine is theoretically linked with GABA levels considering one proposed pathophysiological mechanism for migraine. It has been hypothesized that a cortical excitatory – inhibitory imbalance in migraine leads to headache and other symptoms [42]. GABA may have a putative role in this imbalance. Third, symptoms of emotional states have been shown to involve the GABA system. There is abundant evidence from human and animal studies that anxiety and depression are associated with reduced GABAergic function, yet recent animal studies indicate that symptoms of depression reduce when GABA action through GABA-B receptors is blocked [32]. Fourth, disability in migraine may be viewed as a manifestation of dysregulation in

brain and/or body systems that may have developed in the course of repeated migraine episodes [4]. GABA is a potential mediator in this dysregulation, given its role in regulating excitatory-inhibitory balance in the brain [30]. The potential relationships between GABA levels and central nervous sensitization, emotional state, and disability have not been investigated in migraine.

The primary aim of this study was to explore whether relevant clinical characteristics of migraine including pain, central nervous system sensitization, emotional state and headache-related disability are associated with brain GABA levels. A secondary aim of this study was to compare clinical characteristics, particularly central nervous sensitization and emotional state, between people with migraine and asymptomatic controls. By exploring the relationship of clinical characteristics with GABA levels, we aim to build on the process of validating GABA as a migraine biomarker, inform migraine diagnosis and better understand migraine.

Methods

Design

A secondary analysis of a previous cross-sectional case-control study that compared GABA levels between people with migraine and age-and gender-matched controls [1] was performed to explore the association between GABA levels and migraine clinical characteristics. This research was granted ethics approval by the Human Research Ethics Committee of the University of Sydney (Project Number 2012/581).

Participants

Participants with migraine were eligible for the original study if they were diagnosed with migraine by their attending neurologist/physician and if their headache features fulfilled

the International Classification of Headache Disorders (ICHD)-II criteria for migraine [19]. Participants in the control group were included if they did not experience recurrent headaches, had never experienced a migraine episode, and were not experiencing significant pain nor pain longer than 3 months at the time of the study. Participants in the control group were matched to the migraine group for age and gender. Participants in both groups were excluded if they used medications known to alter GABA levels. Complete inclusion and exclusion criteria and other details of participant recruitment are described elsewhere [1]. In brief, participants were recruited through advertisements posted at university, consumer support groups and primary care sites.

Procedures

We conducted initial telephone screening of potential participants to determine their eligibility. All participants in the migraine group then underwent an interview and physical examination to confirm classification according to ICHD-II criteria and to exclude headache participants with non-migrainous or mixed classification headache. Controls were also interviewed and physically examined.

Participants with migraine provided information on headache characteristics including history of migraine, frequency of episodes, typical duration of each migraine episode, and headache intensity in the last month using the visual analogue scale (VAS: with anchors at 0 and 10: 0 = no pain, 10 = worst pain possible). In addition, participants described the location of their headache, associated symptoms, and any medication and/or treatment received.

All participants satisfying the inclusion and exclusion criteria completed self-administered paper-and-pen questionnaires that were arranged in a standardized manner to ensure consistency. Questionnaires, described below, included information about pain and central nervous system sensitization experience, emotional state, and disability. Completed

questionnaires were checked for any misunderstood or inadvertently missed item. Participants then underwent proton magnetic resonance spectroscopy to determine brain GABA levels. All participants provided written informed consent prior to participation.

Outcomes

Brain GABA Levels

Brain GABA levels were measured in institutional units by single-voxel proton magnetic resonance spectroscopy using the Mescher-Garwood point resolved spectroscopy sequence (TR = 1800 ms; TE = 68 ms; number of excitations (phase cycling), 8; number of acquisitions, 256; number of points, 4096; spectral width, 5000; voxel size, $3 \times 3 \times 3$ cm^3; total scan time, 8 min 24 s). The voxel was positioned lateral to the midline posterior cingulate, and posterior and superior to the splenium of the corpus callosum (Figure 1). Spectroscopy was performed during the interictal period for participants in the migraine group; no one had migraine-related symptoms on the day of testing. Details of the full spectroscopy methods and parameters are reported elsewhere [1].

Clinical Characteristics Based on Self-Report Questionnaires

Migraine pain characteristics were described using the Short-form McGill Pain Questionnaire-2 (SF-MPQ-2) comprising 22 pain quality descriptors scored for intensity on a 0 to 10 Likert scale. SF-MPQ-2 has been validated for use for neuropathic pain [12], as is thought to be present in migraine [3]. For this study, the top and bottom quartiles of intensity scores were considered to reflect the words that people with migraine used the most and least, respectively, to describe their headache. SF-MPQ-2 also provided information on the multidimensional nature of the migraine pain experience by generating summary scores for

continuous, intermittent, neuropathic and affective pain subscales, aside from the total SF-MPQ-2 scores.

Presence of symptoms of central nervous system sensitization was measured using the Central Sensitization Inventory (CSI) [31]. The CSI is a highly reliable and valid screening tool for central sensitivity syndromes (CSS), that is, diseases that have central sensitization as a common feature [34]. Scores of $\geq$40 indicate possible CSS, with higher CSI scores reflecting a higher degree of sensitization. CSI discriminates people with central sensitivity syndromes, including migraine, from those without pain, with a sensitivity = 81%; specificity = 75% [34] and from those with chronic pain without central sensitivity symptoms (sensitivity = 83%; specificity = 55%) [35].

Emotional state was measured using the Depression Anxiety Stress Scales-21 (DASS-21) [29]. The DASS-21 is a short, valid and highly reliable instrument providing depression, anxiety and stress scores based on frequency and severity of symptoms [21]. It has been used to investigate the association of negative emotional state with migraine [6,18,36].

Perceived levels of disability were measured using the Headache Impact Test-6^{TM} (HIT-6), a brief questionnaire on the impact of the headache on work and daily activities [25]. The HIT-6 was shown to have high reliability and good validity in discriminating migraine from other headaches [25].

Statistical Analyses

Spearman's rho and Kendall's tau correlations were used to explore associations between GABA levels and normally and non-normally distributed clinical characteristics, respectively, in individuals with migraine. Correlation coefficients were interpreted as follows: greater than.75, good to excellent relationship; 0.50 to 0.75, moderate to good relationship; 0.25 to 0.50, fair relationship; and 0.00 to 0.25, little or no relationship [39].

These correlation analyses were performed after normality of the distribution of data was tested using the Shapiro-Wilk statistic.

We conducted area under the receiver operating characteristic (ROC) curve analysis for clinical characteristics that had at least a fair association with GABA levels and that might be useful in discriminating migraine. To this end, we computed for optimal cut-off value, area under the curve, sensitivity, and specificity of the questionnaire score. Based on these calculations, we interpreted diagnostic accuracy to be excellent, good, fair or poor [47].

Descriptive statistics (frequency, mean and standard deviation, SD, median and interquartile range, IQR) of headache characteristics and self-report questionnaire scores were used to report clinical characteristics. The Wilcoxon signed rank test was used to determine differences in clinical characteristics based on questionnaire scores between migraine and control groups given that not all were normally distributed. Pairs were excluded from analysis if either case or control data were missing. Glass's $\triangle$ was calculated to compare the difference between mean scores of the migraine and control groups.

Statistical analyses were conducted using Statistical Package for Social Sciences® statistical software, version 21 (SPSS Inc., Chicago, Illinois, USA) for Windows. Significance level was set at 0.05.

As this was an exploratory study using secondary analysis of brain GABA levels from a previous cross-sectional case-control study [1], the sample size of this present study was based on that of the previous study (n = 40). This sample size was powered to detect group differences in brain GABA levels.

Results

Participants

Twenty people with migraine and 20 age- and gender-matched controls participated in this study. The median age (IQR) of the migraine group was 33 (28–47) years while the median age of the control group was 30 (26–48) years. Fourteen out of 20 (70%) participants of each group were female. The average duration of migraine symptoms was 15 years, with a frequency of three to five times per month (Table 1). Migraine characteristics of the participants (Table 1) were consistent with the ICHD diagnostic criteria for migraine. Most participants reported more than one location of headache, with 85% reporting temporal location and 80% reporting frontal location (Figure 2).

Participants most commonly chose aching (95%), tiring-exhausting (80%), throbbing (75%), sickening (70%), and sharp (65%) from the SF-MPQ-2 to describe their headaches (Figure 3). More than half the participants with migraine (55%) were not taking migraine medications at the time of assessment and had neither sought physical treatment such as physiotherapy nor alternative treatment such as acupuncture (Table 1).

Of all the variables considered, only the following variables were normally distributed: history of migraine, intensity of headache in the last month, and scores on HIT-6, CSI, MPQ-continuous, MPQ-affective, and MPQ Total scores.

Association between Clinical Characteristics and GABA Levels among People with Migraine

There was fair positive association between GABA levels and pain scores, specifically total SF-MPQ-2 scores ($\rho = .47$, $P = 0.04$) and SF-MPQ-2 scores on intermittent ($\tau = .33$, $P = 0.04$), neuropathic ($\tau = .37$, $P = 0.03$) and affective ($\rho = .49$, $P = 0.03$) pain subscales (Table 2 and, Figure 4A). There was also fair positive association between GABA levels and scores on the CSI ($\rho = .48$, $P = 0.03$) (Figure 4B). GABA levels were not associated with headache history, frequency, duration or intensity, continuous pain domain

on MPQ, depression, anxiety and stress scales of DASS-21, nor levels of disability ($P > 0.05$; Table 2).

Of those variables having fair association with GABA levels, only CSI scores were suitable for ROC analysis because both migraine and control groups had scores greater than 0 on the CSI. Results of this analysis revealed that CSI appears to have good accuracy for classifying individuals as having migraine or not [AUC (95% confidence interval) = 0.88 (0.76-1.00), $P < 0.001$)] (Figure 5). The optimal CSI cut-off score to distinguish people with migraine from those who do not get regular headaches was 22.5, with sensitivity of 95%, specificity of 80% and positive likelihood ratio of +4.75.

Clinical Characteristics of Migraine and Control Groups Based on Self-Report Questionnaires

There were significant differences between groups for scores on all of the self-report questionnaires (Table 3). The two groups differed the most in their scores on HIT-6 scores, SF-MPQ-2 continuous pain and CSI, as shown by their respective Glass's $\triangle$. Notably, there was no statistically significant between-group difference for the anxiety scale of DASS-21. Participants from both groups had scores categorized as "normal" for this scale.

Discussion

Our results show that pain and central sensitization scores had a fair positive association with GABA levels in migraine. These results support a putative role for GABA in migraine pathophysiology particularly where migraine presents with moderate to severe headache and central nervous system sensitization. This association between these migraine features and GABA also provides some further support in validating GABA as a potential biomarker for migraine.

GABA levels were associated with three of the four summary scales of pain quality and severity contained in the SF-MPQ-2, namely intermittent, neuropathic and affective pain. People with higher pain scores on SF-MPQ-2 scores tended to have higher GABA levels. These results give rise to the question whether the observed relationship between GABA levels and pain scores are characteristic of migraine or of any pain condition. We believe that the association between increased GABA levels and higher pain scores indicates a change in brain chemistry specific to migraine or chronic episodic headache for three reasons. First, we measured GABA levels during the interictal period, when participants were free of headache. Second, two participants in the control group had mild pain in the limb. Third, increased GABA levels in migraine oppose the decreased GABA levels reported in other pain conditions from previous studies, although measured from different brain regions (from the insula in fibromyalgia [15] and thalamus in people with spinal cord injury with neuropathic pain compared to those without neuropathic pain [17]. The association between GABA levels and pain scores also implies that SF-MPQ-2 may be used as a basis for inferring about GABA levels when spectroscopy data are unavailable. Interestingly, GABA levels were not associated with headache intensity based on participant rating of their usual headaches. We speculate that the difference in findings is because participants considered pain differently when presented with words on the SF-MPQ-2 than when asked to rate their usual headaches. Using the SF-MPQ-2, participants rated the intensity associated with the specific words. On the other hand, when asked to rate the intensity of their usual headaches, participants could be thinking of the whole headache experience, how the headache affected their lives or how long they had been dealing with the symptoms.

Increased GABA levels were associated with higher central sensitization scores. This means that increased GABA levels are most likely to be higher when central sensitization symptoms are more frequent. One possible explanation for this relationship may be the role

of GABA in regulating excitatory-inhibitory balance in the brain [30]. The increased GABA levels in migraine may cause abnormal excitability of the trigeminovascular system, as previously postulated for migraine [1,42]. This explanation is plausible given that most of the participants reported having photophobia and/or phonophobia, both considered clinical expressions of sensitization [7,10,42]. We have previously reported that glutamate + glutamine measured from the same cohort did not differ between the migraine and control groups [1]. These findings support the role of increased GABA in the altered excitability of the brain. Another possible explanation for the relationship between increased GABA levels and higher sensitization is based on the role of GABA in neurovascular coupling. GABA has been shown previously to cause vasodilation during neurovascular coupling [23] where cortical blood flow adjusts according to cortical activity. Neurovascular coupling may be impaired in migraine, leading to the progression of migraine symptoms. Therefore the relationship between increased GABA levels and higher central sensitization scores may also be indicative of a role for GABA in migraine symptoms. Further, results of ROC curve analysis indicate that people with CSI scores $\geq$ 22.5 are nearly five times more likely to have migraine than those with scores below this. This cutoff score is lower than the previously reported CSI cutoff score of 40 to identify central sensitization syndromes [34,35], suggesting the possible specific use of the CSI for migraine identification. The CSI provides information beyond ICHD criteria and therefore broadens the diagnostic process and enhances the clinician's appreciation of the patient's experience.

GABA levels were not associated with headache characteristics, emotional state and perceived disability in this cohort. Our results differ from a previous report showing lower GABA levels in more severe headache [2]. The lack of association in this present study may be due to the timing of our GABA measurement (interictal period) and also possibly because

our participants were more homogenous with generally more frequent and more severe headaches than the cohort reported on by Bigal and colleagues [2].

The homogeneity of headache characteristics of the migraine cohort was ideal for investigating potential disease biomarkers [38] and therefore was one of the strengths of this study. We also believe that we were able to detect an association between GABA and pain and central sensitization partly because GABA levels were measured from the cingulate cortex, previously shown to have altered functioning in pain states [14]. Localizing the voxel in this region also allowed the use of a large voxel to maximize signal-to-noise ratio for GABA [1].

Although this study provides new insights on migraine characterization and the role of GABA in pathophysiology, some limitations should be considered. First, GABA levels were measured from just one region to achieve good signal quality in a short acquisition time. We do not know if increased GABA levels, and therefore their association with clinical characteristics, are different in other brain regions. Second, spectroscopy was done during the interictal period so it is not possible to tell if GABA levels are also increased during the ictal period. It seems reasonable to speculate, however, that GABA levels might also be altered if measured during the ictal period. This speculation is based on a previous proposal that the brain in migraine changes in function and structure over time due to repeated migraine episodes [4]. These changes may include a dysregulation of the excitatory-inhibitory balance in the brain involving GABA. Correspondingly, we speculate that GABA levels measured during the ictal period might also be associated with symptoms of central sensitization and pain. Third, this study was intended to be exploratory and therefore was not set up for multivariate analyses and adjustment for multiple comparisons. For the same reason, we did not design the study to include the presence or absence of aura symptoms nor the varied

medications of the participants as covariates in the analyses. Lastly, DASS-21 and HIT-6 scores of our participants had insufficient variability for rigorous analysis.

Further studies are therefore required to confirm the results of our study. Larger, longitudinal cohort studies may investigate the association between GABA levels and clinical characteristics in migraine and other headache types during the ictal and interictal periods. Additional factors that may be related with GABA levels in migraine may be investigated such as other neurotransmitters, presence or absence of aura, and medications. Similarly, it will be useful to determine whether questionnaires can differentiate migraine from other headache types. Further studies can also build on results of this study to validate GABA as a biomarker and address the lack of established biomarkers for migraine [11].

Nevertheless, results of this study strengthen the rationale for the role of GABA in migraine pathophysiology and thus add to the understanding of migraine. The association of pain and central nervous system sensitization symptoms with GABA levels in migraine suggests that patients' subjective reports correlate with brain chemistry. Hence assessing these clinical characteristics using SF-MPQ-2 and CSI is useful, allows more specific characterization of migraine. It is hoped that a better understanding of migraine will eventually pave the way for effective targeted treatment options.

Conclusions

Increased GABA levels were associated with increased pain and more frequent central sensitization symptoms in migraine. These findings contribute to the understanding of migraine. These findings also provide early evidence for the usefulness of measuring GABA and pain and central sensitization in characterizing migraine better and broadening the diagnostic process. In addition to enhancing diagnosis and assessment, using self-report questionnaires in clinical practice may facilitate understanding of a patient's headache

experience. This new information on the association of clinical characteristics of GABA levels in migraine brings us a step closer to demonstrating the validity of GABA as a migraine biomarker.

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Figure Legends

Figure 1. Placement of the single voxel in the (A) axial, (B) coronal, and (C) sagittal planes for proton magnetic resonance spectroscopy analysis

Figure 2. Typical locations of headache as reported by participants with migraine (visual representation according to percentage of participants reporting the site of pain)

Figure 3. Top and bottom five pain descriptors chosen by participants with migraine to describe their headaches (n = 20)

Figure 4. Scatterplot with regression line showing positive association between brain GABA levels and scores on (A) Short-form McGill Pain Questionnaire-2 (ρ = .47, P = 0.04) and (B) Central Sensitization Inventory (ρ = .48, P = 0.03) in the migraine group (n = 20)

Figure 5. Receiver operating characteristic curve evaluating CSI scores of people with migraine and controls. Area under the curve = 0.88 (95% confidence interval 0.76-1.00), P<0.001

Table Legends

Table 1. Descriptive migraine characteristics (*n* = 20)

Table 2. Association of GABA levels and clinical characteristics of migraine using Spearman's rho, ρ, or Kendall's tau, τ, correlation coefficient (*P* values)

Table 3. Comparison of clinical characteristics based on self-report questionnaires between migraine and control groups (*n* = 40)

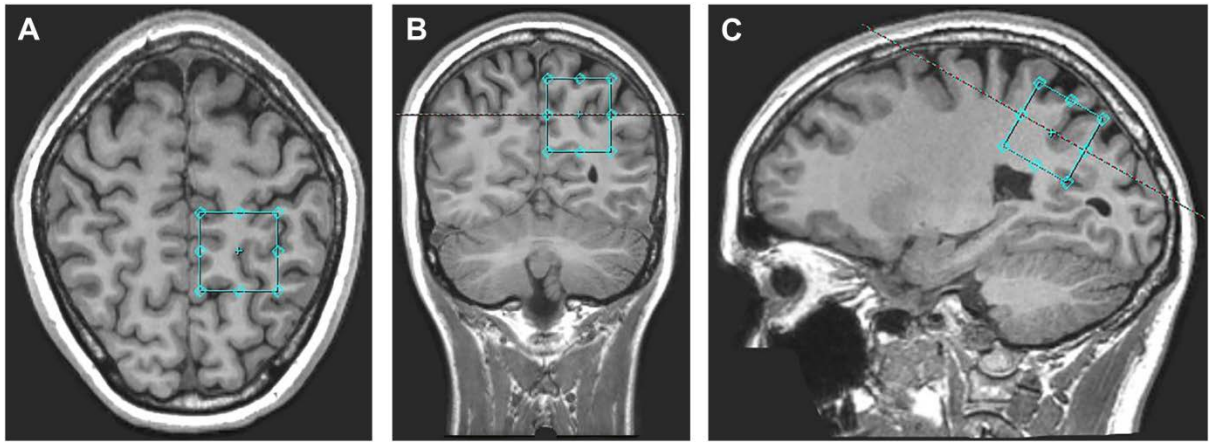
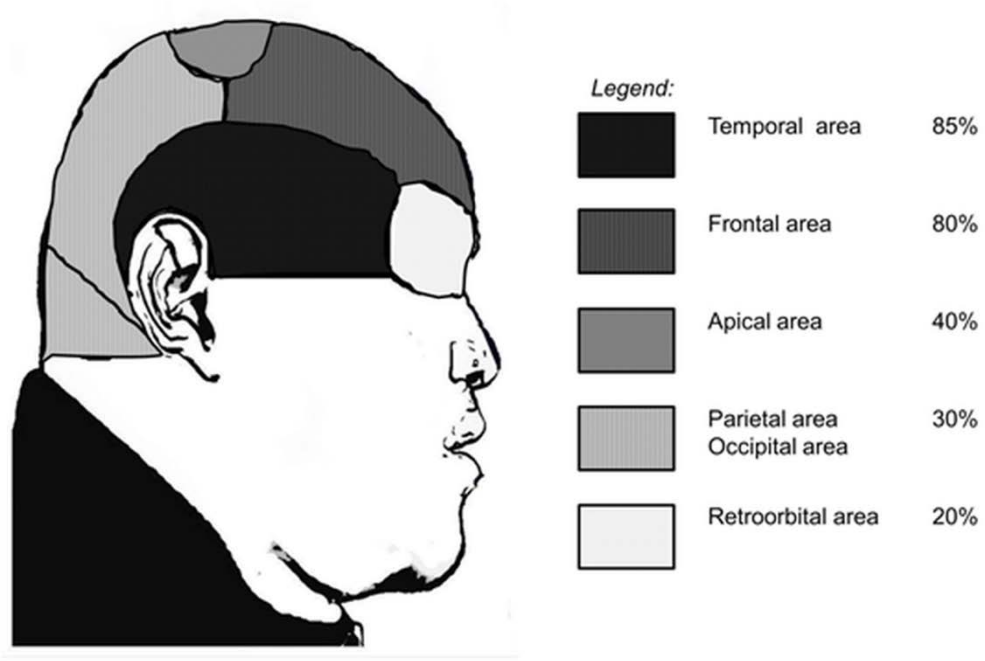


Figure 1. Placement of the single voxel in the (A) axial, (B) coronal, and (C) sagittal planes for proton magnetic resonance spectroscopy analysis



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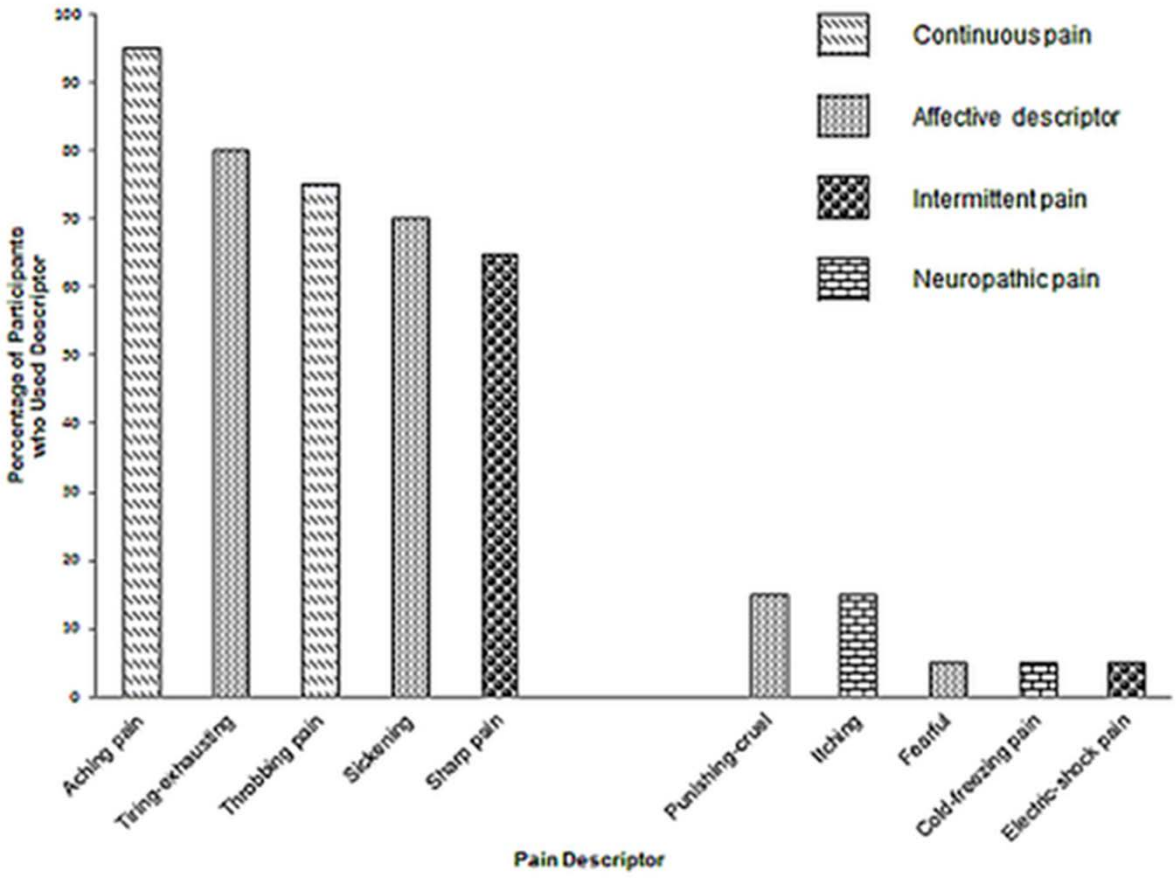

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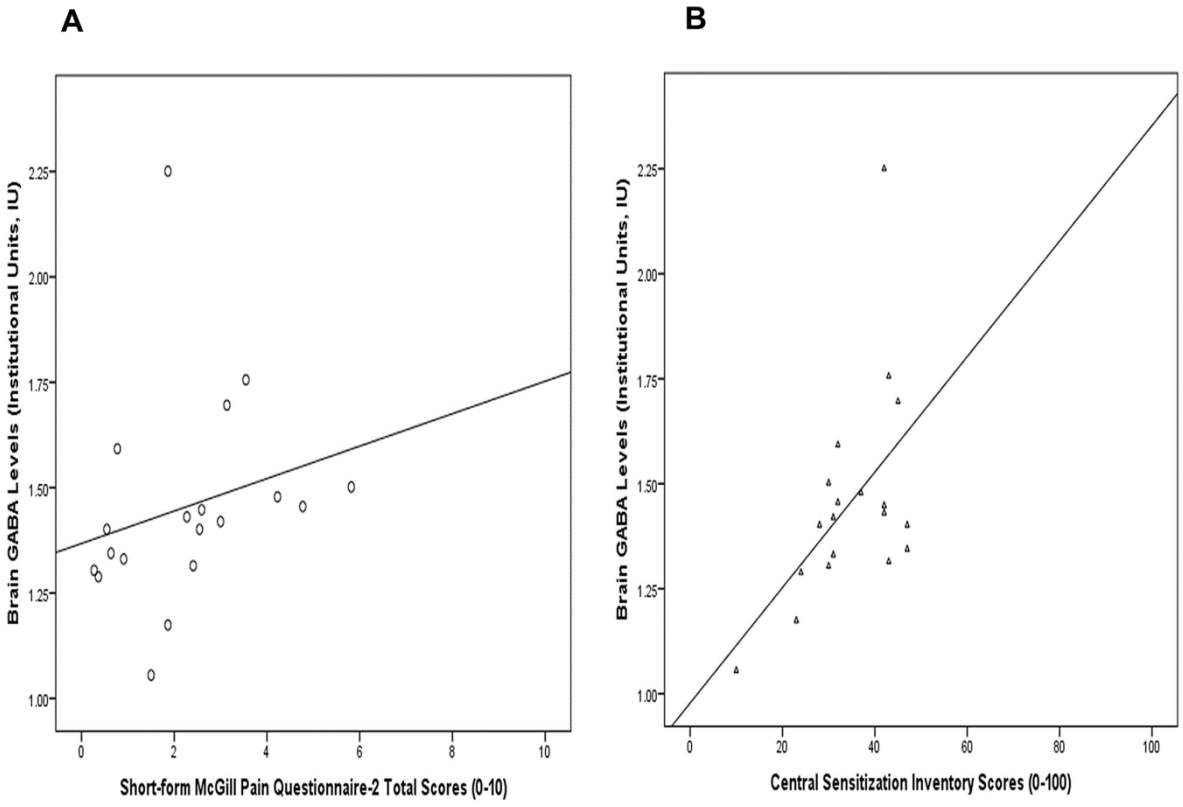

Figure 4. Scatterplot with regression line showing positive association between brain GABA levels and scores on (A) Short-form McGill Pain Questionnaire-2 (ρ = .47, P = 0.04) and (B) Central Sensitization Inventory (ρ = .48, P = 0.03) in the migraine group (n = 20)

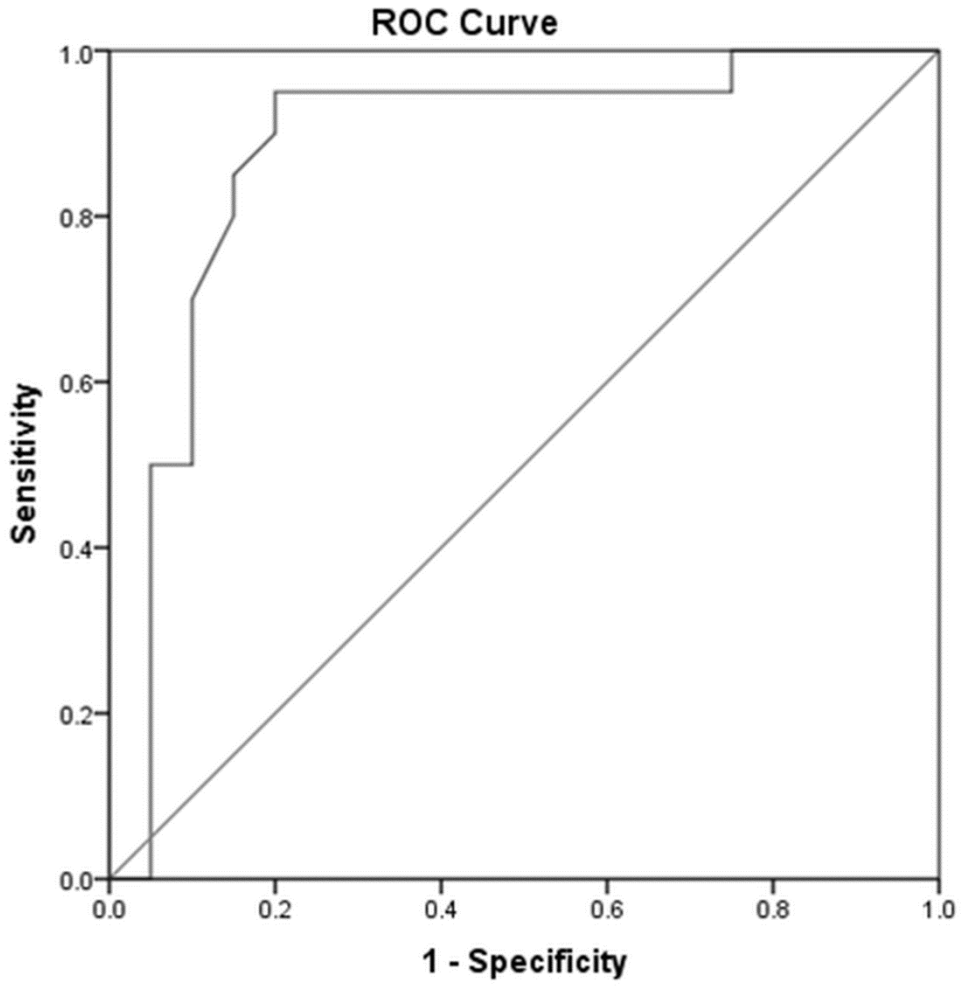

*Figure 5.*Receiver operating characteristic curve evaluating CSI scores of people with migraine and controls. Area under the curve = 0.88 (95% confidence interval 0.76-1.00), *P*<0.001

Table 1. Descriptive migraine characteristics (*n* = 20)

	MEAN (SD)	MEDIAN (IQR)	*n*	%
Migraine history *(years since first episode)*	17.6 (14.6)	15 (5.0-24.0)		
Frequency of headache in a month *(n)*	5.1 (5.2)	2.8 (1.5-8.5)		
Episode duration *(hours)*	38.6 (21.8)	48.0 (24.0-48.0)		
Average headache intensity last month (*0-10*)	6.4 (1.8)	6.0 (6.0-8.0)		
Unilateral			13	65
With aura			9	45
Nausea			18	90
Vomiting			6	30
Photophobia / Phonophobia				
Both photophobia and phonophobia			13	65
Photophobia alone			6	30
Phonophobia alone			0	0
Neither photophobia nor phonophobia			1	5
Physical activity intolerance			15	75

Table 2. Association of GABA levels and clinical characteristics of migraine using Spearman's rho, ρ, or Kendall's tau, τ, correlation coefficient (*P* values)

	GABA LEVELS Correlation Coefficients (*P values*)[1]
Headache characteristics	
Migraine history	ρ = -.40 (0.08)
Frequency of headache in a month	τ = .16 (0.33)
Episode duration	τ = -.01 (0.94)
Average headache intensity last month	ρ = .17 (0.48)
Pain and sensitization	
SF-MPQ-2 Total score	**ρ = .47 (0.04)**[2]
SF-MPQ-2 Continuous pain score	ρ = .21 (0.38)
SF-MPQ-2 Intermittent pain score	**τ = .33 (0.04)**[b]
SF-MPQ-2 Neuropathic pain score	**τ = .37 (0.03)**[b]
SF-MPQ-2 Affective descriptors	**ρ = .49 (0.03)**[b]
CSI Total score	**ρ = .48 (0.03)**[b]
Emotional state	
DASS-21 Depression Score	τ = -.14 (0.42)
DASS-21 Anxiety Score	τ = .17 (0.34)
DASS-21 Stress Score	τ = -.13 (0.43)
Disability (HIT-6 score)	ρ = .06 (0.79)

[1] Spearman's rho, ρ; Kendall's tau, τ
[2] Correlation is significant at the 0.05 level (2-tailed)

Table 3. Comparison of clinical characteristics based on self-report questionnaires between migraine and control groups (*n* = 40)

	MIGRAINE (*n* =20)		CONTROL (*n* = 20)		Glass's △	*P* values
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		
Pain and sensitization						
SF-MPQ-2 Total score	2.2 (1.5)	2.3 (0.8-3.1)	0.0 (0.1)	0.0 (0-0)	***1.47***	***<0.001***
SF-MPQ-2 Continuous pain score	3.3 (1.6)	3.7 (2.0-4.4)	0.1 (0.2)	0.0 (0-0)	***2.00***	***<0.001***
SF-MPQ-2 Intermittent pain score	2.3 (2.3)	1.7 (0.7-3.2)	0.0 (0.0)	0.0 (0-0)	***1.00***	***<0.001***
SF-MPQ-2 Neuropathic pain score	.9 (1.2)	0.3 (00-1.2)	0.0 (0.2)	0.0 (0-0)	***0.75***	***0.006***
SF-MPQ-2 Affective descriptors	2.5 (2.0)	2.2 (1.0-3.8)	0.1 (0.2)	0.0 (0-0)	***1.2***	***<0.001***
CSI Total score	35.0 (9.6)	32.0 (30-42.5)	16.2 (11.8)	14.0 (9.0-20.5)	***1.96***	***<0.001***
Emotional state						
DASS-21 Depression score	3.4 (3.9)	2.0 (0-6.0)	0.8 (1.1)	0.0 (0-1.0)	***0.67***	***0.005***
DASS-21 Anxiety score	3.1 (3.6)	2.0 (0-5.0)	1.5 (2.4)	0.0 (0-3.0)	0.44	0.095
DASS-21 Stress score	9.2 (8.2)	8.0 (2.0-11.0)	3.2 (3.6)	2.0 (0-6.0)	***0.73***	***0.006***
Disability						
HIT-6 Total score[1]	61.6 (7.6)	63.0 (57.2-65.5)	38.5 (5.1)	36.0 (36-39.5)	***3.05***	***<0.001***

[1] HIT-6 scores range from 36 to 78; score less than 49 = little or no impact (grade 1), score 50–55 = moderate impact (grade 2), score 56–59 = substantial impact (grade 3), and score equal to or greater than 60 = severe impact (grade 4).

Highlights

- Increased GABA levels were associated with increased pain and more frequent central sensitization symptoms in migraine.
- Results provide preliminary evidence for the possible involvement of GABA in migraine pathophysiology.
- GABA is a potential biomarker for migraine.
- Measuring clinical characteristics of migraine using self-report questionnaires may be useful in characterizing migraine better and broadening the diagnostic process.

CHAPTER FIVE

Characterizing Cervical Musculoskeletal Impairments and Patient Experience in Migraine as Distinguished from Non-Migraine Headaches

Chapter Five has been submitted as:

Aguila ME, Leaver AM, Hau SA, Ali K, Ng K, Rebbeck T. Characterizing cervical musculoskeletal impairments and patient experience in migraine as distinguished from non-migraine headaches. Submitted to *The Journal of Headache and Pain.*

The study protocol for the study presented in this chapter appears as Appendix 5.

Authorship Statement

As co-authors ofthe paper “Characterizing cervical musculoskeletal impairments and patient experience in migraine as distinguished from non-migraine headaches”, we confirm that Maria Eliza Ruiz Aguila has madethe following contributions:

- Conception and design of the research
- Acquisition of data
- Analysis and interpretation of data
- Drafting and revising of the manuscript and critical appraisal of its content

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Manuscript title: Characterizing cervical musculoskeletal impairments and patient experience in migraine as distinguished from non-migraine headaches

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Abstract

Background: Symptoms of migraine may vary and overlap with those of other recurrent headache types, including tension-type headache and cervicogenic headache. Thus diagnosis and treatment of migraine may potentially be challenging. Cervical musculoskeletal impairments may help characterize migraine further but available evidence is inconsistent. Patient experience of disability and multidimensional pain is also important to detail to possibly differentiate migraine from other recurrent headaches.This research aimed to distinguishmigraine from non-migraine headaches(tension-type headache and cervicogenic headache) based on cervical musculoskeletal impairment and patient experience.

Methods: In this cross-sectional study, participants with migraine and non-migraine headaches and headache-free controlsunderwent physical examination for cervical musculoskeletal impairment and completed questionnaires on patient experience (disability, multidimensional pain, central sensitization, and emotional state).

Results: Fewer participants in the migraine group [*n* (%) 4 (10%)] had cervical articular impairment than the non-migraine group [26 (58%); $p < 0.001$]. Headache groups did not differ on cervical muscle impairment measures when considered independently. Migraine group had more intense pain [median numeric rating scale/10 (IQR)] 7.0 (6.0–7.0) versus 5.0 (4.0–7.0); $p = 0.009$] and higher disability scores [e.g. Headache Disability Questionnaire 43/90 (31–53) versus 27/90 (20–42); $p = 0.006$] than the non-migraine group. A combination of no pain on manual examination of the cervical spine, less change in deep cervical extensors thickness during contraction, less frequent headaches, and higher disability scores had 80.0% sensitivity and 75.6% specificity in identifying migraine.

Conclusions: Less cervical musculoskeletal impairment and higher pain and self-reported disability, considered independently, distinguished migraine from non-migraine headaches. New evidence is presented on cervical muscle behavior measured using the deep cervical

extensor test and self-reported disability as part of a combination of clinical characteristics that distinguishes migraine. Thus results suggest the value of assessing impairments and disability in migraine for differential diagnosis.

Key words*:* migraine, tension-type headache, cervicogenic headache, disability, cervical spine, musculoskeletal impairment

Background

The most common recurrent headaches that present to primary care clinicians and specialists, namely migraine, tension-type headache (TTH) [1] and cervicogenic headache (CGH) [2], are among the most disabling headache types. One critical element in reducing the burden of headaches is effective targeted headache treatment. Effective headache treatment, in turn, requires a clear understanding of underlying disease mechanisms, well-defined distinction of clinical features between headache types, and ultimately, accurate diagnosis.

Distinguishing migraine from other headache types is relevant because migraine is the most disabling headache globally [3], yet is underdiagnosed [4]. Contributing to this difficulty in diagnosis are the complex and varied presentations of migraine within and between individuals and its possible coexistence with other headache types [4, 5]. Migraine features may also overlap with those of other headaches, plausibly due to the common involvement of the trigeminocervical complex in the brainstem in different headache types, including TTH and CGH [6, 7].The bidirectional interaction between nociceptive input from the upper cervical spine and the trigeminocervical complex [8, 9] are hypothesized to result in cervical symptoms that are commonly associated with recurrent headaches [10, 11]. Consequently, cervical musculoskeletal impairment has been treated in headaches, although with variable evidence on effects [9]. To date, it is unknown whether these characteristics distinguish migraine from other frequently presenting recurrent headache types.

Therefore a conceivable way to better distinguish migraine, in addition to those listed as diagnostic criteria in International Classification of Headache Disorders (ICHD) [5], is by assessing symptoms and musculoskeletal impairments arising from the cervical spine [10, 12]. It is plausible that migraine differs from non-migraine headaches in terms of cervical impairments. Migraine primarily involves central nociceptive processing while episodic non-

58 migraine headaches, specifically TTH and CGH, are hypothesized to be primarily initiated by
59 peripheral nociceptive mechanisms [5, 7, 13]. By clarifying whether or not cervical
60 musculoskeletal impairment distinguished migraine, we improve the understanding of
61 migraine especially when its presentation is complex. This improved understanding, then,
62 would help address the issue of underdiagnosis of migraine.

63 To build on knowledge from previous studies and clarify the distinction of migraine
64 from other frequently presenting recurrent headaches, a comprehensive examination of
65 cervical musculoskeletal impairment is warranted. A recent Delphi study that assembled a
66 panel of expert physiotherapists recommended the use of tests for cervical musculoskeletal
67 impairment in headache assessment, including tests previously reported as discriminatory for
68 CGH [14]. Moreover, impairment of the cervical extensor muscle group in headache was
69 proposed to require further investigation [15]. Additionally, cervical musculoskeletal
70 impairment in headaches will be better understood when differentiated from those in
71 headache-free controls, considering the high prevalence of neck pain in the general
72 population [3].

73 In addition to understanding cervical musculoskeletal impairment in headaches more
74 thoroughly, understanding symptoms from a multidimensional biopsychosocial perspective
75 may potentially assist in distinguishing migraine from other headaches. Currently, the ICHD
76 lists unidimensional characteristics of pain, such as quality and severity, among the criteria
77 for classifying headaches [5]. However, these pain characteristics may overlap between
78 headache types. For example, 35.1% of individuals with TTH reported moderate to severe
79 headaches [16], which are severity ratings typically associated with migraine [5]. Therefore,
80 a multidimensional assessment of pain, complemented by information about disability and
81 other characteristics that modulate the pain experience, such as central sensitization

mechanisms [17] and emotional states [18], may provide the opportunity to understand the patient experinece better and distinguish migraine from other headache types.

This study therefore aimed to determine if migraine can be distinguished from frequently presenting non-migraine headaches (TTH and CGH) based on a comprehensive assessment of cervical musculoskeletal impairment and patient experience. Clarifying the distinction between migraine and non-migraine headaches would contribute to a better understanding of frequently presenting headaches, an enhanced diagnostic framework, and eventually research directions for better, targeted treatments for these headache types.

Methods

Design

In this cross-sectional study, we compared characteristics between people with migraine, those with non-migraine headaches and headache-free controls. This research was granted ethics approval by the Human Research Ethics Committee of The University of Sydney (Project Number 2014/536).

Participants

We recruited volunteers aged 18 to 65 with recurrent headache and headache-free controls through advertisements posted at community bulletins, social media, and primary and specialist care clinics. Participants in the headache group were included if they had headaches for at least one year and had at least one headache episode in the previous month. Headache participants were further classified into the migraine group (fulfilling the criteria for migraine only and not those for other headache types) or non-migraine group (with primary diagnosis of TTH and/or CGH, with or without comorbid migraine) using the ICHD-3 beta

criteria [5]. Participants in the control group were included if they had not experienced any headache in the past 3 months.

Exclusion criteria for the headache groups were other known secondary headache classifications without a known pathogenesis in the neck, such as tumor, substance withdrawal, etc., and psychiatric disorders. Exclusion criteria for the control group were severe neck pain, recent head or neck surgery, or conditions requiring medical attention or affecting performance of daily activities.

Procedure

All participants underwent initial telephone screening to confirm their eligibility. All eligible participants provided written informed consent prior to participation.Eligible participants then completed questionnaires that provided information about demographic and headache characteristics as well as their disability and multidimensional pain experience. Participants also attended one assessment session for interview about headache features and physical examination of cervical musculoskeletal impairment. Physical examination was done by a physiotherapist with 20 years of experience for the headache groups and by two novice physiotherapists for the control group. All examiners were trained by a specialist musculoskeletal physiotherapist with clinical and research expertise in cervical spine disorders. Participants were independently classified into migraine and non-migraine groups by two researchers using the ICHD-3 beta criteria. Disagreements were resolved by a third researcher. The process was overseen by a neurologist and a specialist physiotherapist who were blinded to the headache diagnoses of participants and who did not conduct the physical examination.

Outcomes

Cervical musculoskeletal impairment comprised cervical articular impairment and cervical muscle impairment. Cervical articular impairment was measured using the range of motion measures, flexion rotation test [19] and manual examination of the upper cervical spine with passive accessory intervertebral movements (PAIVMs) [12, 20]. The Cervical Range of Motion Instrument (CROM) 3 (Performance Attainment Associates, (Roseville, MN, USA) was used to measure flexion, extension, lateral flexion and rotation, summed to obtain the composite score. The flexion rotation test was deemed positive if headache was provoked and the range of movement was $\leq 32^{o}$ [21]. Manual examination of the cervical spine was deemed positive if headache was provoked.

Cervical muscle impairment was assessed in terms of muscle function (relating to strength and endurance) and muscle behavior (relating to motor control). Cervical flexor and extensor strength was measured using the Lafayette Manual Muscle Tester (Model 01163) handheld dynamometer [22]. Cervical extensor and flexor endurance was measured using the protocol published by Edmondston and colleagues [23]. Upper limits for sustained isometric contraction were set at 60 seconds for flexors and 200 second for extensors [23]. Ratios of extensor to flexor strength and endurance were calculated.

Muscle behavior of the deep flexor and deep extensor muscles were assessed using the cranio-cervical flexion test [24], cervical extensor test [25], and the deep cervical extensor (DCE) test. The DCE test measures changes in thickness of the deep cervical extensor muscle group during low-load using ultrasound imaging [26]. Performance on the cranio-cervical flexion test was scored using the performance index, which was calculated based on the number of times the participant could hold the pressure level achieved for 10 seconds [24]. The cervical extensor test was scored through video analysis of the performance of the participant. The performance of correct movement patterns in maintaining the start position and during the eccentric and concentric phases of movement were scored on

a scale of 0–4, with lower scores indicating better performance. The aggregate score, which is the total of scores for all phases, was reported.

In contrast to the cervical extensor test, the DCE test measures changes in thickness of the deep cervical extensor muscle group during low-load contractions using ultrasound imaging [26]. Thickness of the deep cervical extensors was measured from real-time ultrasound images from the top edge of the lamina to the leading edge of the first fascial plane above the facet joint or spinous process at C4 level [26]. Measurements were done with the muscles at rest and during submaximal contraction. Measurements were taken from the symptomatic side for participants with side-locked headaches. For participants whose headaches were bilateral and for control participants, measurements from the left and right muscle groups were averaged and recorded as the measure for both sides. Analyses of the DCE test were based on the change in thickness of the muscles from the relaxed state to the contracted state and the percentage change in thickness (that is, the difference between contracted and relaxed state divided by the relaxed state multiplied by 100%).

Aspects of patient experience assessed in this studycomprised disability, multidimensional pain, central sensitization, and emotional state using the Henry Ford Headache Disability Inventory (HDI) [27], Headache Disability Questionnaire (HDQ) [28],Headache Impact Test-6^{TM} (HIT-6) [29], World Health Organization Disability Assessment Schedule 2.0 (WHODAS) [30], Short-form McGill Pain Questionnaire-2 (SF-MPQ-2) [31], Central Sensitization Inventory (CSI) [32], and Depression Anxiety Stress Scales-21 (DASS-21) [33].

Statistical analysis

The calculated sample size (n = 32 per group) was based on a hypothesized mean difference of 20 degrees in range of cervical extension and 20 Newtons in strength between migraine

and non-migraine groups [10] and an estimated within-group standard deviation of 35 units,with a significance level of 0.05 with 80% power. Allowing for about 20% attrition, we determined the sample size to be 40 per group.

Distributions of data were examined through visual inspection and using the Shapiro-Wilk test and summarized using descriptive statistics. Comparisons of the continuous variables between migraine, non-migraine and control groups were computed using one-way ANOVA followed by Fisher's least significant difference (LSD) *post-hoc* test when there was an overall significance. Kruskal-Wallis test was used when the assumption of homogeneity of variance was not met (Levene's test, $p< 0.05$), followed by pairwise-comparisons using Mann-Whitney Test with Bonferroni correction. Additionally, comparisons for headache characteristics and pain and disability questionnaire scores between the migraine and non-migraine groups only were computed using the T-test or Mann-Whitney Test, as appropriate. Comparisons of categorical variables between the three groups were computed using the Chi square test, followed by *post-hoc* test with modified Bonferroni correction when there was an overall significance.For characteristics that were significantly different between headache groups, area under the receiver operating characteristic (ROC) curve analysis was used. The discriminative ability of these characteristics were examined by computing for optimal cutoff value, area under the curve (AUC), sensitivity, specificity, and positive likelihood ratio. Stepwise discriminant analysis was used to identify the combination of characteristics that distinguished migraine from non-migraine headaches. The criteria for entry and removal of variables into the model were a significance level of $p< 0.05$ and $p< 0.10$, respectively, of Wilks lambda.Statistical analyses were conducted using Statistical Package for Social Sciences® statistical software, version 24 (SPSS Inc., Chicago, Illinois, USA) for Windows. Significance level was set at 0.05.

Results

Participants

Forty people with migraine, 45 people with non-migraine headache, and 40 controls participated in this study. The non-migraine group comprised 26 participants with predominantly CGH, 16 participants with predominantly TTH, and three participants with both cervicogenic and TTHs. The flow of participants through the study and reasons for exclusion of volunteers are shown in Figure 1.The demographic and headache characteristics of the participants are presented in Table 1 and Table 2, respectively. There were significant differences between the migraine and non-migraine groups in headache characteristics. The migraine group had longer history of headache [median (interquartile range, IQR) 18.50 (10.50–24.50) years versus 9.00 (4.00–20.00) years; p = 0.002], higher average headache intensity in the last month [7.00 (6.00–7.00) versus 5.00 (4.00–7.00); p = 0.009], and less frequent headaches in a month [3.00 (1.00–5.00) versus 8 (3.50–13.00); $p < 0.001$] than the non-migraine group. More participants in the migraine group compared to the non-migraine group had unilateral headache [*n* (%) 32 (80.00%) versus 20 (44.44%); p = 0.001] and experienced vomiting [20 (50.00%) versus 13 (28.89%); p = 0.046], and photophobia and/or phonophobia [36 (90.00%) versus 26 (57.78%), p = 0.001] with their headaches.

Cervical musculoskeletal impairment

There were significant differences between groups in cervical range of extension, pain on flexion rotation test, manual examination of the upper cervical joints, and ratio of extensor-flexor strength (Table 3). *Post-hoc* analyses revealed that the migraine differed from the non-migraine group but not from the control group on cervical articular impairments. Specifically, fewer participants in the migraine [4 (10.00%)] and control groups [6 (15%)] tested positive on the flexion rotation test compared to participants in the non-migraine group [17

231 (37.78%)] (p = 0.003–0.018). Similarly, fewer participants in the migraine group [4 (10.00%)]
232 and control group [0 (0%)] had their headaches provoked on manual examination of the
233 upper cervical joints compared to participants in the non-migraine group [*n* (%) 26 (57.78%)]
234 (p< 0.001). The migraine group had lower ratio of extensor-flexor strength than the control
235 group [1.51 (1.16–1.85) versus 2.15 (1.66–2.64);(p< 0.001)]. The migraine group did not
236 differ from the non-migraine group on all cervical muscle impairment measures (p> 0.05).

237 Table 1. Demographic characteristics of participants (n = 125)[*]

	Median (IQR) or *n* (%)			*p* values[†]
	Migraine (n = 40)	Non-Migraine (n = 45)	Control (n = 40)	
Age	42.00 (28.50–49.50)	29.00 (27.00–42.00)	31.50 (22.00–50.50)	0.06
Gender (female)	32 (80.00%)	40 (88.89%)	31 (77.50%)	0.35
Body mass index	23.44 (21.18–27.62)	22.48 (20.64–27.06)	23.12 (21.26–24.79)	0.69
Marital status				0.48
Single / Divorced / Widowed / Separated	20 (50.00%)	28 (62.22%)	21 (52.50%)	
Married / De facto	20 (50.00%)	17 (37.78%)	19 (47.50%)	
Region of birth				**0.048**
Oceania	**27 (67.50%)**	24 (53.33%)	16 (40.00%)	
Other geographic region	13 (32.50%)	21 (46.67%)	**24 (60.00%)**	
Level of education				0.08
University degree	33 (82.50%)	40 (88.89%)	29 (72.50%)	
No university degree	6 (15.00%)	4 (8.89%)	11 (27.50%)	
No information provided	1 (2.50%)	1 (2.22%)		
Occupation				**0.001**
Professional	13 (32.50%)	**26 (57.78%)**	13 (32.50%)	
Student	9 (22.50%)	12 (26.67%)	**20 (50.00%)**	
Other occupation	**18 (45.00%)**	7 (15.56%)	7 (17.50%)	

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Abbreviation: IQR, interquartile range
NOTE. Bold numbers indicate statistical significance (p< 0.05) or statistically significant difference from the other groups on *post-hoc* analyses

[*] For continuous variables, values are presented as median (IQR); for categorical variable, valuesare presented as frequency (%)
[†]*p*values for Kruskal-Wallis Testfor continuous variables between three groups; *p* values for Chi-square test for categorical variables between three groups

239 Table 2. Headache characteristics of participants with recurrent headaches (n = 85)[‡]

	Median (IQR) or*n* (%)		*p* values[§]
	Migraine (n = 40)	Non-Migraine (n = 45)	
History of headache (*years since first episode*)	18.50 (10.50–24.50)	9.00 (4.00–20.00)	**0.002**
Frequency of headache in a month	3.00 (1.00–5.00)	8 (3.50–13.00)	**<0.001**
Episode duration , minimum (*hours*)	3.50 (1.50–24.00)	4 (2.00–24.00)	0.96
Episode duration , maximum (*hours*)	60.00 (30.00–72.00)	24.00 (12.00–72.00)	0.11
Average headache intensity last month (*0-10*)[**]	7.00 (6.00–7.00)	5.00 (4.00–7.00)	**0.009**
Unilateral location	32 (80.00%)	20 (44.44%)	**0.001**
Throbbing / pulsating quality	31 (77.50%)	27 (60.00%)	0.08
Associated with nausea	35 (87.50%)	32 (71.11%)	0.07
Associated with vomiting	20 (50.00%)	13 (28.89%)	**0.046**
Associated with photophobia/phonophobia	36 (90.00%)	26 (57.78%)	**0.001**
Associated with physical activity intolerance	17 (42.50%)	18 (40.00%)	0.82
Pharmacologic treatment (number of participants, *n*, %)			
Paracetamol	14 (35.00%)	17 (37.78%)	0.06
Non-steroidal anti-inflammatory drug	18 (45.00%)	20 (44.44%)	0.58
Tricyclic antidepressant	6 (15.00%)	3 (6.67%)	0.47
Triptan	19 (47.50%)	10 (22.22%)	**0.006**
Botulinum toxin	8 (20.00%)	11 (24.44%)	0.48
Beta blocker	4 (10.00%)	3 (6.67%)	0.42
Selective serotonin reuptake inhibitor	5 (12.50%)	6 (13.33%)	0.64
Proton pump inhibitor	4 (10.00%)	6 (13.33%)	0.42
Anticonvulsant	5 (12.50%)	7 (15.56%)	0.29
Contraceptive	7 (17.50%)	10 (22.22%)	0.99

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Abbreviation: IQR, interquartile range
NOTE. Bold numbers indicate statistical significance (p<0.05)

[‡]For continuous variables, values are presented median (IQR); for categorical variables, valuesare presented as frequency (%)
[§]*p*values for Mann-Whitney Testfor continuous variables between groups; *p* values for Chi-square test for categorical variables between groups
[**] Headache intensity: Numerical rating scale 0–10; 0= no pain, 10 = worst possible pain

241 *Table 3.* Comparison of performance on cervical musculoskeletal impairment tests between participant groups (n = 125)[††]

	Median (IQR) or *n* (%)			*p* values[‡‡]
	Migraine (n = 40)	Non-Migraine (n = 45)	Control (n = 40)	
Cervical range of motion				
Extension	**70.00 (60.00–70.00)**	**60.00 (60.00–70.00**)	**75.00 (62.50–80.00)**	**0.037**
Composite score	355.00 (312.50–372.50)	349.00 (315.00–375.00)	368.00 (327.50–421.50)	0.14
Upper cervical joint dysfunction (n, %)				
Positive flexion rotation test	4 (10.00%)	**17 (37.78%)**	6 (15.00%)	**0.004**
Pain on manual examination of the upper cervical joints	4 (10.00%)	**26 (57.78%)**	0 (0.00%)	**<0.001**
Muscle performance				
Ratio of extensor-flexor strength	1.51 (1.16–1.85)	1.36 (1.20–1.64)	**2.15 (1.66–2.64)**	**<0.001**
Ratio of extensor-flexor endurance	3.33 (3.24–5.41)	3.33 (2.25–3.33)	3.33 (2.44–4.26)	0.34
Neuromotor control				
Cranio-cervical flexion test performance index	18.00 (6.00–30.00)	8.00 (6.00–26.00)	17.00 (12.00–30.00)	0.09
Cervical extensor test aggregate score	3.00 (3.00–4.50)	3.00 (3.00–5.00)	3.00 (3.00–5.00)	0.99
Deep cervical extensor test[§§]				
Percent change on symptomatic side	5.13 (1.72–10.18)	7.47 (3.07–16.30)	8.44 (3.40–14.60)	0.19
Percent change on asymptomatic side	7.34 (3.19–10.85)	9.32 (6.35–16.30)	8.44 (3.40–14.60)	0.11

Abbreviation: IQR, interquartile range
NOTE. Bold numbers indicate statistical significance (p<0.05) or statistically significant difference from the other groups on *post-hoc* analyses

[††] For continuous variables, values are presented as median (IQR); for categorical variables are presented as frequency (%)
[‡‡] *p* values for Kruskal-Wallis Testfor continuous variables between three groups; *p* values for Chi-square test for categorical variables between three groups
[§§] Difference in thickness between relaxed and contracted deep cervical extensor muscle

Measurement of patient experience using self-report questionnaires

There were significant differences between groups on all questionnaire scores (Table 4). *Post-hoc* analyses revealed that the migraine group had significantly higher scores than the non-migraine group on HDI Total Score [median (IQR) 40 out of 100 (21–56) versus 24 out of 100 (14–44), $p = 0.029$] and HDQ score [43 out of 90 (31–53) versus 27 (20–42), $p = 0.006$]. For all other questionnaires, the control group had significantly lower scores than the headache groups;however there was no difference between headache groups.

Total scores on HDI appeared to have good diagnostic value in classifying individuals as having migraine and not non-migraine headache (AUC = 0.80; 95% confidence interval, CI, 0.73 to 0.88; $p< 0.001$). The optimal HDI cutoff score to distinguish people with migraine from non-migraine headaches was 19 out of 100, with sensitivity of 80.0% and specificity of 67.1%, and positive likelihood ratio of 1.72. Similarly, HDQ score appeared to have good diagnostic value in classifying individuals as having migraine or not (AUC = 0.82; 95% CI 0.75 to 0.90; $p<0.001$). The optimal HDQ cutoff score to distinguish people with migraine from non-migraine headaches was 27.5 out of 90, with sensitivity of 80.0%, specificity of 74.1%, and positive likelihood ratio of 3.09.

Table 4. Comparison of scores on self-report questionnaires between participant groups (n = 125)

	Migraine (n = 40)		Non-Migraine (n = 45)		Control (n = 40)		
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	p values[***]
Disability							
HDI Total Score[†††]	39.45 (23.01)	**40.00 (21.00–56.00)**	30.49 (21.78)	**24.00 (14.00–44.00)**			**0.029**
HDQ[‡‡‡]	41.60 (15.68)	**43.00 (31.00–53.00)**	31.67 (16.04)	**27.00 (20.00–42.00)**			**0.006**
HIT-6 Total score[§§§]	62.10 (5.60)	62.00 (58.00–65.50)	58.67 (6.34)	60.00 (54.00–63.00)			0.06
WHODAS 2.0 Overall score[‡‡‡]	13.65 (13.20)	10.42 (4.17–19.79)	11.62 (10.39)	6.25 (4.17–20.83)	1.09 (3.56)	0.00 (0.00–0.00)	0.70
Pain							
SF-MPQ-2 Total score[****]	2.25 (1.71)	1.98 (0.95–2.66)	1.96 (1.39)	1.64 (1.00–2.59)	0.08 (0.20)	0.00 (0.00–0.02)	0.55
Central sensitization							
CSI Total score[††††]	35.78(14.03)	34.50 (26.50–45.50)	37.16 (12.03)	37.00 (31.00–42.00)	**18.80 (8.86)**	18.50 (12.00–25.50)	**<0.001**
Emotional state[‡‡‡‡]							
DASS-21 Depression score	2.55 (3.64)	1.00 (0.00–3.50)	2.16 (2.32)	1.00 (0.00–4.00)	0.85 (1.61)	**0.00 (0.00–1.00)**	**0.002**
DASS-21 Anxiety score	2.18 (3.39)	1.00 (1.00–3.00)	2.04 (2.34)	1.00 (0.00–3.00)	0.93 (1.42)	**0.00 (0.00–1.50)**	**0.004**
DASS-21 Stress score	5.35 (4.07)	4.50 (2.50–8.00)	4.91 (3.79)	4.00 (2.00–6.00)	2.55 (2.88)	**1.50 (0.00–4.50)**	**0.001**

Abbreviations: CSI, Central Sensitization Inventory; DASS, Depression Anxiety Stress Scales-21; HDI, The Henry Ford Headache Disability Index; HDQ, Headache Disability Questionnaire; HIT-6, Headache Impact Test-6; IQR, interquartile range; SD, standard deviation; SF-MPQ-2, Short-form McGill Pain Questionnaire-2; WHODAS, World Health Organization Disability Assessment Schedule

NOTE. Bold numbers indicate statistical significance (p<0.05) or statisticallysignificant difference from the other groups on *post-hoc* analyses

[***]*p*values for ANOV*A* for CSI scores; *p*values for Mann-Whitney Test for SF-MPQ-2, HDI, HDQ and HIT-6 scores; *p*values for Kruskal-Wallis Testfor WHODAS and DASS scores

†††HDI Total Scores and WHODAS Overall Scores range from 0 to 100, with higher scores reflecting greater disability caused by the headache

[‡‡‡]HDQ scores range from 0 to 90, with higher scores reflecting greater disability caused by the headache

[§§§] HIT-6 scores range from 36 to 78; a score <49 indicates little or no impact (grade 1); a score of 50 to 55 indicates moderate impact (grade 2); a score of 56 to 59 indicatessubstantial impact (grade 3), and score>60 indicates severe impact (grade 4).

[****]SF-MPQ-2 Total Scores range from 0 (no pain) to 10 (worst pain possible)

[††††]CSI scores range from 0 to 100, with higher scores reflecting a higher degree of sensitization

[‡‡‡‡]DASS scores range from 0 (normal) to 21 (extremely severe)

Combination of characteristics predictive of migraine

Discriminant analysis of characteristics revealed significant differences between the migraine and non-migraine groups (Wilk's lambda = 0.60, Chi square =49.22, $p< 0.001$). The discriminant function for characteristics explained 100% of the variance in the groups ($p< 0.001$). A combination of no pain on manual examination of the cervical spine, less change on the DCE test, less frequent headaches, and higher disability scores predicted migraine (Table 5). This prediction model for migraine correctly classified 80.0% of the original grouped cases with a sensitivity of 80.0% and specificity of 75.6% for migraine (Table 6).

Table 5. Discriminant function coefficients (standardized coefficients) for characteristics with highest predictive ability for migraine

Characteristics	Discriminant Function Coefficient
Pain on manual examination of the upper cervical joints	0.736
Frequency of headache	0.523
Headache Impact Test Total Score	-0.513
Percent change in thickness of deep cervical extensor muscle from relaxed state on symptomatic side	0.468

Table 6. The sensitivity and specificity of characteristics to categorize migraine from participants with non-migraine headaches (n = 85)

			Predicted Group Membership		
		Group	Migraine	Non-Migraine and Mixed Headaches	Total
Original classification	Count	Migraine	33	7	40
		Non-Migraine and Mixed Headaches	10	35	45
	Sensitivity / Specificity	Migraine	82.5%	17.5%	100.0%
		Non-Migraine and Mixed Headaches	22.2%	77.8%	100.0%
Cross-validated	Count	Migraine	32	8	40
		Non-Migraine and Mixed Headaches	11	34	45
	Sensitivity / Specificity	Migraine	80.0%	20.0%	100.0%
		Non-Migraine and Mixed Headaches	24.4%	75.6%	100.0%

Discussion

Our results provide information on characteristics that distinguished migraine from non-migraine headaches. Our results indicate that cervical articular impairmentwas worse in people with non-migraine headaches than in people with migraine, while cervical muscle impairmentwas not different between headache groups. In contrast, headache intensity and self-reported disability were worse in migraine than non-migraine headaches. A combination of information on cervical musculoskeletal impairment, headache characteristic and self-reported disability distinguished migraine from non-migraine headaches. These characteristics that distinguished migraine from non-migraine headaches may be assessed to enhance diagnosis especially for complex presentations of migraine.

Cervical articular impairment was significantly less in the migraine group than the non-migraine group in our study, as would be expected. Specifically, both the flexion rotation test [19] and headache provocation with upper cervical spine manual examination [12, 20] more frequently had positive findings in participants with non-migraine headaches than those with migraine. Our results therefore corroborate previousstudies that demonstrated impairments on these tests in people with non-migraine headache, specifically CGH,but not in people with migraine and controls [10,12, 34]. Interestingly, more than half of the participants in both headache groups in the present study reported neck pain.The coexistence of neck pain in headaches is consistent with the hypothesized bidirectional interaction between nociceptive input from upper cervical spine and the trigeminocervical complex [8]. Our findings therefore support examining the upper cervical joints to differentiate migraine from non-migraine headache when neck pain coexists. Doing so would augment the ICHD diagnostic criteria, especially when diagnosing headaches whose clinical features are characteristic of more than one headache type.

In contrast to cervical articular impairment, measures of cervical muscle function and behavior were not different between groups. These results contrast with results of previous studies that showed these impairments to be present in CGH group but not in migraine and control groups [10, 12, 34]. One reason for this difference may be the heterogeneity of our non-migraine group, which comprised participants with predominant tension-type and/or CGH, including 22 participants with comorbid migraine. The heterogeneity of the non-migraine group could have diluted any difference in cervical musculoskeletal impairments between headache types. Another possible explanation for the lack of significant difference in cervical muscle impairment between headache groups may be due to the different experimental protocols used. For example, the equipment we used for measuring strength was different from those used in previous studies [10, 34]. We used a dynamometer which is often available in clinics but may not have been as sensitive as the equipment used in previous studies. This is the first cross-sectional study that evaluated the DCE test, to potentially complement existing evidence on impairment in deep cervical flexors performance in CGH. Given the lack of difference demonstrated between headache groups, examination of the behavior of cervical extensors cannot be recommended at this point in time. In our assessment using the exploratory DCE test using ultrasound imaging, we imaged the extensor muscles at C4 level. Subsequent revised protocols of this test have demonstrated a significant difference when the muscles were imaged higher to the proposed source of symptoms in the spine, namely at C2 level [35].

Nevertheless, the finding that cervical muscle impairment was not significantly different between migraine and non-migraine groups is worth noting and exploring further. Despite the lack of statistically significant difference between groups, cervical spine joint and muscle impairmentswere generally worse in non-migraine headache, consistent with our

hypothesis and previous studies [10, 34].Further work on cervical muscle impairment is recommended, utilizing refined protocols and pure headache groups.

The results also demonstrated that people with migraine had significantly higher pain ratings and disability scores than those with non-migraine headaches. While numerical rating scales of pain intensity were able to distinguish headache types, SF-MPQ-2 and CSI did not appear to do so, suggesting that multidimensional pain and central sensitization experience may be similar in migraine and non-migraine headaches. We also did not find DASS-21 scores to be differentiators of headache types in this cohort, despite previous studies showing an association of negative emotional states with high levels of pain and disability [36]. The high pain rating and disability scores in migraine are consistent with previous studies [37] and with the ICHD definition of migraine as a more intense headache [5]. These results are also consistent with migraine ranking in the top ten disabling conditions globally and the highest headache type on this list [3]. The high disability profile associated with migraine can help distinguish it from non-migraine headaches. Factors that account for the higher disability in migraine versus other headache types may be explored in prospective qualitative and longitudinal cohort studies.

As well, the disability scores from self-report questionnaires had acceptable discriminative ability. This raises a possible role for the use of these questionnaires in the diagnostic workup of people with migraine.Of the disability questionnaires tested in this study, HDI and HDQ appear to be the best questionnaires to use in distinguishing migraine from non-migraine headaches. The diagnostic utility for both HDI and HDQ is promising, given their AUC values on ROC curve analyses of 0.80 and 0.82, respectively. These AUC values suggest that HDI and HDQ could be used to distinguish migraine from non-migraine headaches. Both HDI and HDQ measure the *severity* of the interference of the headache with daily activities and the presence of the *emotional* aspects of disability [27, 28]. Results of this

study therefore indicate that these aspects of disability measured by HDI and HDQ are better differentiators of headaches than the *frequency* of interference of the headache with daily activities measured by other disability questionnaires [29, 30] tested in this study.

When combined tests were considered, we found that a combination of no pain on manual examination of the cervical spine, less change in cervical extensor thickness during contraction,less frequent headaches, and higher self-reported disability distinguished migraine from non-migraine headaches. These results support the combined assessment of aspects of cervical joint function and muscle behavior together with a comprehensive symptom and disability profile as being useful in differentiating migraine from non-migraine headache. This combined assessment is easy to perform and is clinically feasible. Moreover, this combined assessment could complement the presently used model of diagnosing primarily based on headache features to characterize associated impairments and disability. Further, the presence of cervical musculoskeletal impairmentin migraine, although less than in non-migraine, and the disability and multidimensional pain profile in migraine may also inform research directions for modifiable targets of alternative migraine interventions.

Conclusions

Less cervical musculoskeletal impairmentand higher pain and disability, when measured independently,distinguished migraine from non-migraine headaches. A combination of these characteristics and less frequent headaches distinguished migraine with acceptable sensitivity and specificity. Results support the assessment of cervical musculoskeletal impairment and patient-reported outcomes to better characterize and differentially diagnose migraine from non-migraine headaches. Assessing these characteristics could complement diagnosis using existing diagnostic criteria for migraine.

Abbreviations

AUC: area under the curve ; CGH: cervicogenic headache; CROM: Cervical Range of Motion Instrument; CSI: Central Sensitization Inventory; DASS-21: Depression Anxiety Stress Scales-2; DCE test: Deep cervical extensor test; HDI: Henry Ford Headache Disability Inventory; HDQ: Headache Disability Questionnaire; HIT-6: Headache Impact Test-6^{TM}; ICHD: International Classification of Headache Disorders; IQR: interquartile range; LSD: least significant difference; PAIVMs: passive accessory intervertebral movements; ROC: receiver operating characteristic; SF-MPQ-2: Short-form McGill Pain Questionnaire-2; TTH: tension-type headache; WHODAS: World Health Organization Disability Assessment Schedule 2.0

Ethics approval and consent to participate

This research was granted ethics approval by the Human Research Ethics Committee of The University of Sydney (Project Number 2014/536).All participants provided written informed consent prior to participation.

Competing interests

All authors declare no competing interests.

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Authors' contributions

MA, AL, TR conceived and designed the research. MA, SH, KA collected data. MA, AL, TR, KN analysed and interpreted the data. All authors contributed with drafting and revising of the manuscript and critical appraisal of its content. All authors approved the final manuscript.

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519

Table Legends

Table 1. Demographic characteristics of participants (*n* = 125)

Table 2. Headache characteristics of participants with recurrent headaches (*n* = 85)

Table 3. Comparison of performance on cervical musculoskeletal impairment tests between participant groups (*n* = 125)

Table 4. Comparison of scores on self-report questionnaires between participant groups (*n* = 125)

Table 5. Discriminant function coefficients (standardized coefficients) for characteristics with highest predictive ability for migraine

Table 6. The sensitivity and specificity of characteristics to categorize migraine from participants with non-migraine headaches (*n* = 85)

Figure Legend

Figure 1. Flow of participants through the study

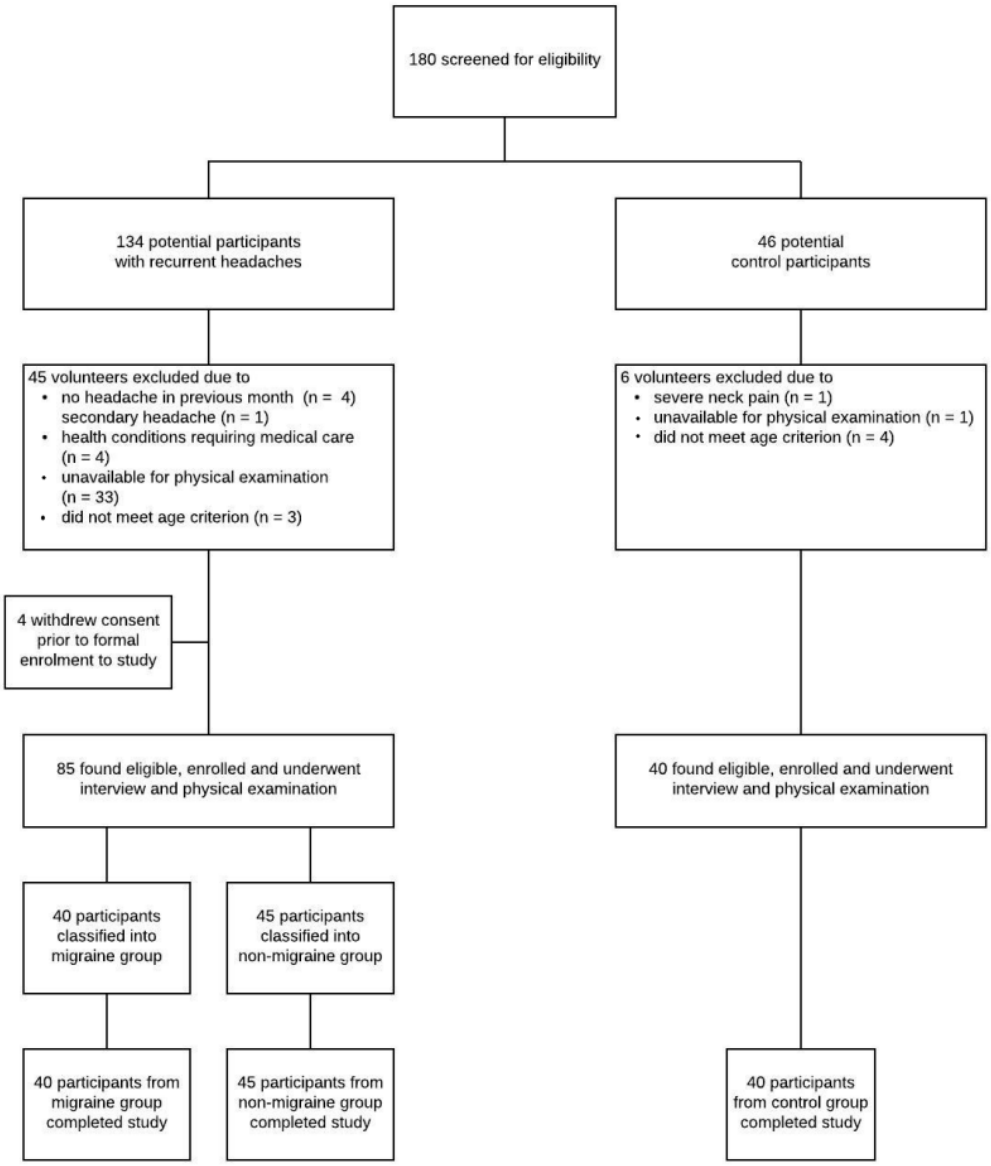

*Figure 1.*Flow of participants through the study

CHAPTER SIX

Six-Month Clinical Course and Factors Associated with Non-Improvement in Migraine and Non-Migraine Headaches

Chapter Six is the peer reviewed version of the following article: Aguila ME, Rebbeck T, Pope A, Ng K, Leaver AM. Six-month clinical course and factors associated with non-improvement in migraine and non-migraine headaches, which has been accepted for publication with revisions in *Cephalalgia* (16 June 2017).

The study protocol for the study presented in this chapter appears as Appendix 5.

Authorship Statement

As co-authors ofthe paper “Six-month clinical course and factors associated with non-recovery in migraine and non-migraine headaches”, we confirm that Maria Eliza Ruiz Aguila has madethe following contributions:

- Conception and design of theresearch
- Acquisition of data
- Analysis and interpretation ofdata
- Drafting and revising of the manuscript and critical appraisal of its content

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Manuscript Title: Six-Month Clinical Course and Factors Associated with Non-Improvement in Migraine and Non-Migraine Headaches

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Abstract:

Background: Evidence on medium-term clinical course of recurrent headaches is scarce. This study explored the six-month course and factors associated with non-improvement in migraine compared with tension-type headache and cervicogenic headache.

Methods: In this longitudinal cohort study, the six-month course of headaches was prospectively examined in participants (n=37 with migraine; n=42 with tension-type or cervicogenic headache). Participants underwent physical examination for cervical musculoskeletal impairments at baseline. Participants also completed questionnaires on pain, disability and other self-report measures at baseline and follow-up, and an electronic diary for 6 months. Course of headaches was examined using mixed within-between analyses of variance and Markov chain modeling. Multiple factors were evaluated as possible factors associated with non-improvement using regression analysis.

Results: Headache frequency, intensity, and activity interference in migraine and non-migraine headaches were generally stable over 6 months but showed month-to-month variations. Day-to-day variations were more volatile in the migraine than the non-migraine group, with the highest probability of transitioning from any headache state to no headache (probability = 0.82–0.85). The odds of non-improvement in disability was nearly 6 times higher with cervical joint dysfunction [odds ratio (95% CI) = 5.58 (1.14–27.42].

Conclusions: Headache frequency, intensity, and activity interference change over 6 months, with day-to-day variation being more volatile in migraine than non-migraine headaches. Cervical joint dysfunction appears to be associated with non-improvement for disability in 6 months. These results may contribute to strategies for educating patients to help align their expectations with the nature of their headaches.

Key words: migraine, tension-type headache, cervicogenic headache, disability, longitudinal study

Introduction

Migraine and other common recurrent headaches such as tension-type headache (TTH) and cervicogenic headache (CGH) may present as episodic attacks, yet persist over time (1-3). To date, knowledge of how these headaches change over time is not fully understood. Evidence from a few longitudinal population-based and clinic-based studies has demonstrated the variable clinical course of migraine and TTH, in particular, in the long term. Specifically, migraine and TTH have been shown to remit in most people, follow a stable course in others, and progress to higher frequency episodes or other poorer outcomes in a few (4-6). For those cases in whom headaches progressed, the following have been identified as predictors: age at onset younger than 20, female, low education and socioeconomic status, white people, head injury, high attack frequency, obesity, medication overuse, stressful life events, caffeine overuse, sleeping problems, and other pain syndromes (6-8). Correspondingly, predictors for remission or recovery from headache have been identified, including less severe headaches at baseline, absence of anxiety and of sleep problems (8), episodes not triggered by alcohol, absence of associated symptoms (4), and short headache duration (5).

However, less is known about how recurrent headaches change and their associated factors in the medium term, which is often considered more important to patients. One longitudinal observational study has shown that clinical characteristics of migraine remain stable over 3 months, with a general trend toward improvement in disability (9). Additionally, improved disability had a moderate positive association with headache frequency in 3 months. Further evidence is required to build on these findings by identifying the short- to medium-term variations in headaches. Specifically, information regarding day-to-day variation in headaches will be relevant to patients with recurrent episodic headaches such as migraine and non-migraine headaches that present frequently to primary care (TTH and

CGH). For many of these patients, daily function is disrupted even on non-headache days because of the unpredictability of their headaches (10) despite undergoing treatment (9).

Knowledge of the medium-term course of common recurrent headaches such as migraine, TTH and CGH will further characterize these headaches and, ultimately, contribute to a greater understanding of their entire clinical course. By knowing the behavior of their headaches in the medium term, patients could form realistic expectations accordingly, which, in turn, could positively influence the way they manage their headaches and reduce their disability. Characterization of migraine and non-migraine headaches could be further broadened when physical impairments that have been reported to be present and treated in these headaches, such as cervical musculoskeletal impairments (11-14), are considered. For example, upper cervical joint dysfunction, as conceivably suggested by the presence of light-headedness, was associated with poor outcome in CGH after one year of active treatment (15). This might be the case for migraine as well; however, this has not been demonstrated. Understanding which factors are associated with poorer short- or medium-term outcomes could assist in mediating or managing these factors toward a more favorable clinical course (7).

Therefore, the primary aim of this study was to describe and compare the medium-term clinical course of migraine and non-migraine headaches in terms of headache frequency, intensity, and activity interference. A secondary aim was to explore factors that are associated with non-improvement in perceived disability, headache frequency and intensity in the medium-term.

Methods

Design

In this longitudinal observational cohort study, we investigated the clinical course of different

headache types and factors that predicted this clinical course by following groups of people with migraine and non-migraine headaches for a period of 6 months. This research was granted ethics approval by the Human Research Ethics Committee of The University of Sydney (Project Number 2014/536).

Participants

We recruited volunteers aged 18 to 65 with recurrent headache through advertisements posted at community bulletins, social media, and primary and specialist care clinics. Participants were included if they had headaches for at least one year and had at least one headache episode in the previous month. Participants were excluded if they had known secondary headache classifications (e.g. tumor, substance withdrawal etc.) or psychiatric disorders. Participants were then classified into the migraine group (fulfilling the criteria for migraine only and not those for other headache types) or non-migraine group (with primary diagnosis of TTH and/or CGH, with or without comorbid migraine) using the ICHD-3 beta criteria (14).

Procedure

All participants underwent initial telephone screening to confirm their eligibility. All eligible participants provided written informed consent prior to participation. Eligible participants then completed questionnaires at baseline regarding demographic and headache characteristics, as well as patient-reported outcomes such as multidimensional pain, disability, and other health measures. Multidimensional pain and disability assessment included the Short-form McGill Pain Questionnaire-2 (SF-MPQ-2) (16), Central Sensitization Inventory (CSI) (17), Henry Ford Headache Disability Inventory (HDI) (18), Headache Disability Questionnaire (HDQ) (19), Headache Impact Test-6^{TM} (HIT-6) (20), and World

Health Organization Disability Assessment Schedule 2.0 (WHODAS) (21). Other health measures comprised those previously shown to predict long-term course of headaches. These included the Depression Anxiety Stress Scales-21 (DASS-21) (22) to assess negative emotional states, the Self-Administered Comorbidity Questionnaire (SCQ) (23) to assess comorbidities (4), the Pittsburgh Sleep Quality Index (PSQI) (24) to assess sleep (6), and the International Physical Activity Questionnaire (IPAQ) (25) to measure physical activity (4).

Participants then attended one assessment for interview and physical examination, in which headaches were classified and data for cervical musculoskeletal impairments were collected. Headache classification used ICHD-3 beta criteria (14) independently done by two researchers. Cervical musculoskeletal impairment data comprised joint dysfunction and cervical muscle behavior. These impairments were shown to be different between migraine and non-migraine headache groups in our previous cross-sectional work. Joint dysfunction was assessed through manual examination of the upper cervical spine with passive accessory intervertebral movements (PAIVMs) (26) and the flexion-rotation test (27). Manual examination of the cervical spine was deemed positive if headache was provoked. The flexion rotation test was deemed positive if headache was provoked and the range of movement was $\leq 32°$. Cervical muscle behavior was assessed using the extensor under load test, a new technique that measures changes in thickness of the deep cervical extensor during low-load using ultrasound imaging (28).

Participants then filled out an electronic diary daily for 6 months, beginning the day after their physical examination. Participants recorded the presence of headaches daily and provided information on headache intensity using the numerical rating scale (NRS: with anchors at 0 and 10: 0 = no headache, 10 = worst headache possible), and interference of the headache with normal daily activities on a scale of not at all (0), a little bit (1), moderately (2), quite a bit (3), and extremely (4). The diary was administered and data were collected

and managed using the Research Electronic Data Capture (REDCap) application (Research Electronic Data Capture, Nashville, Tennessee, USA) (29) hosted at The University of Sydney. Participants also completed the pain and disability questionnaires at 1 month, 3 months, and 6 months after their physical examination.

Statistical Analysis

The sample size of the present study was based on the sample size of our previous cross-sectional study (currently under review) (n = 40 per group). This sample size was powered to detect group differences in cervical musculoskeletal impairments, which was the focus of the cross-sectional study.

Distributions of data were examined through visual inspection by a statistician and using the Shapiro-Wilk test. Accordingly, demographic and headache characteristics, and questionnaire scores were summarized as mean and standard deviation (SD). Additionally, baseline clinical characteristics between the migraine and non-migraine groups were compared using Student *t* test, (for continuous variables) or Chi square test (for categorical variables). The month-to-month variation in the clinical course of headaches over 6 months and between-group comparisons were examined using mixed within-between analyses of variance (ANOVA). The day-to-day variation in clinical course of headaches over 6 months was examined using Markov chain modeling (30). Details of the day-to-day variations derived from Markov chain modeling included the probabilities of transitioning from a given headache intensity and activity interference state to another or the same state on the next day. This approach models the randomness in headache behavior. For Markov chain modeling, intensity was described as ‘no headache’ (NRS 0/10), ‘mild’ (NRS 1–3/10), ‘moderate’ (NRS 4–6/10), or ‘severe’ (NRS 7/10) to simplify the categories. Markov chain modeling also generated simulated models of the clinical course of headache intensity and activity

interference in 30 days in hypothetical individuals with headaches.

The relationship between the dependent variable, absence of clinically meaningful improvement (i.e., non-improvement of headaches) and independent variables, namely demographic and headache characteristics, cervical musculoskeletal impairments, and scores on multidimensional pain, disability, and other health measures were explored using logistic regression analyses. In the absence of a standard definition of non-improvement of headaches, we defined the primary dependent variable, for the purpose of regression analyses, to be < 2.5 point reduction in HIT-6 scores (disability) (31). Secondary dependent variables were < 50% reduction in headache frequency (32) and < 15% reduction in headache intensity (33). The relationship between dependent and independent variables was initially explored using univariate logistic regression analyses. Independent variables with $p < 0.2$ based on the Wald Chi square statistic on univariate analyses were entered into multiple regression analyses using the 'enter' method. In all analyses, headache group was added as an independent variable. Dependent variables were presented as short-term changes (Month 3 minus Month 1) and medium-term changes (Month 6 minus Month 1). Month 1 was considered as the baseline for the change scores in dependent variables; this allowed collection of prospective data from the headache diary for 1 month to serve as baseline data for headache characteristics.

Statistical analyses were conducted using R studio version 3.3.0 2016 (R Foundation for Statistical Computing, Vienna, Austria) and Statistical Package for Social Sciences® statistical software, version 23 (SPSS Inc., Chicago, Illinois, USA) for Windows. Significance level for statistical analyses other than univariate logistic regression was set at 0.05.

Results

Participants

Forty people with migraine and 45 people with non-migraine headache [mean age (standard deviation) = 37.15 (12.88) years] participated in this study. The flow of participants through the study and reasons for exclusion from analyses are shown in Figure 1. Demographic, headache and clinical characteristics of participants at baseline are presented in Table 1. The migraine group had longer history of headache [mean (SD) 20.44 (12.90) years versus 13.44 (12.76) years; $p = 0.014$], less frequent headaches in a month [4.93 (5.89) versus 9.74 (7.66); $p = 0.002$], and higher average headache intensity per month [6.46 (1.65) versus5.57 (1.64); $p = 0.014$] than the non-migraine group. More participants in the migraine group were taking triptan than the non-migraine group [*n* (%) 19 (47.50%) versus 10 (22.22%) participants; $p = 0.014$]. Fewer participants in the migraine group had cervical musculoskeletal impairments than the non-migraine group. For example, 4 (10.00%) participants from the migraine group reported pain on manual examination of the upper cervical joints compared to 26 (57.78%) participants from the non-migraine group.

Clinical course of migraine and non-migraine headaches

Headache characteristics changed over 6 months for both headache groups without fully remitting nor progressing (Figure 2). Headache frequency fluctuated from month to month in both headache groups (Figure 2A; $p = 0.001$), with the migraine group showing more fluctuations than the non-migraine group ($p = 0.005$). The migraine group consistently had fewer headaches per month than the non-migraine group.

Average headache intensity fluctuated from month to month over 6 months for both headache groups (Figure 2B; $p = 0.042$), but this fluctuation was not significantly different between the two headache groups ($p = 0.94$). Average headache intensity oscillated around NRS 4/10 (moderate intensity) for both groups. Considering day-to-day fluctuation in

headache intensity, Markov chain analysis showed that every headache intensity state could be reached from any headache intensity state for both headache groups (Figure 3). The day-to-day transition between headache intensity states of the migraine group ranged from a probability of 0.02 (from mild headache to severe headache the next day) to 0.82 (from no headache to remaining without headache the next day) (Figure 3A).

In contrast, the day-to-day transition between headache intensity states of the non-migraine group ranged from a probability of 0.04 (from no or mild headache to severe headache the next day) to 0.76 (from no headache to remaining without headache the next day) (Figure 3B). The migraine group generally had the greatest probabilities of transition from any headache state to no headache. The transition probabilities for headache intensity differed significantly between the headache groups ($p < 0.001$), with the migraine group showing more volatility. Based on the transition probabilities, any headache intensity would have higher probabilities to have no headache the following day in migraine. In contrast, any headache intensity would have higher probabilities of staying the same or having no headache the following day in non-migraine headaches. The day-to-day volatility of headache intensity in the migraine group was highlighted when modeled using Markov chains (Figure 4).

Average activity interference caused by headaches fluctuated from month to month for both headache groups (Figure 2C; $p = 0.002$) but this fluctuation was not significantly different between the two headache groups ($p = 0.12$). The activity interference for both groups oscillated around NRS 1.5 / 4 (headaches interfered a little bit to moderately with normal daily activities). Considering the day-to-day fluctuation in activity interference, Markov chain modeling showed that every interference state could be reached from any interference state for both headache groups (Figure 5). The day-to-day transition between activity interference states of the migraine group ranged from a probability of 0.01 (from no

interference to extreme interference) to 0.85 (from no interference to remaining without interference) (Figure 5A). In contrast, the day-to-day transition between activity interference states of the non-migraine group ranged from 0.01 (from no interference to extreme interference the next day) to 0.81 (from no interference to remaining without interference the next day) (Figure 5B). The migraine group generally had the greatest probabilities of transition from any interference state to no interference. The transition probabilities for activity interference differed significantly between the headache groups ($p < 0.001$). The day-to-day fluctuation in activity interference was highlighted by simulation models derived from Markov chain analysis (Figure 6).

Factors associated with non-improvement of migraine and non-migraine headaches as to headache-related disability, headache frequency and intensity

The univariate analysis revealed that receiving physical treatment, pain and disability at baseline, and physical activity level were independently associated with non-improvement in headache disability in the short-term (Table 2) and headache intensity, pain, disability scores and physical activity level were associated with non-recovery in the medium term (Table 3).

Multifactorial models were associated with non-improvement in headache-related disability at short- and medium-term. The full model containing migraine headache group, receiving physical treatment, pain on manual examination of the upper cervical joints, higher scores on disability questionnaires (namely HIT-6, HDQ and WHODAS), and lower level of physical activity was statistically significant for predicting non-improvement in headache-related disability at short-term ($p = 0.040$) and explained 27.7% of the variation in disability (Table 4). However, no independent variable made a unique statistically significant contribution to this model. Likewise, the full model containing headache group, age, average headache intensity, average activity interference, pain on manual examination of the upper

cervical joints, scores on disability questionnaires (namely HIT-6, HDQ and WHODAS), and level of physical activity was statistically significant for predicting non-improvement in headache-related disability at medium-term (p = 0.031) and explained 32.3 % of the variation in disability (Table 5). Of these predictors, pain on manual examination of the upper cervical joints made a statistically significant contribution to this model (p = 0.034). Specifically, the odds of non-improvement in disability was nearly 6 times higher when pain on manual examination was present than when it was absent [odds ratio (95% CI) = 5.58 (1.14–27.42]. In contrast, none of the variables examined in this study were associated with non-improvement in headache frequency or intensity after 3 or 6 months (Tables 2–5).

Discussion

This study demonstrated three main findings on the 6-month clinical course and factors associated with outcome in migraine and non-migraine headaches. First, the clinical course of headache characteristics in migraine and non-migraine headaches showed month-to-month variability, but generally did not remit nor progress. Second, day-to-day variations in headache intensity and activity interference were more volatile in the migraine group than the non-migraine group. Third, a number of demographic, clinical and patient-related factors were associated with persistent disability over 3 and 6 months. These findings further characterize and differentiate migraine and non-migraine headaches, thus informing clinical practice and research.

The month-to-month variation in headache frequency, intensity, and activity interference in migraine and non-migraine headaches changed, but did not fully remit nor progress. These results are consistent with existing evidence for the 3-month clinical course of migraine (9) and show a similar trend as the prevailing knowledge on the long-term clinical course of changes in migraine (4, 34). Headache intensity fluctuated around moderate

intensity for both headache groups, challenging the typical picture of migraine as a more severe headache than non-migraine headaches (14). Analogously, activity interference caused by headaches over 6 months hovered between little to moderate interference for both headache groups. This range of activity interference contrasts with the high levels of disability associated especially with migraine and TTH (35). On closer consideration, such disparities in intensity and activity limitation ratings are understandable and may be partly attributed to measuring intensity and activity interference prospectively using a headache diary. First, retrospective rating by patients tends to overestimate headache intensities compared with information from diaries (36). Second, the perceived impact of the headache on daily activities measured each day could be lower compared to perceived disability over extended periods as captured by self-report questionnaires.

This study also presents new evidence that characterizes the day-to-day variation in headache intensity and activity interference as being more volatile in migraine than in non-migraine headaches. This greater volatility in migraine, as demonstrated by Markov chain analyses, is related to the higher probability of having no headache on the following day regardless of the current headache state. Further, the different possible scenarios of transitioning between headache states imply that the extent of volatility may be different between individuals with similar headache diagnoses, undergoing their usual treatment, and having the same level of headache intensity and activity interference on a particular day.

This study also presents preliminary evidence that factors influencing non-improvement in disability in 6 months include headache features, cervical joint dysfunction, disability and physical activity. This preliminary evidence presents prospective directions for future research. Of note is cervical joint dysfunction which appears to be associated with non-improvement in disability in both migraine and non-migraine groups yet was less frequent in the former (10.00% versus 57.78%). The lack of factors significantly associated with non-

improvement in frequency and intensity may most likely be indicative that no factor significantly influences those outcomes in the short-to medium-term. The same can be said for non-improvement in disability in the short-term. However, the multifactorial model for disability explains 27.7% and 32.3% of the variability in the model in the short- and medium-term, respectively. The association of these factors with disability needs to be further investigated in larger cohort studies with pure headache groups. Prospective studies may also explore other factors that would influence non-improvement in disability.

Results of this study inform headache management. First, information about the month-to-month and day-to-day variation in features of migraine and non-migraine headaches can form part of patient education. Importantly, educating patients about the most likely behavior of their headaches will help them align their expectations. This information could also be reassuring for patients who perceive the unpredictability of their headaches as disabling and disquieting (10, 37). Second, the small but statistically significant month-to-month variation in headache characteristics over 6 months justifies continued monitoring of symptoms as part of headache management. Third, the association of cervical joint dysfunction with non-improvement in headache-related disability in 6 months reveals the usefulness of cervical joint assessment and, if necessary, targeting any impairments to help reduce disability in the short- to medium-term.

The study aimed to describe the shorter-term clinical course of migraine and non-migraine headaches with participants having their usual headache management, when interventions were not standardized. As such, we did not control for intervention and other possible confounding factors that could influence the course of headaches. Prospective clinical trials are indicated to investigate those other factors to build on evidence from this study. Such trials can also use evidence presented here concerning the 6-month clinical course of migraine and non-migraine headaches when selecting outcome measures. Further

studies involving pure headache groups and collecting longitudinal data on possible variables influencing non-improvement are also required to validate our results. Investigating the underlying mechanisms explaining the difference in month-to-month and day-to-day variation between migraine and non-migraine headaches also remains an area for future investigation.

In conclusion, headache frequency, intensity, and activity interference show month-to-month and day-to-day variations over 6 months in individuals with migraine and non-migraine headaches who are already receiving treatment. Day-to-day variations in headache intensity and activity interference are more volatile in migraine compared with non-migraine headaches. Cervical joint dysfunction measured using manual examination appears to be associated with non-improvement in headache-related disability in 6 months. These results will contribute to strategies for patient education regarding the nature of their headaches, and also carry implications for outcome measure selection in prospective clinical trials.

Conflict of Interest Statement: All authors declare no conflicts of interest.

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Clinical Implications:

- Headache frequency, intensity and activity interference show variations over 6 months, but generally do not fully remit nor progress, in individuals with migraine and non-migraine headaches.
- Day-to-day variation in headache intensity and activity interference is more volatile in migraine than non-migraine headaches.
- Individuals with migraine or non-migraine headaches who have cervical spine dysfunction are nearly 6 times more likely not to recover in terms of headache-related disability within 6 months.
- These results contribute to strategies for educating patients on the nature of their headaches.
- The need to consider volatility of headache characteristics when selecting outcome measures for prospective clinical trials is highlighted.

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Figure Legends

Figure 1. Flow of participants through the study

Figure 2. Month-to-month variation in headache characteristics in migraine and non-migraine groups. (A) Frequency of headaches. (B) Average headache intensity. (C) Average activity interference due to headache

Figure 3. Transition matrices of headache intensity showing the probability of transitioning from a current headache intensity state (denoted by rows) to the next-day headache intensity state (denoted by columns). (A) Migraine group. (B) Non-migraine group ($p < 0.001$)

Figure 4. Simulated day-to-day clinical course of headache intensity of 12 hypothetical individuals with headaches over 30 days (numerical rating scale; 0, no headache, to 3, severe headache. (A) Migraine group. (B) Non-migraine group ($p < 0.001$)

Figure 5. Transition matrices of activity interference caused by headache for migraine group showing the probability of transitioning from a current activity interference state (denoted by rows) to the next-day activity interference state (denoted by columns). (A) Migraine group. (B) Non-migraine group ($p < 0.001$)

Figure 6. Simulated day-to-day clinical course of activity interference of 12 hypothetical individuals with headaches over 30 days (activity interference rated using a scale; 0, not at all, to 4, extremely. (A) Migraine group. (B) Non-migraine group ($p < 0.001$)

Table Legends

Table 1. Baseline characteristics of participants [mean (SD) or *n* (%) where indicated] (*n* = 85)

Table 2. Univariate logistic regression analysis showing relationships between possible factors associated with non-improvement in headache characteristics in the SHORT-TERM

Table 3. Univariate logistic regression analysis showing relationships between possible factors associated with non-improvement in headache characteristics in the MEDIUM-TERM

Table 4. Multivariate logistic regression predicting likelihood of non-improvement in headache characteristics in the SHORT-TERM

Table 5. Multivariate logistic regression predicting likelihood of non-improvement in headache characteristics in the MEDIUM-TERM

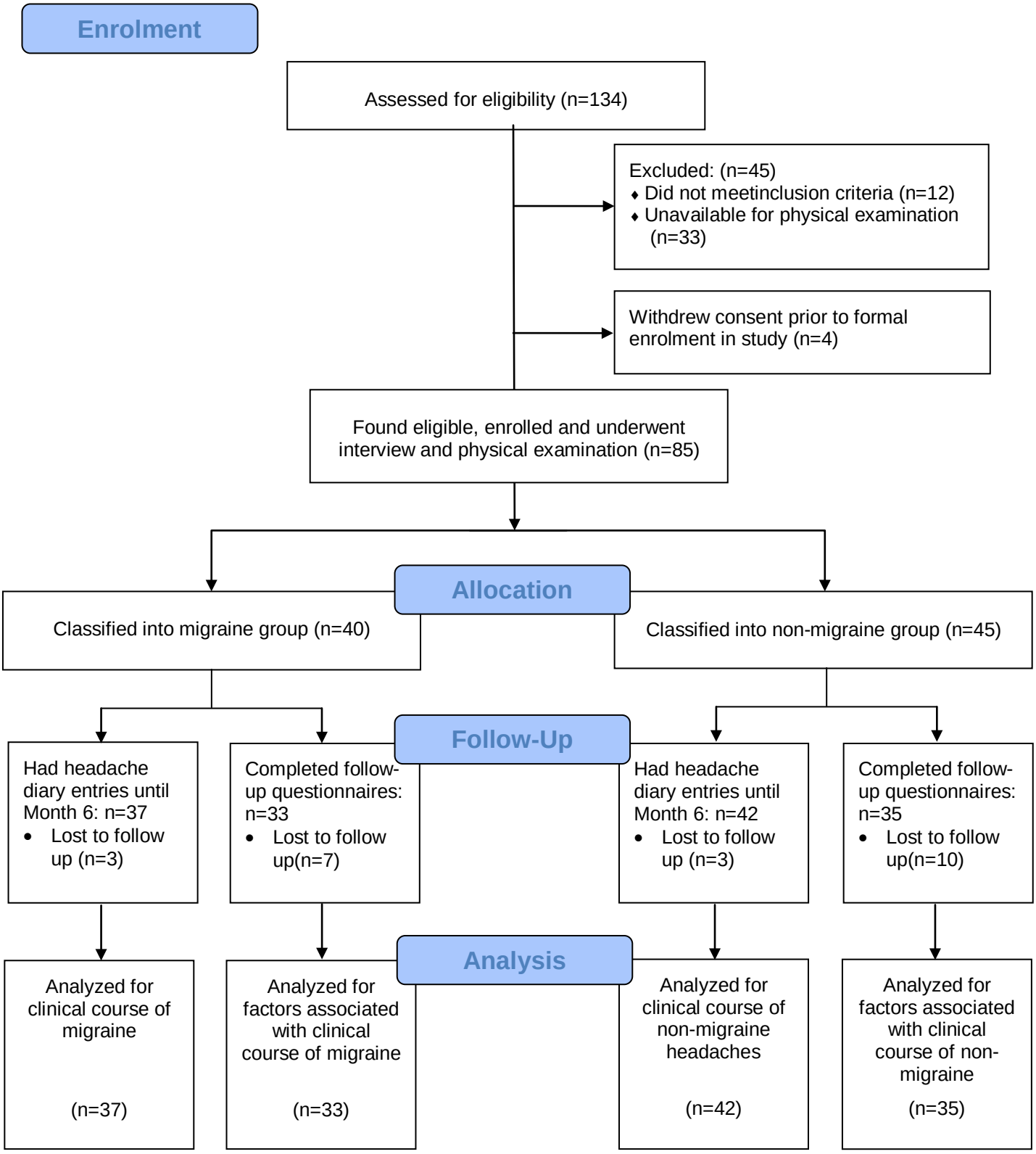


Figure 1. Flow of participants through the study

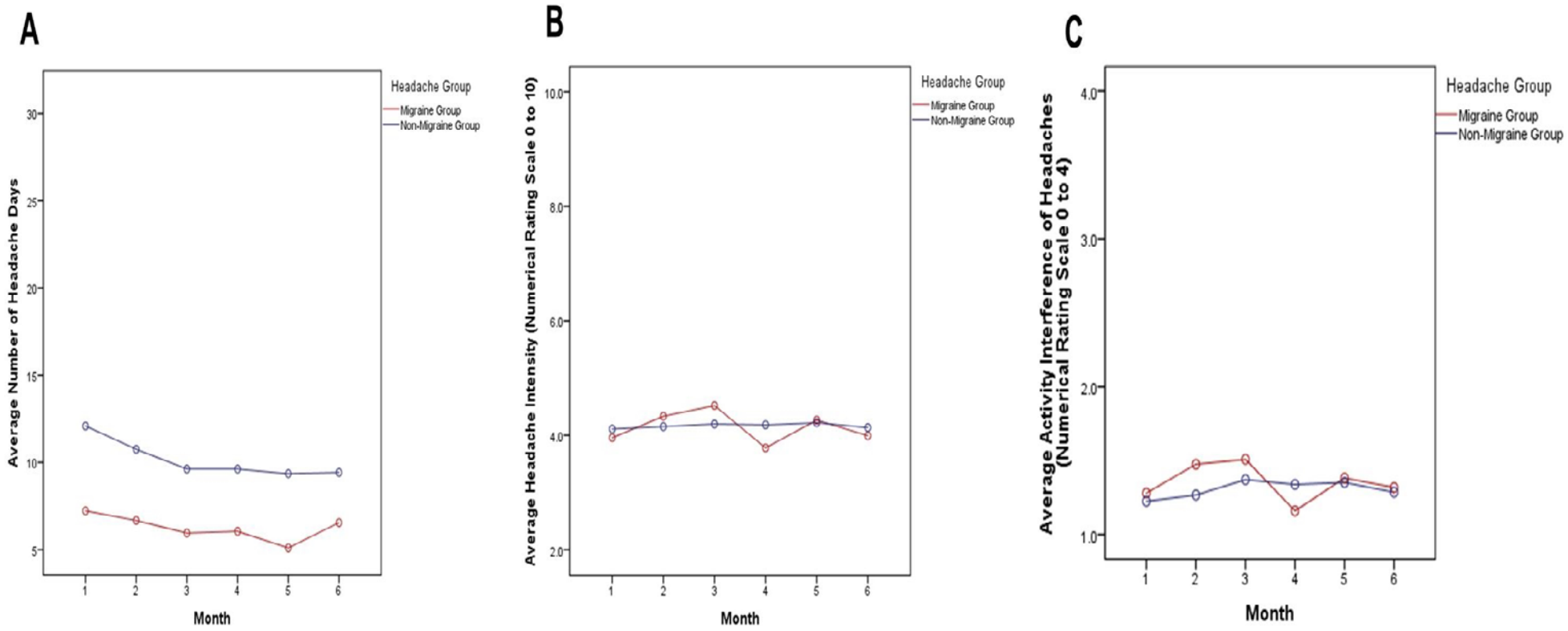


*Figure 2.*Month-to-month variation in headache characteristics in migraine and non-migraine groups. (A) Frequency of headaches. (B) Average headache intensity. (C) Average activity interference due to headache

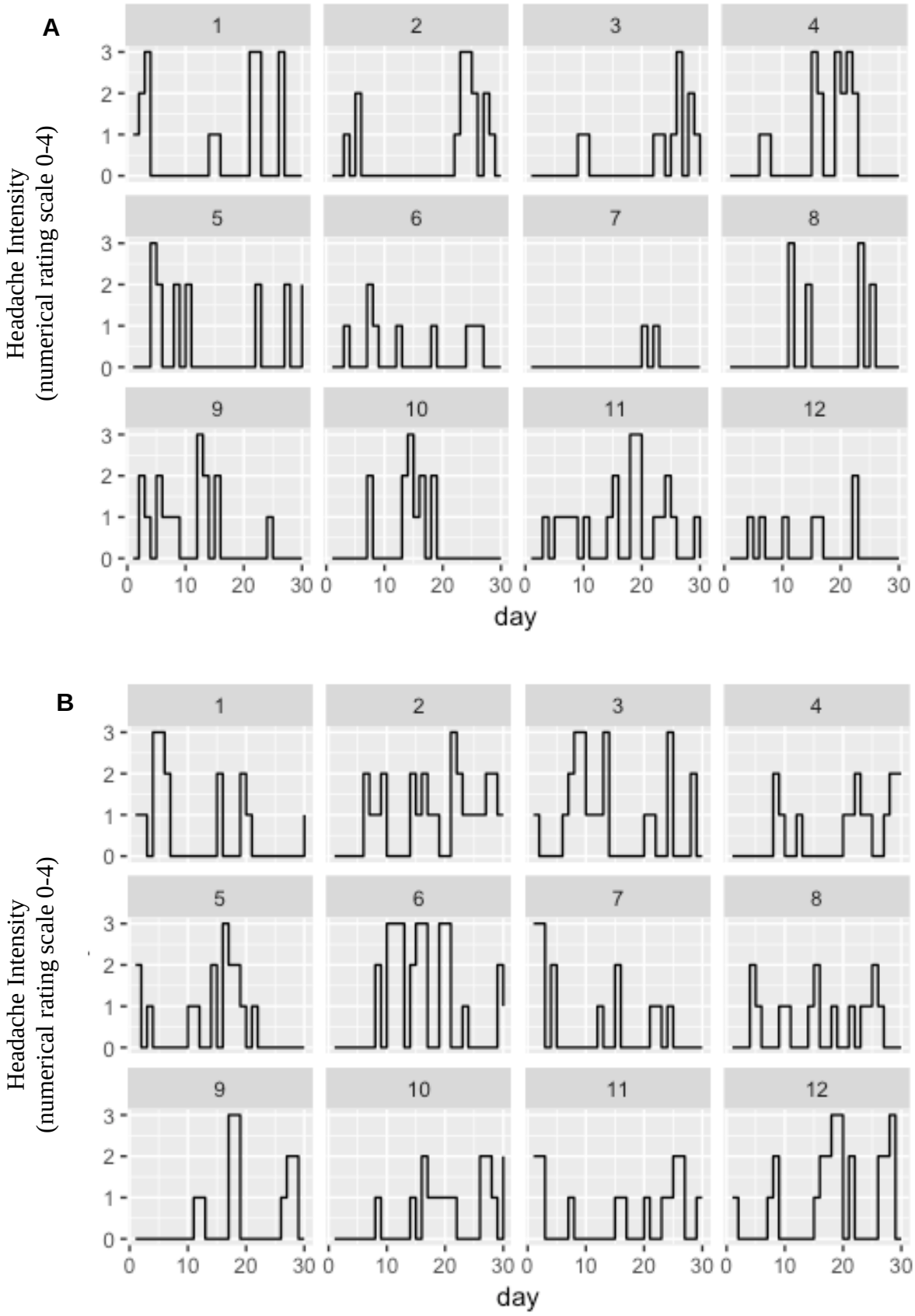
A

Initial State of Headache Intensity	Subsequent State of Headache Intensity			
	No Headache	Mild	Moderate	Severe
No Headache	0.82	0.09	0.06	0.03
Mild	0.61	0.25	0.12	0.02
Moderate	0.48	0.15	0.21	0.16
Severe	0.36	0.06	0.26	0.32

B

Initial State of Headache Intensity	Subsequent State of Headache Intensity			
	No Headache	Mild	Moderate	Severe
No Headache	0.76	0.11	0.09	0.04
Mild	0.45	0.37	0.14	0.04
Moderate	0.36	0.20	0.31	0.13
Severe	0.24	0.11	0.26	0.39

*Figure 3.*Transition matrices of headache intensity showing the probability of transitioning from a current headache intensity state, denoted by rows, to the next-dayheadache intensity state, denoted by columns. (A) Migraine group. (B) Non-migraine group($p < 0.001$)



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A

Initial State of Activity Interference Caused by Headache	Subsequent State of Activity Interference Caused by Headache				
	Not at All	A Little Bit	Moderately	Quite a Bit	Extremely
Not at All	0.85	0.08	0.04	0.02	0.01
A Little Bit	0.63	0.18	0.12	0.06	0.01
Moderately	0.46	0.22	0.22	0.08	0.02
Quite a Bit	0.43	0.14	0.22	0.17	0.04
Extremely	0.44	0.10	0.10	0.13	0.23

B

Initial State of Activity Interference Caused by Headache	Subsequent State of Activity Interference Caused by Headache				
	Not at All	A Little Bit	Moderately	Quite a Bit	Extremely
Not at All	0.81	0.12	0.04	0.02	0.01
A Little Bit	0.52	0.28	0.13	0.05	0.02
Moderately	0.38	0.28	0.20	0.11	0.03
Quite a Bit	0.31	0.19	0.19	0.24	0.07
Extremely	0.26	0.15	0.12	0.20	0.27

Figure 5. Transition matrices of activity interference caused by headache for migraine group showing the probability of transitioning from a current activity interference state, denoted by rows, to the next-day activity interference state, denoted by columns. (A) Migraine group. (B) Non-migraine group

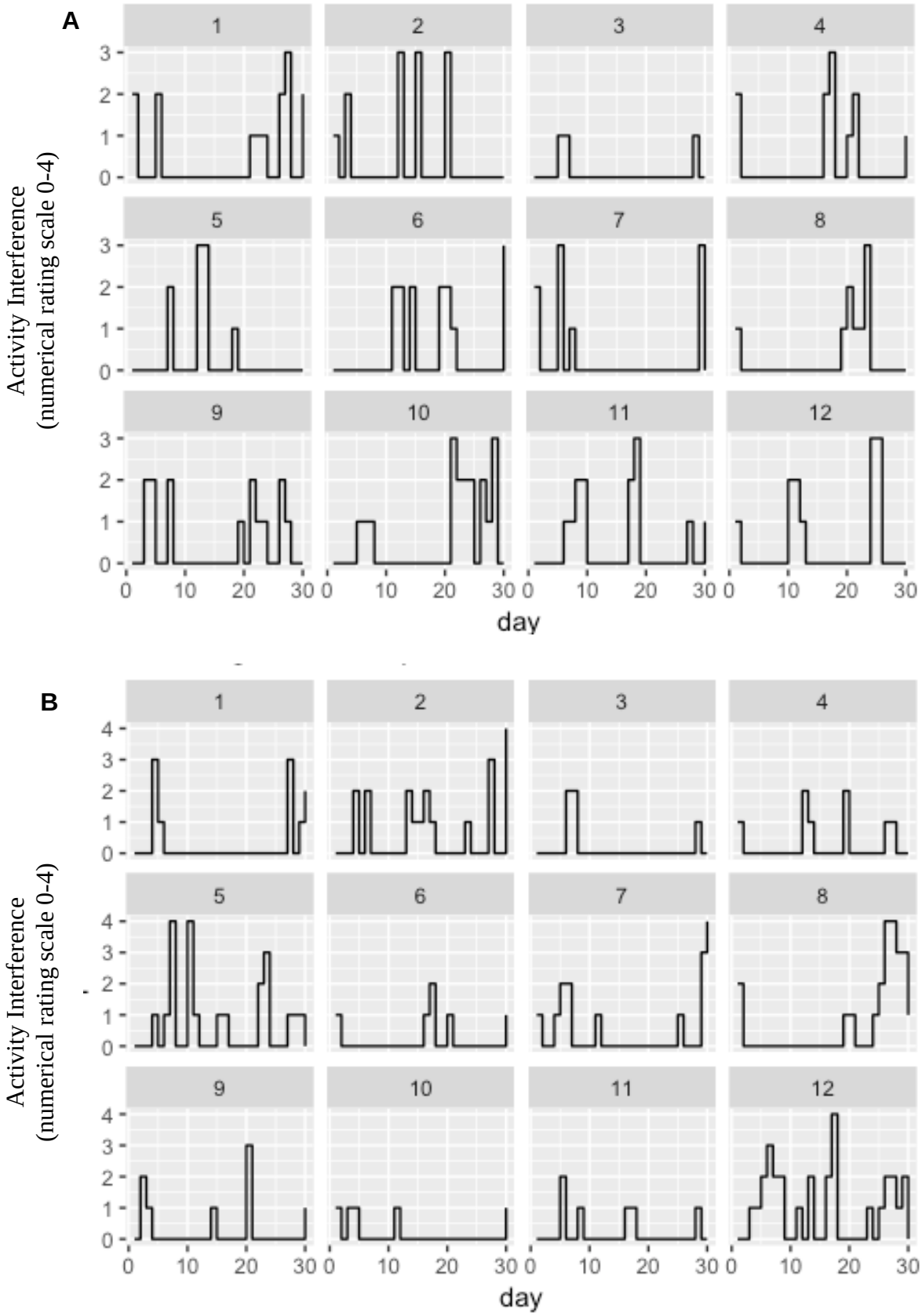

*Figure 6.*Simulated day-to-day clinical course of activity interference of 12hypothetical individuals with headaches over 30 days (activity interference rated using a scale; 0, not at all, to 4, extremely. (A) Migraine group. (B) Non-migraine group ($p < 0.001$)

Table 1. Baseline characteristics of participants [mean (SD) or *n* (%) where indicated)] (*n* = 85)

	Migraine (*n* = 40)	Non-Migraine (*n* = 45)	*p* values*
Demographic characteristics			
Age	40.83 (12.87)	33.89 (12.11)	**0.013**
Gender (female) (*n*, %)	32 (80.00%)	40 (88.89%)	0.26
Body mass index	24.81 (4.93)	24.34 (5.83)	0.70
Headache characteristics			
History of headache (years since first episode)	20.44 (12.90)	13.44 (12.76)	**0.014**
Frequency of headache in a month	4.93 (5.89)	9.74 (7.66)	**0.002**
Episode duration, minimum (hours)	12.45 (16.00)	13.28 (17.61)	0.82
Episode duration, maximum (hours)	58.30 (35.69)	84.97 (168.60)	0.31
Average headache intensity per month (0–10)†	6.46 (1.65)	5.57 (1.64)	**0.014**
Clinical characteristics			
Receiving pharmacologic treatment (*n*, %)			
Paracetamol	14 (35.00%)	17 (37.78%)	0.79
Non-steroidal anti-inflammatory drug	18 (45.00%)	20 (44.44%)	0.96
Tricyclic antidepressant	6 (15.00%)	3 (6.67%)	0.21
Triptan	19 (47.50%)	10 (22.22%)	**0.014**
Botulinum toxin	8 (20.00%)	11 (24.44%)	0.62
Beta blocker	4 (10.00%)	3 (6.67%)	0.58
Selective serotonin reuptake inhibitor	5 (12.50%)	6 (13.33%)	0.91
Proton pump inhibitor	4 (10.00%)	6 (13.33%)	0.63
Anticonvulsant	5 (12.50%)	7 (15.56%)	0.69
Receiving physical treatment (*n*, %)	8 (20.00%)	12 (26.70%)	0.47
Pain on manual examination of the upper cervical joints (*n*, %)	4 (10.00%)	26 (57.78%)	**<0.001**
Positive flexion rotation test (*n*, %)	4 (10.00%)	17 (37.78%)	**0.003**
Extensor under load test (percent change on symptomatic side)	6.17 (8.16)	11.87 (15.34)	**0.035**

NOTE. Bold numbers indicate statistical significance ($p < 0.05$)

* *p* values for Student *t*-test for continuous variables; *p* values for Chi-square test for categorical variables

† Headache intensity: Numerical rating scale 0–10; 0 = no pain, 10 = worst possible pain

Table 2. Univariate logistic regression analysis showing relationships between possible predictors of non-improvement in headache characteristics in the SHORT-TERM

	HIT-6		Headache Frequency		Headache Intensity	
Variable	**Nagelkerke R^2**	***p* value**	**Nagelkerke R^2**	***p* value**	**Nagelkerke R^2**	***p* value**
Demographic characteristics						
Age	0.011	0.46	0.037	**0.196**	0.019	0.38
Sex	0.002	0.78	0.003	0.70	0.001	0.80
BMI	0.001	0.86	0.143	**0.035**	0.042	0.24
Clinical characteristics						
Receiving pharmacologic treatment	0.013	0.42	0.017	0.36	0.003	0.73
Receiving physical treatment	0.066	**0.11**	0.020	0.35	0.015	0.45
Frequency in a month	0.003	0.72	0.007	0.57	0.006	0.62
Average headache intensity last month	0.008	0.54	0.036	0.20	0.065	**0.10**
Average activity interference	0.000	0.90	0.000	0.90	0.000	0.98
Pain on manual examination of the upper cervical joints	0.043	**0.17**	0.005	0.62	0.000	0.89
Positive flexion rotation test	0.001	0.86	0.007	0.55	0.004	0.70
Percent change on symptomatic side on extensor under load test	0.000	0.91	0.019	0.39	0.004	0.68
Pain and sensitization						
SF-MPQ-2 Total score	0.004	0.65	0.000	0.91	0.000	0.90
CSI Total score	0.011	0.46	0.059	**0.11**	0.008	0.55
Disability						
HIT-6 Score at baseline	0.114	**0.028**	0.019	0.35	0.000	0.97
HDI Total Score at baseline	0.012	0.45	0.025	0.29	0.003	0.71
HDQ Total Score at baseline	0.109	**0.025**	0.038	**0.19**	0.001	0.85
WHODAS Overall Score at baseline	0.113	**0.029**	0.175	**0.018**	0.014	0.42
Emotional state						
DASS-21 Depression Score	0.021	0.33	0.006	0.625	0.007	0.61
DASS-21 Anxiety Score	0.015	0.39	0.005	0.633	0.004	0.71
DASS-21 Stress Score	0.013	0.45	0.064	**0.106**	0.001	0.85
Other health measures						
SCQ Overall Score	0.013	0.44	0.029	0.277	0.000	0.95
PSQI Total Score	0.011	0.47	0.010	0.496	0.027	0.28
Physical activity level	0.058	**0.099**	0.025	0.289	0.000	0.94

Abbreviations: BMI, body mass index; CSI, Central Sensitization Inventory; DASS-21, Depression Anxiety Stress Scales-21; HDI, The Henry Ford Headache Disability Inventory; HDQ, Headache Disability Questionnaire; HIT-6, Headache Impact Test-6; PSQI, Pittsburgh Sleep Quality Index; SCQ, the Self-Administered Comorbidity Questionnaire; SF-MPQ-2, Short-form McGill Pain Questionnaire-2; WHODAS, World Health Organization Disability Assessment Schedule

Bold numbers indicate possible predictors with $p < 0.2$

Table 3. Univariate logistic regression analysis showing relationships between possible predictors of non-improvement in headache characteristics in the MEDIUM-TERM

	HIT-6		**Headache Frequency**		**Headache Intensity**	
Variable	**Nagelkerke R^2**	***p* value**	**Nagelkerke R^2**	***p* value**	**Nagelkerke R^2**	***p* value**
Demographic characteristics						
Age	0.040	**0.17**	0.002	0.79	0.067	**0.09**
Sex	0.001	0.82	0.001	0.84	0.040	0.22
BMI	0.009	0.53	0.041	0.23	0.109	**0.06**
Clinical characteristics						
Receiving pharmacologic treatment	0.005	0.64	0.026	0.26	0.000	0.96
Receiving physical treatment	0.026	0.27	0.010	0.51	0.001	0.85
Frequency in a month	0.001	0.85	0.004	0.68	0.067	**0.09**
Average headache intensity last month	0.070	**0.07**	0.068	**0.09**	0.016	0.38
Average activity interference	0.052	**0.11**	0.008	0.56	0.001	0.82
Neck impairments						
Pain on manual examination of the upper cervical joints	0.057	**0.10**	0.017	0.37	0.002	0.76
Positive flexion rotation test	0.017	0.36	0.510	**0.12**	0.004	0.67
Percent change on symptomatic side on extensor under load test	0.007	0.55	0.012	0.50	0.000	0.99
Pain and sensitization						
SF-MPQ-2 Total score	0.002	0.76	0.022	0.34	0.018	0.37
CSI Total score	0.000	0.92	0.005	0.65	0.051	**0.13**
Disability						
HIT-6 Score at baseline	0.049	**0.13**	0.011	0.48	0.029	0.24
HDI Total Score at baseline	0.001	0.83	0.000	0.97	0.087	**0.06**
HDQ Total Score at baseline	0.104	**0.026**	0.015	0.42	0.008	0.55
WHODAS Overall Score at baseline	0.040	**0.17**	0.004	0.69	0.059	**0.13**
Emotional state						
DASS-21 Depression Score	0.005	0.61	0.012	0.50	0.035	0.27
DASS-21 Anxiety Score	0.018	0.36	0.002	0.74	0.010	0.52
DASS-21 Stress Score	0.030	0.24	0.003	0.72	0.079	**0.07**
Other health measures						
SCQ Overall Score	0.014	0.42	0.005	0.61	0.005	0.62
PSQI Total Score	0.000	0.89	0.013	0.43	0.009	0.53
Physical activity level	0.078	**0.05**	0.007	0.57	0.004	0.65

Abbreviations: BMI, body mass index; CSI, Central Sensitization Inventory; DASS-21, Depression Anxiety Stress Scales-21; HDI, The Henry Ford Headache Disability Inventory; HDQ, Headache Disability Questionnaire; HIT-6, Headache Impact Test-6; PSQI, Pittsburgh Sleep Quality Index; SCQ, the Self-Administered Comorbidity Questionnaire; SF-MPQ-2, Short-form McGill Pain Questionnaire-2; WHODAS, World Health Organization Disability Assessment Schedule 2.0

Bold numbers indicate possible predictors with $p < 0.2$

Table 4. Multivariate logistic regression predicting likelihood of non-improvement in headache characteristics in the SHORT-TERM

Outcome	Predictor variables	B (SE)	Wald test	*p* value	OR (95% CI)
Headache frequency	Headache group	0.36 (0.81)	0.20	0.66	1.44 (0.29–7.08)
	Age	0.03 (0.03)	0.77	0.38	1.03 (0.97–1.09)
	BMI	0.17 (0.11)	2.42	0.12	1.18 (0.96–1.46)
	CSI Total Score	-0.04 (0.04)	1.17	0.28	0.96 (0.89–1.03)
	HDQ Total Score	0.004 (0.03)	0.03	0.87	1.00 (0.95–1.06)
	WHODAS Overall Score	0.10 (0.06)	2.45	0.12	1.10 (0.98–1.25)
	DASS-21 Stress Score	0.05 (0.12)	0.19	0.66	1.05 (0.84–1.33)
Chi square 12.96, $p = 0.07$; Nagelkerke R^2: 0.273					
HIT-6 score	Headache group	-0.68 (0.72)	0.89	0.34	0.51 (0.12–2.08)
	Receiving physical treatment	1.63 (0.89)	3.36	0.07	5.10 (0.89–29.09)
	Pain on manual examination of the upper cervical joints	1.23 (0.81)	2.30	0.13	3.43 (0.70–16.90)
	HIT-6 Score at baseline	-0.06 (0.07)	0.65	0.42	0.94 (0.81–1.09)
	HDQ Total Score at baseline	-0.01 (0.03)	0.03	0.87	1.00 (0.94–1.06)
	WHODAS Overall Score at baseline	-0.02 (0.03)	0.52	0.47	0.98 (0.92–1.04)
	Physical activity level at baseline	0.72 (0.51)	2.01	0.16	2.05 (0.76–5.55)
Chi square 14.70, $p = 0.040$; Nagelkerke R^2: 0.277					
Headache intensity	Headache group	0.33 (0.64)	0.27	0.60	1.39 (0.40–4.84)
	Average headache intensity	-0.34 (0.20)	2.75	0.10	0.71 (0.48–1.06)
Chi square 3.10, $p = 0.21$; Nagelkerke R^2: 0.072					

Abbreviations: BMI, body mass index; CSI, Central Sensitization Inventory; DASS-21, Depression Anxiety Stress Scales-21; HDQ, Headache Disability Questionnaire; HIT-6, Headache Impact Test-6; WHODAS, World Health Organization Disability Assessment Schedule 2.0

Bold numbers indicate statistical significance ($p < 0.05$)

Table 5. Multivariate logistic regression predicting likelihood of non-improvement in headache characteristics in the MEDIUM-TERM

Outcome	Predictor variables	B (SE)	Wald test	*p* value	OR (95% CI)
Headache frequency	Headache group	0.21 (0.62)	0.11	0.74	1.23 (0.36–4.20)
	Average headache intensity	0.31 (0.19)	2.63	0.11	1.36 (0.94–1.97)
	Positive flexion rotation test	-0.97 (0.66)	2.18	0.14	0.38 (0.10–1.38)
Chi square 5.37 p = 0.15; Nagelkerke R^2: 0.112					
HIT-6 score	Headache group	-0.59 (0.70)	0.72	0.40	0.55 (0.14–2.16)
	Age	0.05 (0.03)	3.65	0.06	1.05 (1.00–1.11)
	Average headache intensity	-0.14 (0.26)	0.29	0.59	0.87 (0.52–1.45)
	Average activity interference	-0.28 (0.69)	0.16	0.69	0.76 (0.20–2.92)
	Pain on manual examination of the upper cervical joints	1.72 (0.81)	4.48	**0.034**	5.58 (1.14–27.42)
	HIT-6 Score at baseline	0.01 (0.07)	0.02	0.89	1.01 (0.87–1.17)
	HDQ Total Score at baseline	-0.04 (0.04)	1.31	0.25	0.96 (0.90–1.03)
	WHODAS Overall Score at baseline	0.02 (0.03)	0.43	0.51	1.02 (0.96–1.09)
	Physical activity level	1.06 (0.56)	3.64	0.06	2.89 (0.97–8.61)
Chi square 18.34, p = 0.031; Nagelkerke R^2: 0.323					
Headache intensity	Headache group	-0.004 (0.76)	0.00	1.00	1.00 (0.23–4.41)
	Age	0.03 (0.03)	0.63	0.43	1.03 (0.96–1.09)
	BMI	0.10 (0.09)	1.11	0.29	1.10 (0.92–1.32)
	Frequency of headaches	0.09 (0.06)	2.28	0.13	1.10 (0.97–1.24)
	CSI Total Score	-0.04 (0.03)	1.11	0.29	0.96 (0.90–1.03)
	HDI Total Score	0.02 (0.02)	0.69	0.41	1.02 (0.98–1.06)
	WHODAS Overall Score	0.005 (0.05)	0.01	0.93	1.00 (0.90–1.12)
	DASS-21 Stress Score	0.15 (0.12)	1.63	0.20	1.17 (0.92–1.47)
Chi square 12.61, p = 0.13; Nagelkerke R^2: 0.266					

Abbreviations: BMI, body mass index; CSI, Central Sensitization Inventory; DASS, Depression Anxiety Stress Scales-21; HDI, The Henry Ford Headache Disability Inventory; HDQ, Headache Disability Questionnaire; HIT-6, Headache Impact Test-6; WHODAS, World Health Organization Disability Assessment Schedule 2.0

Bold numbers indicate statistical significance ($p < 0.05$)

CHAPTER SEVEN

Responsiveness of Disability Questionnaires in Migraine and Non-Migraine Headaches

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Authorship Statement

As co-authors ofthe paper “Responsiveness of disability questionnaires in migraine and non-migraine headache”, we confirm that Maria Eliza Ruiz Aguila has madethe following contributions:

- Conception and design of the research
- Acquisition of data
- Analysis and interpretation of data
- Drafting and revising of the manuscript and critical appraisal of its content

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Abstract

Purpose To examine the responsiveness of disability questionnaires for migraine and other frequently presenting non-migraine headaches in primary care (tension-type headache and cervicogenic headache).

Methods Data were collected from a longitudinal cohort study distinguishing migraine and non-migraine headaches. Participants fulfilled the International Classification of Headache Disorders-3 beta criteria for migraine, tension-type headache and/or cervicogenic headache. Participants completed the Headache Impact Test-6, Headache Disability Inventory, Henry Ford Headache Disability Inventory, Headache Disability Questionnaire, and the World Health Organization Disability Assessment Schedule 2.0 at baseline and at 1, 3 and 6 months. Participants also filled out a headache diary daily for 6 months. Internal responsiveness of the questionnaires was evaluated by calculating effect size, and external responsiveness by receiver operating characteristic curve analysis of change scores with headache frequency.

Results Headache Impact Test-6 and Headache Disability Questionnaire had the best internal responsiveness for individuals with migraine and non-migraine. At short-term, effect sizes (84% confidence intervals) ranged from 0.31 (0.07–0.56) to 0.47 (0.11–0.82). At medium-term, effect sizes ranged from 0.40 (0.06–0.74) to 0.60 (0.26–0.94). Headache Disability Questionnaire generally had the best external responsiveness to change in headache frequency at both short- and medium-term [areas under the curve (95% confidence intervals) 0.52 (0.32–0.72) to 0.69 (0.49–0.89)].

Conclusions Headache Impact Test-6 and Headache Disability Questionnaire were the most responsive disability questionnaires for individuals with migraine and non-migraine headaches. These results add to the evidence on the usefulness of these measures in routine assessment of outcomes in clinical practice.

Keywords: migraine, tension-type headache, cervicogenic headache, disability, outcome assessment

Introduction

Headaches that most frequently present to primary care include migraine [1] and non-migraine headaches such as tension-type headache [1] and cervicogenic headache [2]. These headaches are associated with significant impact on the individuals [3, 4], who experience disability when their headache and associated symptoms are active, as well as between headache episodes. Disability must therefore be assessed in individuals with headaches because it cannot be fully explained by headache frequency, intensity and symptoms [5].

Disability assessed using self-report questionnaires is among the outcomes recommended for headache research [6–9]. A number of these questionnaires are specific to migraine and assess disability during, but not between, migraine episodes [10]. Aside from migraine-specific questionnaires, there are headache-specific questionnaires that are applicable across different episodic or chronic headache types. These questionnaires include the Headache Impact Test-6^{TM} (HIT-6) [11], The Henry Ford Headache Disability Inventory (HDI) [12], and the Headache Disability Questionnaire (HDQ) [13]. In addition to these headache-specific questionnaires, generic disability questionnaires [e.g. 14, 15], including the World Health Organization Disability Assessment Schedule 2.0 (WHODAS) [16], have also been used. The above questionnaires differ in their constructs, reference time periods and scoring, however all are reliable and valid measures of disability for individuals with headache [6, 10, 11, 14, 17]. To date, however, evidence is still lacking regarding which of these questionnaires are most responsive, and therefore can be recommended to clinicians for their ability to detect improvement or worsening of symptoms across migraine and non-migraine headaches.

Responsiveness of self-report questionnaires is important to clinicians and patients

because it denotes ability to measure true change over time. Internal responsiveness describes the ability of a measure to detect change over a particular time period [18], whilst external responsiveness measures this change in relation to an external reference measure of health status [18]. Thus far, only the responsiveness of the HIT-6 has been evaluated in specific headache populations [11]. The HIT-6 has been shown to be responsive to self-reported change in severity [19] and headache frequency and duration [20] in migraine and to self-reported change and headache frequency in tension-type headache [21]. Other disability questionnaires measuring slightly different constructs than HIT-6 (see Table 1) are available for headache populations. The responsiveness of HDQ has been shown to be acceptable in a general headache population who are seeking physiotherapy treatment [22] and the responsiveness of WHODAS has been shown to be acceptable in a population with chronic conditions, including migraine [23]. However, the responsiveness of these questionnaires has not been compared across headache types nor compared with HIT-6. Comparing the responsiveness of these questionnaires between migraine and non-migraine headache populations could build on early evidence from our previous work indicating greater day-to-day variability in disability in migraine compared to non-migraine headaches (forthcoming publication). Investigating the responsiveness of HIT-6 compared with that of other disability questionnaires in different headache types could reveal the ability of the questionnaires to capture clinically meaningful changes and, therefore, the utility of these questionnaires as outcome measures.

Therefore the primary aim of the study was to examine the responsiveness of disability questionnaires for headache types presenting frequently in primary care, namely migraine and non-migraine headaches. A secondary aim of the study was to explore whether responsiveness of questionnaires differed between headache types.

Methods

Participants and study design

Data were collected from a longitudinal cohort study distinguishing migraine and non-migraine headaches. This research was granted ethics approval by the Human Research Ethics Committee of The University of Sydney (Project Number 2014/536).

Recruitment of participants with recurrent headaches for the longitudinal cohort study was done through advertisements posted at University, consumer support groups, community bulletins, social media, and primary care and neurology clinics. Volunteers were eligible if they were aged 18-65 years, had headaches for at least a year and had at least one headache episode in the previous month.

Participants in the migraine group were those who were diagnosed as having migraine by their attending neurologist/physician, whose headache features fulfilled the International Classification of Headache Disorders (ICHD)-3 beta criteria for migraine [24] and in whom other headache types were excluded as diagnosis. Participants in the non-migraine headache group were those diagnosed as having tension-type or cervicogenic headache by a clinician and whose headache features fulfilled the ICHD 3 beta criteria for tension-type headache or cervicogenic headache.

Volunteers were excluded from either of the headache groups if their headaches were due to any known secondary cause (other than cervicogenic) such as tumour, substance withdrawal, surgery, etc. or if they had a pacemaker or fibrillator.

Procedures

All participants underwent initial telephone screening to confirm their eligibility. All eligible participants completed self-administered questionnaires which covered information on demographics and disability. Written informed consent was provided by all participants prior to participation. Participants also provided baseline information on headache characteristics including history, frequency of episodes, typical duration of each episode, and headache intensity in the last month using the numerical rating scale (with anchors at 0 and 10: 0 = no pain, 10 = worst pain possible). Participants then filled out an electronic diary administered using the Research Electronic Data Capture (REDCap) application (Research Electronic Data Capture, Nashville, Tennessee, USA) [25] hosted at The University of Sydney. Participants recorded the presence of headaches daily for 6 months. Disability questionnaires were also completed at baseline, 1 month, 3 months and 6 months.

Outcomes

Disability Disability was measured using the Headache Impact Test-6^{TM} (HIT-6) [11], Henry Ford Headache Disability Inventory (HDI) [12], Headache Disability Questionnaire [13], and the 12-item version of the World Health Organization Disability Assessment Schedule 2.0 (WHODAS) [16]. The characteristics of these questionnaires are described in Table 1.

Headache frequency Frequency of headache episodes was counted from the number of headache days reported in diary entries and summarized as number of headache episodes per month. External responsiveness for headache frequency was calculated using 50% reduction in headache frequency as the external criterion. This external criterion was selected because it was among the recommended outcome measures in headache trials [6, 8, 9] and

was the primary indicator of recovery nominated as most important by patients [26, cited in 13]. This was used as the external criterion for external responsiveness. (See statistical analysis.)

Statistical analyses

Demographic and baseline headache characteristics were summarized as mean and standard deviation (SD) and frequency and percentage as appropriate. Additionally, questionnaire scores at baseline, and at 1, 3 and 6 months were summarized as mean and SD.

Internal and external responsiveness were calculated for short-term and medium-term changes for all questionnaire scores. Internal responsiveness was calculated using effect size = mean change between baseline and follow-up scores (at 3 months for short-term and at 6 months for medium-term) divided by the standard deviation of the baseline score [27]. Effect sizes of 0.2, 0.5 and 0.8 were interpreted as small, medium and large, respectively [18]. Statistical significance of effect size was established based on non-overlapping 84% confidence intervals (CI), equivalent to Z test of means at the 0.05 level [28]. External responsiveness was calculated using receiver operating characteristic (ROC) curve analysis. ROC curves were plotted for each disability measure against the external criterion for short-term change (from 1 month to 3 months) and medium term change (from 1 month to 6 months). The area under the curve (AUC) and 95% CI were then calculated to determine the capacity of each questionnaire to discriminate between participants who improved on the external criteria and those who did not. AUC values were interpreted as follows: 0.90 as excellent; 0.80 and < 0.90 as good; 0.70 and < 0.80 as fair; and < 0.70 as poor [29]. ROC curves between HIT-6 and the other disability questionnaires were compared using the

DeLong approach [30]. Data were excluded from analyses if any of the follow up questionnaires was missing.

The calculated sample size for this study had 80% power to detect an effect size of 0.7, within the range of previously published responsiveness effect size of HIT-6 for chronic migraine [20], at significance level of 0.05, whilst allowing for about 20% attrition. Statistical analyses were conducted using Statistical Package for Social Sciences® statistical software, version 24 (SPSS Inc., Chicago, Illinois, USA) for Windows and Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA; 2010), and Analyse-it for Microsoft Excel (standard edition) (Analyse-it Software, Ltd, Leeds, England, UK; 2009).

Results

Participants

Eighty five eligible participants were included in the longitudinal study. Of these, 68 participants, 33 from the migraine group and 35 from the non-migraine group, had complete baseline and follow-up questionnaires and therefore were included in analyses. Sixty participants (88.2%) were female. Mean age (standard deviation, SD) was 37.74 (13.06) years. Participants in the migraine group had longer history of headache, less frequent episodes and more severe headache intensities than the non-migraine group (Table 2).

Questionnaire responses

Mean scores on all questionnaires at baseline and the three follow-up periods are shown in Table 3. HIT-6 scores ranged from substantial to severe categories for the migraine group and

from moderate to substantial categories for the non-migraine group. None of the mean scores were at the lowest 10% or highest 10% of the total score range for all the questionnaires.

Internal responsiveness

At short-term, internal responsiveness based on effect sizes (84% CI) was highest for HDQ [0.37 (0.13–0.61)] and HIT-6 [0.31 (0.07–0.56)] for the total cohort (Table 4). Similarly, HDQ and HIT-6 had the highest internal responsiveness for the migraine group [0.47 (0.11–0.82) and 0.34 (-0.01–0.69), respectively] and for the non-migraine group [0.31 (-0.02–0.65) and 0.32 (-0.02–0.66), respectively]. These effect sizes are interpreted as small. The overlap in confidence intervals of effect sizes for HIT-6 and HDQ indicates no statistically significant difference between these two questionnaires in short-term internal responsiveness.

At medium-term, internal responsiveness based on effect sizes (84% CI) was highest for HIT-6 [0.52 (0.27–0.76) and HDQ [0.41 (0.16–0.65)] for the total cohort (Table 4). Similarly, HIT-6 and HDQ had the highest internal responsiveness for the migraine group [0.47 (0.12–0.83) and 0.46 (0.11–0.81), respectively] and for the non-migraine group [0.60 (0.26–0.94) and 0.40 (0.06–0.74), respectively]. These effect sizes are interpreted as small to medium. The overlap in confidence intervals for HIT-6 and HDQ indicates no statistically significant difference between these two questionnaires in medium-term internal responsiveness based on effect sizes.

External responsiveness

At short-term, HDQ was the most responsive to change in headache frequency, considering the total cohort, with AUC value (95% CI) of 0.61 (0.47–0.74) (Table 4). This AUC value is

interpreted as poor but better than chance probability of differentiating between participants who improved and those who did not improve on headache frequency. For the migraine group, HIT-6 was the most responsive disability questionnaire, with AUC value (95% CI) of 0.53 (0.29–0.77). This value is also interpreted as poor. For the non-migraine group, HDQ was the most responsive, with AUC value (95% CI) of 0.69 (0.49–0.89), interpreted as fair.

At medium-term, HDQ was the most responsive to change in headache frequency for the total cohort as well as the migraine and non-migraine groups. HDQ AUC values ranged from 0.52–0.55, interpreted as poor in differentiating between participants who improved and those who did not improve on headache frequency.

There were no significant differences for the AUC of the HIT-6 compared with the other questionnaires for short-term and medium-term ($P > 0.05$) (Table 4). These results were consistent for the whole cohort, for the migraine group, and for the non-migraine group.

Discussion

Results of this study indicate that HIT-6 and HDQ were the most responsive disability questionnaires for individuals with migraine and non-migraine headaches with clinical characteristics similar to the cohorts in this study. As expected, responsiveness was better for headache-specific than generic questionnaires. Additionally, responsiveness was better at medium-term than short-term. These results suggest that either HIT-6 or HDQ may be used in assessing outcomes at 6 months in individuals with migraine and non-migraine headaches undergoing their usual headache management.

The relative ranking of responsiveness for HIT-6 and HDQ differed for internal and external responsiveness and between headache groups. However, these two questionnaires consistently ranked first or second on any responsiveness calculation and headache group.

Additionally, there were no statistically significant differences in their responsiveness scores. Collectively, these findings show that either HIT-6 or HDQ could be used in assessing clinically important changes for migraine or non-migraine at 3 or 6 months.

Interestingly, HIT-6 showed the largest effect size for migraine and non-migraine headaches at medium-term. These results support previous evidence on the responsiveness of HIT-6 for people with recurrent headaches, in general [11], and for chronic migraine [20] and tension-type headache in particular [21]. Results of this study also present new evidence on the responsiveness of HDQ for both migraine and non-migraine headaches. The comparatively high responsiveness of HDQ could be due to the scale options in the individual items, allowing detection of small clinical changes. For example, one HDQ item asks "When you have a headache while you work (or school), how much is your ability to work reduced?" and presents options ranging from 0 (no reduction) to 10 (100% reduction) [13]. The HDQ thus provides a greater range of options than the scales in the other disability questionnaires. Further, HDQ had the best external responsiveness for the whole cohort, indicating that HDQ related better than the other questionnaires with short-term and medium-changes in headache frequency. This finding may reflect the fact that the HDQ includes items on frequency (number of days) of specific headache symptoms and associated disability [13] while the others do not.

The external responsiveness of the questionnaires was nearly no better than chance at differentiating between those who improved on headache frequency and those who did not after 3 or 6 months. These findings could be specific for individuals with clinical characteristics similar to the cohorts in this study or could be due to the natural course of these headaches in the absence of intervention in this study.

Results of external responsiveness may have also been different if other external criteria were used. For example, higher external responsiveness scores for HDQ (ROC =

0.76) were demonstrated in a general headache population when global change scores as perceived by patients was used as the external criterion [22]. In another study, small to large effect sizes were demonstrated for WHODAS in a population with chronic conditions when improvement in severity of condition, categorized as mild, moderate or severe, was used as the external criterion [23]. However we are confident that our choice of external criterion is the most relevant to patients, as indicated by patients' perception of its importance as an outcome measure [26, cited in 13]. In addition, a reduction in headache frequency is among the recommended external criteria based on guidelines for headache trials [6–9].

Findings of this study must therefore be considered whilst recognising a number of methodological limitations. The heterogeneity of the non-migraine group restricts any conclusion that can be drawn about the relative responsiveness of the questionnaires for specific headache types. Whilst this study did not aim to compare responsiveness of questionnaires between specific headache types, future studies could address such aim by building on results of this present study. The sample size was relatively small and may not have been adequate to detect effect sizes smaller than that hypothesised for this study. The short observation period could have restricted the differences in responsiveness of questionnaires between migraine and non-migraine groups. Therefore the responsiveness of these questionnaires should be explored for longer-term changes in larger, homogenous headache groups in controlled treatment efficacy trials.

Nevertheless, given the equal responsiveness of the HIT-6 and HDQ in migraine and non-migraine headaches, clinicians could use either questionnaire, depending on the aspect of disability of interest. For example, HDQ could be preferred when the goal is to measure the percentage decrease in efficiency of tasks while HIT-6 may be preferred when the goal is to measure the frequency of activity limitation.

Conclusions

In this study comparing responsiveness of disability questionnaires, HIT-6 and HDQ were the most responsive to short-term and medium-term clinically relevant changes. These findings are applicable to individuals with migraine and non-migraine headaches undergoing their usual headache treatment. These findings add to the evidence on the usefulness of HIT-6 and HDQ in routine assessment of outcomes in the clinics.

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Compliance with ethical standards

Conflicts of interest The authors declare no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Table 1. Characteristics of Headache Impact Test-6 [11], The Henry Ford Headache Disability Inventory [12], Headache Disability Questionnaire [13], and World Health Organization Disability Assessment Schedule 2.0) [16]

Questionnaire	Construct	Reference Period	Number of Items	Number of Response Options	Score Range	Better State Indicated By
Headache Impact Test-6 (HIT-6)	Impact of headache on work and daily activities	When headache is present or past 4 weeks	6	5	36–78*	Lower scores
The Henry Ford Headache Disability Inventory (HDI)	Emotional and functional disabilities due to headaches	Not specified	25	3	0–100	Lower scores
Headache Disability Questionnaire (HDQ)	Headache severity and effect of headache on activity	When headache is present or past month	9	11	0–90	Lower scores
World Health Organization Disability Assessment Schedule 2.0 (WHODAS)	Functioning in the domains of cognition, mobility, self-care, getting along, life activities, and participation	Past 30 days	12	5	0–100	Lower scores

* HIT-6 scores <49 indicate little or no effect (grade 1); scores of 50 to 55 indicate moderate effect (grade 2); scores of 56 to 59 indicate substantial effect (grade 3), and scores ≥60 indicate severe effect (grade 4).

Table 2. Baseline characteristics of participants (n = 68)[†]

	Migraine (n = 33)	Non-Migraine (n = 35)
	Mean (SD) or *n* (%)	Mean (SD) or *n* (%)
Demographic characteristics		
Age	39.91 (13.30)	35.69 (12.68)
Gender (female)	28 (84.8%)	32 (91.4%)
Clinical characteristics		
History of headache (*years since first episode*)	20.24 (12.51)	14.33 (14.90)
Frequency of headache in a month	4.89 (6.12)	9.31 (7.18)
Episode duration , minimum (*hours*)	15.12 (17.86)	12.58 (18.31)
Episode duration , maximum (*hours*)	64.73 (38.47)	95.13 (189.30)
Average headache intensity last month (*0-10*)[‡]	6.41 (1.74)	5.80 (1.57)
Taking medication for headache	30 (90.9%)	31 (81.6%)
Receiving physical therapy for headache	6 (18.2%)	10 (28.6%)
Receiving alternative treatment for headache	14 (42.4%)	15 (42.9%)

Abbreviation: SD, standard deviation

[†] For continuous variables, values are presented as mean (SD); for categorical variables, values are presented as frequency (%).
[‡] Headache intensity: Numerical rating scale 0–10; 0 = no pain, 10 = worst possible pain

Table 3. Scores on self-report questionnaires at baseline and after 1, 3 and 6 months [mean (SD)]

Questionnaire	Baseline		After 1 Month		After 3 Months		After 6 Months	
	Migraine	Non-Migraine	Migraine	Non-Migraine	Migraine	Non-Migraine	Migraine	Non-Migraine
	n = 33	*n* = 35	*n* = 33	*n* = 35	*n* = 33	*n* = 35	*n* = 33	*n* = 35
Headache Impact Test-6 (HIT-6)[§]	62.45 (5.81)	58.26 (6.55)	59.97 (6.56)	56.00 (8.14)	60.48 (5.42)	56.14 (8.35)	59.70 (8.21)	54.31 (9.30)
The Henry Ford Headache Disability Inventory (HDI)	37.45 (21.06)	28.57 (20.36)	36.36 (20.91)	29.60 (24.51)	38.36 (23.51)	27.60 (20.95)	37.58 (23.65)	28.57 (24.29)
Headache Disability Questionnaire (HDQ)	42.24 (16.41)	30.89 (15.73)	34.30 (16.96)	26.09 (17.36)	34.61 (17.42)	25.94 (16.07)	34.73 (18.29)	24.54 (16.49)
World Health Organization Disability Assessment Schedule 2.0 (WHODAS)	13.57 (13.95)	11.25 (10.38)	12.37 (14.70)	11.61 (11.17)	12.25 (14.15)	10.24 (9.55)	14.65 (16.84)	10.36 (10.60)

[§] HIT-6 scores range from 36 to 78; scores <49 indicate little or no effect (grade 1); scores of 50 to 55 indicate moderate effect (grade 2); scores of 56 to 59 indicate substantial effect (grade 3), and scores 60 indicate severe effect (grade 4).

Abbreviation: SD, standard deviation

Table 4. Short-term and medium-term internal responsiveness of disability questionnaires

Questionnaires	Effect Size (84% CI)	
	Short-Term	Medium-Term
Total participants		
Headache Impact Test-6 (HIT-6)	0.31 (0.07–0.56)	0.52 (0.27–0.76)
The Henry Ford Headache Disability Inventory (HDI)	0.003 (-0.24–0.24)	-0.003 (-0.24–0.24)
Headache Disability Questionnaire (HDQ)	0.37 (0.13–0.61)	0.41 (0.16–0.65)
World Health Organization Disability Assessment Schedule 2.0 WHODAS)	0.10 (-0.15–0.34)	-0.01 (-0.25–0.24)
Migraine Group		
Headache Impact Test-6 (HIT-6)	0.34 (-0.01–0.69)	0.47 (0.12–0.83)
The Henry Ford Headache Disability Inventory (HDI)	-0.04 (-0.39–0.30)	-0.01 (-0.35–0.34)
Headache Disability Questionnaire (HDQ)	0.47 (0.11–0.82)	0.46 (0.11–0.81)
World Health Organization Disability Assessment Schedule 2.0 WHODAS)	0.10 (-0.25–0.44)	-0.08 (-0.42–0.27)
Non-Migraine Group		
Headache Impact Test-6 (HIT-6)	0.32 (-0.02–0.66)	0.60 (0.26–0.94)
The Henry Ford Headache Disability Inventory (HDI)	0.05 (-0.29–0.38)	0.00 (-0.34–0.34)
Headache Disability Questionnaire (HDQ)	0.31 (-0.02–0.65)	0.40 (0.06–0.74)
World Health Organization Disability Assessment Schedule 2.0 WHODAS)	0.10 (-0.24–0.43)	0.08 (-0.25–0.42)

Abbreviation: CI, confidence interval

Table 5. Short-term and medium-term external responsiveness of disability questionnaires

Questionnaires	Area Under the Curve (95% CI)	DeLong Test Statistic, *P*	Area Under the Curve (95% CI)	DeLong Test Statistic, *P*
	Short-Term		Medium-Term	
Total participants				
Headache Impact Test-6 (HIT-6)	0.52 (0.37–0.68)		0.44 (0.28–0.61)	
The Henry Ford Headache Disability Inventory (HDI)	0.38 (0.24–0.52)	0.42	0.38 (0.22–0.54)	0.52
Headache Disability Questionnaire (HDQ)	0.61 (0.47–0.74)	0.32	0.54 (0.40–0.69)	0.92
World Health Organization Disability Assessment Schedule 2.0 WHODAS)	0.55 (0.41–0.68)	0.77	0.44 (0.28–0.60)	0.96
Migraine Group				
Headache Impact Test-6 (HIT-6)	0.53 (0.29–0.77)		0.49 (0.26–0.71)	
The Henry Ford Headache Disability Inventory (HDI)	0.36 (0.15–0.58)	0.60	0.36 (0.12–0.59)	0.17
Headache Disability Questionnaire (HDQ)	0.49(0.30–0.68)	0.90	0.55 (0.32–0.77)	0.88
World Health Organization Disability Assessment Schedule 2.0 WHODAS)	0.49 (0.29–0.69)	0.90	0.46 (0.23–0.68)	0.85
Non-Migraine Group				
Headache Impact Test-6 (HIT-6)	0.54 (0.34–0.74)		0.39 (0.15–0.62)	
The Henry Ford Headache Disability Inventory (HDI)	0.41 (0.22–0.60)	0.73	0.41 (0.18–0.64)	0.88
Headache Disability Questionnaire (HDQ)	0.69 (0.49–0.89)	0.12	0.52 (0.32–0.72)	0.62
World Health Organization Disability Assessment Schedule 2.0 WHODAS)	0.58 (0.39–0.77)	0.71	0.42 (0.19–0.64)	0.81

Abbreviation: CI, confidence interval

CHAPTER EIGHT

Conclusions

Conclusions

8.1 Overview of findings

The current standard in defining, classifying and diagnosing migraine and non-migraine headaches involves differentiating each headache type based on headache characteristics following the International Classification of Headache Disorders (ICHD) (1).The ICHD is continuously being reviewed and revised according to evidence regarding pathophysiology and characteristics of the headache type. Thus the application of ICHD, and therefore classification and diagnosis of migraine and non-migraine headaches, may be augmented by a better understanding of their pathophysiology and clinical characteristics. This thesis verifiesthe ICHD as the standard for classifying headaches. It submits new evidence on the potential of gamma-aminobutyric acid (GABA) as a biomarker for migraine and on the day-to-day volatility and six-month clinical course of migraine and non-migraine headaches. This thesis also presents additional data on clinical characteristics that differentiate migraine from non-migraine headaches beyond the ICHD diagnostic criteria, such as impairments in cervical muscle behaviour measured using the deep cervical extensor test and self-reported disability measured using the Headache Disability Questionnaire or the Headache Impact Test-6 as part of a combination of clinical characteristics differentiating migraine.

The aim of this thesis was to characterise migraine on the basis of its neurochemical profile and clinical features not listed as diagnostic criteria in the ICHD, compared with non-migraine headaches (TTH and CGH) that frequently present in primary care. Chapter Two verified that ICHD is generally used to define patient populations of migraine and non-migraine headaches in defined in clinical trials. Cutting-edge evidence is presented in

Chapters Three, Four and Six. First, GABA is a potential diagnostic biomarker for migraine, given the higher concentration found in people with migraine compared with headache-free controls (Chapter Three) and its association with pain and disability (Chapter Four). This is the first time that the potential of GABA as a migraine biomarker is demonstrated, providing direction for future research to investigate the pathophysiology of migraine, leading to targeted management. Second, the day-to-day volatility of headache intensity and disability is worse in migraine compared to non-migraine headaches as presented in Chapter Six. This is the first time that the day-to-day volatility of migraine is depicted in detail, carrying significance for addressing patients' concern about the unpredictability of their headaches. Evidence in addition to existing knowledge is presented in Chapter Five. Evidence is presented suggesting that a combination of less pain on manual examination of the upper cervical spine, less change in deep cervical extensors thickness during contraction, less frequent headaches, and higher disability distinguished migraine from non-migraine headaches. Chapter Six also showed that the disability changed in migraine and non-migraine headaches, with a tendency to decline, over six months. This medium-term reduction in disability was associated with the absence of painful cervical joint dysfunction. Chapter Seven found that the best way to measure this change in disability over time could be using the Headache Impact Test-6 (HIT-6) or the Headache Disability Questionnaire (HDQ). The findings of this thesis addressgaps in the understanding of migraine, with implications including expanding details in headache definitions, improving clinical practice, as well asinforming future research. Ultimately, this thesis advances the search for effective treatments and better health outcomes for people with migraine.

8.2 Implications of the thesis

8.2.1. Implications for headache definitions

The evidence presented by this thesis provides impetus for the definitions of migraine and non-migraine headache to be explained in more detail and broadened. The systematic review in Chapter Two is the first study to provide an understanding of the characteristics of study populations in treatment efficacy trials for migraine and non-migraine headaches. Whilst 89.5% of the trials reported adherence to the ICHD criteria in selecting the study populations, details on the definition of study populations were unclear. First, 44.5% of the trials included in the review did not report the method used to arrive at a headache diagnosis. Second, the specific diagnostic criteria present among the study populations at baseline were generally not provided. Such details are important, as they provide a clear description of study populations, improving the transparency on the possible inclusion of people with overlapping features or coexistent headache types. Such details could enable clinicians to decide on the applicability of evidence to their patients (2), enhancing research translation. (3). Results of this review therefore suggest that minimum standards for reporting characteristics of study populations at baseline would be beneficial. Specifying the extent to which study populations demonstrated ICHD diagnostic criteria at baseline should be among these minimum standards. More detailed reporting of characteristics of study populations allow clarity of headache populations in trials and ensure transparency and generalisabiltiy of evidence to clinical practice(1, 4). This consideration of minimum standards could be a course of action forguideline developers,who are involved in refining existing guidelines for clinical trials in specific headache types (5-7).

The definition of migraine could be expanded by differentiating migraine as being associated with more severe disability than non-migraine headaches. Whilst the ICHD presents migraine as a more severe headache type than TTH based on headache intensity (1), the results of the cross-sectional study demonstrated that migraine is more severe than non-migraine headaches based on disability. Greater disability differentiates migraine from non-migraine headaches when disability is considered in isolation or in combination with cervical musculoskeletal impairments. Results of the cross-sectional cohort study also validate that cervical joint dysfunction is less in migraine than in non-migraine headaches and present preliminary evidence that cervical muscle behaviour is also impaired in migraine. Cervical musculoskeletal impairments in migraine may be investigated further to determine their utility in defining migraine. Nevertheless, the additional evidence presented in this thesis on characteristics of migraine that may be useful in differential diagnosis therefore contributes to the continued efforts of the headache community to clarify characteristics of headache types to improve clinical practice and research.

8.2.2. Implications for clinical practice

The findings of Chapters Four, Five and Six have important implications in clinical practice namely, headache assessment and differential diagnosis, prognosis and management. The findings of this thesis show that the clinical characteristics that are relevant to assess and consider in prognosis and management include cervical musculoskeletal impairments and disability.

8.2.2.1. Assessment of cervical musculoskeletal impairments

Measuring cervical joint dysfunction will enable clinicians to characteriseand potentially distinguish migraine from non-migraine headaches. The findings presented in Chapter Five further validate that migraine has less upper cervical joint dysfunction than non-migraine headaches as demonstrated by less frequent pain on manual provocation of the upper cervical joints ($p< 0.001$) and less frequent positive flexion rotation test ($p = 0.004$). These findings were consistent with previous reports of greater joint dysfunction in non-migraine headaches compared to migraine (8-10). Taken together, clinicians can be confident that examination of cervical joint dysfunction by palpation and the flexion rotation test should be retained to assist with characterisation and differential diagnosis of migraine from non-migraine headaches.

Cervical joint dysfunction was also one of the factors in a multifactorial model that explained 32.3 % of the variation in non-improvement in disability in the medium-term ($p = 0.031$) (Chapter Six). Painful joint dysfunction was associated with 6 times higher odds of non-improvement in disability [odds ratio (95% confidence interval) = 5.58 (1.14 to 27.42] ($p = 0.040$). Clinicians should therefore treatcervical dysfunction when present to potentially improve the outcome in disability.

In contrast, measurement of cervical muscle impairment by clinicians to assist in differential diagnosis of headaches was not supported by this thesis. However, its assessment may direct management. We investigated a new test, the deep cervical extensor test (11), in Chapter Five that measured muscle behaviour of deep cervical extensors during low-load contractions, detected using real-time ultrasound imaging, We found no difference in muscle behaviour

between headache types when directly compared. However, there is some preliminary evidence to explore this test further, given that this test contributed significantly (discriminant function coefficient = 0.47) to a combination of measures distinguishing migraine from non-migraine (Chapter Five). This test had not been evaluated in other cross-sectional studies to date. Given the lack of difference demonstrated between headache groups, examination of the behaviour of cervical extensors for the purposes of differential diagnosis cannot be recommended at this point in time. However, as pointed out earlier, there is evidence that it could be included amongst a battery of tests to characterise and possibly differentially diagnose migraine.

Assessment of other domains of cervical muscle impairment such as muscle function, i.e., strength and endurance, to assist in the differentiation of migraine from non-migraine headaches was also not supported by this thesis. However assessment of impairment to direct treatment would be supported. Chapter Five found no difference in strength or endurance of either cervical flexors or extensors between migraine and non-migraine headaches. Unexpectedly, it was found that people with migraine also displayed these impairments compared with controls. This supports the only other study that demonstrated reduced strength in cervical muscles in episodic migraine compared to controls (12). Thus evidence from this thesis indicates that impairments in cervical muscle function may also be present in migraine. Considering this evidence, clinicians should assess cervical muscle function impairment in migraine to identify possible targets for treatment.

Finally, clinicians are recommended to examine cervical musculoskeletal impairment in combination with other clinical characteristics such as headache frequency and higher disability scores. The findings of Chapter Five support that the combination of these tests

results in distinguishing migraine from non-migraine headaches with a sensitivity of 80% and specificity of 75.6%. Clinicians now have additional evidence to consider when differentially diagnosing, especially when the presenting case is ambiguous as to being pure migraine or a non-migraine headache (Chapter Five).

a. Assessment of multidimensional pain and central sensitisation symptoms

Implications of results of Chapter Four include measuring the multidimensional nature of pain and central sensitisation symptoms to gain greater insight into the patient experience of migraine as well as providing an association with the diagnosis and neurochemical profile.These characteristics can be easily measured using self-report questionnaires such as the Short-form McGill Pain Questionnaire-2 (SF-MPQ-2) (13) and the Central Sensitization Inventory (CSI) (14), respectively. Responses to these questionnairesprovide rich information on the sensory and emotional dimensions of the pain experience (13, 15) and underlying pathophysiological mechanisms (14, 16). Consequently, clinicians are provided with a deeper understanding of the patient's headache experience, ultimately facilitating a more specific, patient-centred approach to treatment.

In addition, both SF-MPQ-2 and CSI are useful in diagnosis and have an association with the neurochemical profile of migraine. Individuals with CSI scores of $\geq$ 22.5 out of 100 are nearly five times more likely to be indicative of migraine than no headache, with sensitivity of 95% and specificity of 80% (Chapter Four). This cut-off score of 22.5 is lower than previously published cut-off score of 40 for central sensitisation syndromes in general (17), As such, this lower cut-off score means that migraine can be strongly suspected in individuals

with CSI scores of 22.5, improving the clinical utility of this index. Additionally, the fair correlations of pain and central sensitisation scores with increased GABA levels in migraine (Chapter Three) suggest that information from SF-MPQ-2 and CSI could be used to understand the neurochemical profile of patients in the absence of spectroscopy data. However, whether the association between multidimensional pain and central sensitisation and brain GABA levels is specific for migraine, or true for any recurrent headache or chronic pain condition,will be investigated in prospective research.

b. Assessment of disability

The findings of Chapters Five, Six and Seven support that clinicians should assess disability for several reasons: to differentiate migraine, to predict the course of headache and to assess outcome. Firstly, Chapter Five found that people with migraine had greater disability than non-migraine. Disability is best assessed using the Headache Disability Questionnaire (HDQ) (18), The Henry Ford Headache Disability Inventory (HDI) (19),or Headache Impact Test -6 (HIT-6) (20) because they showed good discriminative ability for migraine. For example, scores on HDQ $\geq$ 27.5 out of 90 distinguish people with migraine from non-migraine headaches, with sensitivity = 80.0%, specificity = 74.1%, and positive likelihood ratio = 3.09. Similarly, total scores on HDI $\geq$19 out of 100 distinguish having migraine, with sensitivity = 80.0%, specificity = 67.1%, and positive likelihood ratio = 1.72. Scores on HIT-6, when combined with results of musculoskeletalimpairment and headache frequency,also showed good discriminative validity for migraine from non-migraine headaches (sensitivity = 80.0%, specificity = 75.6%).

Further, clinicians should also assess disability because it may be associated with poor prognosis and therefore could be targeted to potentially change the course of the headache. The findings in Chapter Six demonstrated that higher disability at baseline was one factor in a multifactorial model that explained 32.3 % of the variation in non-improvement in disability in the medium-term (p = 0.031). Further, the results presented in Chapter Six showed that disability changed over the medium-term in migraine and non-migraine headaches. Given this, assessment of disability at baseline may assist clinicians with understanding the prognosis and course of headache.

Finally the findings of Chapter Seven support the use of disability questionnaires by clinicians to measure outcome. Clinically relevant changes in disability may be measured using the HIT-6 or HDQ, with acceptable responsiveness [effect sizes (95% confidence interval) ranging from 0.40 (0.06 to 0.74) to 0.69 (0.49 to 0.89)].Chapter Seven thus builds on the evidence presented in Chapter Five on the usefulness of HIT-6 and HDQ, not only to characterise disability in migraine and non-migraine headaches,but also to measure clinically relevant change over time in migraine (21, 22) and non-migraine headaches (23).

c. Implications for patient education

Overall, the results of this thesis have implications for patient education with regard to diagnosis, prognosis and management. As a result of findings of Chapters Three, Four and Five, clinicians can have greater confidence to differentiate migraine on the basis of clinical and characteristics, including disability profile, and can communicate this to their patients. Clinicians will be able to educate patients with migraine about the nature of their headaches with greater clarity. The factors associated with non-improvement in disability and the high

day-to-day volatility especially of migraine headaches presented in Chapter Six could be included in patient education strategies. Previous work has established the critical role of patient education in effective multidisciplinary headache management. Educating patients about the characteristics of their headaches enhances self-efficacy, motivation and treatment adherence, eventually resulting in improved outcomes (24-26). In particular, providing patients with information on the behaviour of headaches addresses their frustration because of the unpredictability of their headaches (27, 28) and potentially helps them align their expectations accordingly. Finally, the work in Chapters Five and Six demonstrated that cervical musculoskeletal impairments are present in 10% of participants with migraine.. Explaining to patients that these impairments could be targeted when present, potentially reducing disability (Chapter Six), may provide patients with some hope.

8.2.3. Limitations of the thesis

The findings of this thesis must be interpreted with caution in light of a number of methodological limitations of the studies. One limitation of this thesis is that the spectroscopy technique employed in Chapters Three and Fourmight not provide a complete profile of brain neurochemicals in migraine. Although MEGA-PRESS is considered to be the best available technique for separating and quantifying GABA, it is possible that even this best spectroscopy technique might not have achieved complete separation of GABA from macromolecules. Future advances in spectroscopy might allow more complete separation, and therefore more accurate measurement of GABA. As regards distinguishing migraine from non-migraine headaches, an important caveat in considering the findings presented in Chapters Five through Seven is that the heterogeneity of the non-migraine group prevents any

conclusion to be drawn about cervical musculoskeletal impairments and clinical course specifically for CGH or TTH. Prospective studies with pure headache groups that have larger sample sizes would be better suited to distinguish specific headache types. Larger sample sizes of prospective population- or clinic-based research could also allow for a more in-depth investigation of numerous possible predictors of non-improvement in headaches. Such research could build on findings of our exploratory longitudinal cohort study presented in Chapter Six. There is also reason for cautious interpretation of results related to self-report questionnaires in Chapters Four through Seven due to possible test order effects. Although the consistent presentation of questionnaires across participants eliminated one possible confounding variable, we did not test any effect the order of administration of questionnaires may have on the responses of the participants. Lastly, the lack of follow up measurements of cervical musculoskeletal impairments and the limited observation period in the study presented in Chapter Six do not allow any conclusion on long-term clinical courses of headaches and possible association of any change in cervical musculoskeletal impairments. These limitations may be addressed in future research.

8.2.4. Directions for future research

Evidence presented in this thesis has implications for future research to further elucidate the nature of migraine toward enhancing treatment. These include validating GABA as a biomarker for migraine, specifying cervical musculoskeletal impairments in headaches, and further characterising the clinical course and prognosis of migraine and non-migraine headaches.

8.2.4.1 Validating GABA as a biomarker for migraine

The breakthrough presented in Chapters Three and Four regarding the potential of GABAas a biomarker for migraine may be explored further in future studies. Validating GABA as a migraine biomarker would address the lack of established biomarkers (29, 30)and would consequently allow refinement of headache definitions to be based on more objective markers than headache features. In the process of validating GABA as a biomarker for migraine, its role in migraine pathophysiology may be investigated.

The first step toward validating GABA as a biomarker is to examine the association of brain GABA levels with other clinical characteristics of migraine (31). Such characteristics should include those related to the headache (such as triggers, aura, associated symptoms during the headache phase, e.g. nausea and photophobia, and symptoms during the postdrome phase). Also it may be worth exploring the associations of brain GABA levels with personal factors, including multidimensional pain, central sensitisation, emotional state and lifestyle habits (32, 33), and other known risk factors for migraine progression [such as obesity (34), genetic predisposition and medication overuse (32)]. Whilst multidimensional pain and central sensitisation were found to be associated with brain GABA levels in this thesis (Chapter Four), these findings need to be cross-validated in future cross sectional studies with larger sample sizes.

The second step in establishing GABA as a biomarker is to determine that increased concentration of GABA in the brain is unique to migraine. Hence concentration of GABA should be compared between different headache types, chronic pain conditions and pain-free controls in a larger cross sectional studies. This would elucidate whether the increase in

GABA concentrations in migraine is specific for migraine, to headaches in general or to any chronic pain condition.

A longitudinal study would enable identification of causal relationships between GABA levels and the onset and phases of migraine, and any change in clinical characteristics such as pain and disability. Identifying these causal relationships would clarify the pathophysiology of migraine and the mechanisms causing the increased GABA levels. Next, to identify the GABA-related mechanisms, preclinical studies using animal models may help inform the design of randomised controlled trials targeting reduction in GABA levels. Ultimately curing migraine with an intervention (e.g. pharmaceutical agent) aimed at the potential cause (increased GABA levels would confirm the role of GABA in migraine pathophysiology. Proving the efficacy of the intervention targeting GABA would then complete the validation of GABA as a migraine biomarker.

8.2.4.2 Specifying cervical musculoskeletal impairments in headaches

Cervical musculoskeletal impairments in migraine compared to non-migraine headaches demonstrated in Chapter Five need to be exploredfurther. First, larger cross-sectional cohort studies with pure groups for migraine, TTH and CGH would enable differentiation between specific headache types. Second, the discriminative validity of the combination of tests to differentiate migraine from non-migraine headaches should be evaluated in future cohort studies. To accomplish this, headache classification using the combination of manual examination of the upper cervical spine, real-time ultrasound measurement of the change in deep cervical extensors thickness during low-load contraction, frequency of headaches, and disability may be compared with classification using the ICHD. Such studies would hopefully

resolve the conflicting findings regarding the presence of these cervical musculoskeletal impairments in migraine.

8.2.4.3 Characterising the clinical course and prognosis of migraine and non-migraine headaches better

Lastly, the clinical course and prognosis of migraine and non-migraine headaches may be studied further to build on findings of Chapters Six and Seven. This may be achieved through a longitudinal clinical trial over at least one year, preferably longer to consider the volatility of headache symptoms demonstrated in the medium-term in Chapter Six. Such longitudinal clinical trial study should entail at least one intervention and prospective measurements of headache characteristics and other putative predictors repeated over time. Additional studies on clinical course would address the scarcity of evidence in this area and may eventually open avenues for specific management of headaches.

The recommendations presented in this chapter for guideline expansion, clinical practice and research are envisioned to inform the design of targeted and effective treatment for migraine and for headaches in general. Whilst much is still left to be known about headaches, every effort to increase the understanding of the nature of headaches contributes toward improved definitions of headaches. Correct headache classification is a necessary step toward development of effective treatments. The application of findings presented in this thesis will therefore contribute to better health outcomes for patients and, ultimately, to the reduction of the global burden of headaches.

For Meg, this is, pardon the pun, MIND-BLOWING news!…Meg now awaits studies that will solve exactly how GABA links with migraine: Does GABA start her migraine attack? Does GABA stop it? Much more remains unknown, but each piece to the migraine puzzle raises hope for its cure.

Illustration by David Val Christian B. Agoncillo, 2014
for presentations related to studies in this thesis

[Excerpt from Three-Minute Thesis Presentation (3MT®) by Maria Eliza Ruiz Aguila; Winner, Faculty of Health Sciences 3MT® 2014]

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APPENDICES

List of appendices

APPENDIX 1

Supplemental Materials for Chapter Two:

Definitions and Participant Characteristics of Frequent Recurrent Headache Types in Clinical Trials:

A Systematic Review

Appendix 1is the peer reviewed version of supplemental materials to the following article: Aguila ME, Rebbeck T, Mendoza KG, De La Peña MG, Leaver AM. Definitions and participant characteristics of frequent recurrent headache types in clinical trials: A systematic review. *Cephalalgia*.Epub2017 Apr 25. doi: 10.1177/0333102417706974, which has been published in online form ahead of print at http://journals.sagepub.com/doi/suppl/10.1177/0333102417706974

Appendix A

Search Strategy: MEDLINE OVID

Definitions and participant characteristics of frequent recurrent headache types in clinical studies: A systematic review

1	exp Headache/
2	exp Cluster Headache/
3	exp Tension-Type Headache/
4	exp Migraine Disorders/
5	exp Post-Traumatic Headache/
6	cervicogenic headache.mp.
7	exp Headache Disorders, Primary/
8	exp Headache Disorders/
9	primary headache.mp.
10	(headache* or cephalagi* or migrain*).mp
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp Clinical Trial/
13	(clin* adj25 trial*).ti,ab.
14	((singl* or doubl* or trebl* or tripl*) adj25 blind*).mp. or mask*.ti,ab.
15	((singl* or doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ti,ab.
16	exp Placebos/
17	placebo*.ti,ab.
18	random*.ti,ab.
19	exp Cross-Over Studies/
20	exp Double-Blind Method/
21	double-blind procedure*.mp.
22	exp Randomized Controlled Trial/
23	exp Single-Blind Method/
24	Single-Blind Procedure*.mp.
25	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26	11 and 25
27	limit 26 to (English language and yr="2005 -Current")
28	limit 27 to humans

Appendix B

Data extraction form

Definition of study population in headache studies based on selection and diagnosis of participants

and ICHD headache features at baseline

B.1 Migraine studies

Study by first author, year	Participant selection and diagnosis				ICHD diagnostic criteria reported as baseline characteristics						
	Method of diagnosis	Diagnostic classification used	Inclusion criteria other than diagnostic criteria	Exclusion criteria	Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)	Unilateral location	Pulsating quality	Moderate or severe pain intensity	Aggravation by or causing avoidance of routine physical activity	Nausea and/or vomiting	Photophobia and phonophobia

B.2 Tension-type headache studies

Study by first author, year	Participant selection and diagnosis				ICHD diagnostic criteria reported as baseline characteristics							
	Method of diagnosis	Diagnostic classification used	Inclusion criteria other than diagnostic criteria	Exclusion criteria	Headache lasting from 30 minutes to 7 days	Bilateral location	Pressing/tightening (non-pulsating) quality	Mild or moderate intensity	Not aggravated by routine physical activity	No nausea or vomiting	No more than one of photophobia or phonophobia	Headache occurring on ≥15 days/month on average for >3 months (≥180 days/year)

B.3 Cluster headache studies

Study by first author, year (Appendix B reference)	Participant selection and diagnosis				ICHD diagnostic criteria reported as baseline characteristics							
	Method of diagnosis	Diagnostic classification used	Inclusion criteria other than diagnostic criteria	Exclusion criteria	Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes if untreated	Ipsilateral conjunctival injection and/or lacrimation	Ipsilateral nasal congestion and/or rhinorrhoea	Ipsilateral eyelid oedema	Ipsilateral forehead and facial sweating	Ipsilateral miosis and/or ptosis	A sense of restlessness or agitation	Attacks have a frequency from one every other day to 8 per day

B.4 Cervicogenic headache studies

Study by first author, year	Participant selection and diagnosis				ICHD diagnostic criteria reported as baseline characteristics			
	Method of diagnosis	Diagnostic classification used	Inclusion criteria other than diagnostic criteria	Exclusion criteria	Pain from neck and perceived in head and/or face	Related diagnostic evidence	Abolition of headache following blockade	Pain resolution after treatment

Appendix C

Reference List for Studies Included in the Review

Migraine studies

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APPENDIX 2

Ethics Approvals

Appendix 2 presents ethics approvals from The University of Sydney Human Research Ethics Committee for studies presented in Chapters Three through Seven.

THE UNIVERSITY OF SYDNEY

RESEARCH INTEGRITY
Human Research Ethics Committee
Web: http://sydney.edu.au/ethics/
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The University of Sydney
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Ref: [SA/KFG]

31 October 2012

Prof Kathryn Refshauge
Dean, Faculty of Health Sciences
The University of Sydney
Email: kathryn.refshauge@sydney.edu.au

Dear Professor Refshauge

Thank you for your correspondence dated 17 August 2012 (received 25 October 2012), addressing comments made to you by the Human Research Ethics Committee (HREC).

On 30 October 2012 the Chair of the HREC considered this information and approved your protocol entitled **"Development of "neurochemical signatures" as a novel diagnostic technique for headache."**

Details of the approval are as follows:

Protocol No.: **15048**

Approval Date: **30 October 2012**

First Annual Report Due: **31 October 2013**

Authorised Personnel: **Prof Kathryn Refshauge**
A/Prof Jim Lagopoulos
Prof Patrick Brennan
Dr Markus Huebscher
Dr Andrew Leaver
Dr Trudy Rebbeck

Documents Approved:

Document	Version Number	Date
Recruitment Advertisement	Version 2	22nd October 2012
Participant Information Statement	Version 2	22nd October 2012
Participant Consent Form	Version 1	23rd December 2011
Letter to neurologists	Version 2	18th August 2012
Standardised Measures: Headache Disability Index, Short-Form McGill Pain Questionnaire,	n/a	n/a

HREC approval is valid for four (4) years from the approval date stated in this letter and is granted pending the following conditions being met:

Manager Human Ethics
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CRICOS 00026A

THE UNIVERSITY OF SYDNEY

Condition/s of Approval

- Continuing compliance with the National Statement on Ethical Conduct in Research Involving Humans.
- Provision of an annual report on this research to the Human Research Ethics Committee from the approval date and at the completion of the study. Failure to submit reports will result in withdrawal of ethics approval for the project.
- All serious and unexpected adverse events should be reported to the HREC within 72 hours.
- All unforeseen events that might affect continued ethical acceptability of the project should be reported to the HREC as soon as possible.
- Any changes to the protocol including changes to research personnel must be approved by the HREC by submitting a Modification Form before the research project can proceed.

Chief Investigator / Supervisor's responsibilities:

1. You must retain copies of all signed Consent Forms (if applicable) and provide these to the HREC on request.
2. It is your responsibility to provide a copy of this letter to any internal/external granting agencies if requested.

Please do not hesitate to contact Research Integrity (Human Ethics) should you require further information or clarification.

Yours sincerely

Dr Stephen Assinder
Chair
Human Research Ethics Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice.

2012/581 - Change in Personnel Outcome

Human Ethics [ro.humanethics@sydney.edu.au]

Sent: Monday, 27 May 2013 11:30 AM
To: Kathryn Refshauge [kathryn.refshauge@sydney.edu.au]
Cc: Maria Eliza Aguila; Andrew Leaver [andrew.leaver@sydney.edu.au]; markus.heubscher@sydney.edu.au; Trudy Rebbeck [trudy.rebbeck@sydney.edu.au]; Patrick Brennan [patrick.brennan@sydney.edu.au]; Jim Lagopoulos [jim.lagopoulos@sydney.edu.au]

Dear Professor Refshauge

Project Title: Development of "neurochemical signatures" as a novel diagnostic technique for headache.

Project No: 2012/581

Thank you for submitting a Change in Personnel form for the above project. Your request was considered by Research Integrity (Human Ethics).

The change has been approved.

All current investigators: Refshauge Kathryn; Aguila Maria; Leaver Andrew; Heubscher Marcus; Rebbeck Trudy; Brennan Patrick; Lagopoulos Jim;

Please do not hesitate to contact Research Integrity (Human Ethics) should you require further information or clarification.

Regards,
Human Ethics Administration
The University of Sydney

THE UNIVERSITY OF SYDNEY

Research Integrity
Human Research Ethics Committee

Tuesday, 27 August 2013

Professor Kathryn Refshauge
Clinical and Rehabilitation Sciences; Faculty of Health Sciences
Email: kathryn.refshauge@sydney.edu.au

Dear Professor Kathryn Refshauge,

Your request to modify the above project submitted on 28th May 2013 was considered by the Executive of the Human Research Ethics Committee.

The Committee had no ethical objections to the modification/s and has approved the project to proceed.

Details of the approval are as follows:

Project No.: **2012/581**

Project Title: **Development of "neurochemical signatures" as a novel diagnostic technique for headache.**

Approved Documents:

Date Uploaded	Type	Document Name
28/05/2013	Questionnaires/Surveys	Headache questionnaires
28/05/2013	Advertisements/Flyer	Web advertisement

Please do not hesitate to contact Research Integrity (Human Ethics) should you require further information or clarification.

Yours sincerely

Dr Stephen Assinder
Chair
Human Research Ethics Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice.

Research Integrity
Human Research Ethics Committee

Monday, 4 August 2014

Dr Trudy Rebbeck
Clinical and Rehabilitation Sciences; Faculty of Health Sciences
Email: trudy.rebbeck@sydney.edu.au

Dear Trudy

I am pleased to inform you that the University of Sydney Human Research Ethics Committee (HREC) has approved your project entitled "**Natural Course and Predictors of Recovery of Migraine and Other Headache Types"**.

Details of the approval are as follows:

Project No.: **2014/536**

Approval Date: **1 August 2014**

First Annual Report Due: **1 August 2015**

Authorised Personnel: **Rebbeck Trudy; Aguila Maria; Brennan Patrick; Lagopoulos Jim; Leaver Andrew; Refshauge Kathryn;**

Documents Approved:

Date	Type	Document
16/05/2014	Questionnaires/Surveys	Disability Assessment Scale
16/05/2014	Questionnaires/Surveys	McGill Pain Questionnaire
20/05/2014	Questionnaires/Surveys	Headache Disability Questionnaire
20/05/2014	Questionnaires/Surveys	Comorbidity Questionnaire
20/05/2014	Questionnaires/Surveys	Central Sensitization Inventory
20/05/2014	Questionnaires/Surveys	Headache Impact Test
20/05/2014	Questionnaires/Surveys	Depression Anxiety Stress Scale
20/05/2014	Questionnaires/Surveys	Pittsburgh Sleep Quality Index
20/05/2014	Questionnaires/Surveys	Henry Ford Headache Disability Index
20/05/2014	Participant Consent Form	Consent Form
21/05/2014	Questionnaires/Surveys	International Physical Activity Questionnaire
29/05/2014	Recruitment Letter/Email	Recruitment letter to physicians
23/07/2014	Advertisements/Flyer	Ad for posting v2
23/07/2014	Participant Info Statement	Participant Information Statement v2
23/07/2014	Advertisements/Flyer	Web ad v2
23/07/2014	Interview Questions	Baseline questions v2

HREC approval is valid for four (4) years from the approval date stated in this letter and is granted pending the following conditions being met:

Condition/s of Approval

- Continuing compliance with the National Statement on Ethical Conduct in Research Involving Humans.
- Provision of an annual report on this research to the Human Research Ethics Committee from the approval date and at the completion of the study. Failure to submit reports will result in withdrawal of ethics approval for the project.
- All serious and unexpected adverse events should be reported to the HREC within 72 hours.
- All unforeseen events that might affect continued ethical acceptability of the project should be reported to the HREC as soon as possible.
- Any changes to the project including changes to research personnel must be approved by the HREC before the research project can proceed.
- Note that for student research projects, a copy of this letter must be included in the candidate's thesis.

Chief Investigator / Supervisor's responsibilities:

1. You must retain copies of all signed Consent Forms (if applicable) and provide these to the HREC on request.
2. It is your responsibility to provide a copy of this letter to any internal/external granting agencies if requested.

Please do not hesitate to contact Research Integrity (Human Ethics) should you require further information or clarification.

Yours sincerely

Dr Stephen Assinder
Chair
Human Research Ethics Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice.

Research Integrity
Human Research Ethics Committee

Tuesday, 30 June 2015

Dr Trudy Rebbeck
Clinical and Rehabilitation Sciences; Faculty of Health Sciences
Email: trudy.rebbeck@sydney.edu.au

Dear Trudy

Your request to modify the above project submitted on 9th June 2015 was considered by the Executive of the Human Research Ethics Committee at its meeting on 23rd June 2015.

The additional information provided was reviewed by the Ethics Office on **30th June 2015.**

The Committee had no ethical objections to the modification/s and has approved the project to proceed.

Details of the approval are as follows:

Project No.: **2014/536**

Project Title: **Natural Course and Predictors of Recovery of Migraine and Other Headache Types**

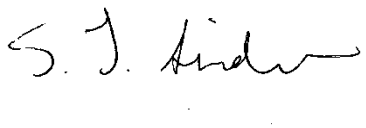
Approved Documents:

DATE	TYPE	DOCUMENT NAME
16/05/2014	Questionnaires/Surveys	McGill Pain Questionnaire
20/05/2014	Questionnaires/Surveys	Headache Disability Questionnaire
20/05/2014	Questionnaires/Surveys	Comorbidity Questionnaire
20/05/2014	Questionnaires/Surveys	Central Sensitization Inventory
20/05/2014	Questionnaires/Surveys	Headache Impact Test
20/05/2014	Questionnaires/Surveys	Depression Anxiety Stress Scale
20/05/2014	Questionnaires/Surveys	Pittsburgh Sleep Quality Index
20/05/2014	Questionnaires/Surveys	Henry Ford Headache Disability Index
20/05/2014	Participant Consent Form	Consent Form
21/05/2014	Questionnaires/Surveys	International Physical Activity Questionnaire
21/05/2014	Interview Questions	Baseline Questions
16/05/2014	Questionnaires/Surveys	Disability Assessment Scale
29/05/2014	Advertisements/Flyer	Web advertisement
29/05/2014	Participant Info Statement	Participant Information Statement
29/05/2014	Advertisements/Flyer	Advertisement for posting
23/07/2014	Advertisements/Flyer	Ad for posting v2

23/07/2014	Participant Info Statement	Participant Information Statement v2
23/07/2014	Advertisements/Flyer	Web ad v2
23/07/2014	Interview Questions	Baseline questions v2
09/06/2015	Participant Info Statement	Participant Information Statement (tracked changes)
09/06/2015	Advertisements/Flyer	Advertisement for posting (tracked changes)
09/06/2015	Advertisements/Flyer	Web advertisement (tracked changes)

Please do not hesitate to contact Research Integrity (Human Ethics) should you require further information or clarification.

Yours sincerely



Dr Stephen Assinder
Chair
Human Research Ethics Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice.

APPENDIX 3

Levels of Excitatory and Other Brain Chemicals in Migraine Detected Using Proton Magnetic Resonance Spectroscopy

Appendix 3 presents supplementary methods and findings for Chapter Three.

INTRODUCTION

This report presents the levels of excitatory and other brain chemicals in migraine, to supplement findings presented in Chapter 3. In Chapter 3, new evidence was presented on elevated levels of the inhibitory brain chemical, gamma-aminobutyric acid (GABA), in people with migraine compared to age- and gender- matched controls and on the good diagnostic accuracy of GABA for classifying individuals with and without migraine. In light of this new evidence and the hypothesis that migraine pathophysiology involves an imbalance between excitatory and inhibitory mechanisms (1, 2), levels of excitatory and other brain neurochemicals in migraine are worth exploring.

Abnormalities in the brain concentrations of N-acetyl-aspartate (NAA), glutamate (Glu), glutamate + glutamine (Glx), creatine (Cr), choline (Cho), and myoInositol (mI) have been associated with various pathological changes in the brain. NAA is considered a marker of neuronal integrity and lower NAA levels are interpreted as neuronal loss or injury (3, 4). Glu and Glx are associated with excitatory neurotransmission. Cr reflects energy metabolism and is also used as a reference metabolite in measuring brain chemicals because of its relative stability across the brain (4). Cho is typically found in cell membranes and is believed to be a marker of cell turnover. mI maintains glial cell volumes and elevated mI levels are interpreted as glial activation due to inflammation (5).

Previous studies have investigated these brain chemicals in migraine. For example, decreased levels of NAA in the cerebellum have been reported in individuals with familial hemiplegic migraine compared to controls (6). There is also evidence on excitatory abnormalities in migraine. Elevated levels of Glu have been suggested to be related with central sensitization mechanisms in animal models of migraine (7). Consistent with this finding, there is evidence

for higher Glu levels in the anterior paracingulate cortex of individuals with migraine compared with controls. Similarly, low ratios of N-acetyl aspartylglutamate and Gln have been shown in the anterior cingulate cortex and insula in patients with migraine (8). Alterations in brain chemicals in migraine have also been found in the presence of comorbidities. For example, elevated levels of mI in the prefrontal cortex were observed in individuals with migraine and major depressive disorder compared to individuals with migraine without major depressive disorder(9).Further studies are required to replicateand validatethese findings to fully understand the neurochemical profile of migraine.

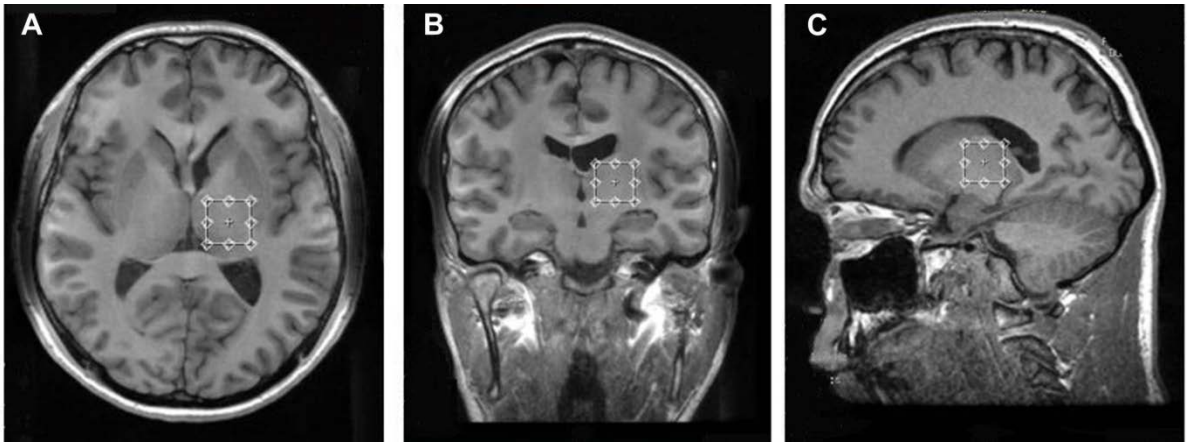
Therefore this report presents the methods and results of proton magnetic resonance spectroscopy for the following brain chemicals measured during the interictal period from the same cohort described in Chapter 3: NAA, Glu, Glx, Cr, Cho, and mI. The aim of this report was to characterise migraine in terms of its neurochemical profile, in addition to the evidence for GABA presented in Chapter 3.

MAGNETIC RESONANCE SPECTROSCOPY DATA ACQUISITION

Imaging was conducted at the Brain and Mind Research Institute imaging centre on a 3-Tesla GE Discovery MR750 scanner (GE Medical Systems, Milwaukee, Wisconsin) using an 8-channel phased array head coil. The protocol comprised three-dimensional sagittal whole-brain scout for orientation and positioning of all subsequent scans (repetition time, TR=50ms; echo time, TE=4ms; 256matrix; no averaging, z=5mm thickness). To aid in the anatomical localisation of all sampled voxels, a T1-weighted Magnetization Prepared RApid Gradient-Echo (MPRAGE) sequence producing 196 sagittal slices (TR=7.2ms; TE=2.8ms; flip angle = 10°; matrix 256x256; 0.9mm isotropic voxels) was acquired. Next, single voxel 1H-MRS using a Point RESolved Spectroscopy (PRESS) acquisition with two chemical shift-selective

imaging pulses for water suppression was acquired separately from voxels placed in the thalamus and anterior cingulate cortex using the following parameters: TE=35ms, TR=2000ms, 128 averages voxel size 2x2x2cm(see Figure 1). Anatomical localisation of voxel placement was based on the Talairach and Tournoux brain atlas (10) and positioning was guided by the T1-weighted image. Prior to any post-processing, all spectra were visually inspected separately by two independent raters to ensure the consistency of the data. Poorly fitted neurochemical peaks as reflected by large Cramer–Rao Lower Bounds (CRLB) were excluded from further analysis (CRLB less than 20). Finally, prior to determination of neurochemical ratios, all spectroscopy data were corrected for grey and white matter and cerebrospinal fluid content within the acquisition voxel.

Thalamus



Anterior Cingulate Cortex

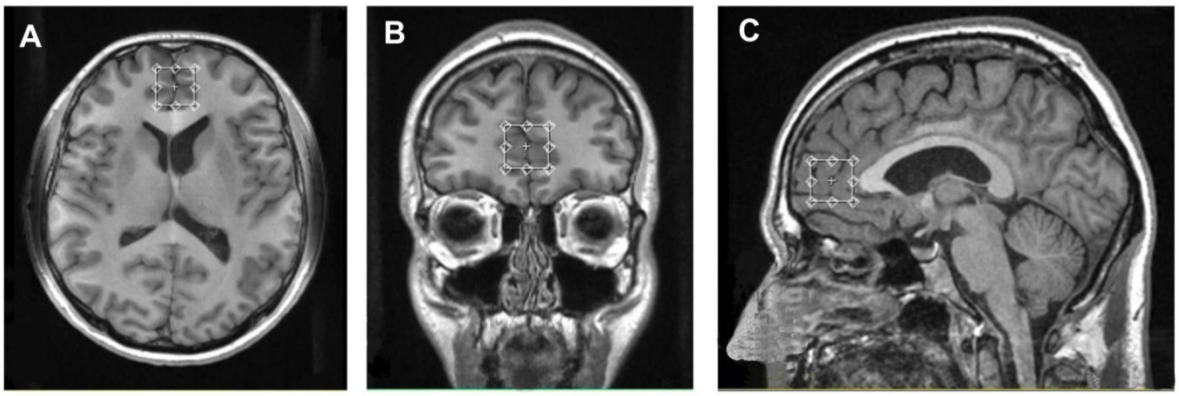


Figure 1. Placement of the single voxel in the thalamus (top panel) and anterior cingulate cortex (bottom panel) in the (A) axial, (B) coronal, and (C) sagittal planes for proton magnetic resonance spectroscopy analysis.

All spectra were quantified with the LCModel software package (11, 12) using a PRESS TE=35 basic set of 15 neurochemicals that included NAA, Glu, Glx, Cr, cho, and mI and incorporated macromolecule and baseline fitting routines. The radiographers, the neuroimaging expert who read the spectroscopy data and the neuroradiologist were blinded to group allocation.

Other methods, including study design, participant inclusion, procedures and statistical analyses have been detailed in Chapter 3.

RESULTS

Spectroscopy data were of sufficient quality to allow analysis from 18 participants each from the control group and their matched participants in the migraine group.

Profiles of NAA, Glu, Glx, Cr, Cho, and mI in migraine and controls are depicted in representative spectra in Figure 2. The spectra are plots of signal intensity against the frequency of the signal. The peaks for the neurochemicals in the spectra therefore represent the concentration of the neurochemicals, where the height of the peaks is proportional to the concentration of the neurochemicals (3). Thus the concentrations of NAA, Glu, Glx, Cr, Cho, and mI in migraine were not significantly different from those in matched controls (Figure 2, Table 1). Consequently, these brain chemicals also demonstrated poor diagnostic accuracies in classifying individuals as having migraine or not (Table 2).

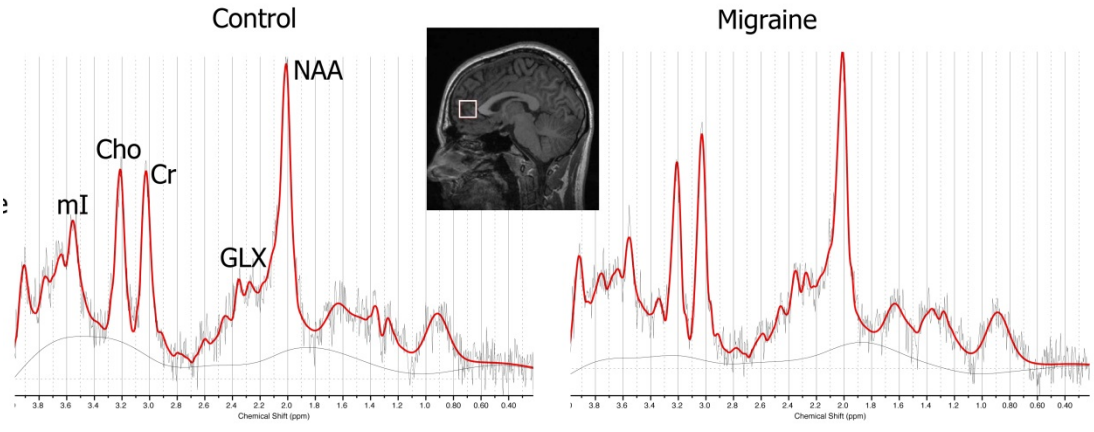


Figure 2.Representative spectra from the anterior cingulate cortex of a participant with migraine (right) and a matched control (left).

Table 1. Median and interquartile range of concentrations (in institutional units) of N-acetyl-aspartate, glutamate, glutamate + glutamine, creatine, choline, and myoInositol in the thalamus and anterior cingulate cortex in in people with migraine and controls

	Migraine	Control	*p* values
Thalamus			
N-acetyl-aspartate	17.35 (16.06–18.18)	17.59 (16.96–18.14)	0.647
Glutamate	15.84 (14.41–16.87)	16.33 15.18–17.66)	0.215
Glutamate + glutamine	17.08 (15.86–18.22)	17.61 (16.65–18.67)	0.528
Creatine	3.64 (1.35–5.36)	3.71 (2.37–5.26)	0.845
Choline	3.04 (2.77–3.33)	3.12 (2.88–3.44)	0.679
MyoInositol	7.06 (6.18–7.88)	7.10 (6.42–8.09)	0.112
Anterior cingulate cortex			
N-acetyl-aspartate	15.28 (14.14–17.60)	15.25 (13.56–16.31)	0.841
Glutamate	21.08 (17.88–23.22)	19.85 (17.93–22.75)	0.478
Glutamate + glutamine	25.63 (22.41–28.05)	24.13 (20.12–28.26)	0.167
Creatine	4.43 (3.13–6.33)	3.84 (3.16–4.58)	0.455
Choline	3.08 (2.74–3.62)	3.35(3.15–3.65)	0.575
MyoInositol	11.32 (10.47–12.37)	11.78 (8.47–12.61)	0.067

Table 2. Areas under the curve (95% confidence intervals) from receiver operating characteristic curve analyses evaluating N-acetyl-aspartate, glutamate, glutamate + glutamine, creatine, choline, and myoInositol in the thalamus and anterior cingulate cortex in in people with migraine and controls

	Area Under the Curve (95% CI)	*p* values
Thalamus		
N-acetyl-aspartate	0.43 (0.25–0.62)	0.46
Glutamate	0.41 (0.22–0.59)	0.32
Glutamate + glutamine	0.39 (0.21–0.57)	0.24
Creatine	0.51 (0.32–0.70)	0.94
Choline	0.43 (0.24–0.62)	0.46
MyoInositol	0.47 (0.28–0.66)	0.74
Anterior cingulate cortex		
N-acetyl-aspartate	0.57 (0.38–0.75)	0.48
Glutamate	0.56 (0.37–0.74)	0.56
Glutamate + glutamine	0.58 (0.39–0.77)	0.41
Creatine	0.61 (0.42–0.79)	0.27
Choline	0.39 (0.20–0.58)	0.24
MyoInositol	0.52 (0.32–0.72)	0.815

Abbreviation: CI, confidence interval; ROC, receiver operating characteristic

These findings differ from previous reports on brain chemicals in migraine, possibly due to different methods, region of measurement, and characteristics of the cohort in the studies. Still, these findings add to the scarce evidence on the neurochemical basis and pathophysiology of migraine. Considering the elevated levels of GABA detected in the same migraine cohort, these findings on NAA, Glu, Glx, Cr, Cho, and mI suggest the relative importance of GABA in the pathophysiology and diagnosis of migraine compared to these chemicals. Further cross-sectional and longitudinal studies could investigate these brain chemicals and their changes over time in different brain regions hypothesised to be involved in migraine, in individuals with migraine with different characteristics from participants of this study, and during the ictal period.

CONCLUSIONS

Our results demonstrate no significant difference in metabolic profile for NAA, Glu, Glx, Cr, Cho, and mI in individuals with migraine during the interictal period compared with matched controls. These findings, taken together with elevated levels of GABA detected in the same migraine cohort presented in Chapter 3, contribute to the characterisation of the neurochemical profile of migraine and provide basis to further explore neurochemical alterations and their probable link with the pathophysiology of migraine.

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APPENDIX 4

Project Protocol:

Can Neurochemicals Distinguish Headache Types?

Appendix 4 presents the project protocol for studies in Chapters Three and Four.

Project Title:

CAN NEUROCHEMICALS DISTINGUISH HEADACHE TYPES?

Project Protocol

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    - 1.3.1.1 Participant information statement
    - 1.3.1.2 Participant consent form
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  - 1.3.2 Questionnaires
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    - 1.5.2.5 Flexion rotation test
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- 1.6 Spectroscopy

2.0Initial telephone screening for patient groups

Potential subjects are recruited by advertisement or from referring doctors as per the ethics document. Potential subjects will initially be screened over the telephone by either Marilie or Andrew. During the current (pilot phase) subjects will be recruited with migraine or as controls.

2.1 General screening and demographic details

Name:

Found about study by:
DOB: Gender: F ☐ M ☐

Contact: Address:

Phone:
Email:

2.2 Initial screening for either migraine or control group

Have you experienced headaches?	**Yes ☐ Proceed to 1.3 Telephone screening for migraine**	**No ☐ Proceed to 1.4 Telephone screening for control**

2.3 Telephone screening for migraine

ICHD-II criteria 1.1 Migraine without aura	Sample screening question	Participant response
A. At least 5 attacks fulfilling criteria B-D	How often do you have headaches? (Or how many headaches have you have had so far?)	
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)	How long do your headaches typically last?	
C. Headache has at least two of the following characteristics: ☐ **Unilateral location** ☐ **Pulsating quality** ☐ **Moderate or severe pain intensity** ☐ **Aggravation by or causing avoidance of routine physical activity (eg walking or climbing stairs)**	Can you describe your headache/ how does it feel? (If needing further prompting: would you describe it as sickening?splitting? nauseating?) Where do you feel your headache usually? How would you rate the average intensity of your headacheon a scale of 0 (no pain at all) to 10/10(worst possible pain?) What happens to your headachewith exercise such as walking or climbing stairs? Does it get better or worse?	
D. During headache at least one of the following ☐ **Nausea and/or vomiting** ☐ **Photophobia** ☐ **Phonophobia**	Do you experience any other symptoms with your headache? Can you describe them? Or more leading questions: Do you ever feel nauseas or vomit when you have a headache? Are you sensitive to light or sound during a headache?	
(Other info)	What do you need to do to relieve your headache and the other symptoms?	
	Do you take any medication for your headache? What meds?	
	What do you think triggers your headaches? (Or more leading: Do you think your headache is associated with chocolate intake, alcohol consumption, hormonal changes, etc.?)	
	Do you have a family member who has migraine?	
E. Not attributed to another disorder	Have you been diagnosed with any other condition that may be related to your headache? Have you received treatment any other condition that may be related to your headache?	

ICHD-II criteria 1.1 Migraine with aura	Sample screening question	Participant response
A. At least 2 attacks fulfilling criteria B-D	How often do you have headaches?	
B. Aura consisting of at least one of the following, but ☐ **No motor weakness;** ☐ **Fully reversible visual symptoms** o **positive features: flickering lights, spots or lines** o **negative features: loss of vision** ☐ **Fully reversible sensory symptoms** o **positive features: pins and needles** o **negative features: numbness** ☐ **Fully reversible dysphasic speech disturbance**	Do you experience any other symptoms with your headache? Can you describe them? Do you feel these before or after your headache? Or more leading questions: Do you have visual symptoms with your headache such as flickering lights, etc. Do you feel pins and needles? Numbness? Does your speech get affected during attacks?	

ICHD-II criteria 1.1 Migraine with aura	Sample screening question	Participant response
C. At least two of the following: ☐ **Homonymous visual symptoms and/or unilateral sensory symptoms** ☐ **At least one aura symptom develops gradually over ≥ 5minutes and/or different aura symptoms occur in succession over ≥ 5minutes** ☐ **Each symptom lasts ≥ 5 and less than ≤60 minutes**	**Are your visual symptoms sensory on one side or both sides?** **How long does it take for the visual / sensory / speech symptom (aura) to develop?** **How long does the visual / sensory / speech symptom (aura) last?**	
D. Headache fulfilling criteria B-D for migraine without aura begins during the aura or follows aura within 60 minutes	Once you have the visual / sensory / speech symptom (aura), how long does it take before you get a headache? Can you describe this headache?	
(Other info)	What do you need to do to relieve your headache and the other symptoms?	
	Do you take any medication for your headache? What meds?	
	What do you think triggers your headaches? (Or more leading: Do you think your headache is associated with chocolate intake, alcohol consumption, hormonal changes, etc.?)	
	Do you have a family member who has migraine?	
E. Not attributed to another disorder	Have you been diagnosed with any other condition that may be related to your headache? Have you received treatment any other condition that may be related to your headache?	

Fulfilled criteria for migraine?

☐ **Yes: Included in migraine group**

☐ **No: Excluded**

2.4 Telephone screening for controls

2.4.1	Have you had a headache in the past 3 months?	Yes ☐	No ☐
2.4.2	If you experience headaches, are they regular? (N.B. "regular" ~ once in 3mos)	Yes ☐	No ☐
2.4.3	Do you experience significant pain?	Yes ☐	No ☐
2.4.4	Do you experience significant neck pain?	Yes ☐	No ☐
2.4.5	Do you have any other chronic complaints, say pain that lasts for more than 3 months?	Yes ☐	No ☐

Responded "no" to screening questions 1.4.1 to 1.4.5?

☐ **Yes: Included as control**

☐ **No: Excluded**

2.5 Telephone screening for exclusion criteria

I need to ask a few more questions to make sure that you can undergo MRI scanning.

- Do you have entrapment neuropathy? Myelopathy?Stent? Epilepsy? Yes ☐ No ☐
- Are you pregnant? Yes ☐ No ☐
- Have you had cervical spine surgery? Whiplash or trauma to the head or neck? Amputation? Yes ☐ No ☐
- Do you use a wheelchair? Yes ☐ No ☐
- Have you had any health complaints in the last 5 days? Yes ☐ No ☐
- Have you been diagnosed with severe depression, since symptoms of depression influence neurochemistry in the cortical regions of interest in this study? Yes ☐ No ☐
- Did you take any medicine for a neck condition or headache in the previous 6 hours? Yes ☐ No ☐
- Do you have any metal in your body? This may be a reason for not going through MRI scanning. Do you have any metal in your head? An aneurysm clip? Cochlear implants? Neurostimulators in your head? Braces on your teeth? Head tattoos? Metal piercings in your head? Do you have any metal in your heart? Have you done any welding, because that might leave metal in your eyes? Yes ☐ No ☐
- Do you have claustrophobia or fear of enclosed spaces? Are you afraid of tight spaces? Yes ☐ No ☐
- Do you think you do not have reasonable command of English to understand instructions? Yes ☐ No ☐

Responded "yes" to any of the exclusion criteria?

☐ **Yes: Excluded**

☐ **No: Included**

If individual meets inclusion and exclusion criteria (for either migraine or control), proceed to explain that they are eligible for study. Explain briefly the following:

- Will you be interested to participate in our project? This is a study about natural chemicals in your brain that might be associated with different types of headache. We think there might be different natural chemicals in your brain when you have migraines and when you do not have migraines. We are doing this study to better understand these natural chemicals in the brain and maybe eventually better decide on treatment for headaches.
- You might be interested in the findings
- You will be required to undertake a series of brain scans at the Brain & Mind Research Institute on Mallett St., Camperdown

If individual has more questions or if he/she is interested to participate in the study, say that you will send further information and some questionnaires that need to be filled out before the MRI appointment. These may be sent by email or post, according to preference.

- patient information statement (PIS)
- consent form
- baseline demographic information (other than that collected above)
- baseline questionnaires (SF-MPQ-2, DASS-21, Headache Disability Questionnaire, Headache Impact Test-6, Headache Disability Inventory)
- information about how to access the BMRI (where to parkand meet etc)

Once participant has had time to read the PIS, explain that we will telephone to book the MRI time. Remind that he/she should come to the appointment with the questionnaires completed.

3.0Participant forms and questionnaires

3.1 Patient information statement and consent form

PARTICIPANT INFORMATION STATEMENT

Can neurochemicals distinguish headache types?

(1) What is the study about?

You are invited to participate in a study of brain chemicals that are associated with different types of headache. We will measure the levels of chemicals in different parts of your brain to determine whether any changes are specific to different types of headache. You are eligible to participate in this study if you experience frequent headaches, or you never experience headaches.

You are not eligible to participate if you have any of the following:

- Any disease or injury affecting the neck
- Epilepsy
- A physical condition that prevents you from being positioned in the scanner, such as being in a wheelchair
- Severe depression
- Any metal in your head or neck, including orthodontic braces for your teeth, or neck tattoos
- Claustrophobia

If you are not certain whether you are eligible, please ask the researchers. You will have to complete a questionnaire to ensure there are no contraindications to your participation. This is routine before any scanning.

(2) Who is carrying out the study?

The study is being conducted by Professors Kathryn Refshauge, Jim Lagopoulos and Patrick Brennan and Drs Trudy Rebbeck and Andrew Leaver, at The University of Sydney.

(3) What does the study involve?

You will be required to attend the Brain and Mind Research Institute at Mallett St, Camperdown, to undertake a series of brain scans. We will first ask you a series of questions about your headache status and general health. We will then scan your brain using a particular type of imaging equipment, proton magnetic resonance spectroscopy, to enable us to measure the concentration of five different chemicals in four regions of your brain. Some people may experience some mild anxiety when placed in the MRI scanner. However, the imaging staff involved with this study are trained to deal with these issues and will be available for immediate support. We will reimburse you for travel and inconvenience.

(4) How much time will the study take?

Your involvement in the study will take 1 hr. We will follow up your progress in 3 months, and measure the level of these chemicals again as well as your headache status.

(5) Can I withdraw from the study?

Being in this study is completely voluntary - you are not under any obligation to consent and - if you do consent - you can withdraw at any time without affecting your relationship with The University of Sydney.

(6) Will anyone else know the results?

All aspects of the study, including results, will be strictly confidential and only the researchers will have access to information on participants.
A report of the study may be submitted for publication, but individual participants will not be identifiable in such a report.

(7) Will the study benefit me?

We cannot and do not guarantee or promise that you will receive any benefits from the study.

(8) Can I tell other people about the study?

You can tell other people about the study. If they are interested in participating, they would be welcome to ring one of the researchers named on this Participant Information Sheet.

(9) What if I require further information about the study or my involvement in it?

When you have read this information, one of the chief investigators will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact:

Ms Maria Eliza Aguila
9351 9453
magu5636@uni.sydney.edu.au

Associate Professor Jim Lagopoulos
93510783
Jim.Lagopoulos@sydney.edu.au

Dr Andrew Leaver
9351 9545
Andrew.Leaver@sydney.edu.au

(10) What if I have a complaint or any concerns?

Any person with concerns or complaints about the conduct of a research study can contact The Manager, Human Ethics Administration, University of Sydney on +61 2 8627 8176 (Telephone); +61 2 8627 8177 (Facsimile) or ro.humanethics@sydney.edu.au (Email).

PARTICIPANT CONSENT FORM

I, ...[PRINT NAME], give consent to my participation in the research project

TITLE: **Can neurochemicals distinguish headache types?**

In giving my consent I acknowledge that:

1. The procedures required for the project and the time involved have been explained to me and any questions I have about the project have been answered to my satisfaction.

2. I have read the Participant Information Statement and have been given the opportunity to discuss the information and my involvement in the project with the researcher/s.

3. I understand that being in this study is completely voluntary – I am not under any obligation to consent.

4. I understand that my involvement is strictly confidential. I understand that any research data gathered from the results of the study may be published however no information about me will be used in any way that is identifiable.

5. I understand that I can withdraw from the study at any time, without affecting my relationship with the researcher(s) or the University of Sydney now or in the future.

I consent to:
Receiving Feedback YES ☐ NO ☐

If you answered YES to the “Receiving Feedback” question, please provide your details i.e. mailing address, email address.

Feedback Option

Address: _____

_____

Email: _____

....
Signature

....
Please PRINT name

.....
Date

3.2Demographic details

Marital status: **single☐ married☐ divorced☐ widowed☐**

Highest education level: **Primary ☐ secondary ☐ tertiary☐**

Occupation:

Height: **Weight:**

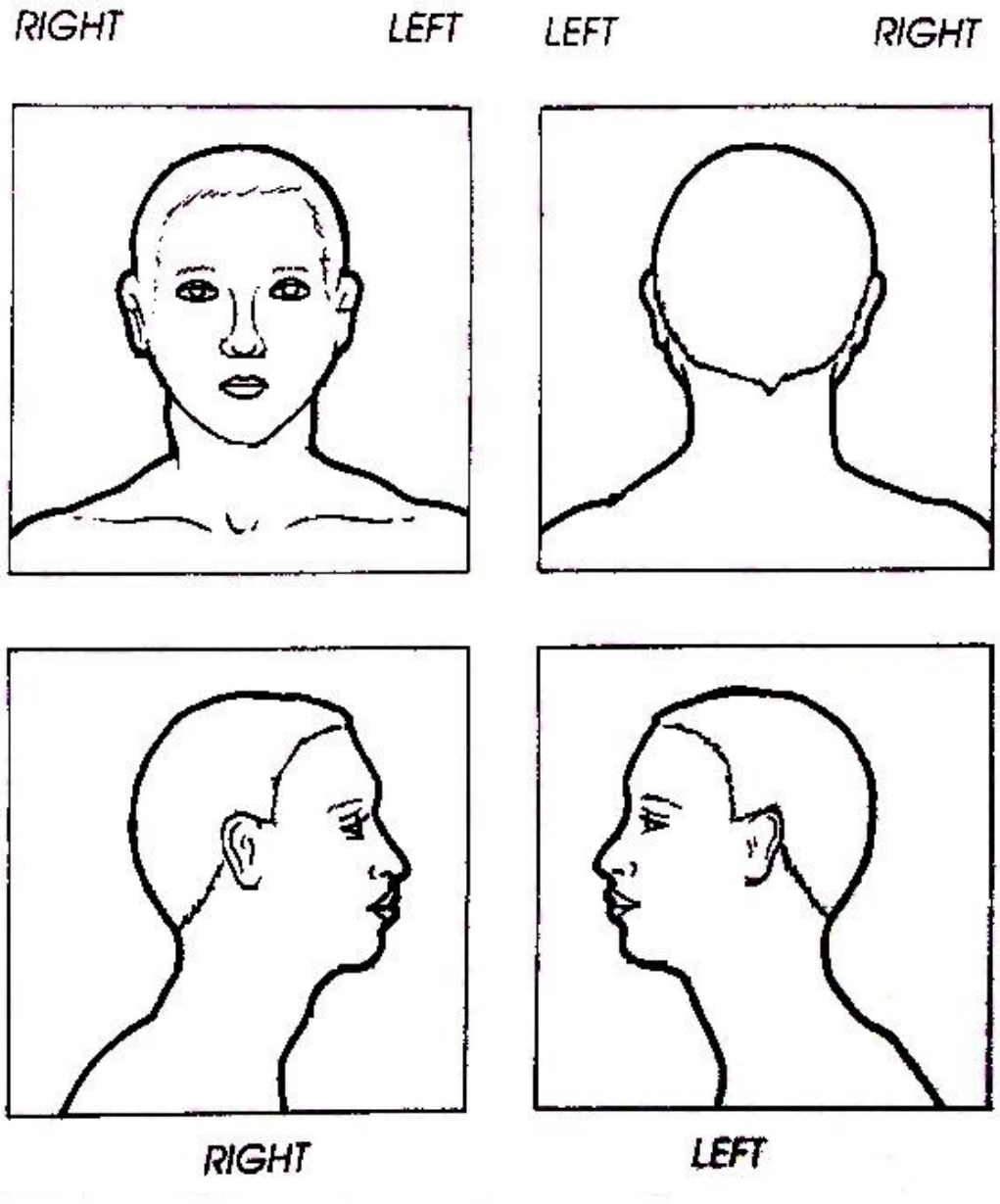
Medications:

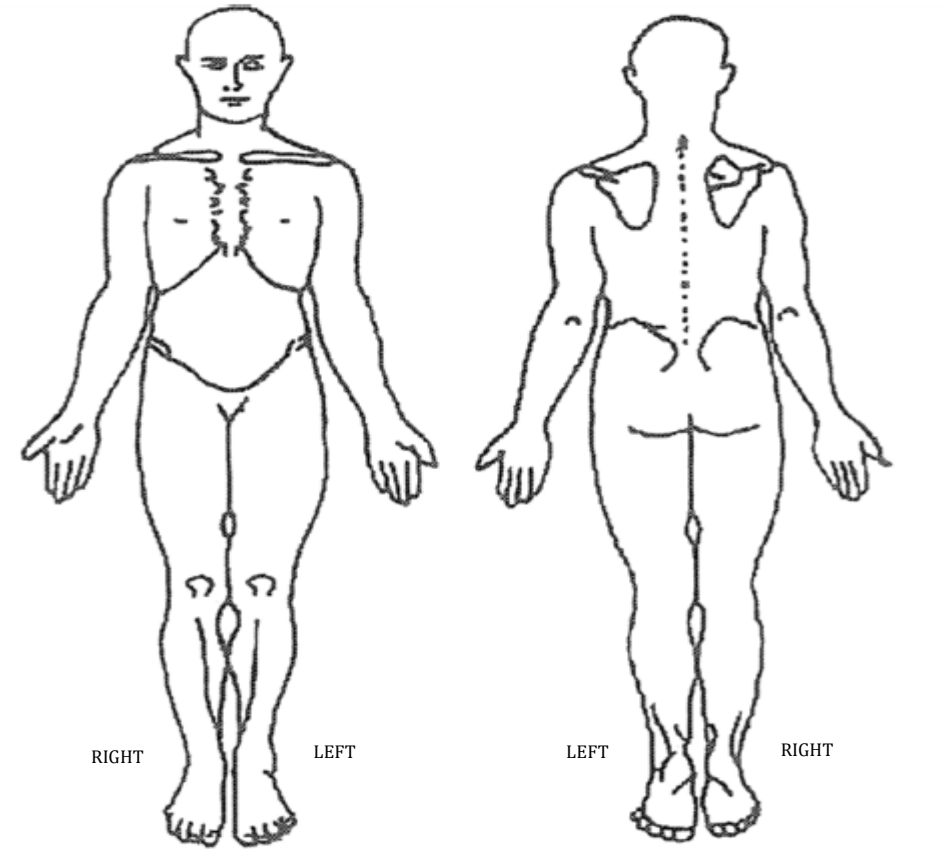
Drug name	Dose	Frequency	Length of time taken	Time/ date last taken

3.3Headache duration, location, intensity and frequency

2.3.1 How long have you been experiencing headaches? _____ months/ years

Please shade areas on the head and body charts below to indicate where you are currently experiencing pain including headaches. If you have pain in more than one location, indicate additional locations also.





You should then rate the **headache intensity** using the following two 0 – 10 scales:

2.3.2 Average headache pain intensity over the last month (Circle the most appropriate)

0	1	2	3	4	5	6	7	8	9	10
No pain								Worst possible pain		

2.3.3 Average headache intensity over the last 24 hours (Circle the most appropriate)

0	1	2	3	4	5	6	7	8	9	10
No pain							Worst possible pain			

2.3.4 How often do you experience headaches _____times per month

2.3.5 Global perceived effect

With respect to your headache pain, compared to when you first entered the study, how would you describe your headaches these days?
(Circle the most appropriate)

-5	-4	-3	-2	-1	0	1	2	3	4	5
Vastly worse				Unchanged			Completely recovered			

3.4 Pain questionnaires

Short-Form McGill Pain Questionnaire-2(SF-MPQ-2)[1]

This questionnaire provides you with a list of words that describe some of the different qualities of pain and related symptoms. Please put an **X** through the numbers that best describe the intensity of each of the pain and related symptoms you felt during the past week. Use 0 if the word does not describe your pain or related symptoms.

1. Throbbing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
2. Shooting pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
3. Stabbing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
4. Sharp pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
5. Cramping pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
6. Gnawing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
7. Hot-burning pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
8. Aching pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
9. Heavy pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
10. Tender	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
11. Splitting pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
12. Tiring-exhausting	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
13. Sickening	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
14. Fearful	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
15. Punishing-cruel	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
16. Electric-shock pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
17. Cold-freezing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
18. Piercing	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
19. Pain caused by light touch	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
20. Itching	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
21. Tingling or 'pins and needles'	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
22. Numbness	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*

CENTRAL SENSITIZATION INVENTORY[2]: PART A

Please circle the best response to the right of each statement

1	I feel unrefreshed when I wake up in the morning	Never	Rarely	Sometimes	Often	Always
2	My muscles feel stiff and achy	Never	Rarely	Sometimes	Often	Always
3	I have anxiety attacks	Never	Rarely	Sometimes	Often	Always
4	I grind or clench my teeth	Never	Rarely	Sometimes	Often	Always
5	I have problems with diarrhea and/or constipation	Never	Rarely	Sometimes	Often	Always
6	I need help in performing my daily activities	Never	Rarely	Sometimes	Often	Always
7	I am sensitive to bright lights	Never	Rarely	Sometimes	Often	Always
8	I get tired very easily when I am physically active	Never	Rarely	Sometimes	Often	Always
9	I feel pain all over my body	Never	Rarely	Sometimes	Often	Always
10	I have headaches	Never	Rarely	Sometimes	Often	Always
11	I feel discomfort in my bladder and/or burning when I urinate	Never	Rarely	Sometimes	Often	Always
12	I do not sleep well	Never	Rarely	Sometimes	Often	Always
13	I have difficulty concentrating	Never	Rarely	Sometimes	Often	Always
14	I have skin problems such as dryness, itchiness, or rashes	Never	Rarely	Sometimes	Often	Always
15	Stress makes my physical symptoms get worse	Never	Rarely	Sometimes	Often	Always
16	I feel sad or depressed	Never	Rarely	Sometimes	Often	Always
17	I have low energy	Never	Rarely	Sometimes	Often	Always
18	I have muscle tension in my neck and shoulders	Never	Rarely	Sometimes	Often	Always
19	I have pain in my jaw	Never	Rarely	Sometimes	Often	Always
20	Certain smells, such as perfumes, make me feel dizzy and nauseated	Never	Rarely	Sometimes	Often	Always
21	I have to urinate frequently	Never	Rarely	Sometimes	Often	Always
22	My legs feel uncomfortable and restless when I am trying to go to sleep at night	Never	Rarely	Sometimes	Often	Always
23	I have difficulty remembering things	Never	Rarely	Sometimes	Often	Always
24	I suffered trauma as a child	Never	Rarely	Sometimes	Often	Always
25	I have pain in my pelvic area	Never	Rarely	Sometimes	Often	Always
					Total =	

CENTRAL SENSITIZATION INVENTORY: PART B

Have you been diagnosed by a doctor with any of the following disorders?
Please check the box to the right for each diagnosis and write the year of the diagnosis

		No	Yes	Year Diagnosed
1	Restless leg syndrome			
2	Chronic fatigue syndrome			
3	Fibromyalgia			
4	Temporomandibular joint disorder (TMJ)			
5	Migraine or tension headaches			
6	Irritable bowel syndrome			
7	Multiple chemical sensitivities			
8	Neck injury (including whiplash)			
9	Anxiety or panic attacks			
10	Depression			

[2]From Mayer, T.G.,Neblett, R., Cohen, H., Howard, K.J., Choi, Y.H., Williams, M.J., Perez, Y., &Gatchel, R.J. (2012). The development and psychometric validation of the Central Sensitization Inventory. *Pain Practice, 12*(4), 276-285. With permission.

3.5 DASS-21

DASS21

Name: *Date:*

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

1	I found it hard to wind down	0	1	2	3
2	I was aware of dryness of my mouth	0	1	2	3
3	I couldn't seem to experience any positive feeling at all	0	1	2	3
4	I experienced breathing difficulty (eg, excessively rapid breathing,breathlessness in the absence of physical exertion)	0	1	2	3
5	I found it difficult to work up the initiative to do things	0	1	2	3
6	I tended to over-react to situations	0	1	2	3
7	I experienced trembling (eg, in the hands)	0	1	2	3
8	I felt that I was using a lot of nervous energy	0	1	2	3
9	I was worried about situations in which I might panic and makea fool of myself	0	1	2	3
10	I felt that I had nothing to look forward to	0	1	2	3
11	I found myself getting agitated	0	1	2	3
12	I found it difficult to relax	0	1	2	3
13	I felt down-hearted and blue	0	1	2	3
14	I was intolerant of anything that kept me from getting on withwhat I was doing	0	1	2	3
15	I felt I was close to panic	0	1	2	3
16	I was unable to become enthusiastic about anything	0	1	2	3
17	I felt I wasn't worth much as a person	0	1	2	3
18	I felt that I was rather touchy	0	1	2	3
19	I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	0	1	2	3
20	I felt scared without any good reason	0	1	2	3
21	I felt that life was meaningless	0	1	2	3

Participants with a score of $\geq$ 21 on the Depression Scale of on the DASS 21 will be excluded.

3.6 Headache disability questionnaires

HEADACHE DISABILITY QUESTIONNAIRE

Name:…… Date:……/……/…… Score / 90

Please read each question and circle the response that best applies to you

1. How would you rate the usual pain of your headache on a scale from 0 to 10?

0 NO PAIN	1	2	3	4	5	6	7	8	9	10	WORST PAIN

2. When you have headaches, how often is the pain severe?

NEVER	1-9%	10-19%	20-29%	30-39%	40-49%	50-59%	60-69%	70-79%	80-89%	90-100%	ALWAYS
0	1	2	3	4	5	6	7	8	9	10	

3. On how many days in the last month did you actually lie down for an hour or more because of your headaches?

NONE	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-31	EVERY DAY
0	1	2	3	4	5	6	7	8	9	10	

4. When you have a headache, how often do you miss work or school for all or part of the day?

NEVER	1-9%	10-19%	20-29%	30-39%	40-49%	50-59%	60-69%	70-79%	80-89%	90-100%	ALWAYS
0	1	2	3	4	5	6	7	8	9	10	

5. When you have a headache while you work (or school), how much is your ability to work reduced?

NOT	1-9%	10-19%	20-29%	30-39%	40-49%	50-59%	60-69%	70-79%	80-89%	90-100%	UNABLE TO
0 REDUCED	1	2	3	4	5	6	7	8	9	10	WORK

6. How many days in the last month have you been kept from performing housework or chores for at least half of the day because of your headaches?

NONE	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-31	EVERY DAY
0	1	2	3	4	5	6	7	8	9	10	

7. When you have a headache, how much is your ability to perform housework or chores reduced?

NOT	1-9%	10-19%	20-29%	30-39%	40-49%	50-59%	60-69%	70-79%	80-89%	90-100%	UNABLE
0 REDUCED	1	2	3	4	5	6	7	8	9	10	TO PERFORM

8. How many days in the last month have you been kept from non-work activities (family, social or recreational) because of your headaches?

NONE	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-31	EVERY DAY
0	1	2	3	4	5	6	7	8	9	10	

9. When you have a headache, how much is your ability to engage in non-work activities (family, social or recreational) reduced?

NOT	1-9%	10-19%	20-29%	30-39%	40-49%	50-59%	60-69%	70-79%	80-89%	90-100%	UNABLE
0 REDUCED	1	2	3	4	5	6	7	8	9	10	TO PERFORM

HIT-6™ HEADACHE IMPACT TEST

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please check one box for each question.

1.When you have headaches, how often is the pain severe?

☐ **Never** ☐ **Rarely** ☐ **Sometimes** ☐ **Very Often** ☐ **Always**

2.How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

☐ **Never** ☐ **Rarely** ☐ **Sometimes** ☐ **Very Often** ☐ **Always**

3. When you have a headache, how often do you wish you could lie down?

☐ **Never** ☐ **Rarely** ☐ **Sometimes** ☐ **Very Often** ☐ **Always**

4.In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

☐ **Never** ☐ **Rarely** ☐ **Sometimes** ☐ **Very Often** ☐ **Always**

5.In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

☐ **Never** ☐ **Rarely** ☐ **Sometimes** ☐ **Very Often** ☐ **Always**

6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

☐ **Never** ☐ **Rarely** ☐ **Sometimes** ☐ **Very Often** ☐ **Always**

COLUMN 1	*COLUMN 2*	*COLUMN 3*	*COLUMN 4*	*COLUMN 5*
(6 points each)	*(8 points each)*	*(10 points each)*	*(11 points each)*	*(13 points each)*

To score, add points for answers in each column
Please share your HIT-6 results with your doctor.

Total Score: _____

Higher scores indicate greater impact on your life.
Score range is 36-78.

THE HENRY FORD HEADACHE DISABILITY INVENTORY[3]

Please read carefully: The purpose of the scale is to identify difficulties that you may be experiencing because of your headache. Please check off "YES", "SOMETIMES", or "NO" to each item. Answer each question as it pertains to your headache only.

	YES	SOMETIMES	NO
E1. Because of my headaches I feel handicapped.			
F2. Because of my headaches I feel restricted in performing my routine daily activities.			
E3. No one understands the effect that my headaches have on my life.			
F4. I restrict my recreational activities (eg, sports, hobbies) because of my headaches.			
E5. My headaches make me angry.			
E6. Sometimes I feel that I am going to lose control because of my headaches.			
F7. Because of my headaches I am less likely to socialize.			
E8. My spouse (significant other), or family and friends, have no idea what I am going through because of my headaches.			
E9. My headaches are so bad that I feel that I am going to go insane.			
E10. My outlook on the world is affected by my headaches.			
E11. I am afraid to go outside when I feel that a headache is starting.			
E12. I feel desperate because of my headaches.			
F13. I am concerned that I am paying penalties at work or at home because of my headaches.			
E14. My headaches place stress on my relationships with family or friends.			
F15. I avoid being around people when I have a headache.			
F16. I believe my headaches are making it difficult for me to achieve my goals in life.			
F17. I am unable to think clearly because of my headaches.			
F18. I get tense (eg, muscle tension) because of my headaches.			
F19. I do not enjoy social gatherings because of my headaches.			
E20. I feel irritable because of my headaches.			
F21. I avoid traveling because of my headaches.			
E22. My headaches make me feel confused.			
E23. My headaches make me feel frustrated.			
F24. I find it difficult to read because of my headaches.			
F25. I find it difficult to focus my attention away from my headaches and on other things.			

[3]From Jacobson, G.P., Ramadan, N.M., Aggarwal, S.K., & Newman, C.W. (1994). The Henry Ford Hospital Headache Disability Inventory (HDI). *Neurology, 44,* 837-842.With permission.

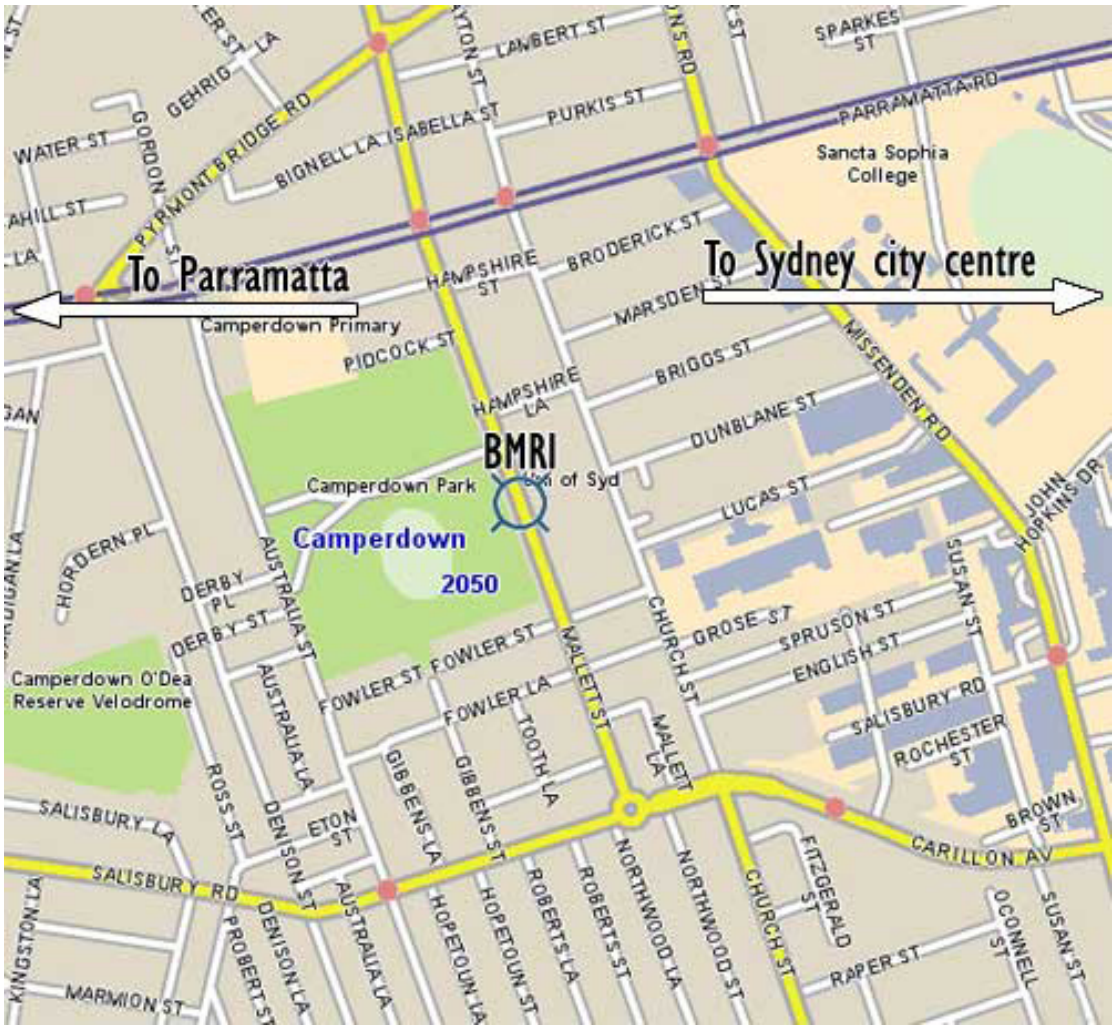
4.0 Where do I go for the MRI?

Please come to the Brain & Mind Research Institute, 94 Mallett Street, Camperdown, where a member of the research team (Ms. Marilie Aguila, Dr Andrew Leaver or Dr Trudy Rebbeck) will meet you at the foyer of Building F.

By public transport, get off at Central station, walk to the bus stop Railway Square D, Sydney and then catch a bus (438, 439, 440, or 461, any bus that will go on Paramatta Road). Get off at Parramatta Rd NrMallett St. The BMRI is a short walk from there.

If you are driving, there are a number of parking spots on Australia St. near the BMRI that are all day parking, although these are limited and may be full early.

Contact: Ms Maria Eliza Aguila, **T** 02 9351 9010, **M** 0405-756675
Brain & Mind Research Institute **T** 02 9351 0672

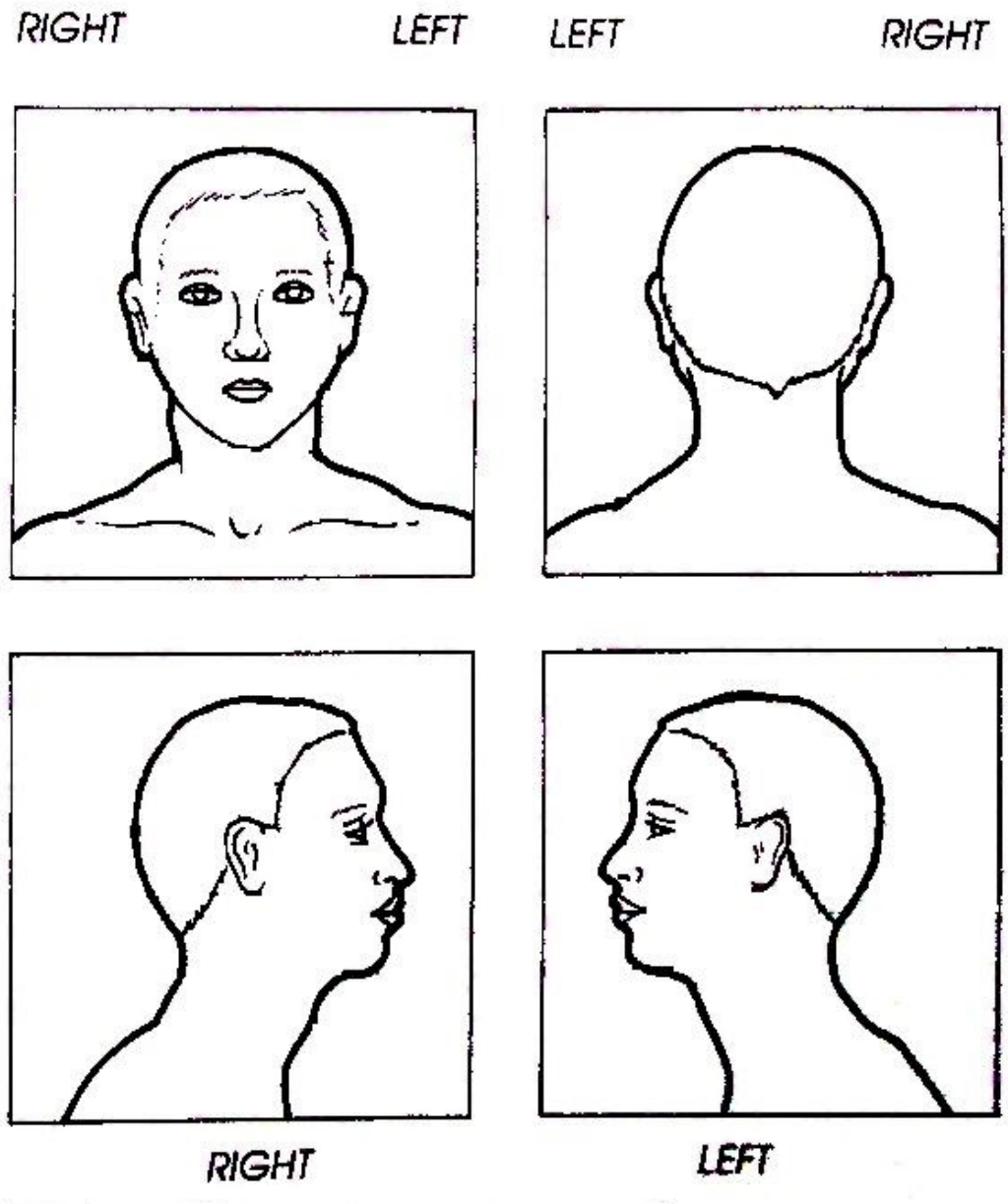


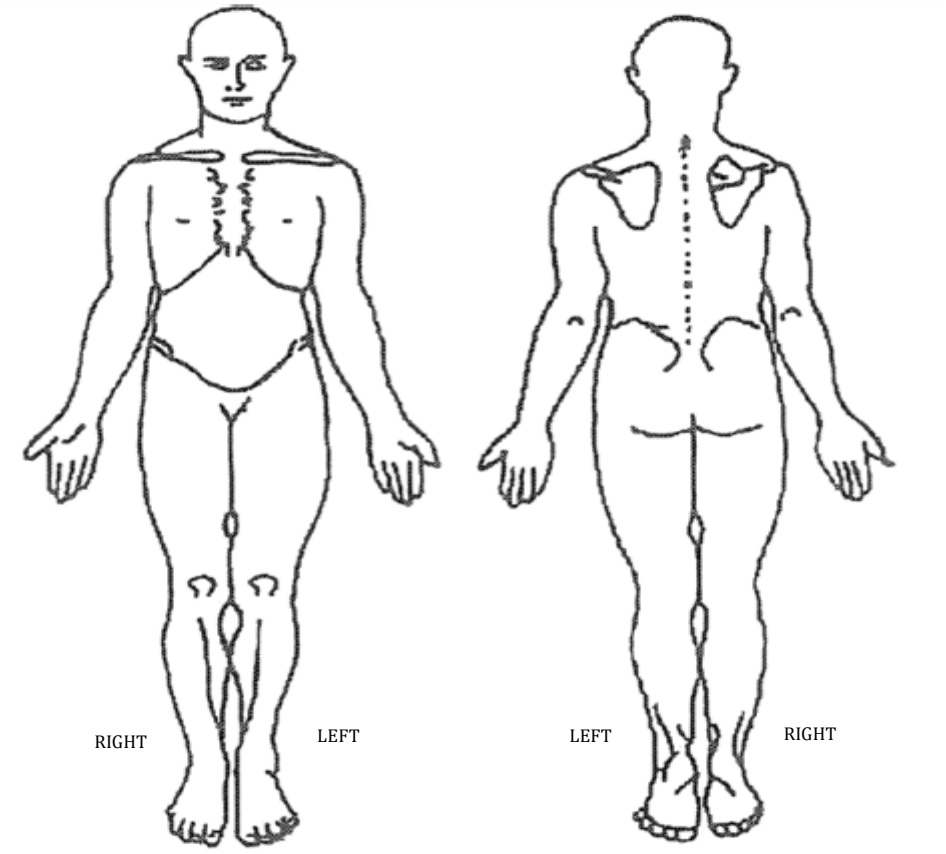
4.0 Clinical screening

CLINICAL NOTES for assessing physiotherapist

Subjective Examination

Clarify body chart as provided by patient:





Do the painful areas become painful together or separately?

History:

- Have you seen a neurologist? Yes ☐ No ☐

  If yes, what was the diagnosis given? _____

- Have you taken any medication to reduce the pain? Yes ☐ No ☐

- Have you received physical treatment for the pain? Yes ☐ No ☐

  If yes, what are these? _____

- Have you received alternative treatment for the pain? Yes ☐ No ☐

  If yes, what are these? _____ No ☐

Pain behaviour:

- Do movements affect your pain? Yes ☐ No ☐
- Do certain positions affect your pain? Yes ☐ No ☐

Other: general health etc

- Are you comfortable to go through MRI scanning? Yes ☐ No ☐

Clinical Examination

Cervical ROM:

Movement	Range	Comment
Flexion		
Extension		
Left lateral flexion		
Right lateral flexion		
Left rotation		
Right rotation		

Test for Mechanosensitivity of Neural Tissue:

Tests for mechanosensitivity of the upper cervical neural tissues will be done following the protocol described in Hall &Elvey (2004) In J.D. Boyling& G.A. Jull (Eds.), *Grieve's modern manual therapy: The vertebral column* (3rd ed.). (pp. 413-431). Edinburgh: Churchill Livingstone and Hall, T., Briffa, K., & Hopper, D. (2008). Clinical Evaluation of Cervicogenic Headache: A Clinical Perspective. *J Man ManipTher, 16*(2): 73–80.

☐ **Yes**
☐ **No**

Spurling's: Extension/Lateral Flexion: +/- rotation + compression

Positive ☐ Negative☐

Positive Spurling's?

☐ **Yes: Excluded**
☐ **No: Confirm inclusion as participant**

Palpation:

Manual examination of the upper cervical joints will be done following the protocol of Zito, Jull & Story, 2006

0/C1	Provoked ☐	VAS:	Relieved ☐	VAS:
C1/C2	Provoked ☐	VAS:	Relieved ☐	VAS:
C2/C3	Provoked ☐	VAS:	Relieved ☐	VAS:
C3/C4	Provoked ☐	VAS:	Relieved ☐	VAS:

Cervical Flexion Rotation Test:

Cervical flexion rotation test will be done following the protocol described in Hall, Briffa, Hopper, & Robinson, 2010.

Positive ☐ Negative ☐

Neurological Tests:

Two or more neurologic signs present?

- ☐ **Yes: Excluded**
- ☐ **No: Confirm inclusion as participant**

APPENDIX 5

Project Protocol:

Natural Course and Predictors of Recovery of

Migraine and Other Headache Types

Appendix 5 presents the project protocol for studies in Chapters Five through Seven.

Project Title:

NATURAL COURSE AND PREDICTORS OF RECOVERY OF MIGRAINE AND OTHER HEADACHE TYPES

Project Protocol

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2.0 Initial telephone screening for participant groups

Potential participants are recruited by advertisement or from referring doctors as per the ethics document. Potential participants will initially be screened over the telephone by Marilie (headache or control groups) and Kanzah (control group).

2.1 Demographic details

Name:

Found about study by:
DOB: Sex: F ☐ M ☐

Contact: Address:

Phone:
Email:

Is the volunteer aged 18-65 years old?

- ☐ **Yes: Proceed to screening for inclusion criteria**
- ☐ **No: Excluded**

2.2 Initial screening for either headache or control group

Have you experienced headaches?	**Yes ☐** **Proceed to 2.3.1 Telephone screening for headache groups**	**No ☐** **Proceed to 2.3.2 Telephone screening for control**

2.3 Telephone screening for inclusion criteria

2.3.1 Telephone screening for inclusion criteria for headache groups

Do you experience recurrent headaches?	☐	Yes	☐	No
Did you experience headache in the last month?	☐	Yes	☐	No
Have you had your headache for more than a year?	☐	Yes	☐	No

Responded "yes" to screening questions 2.3.1?

- ☐ **Yes: Included in headache group; proceed to screening for exclusion criteria for headache group**
- ☐ **No: Excluded**

2.3.2 Telephone screening for inclusion criteria for control group

Have you had a headache in the past 3 months?	☐	Yes	☐	No
If you experience headaches, are they regular? (N.B. "regular" ~ once in 3mos)	☐	Yes	☐	No
Did you have any recent head or neck surgery?	☐	Yes	☐	No
Do you experience significant neck pain?	☐	Yes	☐	No
Do you have other conditions requiring medical attention or that affect performance of daily activities (e.g. diabetes mellitus, malignant cancers, demyelinating, inflammatory and degenerative neurological conditions, class3 obesity (BMI >40), severe cardiac or pulmonary disease, infectious or inflammatory arthropathies)	☐	Yes	☐	No
Do you have severe mobility impairment necessitating dependence on mobility aids for ambulation?	☐	Yes	☐	No

Responded "no" to screening questions 2.3.2?

- ☐ **Yes: Included as control; proceed to screening for exclusion criteria for control group**
- ☐ **No: Excluded**

2.4 Telephone screening for exclusion criteria

I need to ask a few more questions to make sure that you are eligible to participate in this research project.

2.4.1 Telephone screening for exclusion criteria for headache groups

Do you have a known reason for your headache such as dehydration or a substance or its withdrawal?	☐	Yes	☐	No
Have you not had a craniotomy?	☐	Yes	☐	No
Do you have no access to internet using a computer or a mobile phone?	☐	Yes	☐	No
Do you have a pacemaker or fibrillator?	☐	Yes	☐	No
Will you not be willing to fill out an online headache diary for 6 months?	☐	Yes	☐	No
Do you think you do not have reasonable command of English to understand instructions?	☐	Yes	☐	No

Responded "yes" to any of the screening questions 2.4.1?

- ☐ **Yes: Excluded**
- ☐ **No: Included in headache group**

2.4.2 Telephone screening for exclusion criteria for control group

I need to ask a few more questions to make sure that you are eligible to participate in this research project.

Do you have a pacemaker or fibrillator?	☐	Yes	☐	No
Do you think you do not have reasonable command of English to understand instructions?	☐	Yes	☐	No

Responded "yes" to any of the screening questions 2.4.2?

- ☐ **Yes: Excluded**
- ☐ **No: Included in control group**

If the volunteer meets the inclusion and exclusion criteria, proceed to explain that they are eligible for study. Explain briefly the following:

- Will you be interested to participate in our project? This is a study about differentiating migraine from other types of headaches. If you experience recurrent headaches, we will monitor changes in your headaches, and determine what affects your headaches.
  We are doing this study to better understand the similarities and differences between headache types and maybe eventually to better decide on diagnosis and treatment for headaches.
- You might be interested in the findings.
- You will be required to undertake a series of clinical tests, including real-time ultrasound imaging at the Arthritis and Musculoskeletal Research Group Laboratory at The University of Sydney Cumberland Campus in Lidcombe. If more convenient, they may also do the assessment at a city clinic(Sydney Specialist Physiotherapy Centre, Level 1, 50 York St. Sydney).

If the individual has more questions or if he/she is interested to participate in the study, say that you will send further information and some questionnaires that need to be filled out before the clinical assessment. These may be sent by email or post, according to their preference.

- participant information statement (PIS)
- consent form
- baseline questionnaire on demographic (and headache information for headache groups)
- baseline questionnaires
  - McGill Pain Questionnaire
  - Central Sensitization Inventory
  - Headache Impact Test-6
  - The Henry Ford Headache Disability Index
  - Headache Disability Questionnaire
  - WHO Disability Assessment Schedule 2.0
  - Self-Administered Comorbidity Questionnaire
  - Depression Anxiety Stress Scales-21
  - Pittsburgh Sleep Quality Index
  - Long Form International Physical Activity Questionnaire
- information about how to get to The University of Sydney Cumberland Campus or to alternative assessment site (where to parkand meet etc)

Once participant has had time to read the PIS, explain that we will do the assessment, preferably done within 3 days of the last headache episode of participants with headaches. Inform the participant that you need the neck and shoulders exposed. Suggest for the participant to come in singlet. Remind that he/she should come to the appointment with the questionnaires completed.

3.0 Participant questionnaires

3.1 Participant information statement and consent form

PARTICIPANT INFORMATION STATEMENT

Distinguishing Migraine from Other Headache Types

(1) What is the study about?

You are invited to participate in a study which will investigate if migraine is different from other headaches. We will monitor changes in your headaches, and determine whether physical activity, movement or neck muscle function affects your headache. This study will also investigate the usefulness of clinical tests to distinguish different types of headaches.
You are eligible to participate in this study if you experience recurring headaches.

You are not eligible to participate if you have recurring headaches due to dehydration, a substance or substance withdrawal, if you have had craniotomy, or if you have no access to internet using a computer or a mobile phone.

If you are not certain whether you are eligible, please ask the researchers.

(2) Who is carrying out the study?

The study is being conducted by Dr Trudy Rebbeck, Dr Andrew Leaver, Mrs Maria Eliza Aguila, Prof Patrick Brennan, Prof Jim Lagopoulos, and Prof Kathryn Refshaugeat The University of Sydney.

(3) What does the study involve?

You will be required to attend an assessment session. We will first ask you to answer some questions about your headache, its effects on your life and general health. We will then perform a series of clinical tests to analyse your neck muscles and movements. These tests are part of standard clinical assessment for neck pain. We will also measure the size of your neck muscles using ultrasound imaging. Images and videos will be obtained during some of these tests to aid in analysing movements. You will also be asked to record details of each of your headache episodes such as headache intensity, duration, triggers, and associated symptoms, over 6 months since your first assessment using an electronic web-based diary. You will also answer headache and disability questionnaires at 1 month, 3 months and 6 months after the assessment.

(4) How much time will the study take?

Your involvement in the study will take a maximum of 1.5 hours for the assessment in the laboratory or clinic. You will then record features of your headache episodes on an electronic web-based headache diary on days when you have headache for 6 months after the assessment session. Filling out this diary will take about 10 minutes each

time. The headache and disability questionnaires on follow up will take about 20 minutes to answer.

(5) Can I withdraw from the study?

Being in this study is completely voluntary. You are not under any obligation to consent and, if you do consent, you can withdraw at any time without affecting your relationship with the investigators or The University of Sydney.

(6) Will anyone else know the results?

All aspects of the study, including results, will be strictly confidential and only the researchers will have access to information on participants. Images and videos obtained in this study will be used for purposes of analysis of neck muscles and movements only.

A report of the study may be submitted for publication, but individual participants will not be identifiable in such a report.

(7) Will the study benefit me?

We cannot and do not guarantee or promise that you will receive any benefits from the study.

(8) Can I tell other people about the study?

You can tell other people about the study. If they are interested in participating, they would be welcome to ring one of the researchers named on this Participant Information Sheet.

(9) What if I require further information about the study or my involvement in it?

When you have read this information, one of the chief investigators will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact:

Ms Maria Eliza Aguila
9351 9010
maria.aguila@sydney.edu.au

Dr Trudy Rebbeck
9351 9534
trudy.rebbeck@sydney.edu.au

Dr Andrew Leaver
9351 9545
andrew.leaver@sydney.edu.au

(10) What if I have a complaint or any concerns?

Any person with concerns or complaints about the conduct of a research study can contact The Manager, Human Ethics Administration, University of Sydney on +61 2 8627 8176 (Telephone); +61 2 8627 8177 (Facsimile) or ro.humanethics@sydney.edu.au (Email).

This information sheet is for you to keep

PARTICIPANT CONSENT FORM

I, ...[PRINT NAME], give consent to my participation in the research project

TITLE: **Distinguishing Migraine from Other Headache Types**

In giving my consent, I acknowledge that:

1. The procedures required for the project and the time involved have been explained to me and any questions I have about the project have been answill bed to my satisfaction.

2. I have read the Participant Information Statement and have been given the opportunity to discuss the information and my involvement in the project with the researcher/s.

3. I understand that being in this study is completely voluntary – I am not under any obligation to consent.

4. I understand that my involvement is strictly confidential. I understand that any research data gathered from the results of the study may be published however no information about me will be used in any way that is identifiable.

5. I understand that I can withdraw from the study at any time, without affecting my relationship with the researcher(s) or the University of Sydney now or in the future.

6. I consent to:

    - Receiving Feedback YES ☐ NO ☐

    If you answill bed YES to the "Receiving Feedback" question, please provide your details i.e. mailing address, email address.

    Feedback Option

    Address: _____

    _____

    Email: _____

.....
Signature

....
Please PRINT name

.....
Date

3.2 Baseline Questions

3.2.1 Demographic details

PERSONAL DETAILS

1. Name _____
2. Sex ☐ Male ☐ Female
3. Height (cm) _____
4. Weight (kg) _____
5. Marital status ☐ Single ☐ Married / Defacto
   ☐ Divorced / Widowed / Separated
6. Country of birth _____
7. Highest education level ☐ Primary ☐ Secondary
   ☐ Certificate
   ☐ Diploma or advanced diploma
   ☐ Bachelor degree
   ☐ Graduate
   ☐ Bachelor degree
   ☐ Graduate diploma or graduate certificate
   ☐ Postgraduate degree
8. Occupation _____
9. Medications:

Drug name	Dose	Frequency	Length of time taken	Time/ date last taken

3.2.2 Headache duration, location, intensity and frequency

QUESTIONS ON HEADACHE

10. How long have you been experiencing headaches? _____ months/ years

11. Have you been seen by a health professional for your headaches?

☐ Yes ☐ No

12. Have you been given a headache diagnosis?

☐ Yes ☐ No

If yes,

a. What is your headache diagnosis?

☐ Tension-type headache

☐ Migraine, please specify _____

☐ Cervicogenic headache

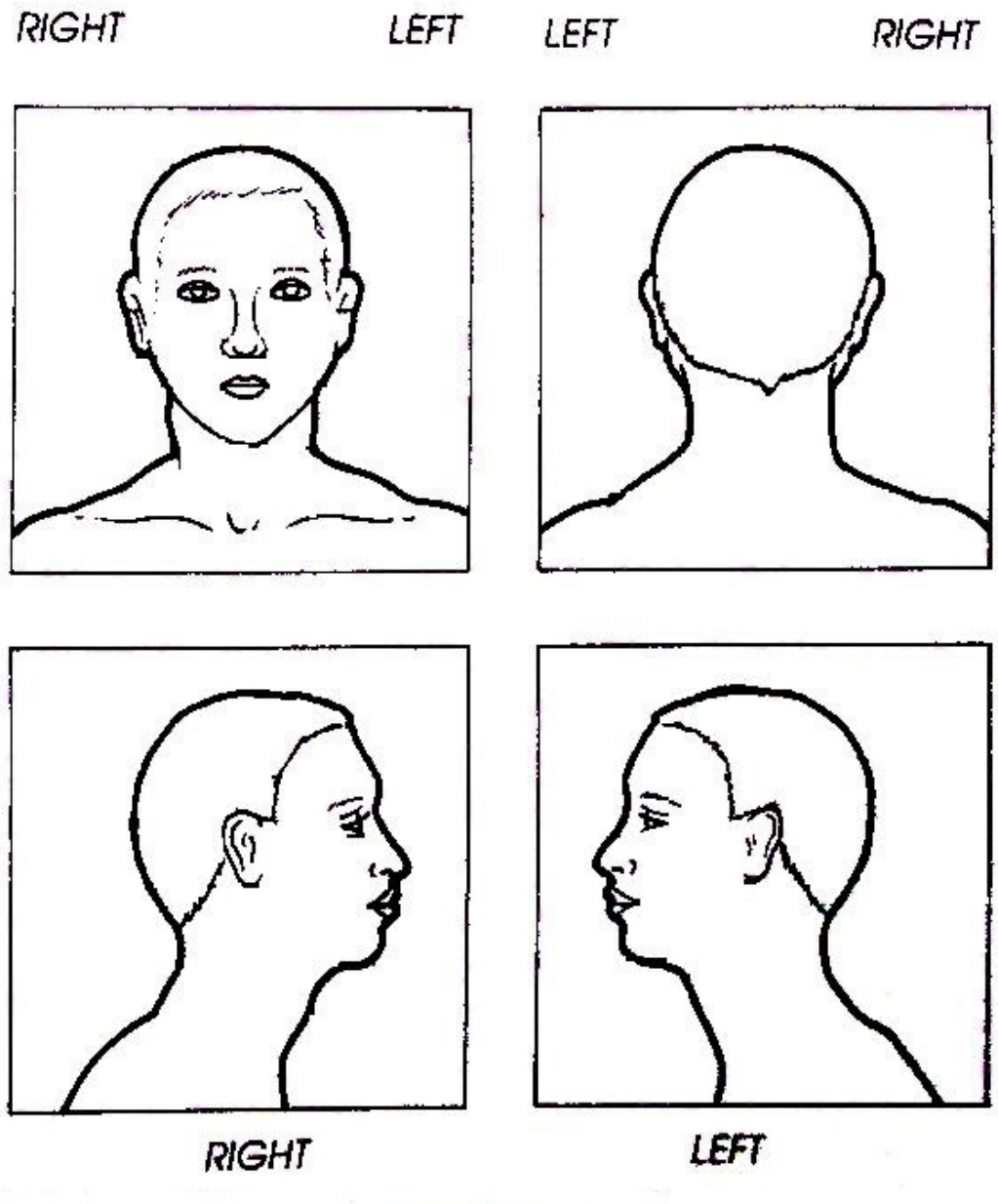
☐ Post-traumatic headache, please specify _____

☐ Other, please specify _____

b. Who diagnosed your headache type?

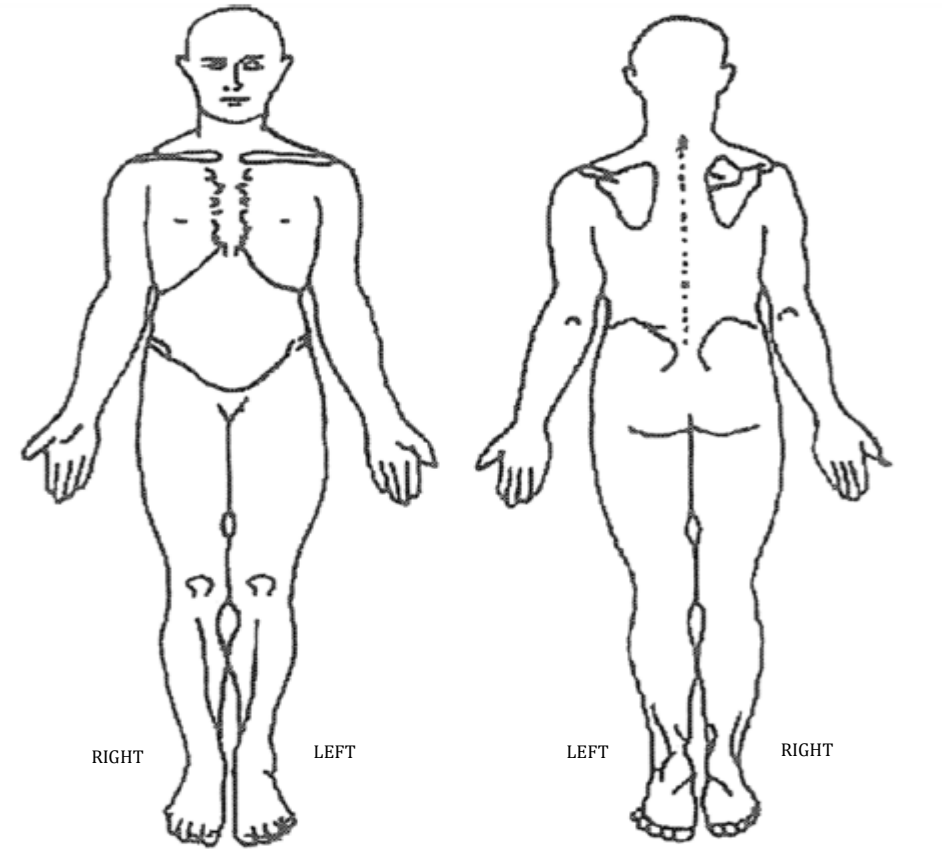
☐ GP ☐ Neurologist ☐ Other, please specify _____

13. Please shade areas on the head and body charts below to indicate where you are currently experiencing pain including headaches. If you have pain in more than one location, indicate additional locations also.



Please proceed to question 14, next page.

RESEARCH TEAM USE ONLY:
Frequency:
Duration:
Intensity:
Associated symptoms:
Triggers:
History:
Previous treatment:



You should then rate the **headache intensity** using the following two 0 – 10 scales:

14. Average headache pain intensity over the last month (Circle the most appropriate)

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

15. Average headache intensity over the last 24 hours (Circle the most appropriate)

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

16. How many times in a <u>day</u> do you experience headaches? _____times per day

17. How many times in a <u>month</u> do you experience headaches? _____ times per month

3.3 Pain questionnaires

3.3.1 Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2)

This questionnaire provides you with a list of words that describe some of the different qualities of pain and related symptoms. Please put an **X** through the numbers that best describe the intensity of each of the pain and related symptoms you felt during a typical headache episode. Use 0 if the word does not describe your pain or related symptoms.

1.	**Throbbing pain**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
2.	**Shooting pain**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
3.	**Stabbing pain**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
4.	**Sharp pain**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
5.	**Cramping pain**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
6.	**Gnawing pain**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
7.	**Hot-burning pain**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
8.	**Aching pain**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
9.	**Heavy pain**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
10.	**Tender**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
11.	**Splitting pain**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
12.	**Tiring-exhausting**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
13.	**Sickening**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
14.	**Fearful**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
15.	**Punishing-cruel**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
16.	**Electric-shock pain**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
17.	**Cold-freezing pain**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
18.	**Piercing**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
19.	**Pain caused by light touch**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
20.	**Itching**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
21.	**Tingling or 'pins and needles'**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
22.	**Numbness**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*

22.	**Pulsating**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
22.	**Band-like**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
22.	**Tightness**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*
22.	**Excruciating**	*none*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	*worst possible*

3.3.2 Central Sensitization Inventory[1]: Part A

Please circle the best response to the right of each statement

1	I feel unrefreshed when I wake up in the morning	Never	Rarely	Sometimes	Often	Always
2	My muscles feel stiff and achy	Never	Rarely	Sometimes	Often	Always
3	I have anxiety attacks	Never	Rarely	Sometimes	Often	Always
4	I grind or clench my teeth	Never	Rarely	Sometimes	Often	Always
5	I have problems with diarrhea and/or constipation	Never	Rarely	Sometimes	Often	Always
6	I need help in performing my daily activities	Never	Rarely	Sometimes	Often	Always
7	I am sensitive to bright lights	Never	Rarely	Sometimes	Often	Always
8	I get tired very easily when I am physically active	Never	Rarely	Sometimes	Often	Always
9	I feel pain all over my body	Never	Rarely	Sometimes	Often	Always
10	I have headaches	Never	Rarely	Sometimes	Often	Always
11	I feel discomfort in my bladder and/or burning when I urinate	Never	Rarely	Sometimes	Often	Always
12	I do not sleep well	Never	Rarely	Sometimes	Often	Always
13	I have difficulty concentrating	Never	Rarely	Sometimes	Often	Always
14	I have skin problems such as dryness, itchiness, or rashes	Never	Rarely	Sometimes	Often	Always
15	Stress makes my physical symptoms get worse	Never	Rarely	Sometimes	Often	Always
16	I feel sad or depressed	Never	Rarely	Sometimes	Often	Always
17	I have low energy	Never	Rarely	Sometimes	Often	Always
18	I have muscle tension in my neck and shoulders	Never	Rarely	Sometimes	Often	Always
19	I have pain in my jaw	Never	Rarely	Sometimes	Often	Always
20	Certain smells, such as perfumes, make me feel dizzy and nauseated	Never	Rarely	Sometimes	Often	Always
21	I have to urinate frequently	Never	Rarely	Sometimes	Often	Always
22	My legs feel uncomfortable and restless when I am trying to go to sleep at night	Never	Rarely	Sometimes	Often	Always
23	I have difficulty remembering things	Never	Rarely	Sometimes	Often	Always
24	I suffered trauma as a child	Never	Rarely	Sometimes	Often	Always
25	I have pain in my pelvic area	Never	Rarely	Sometimes	Often	Always
					Total =	

CENTRAL SENSITIZATION INVENTORY: PART B

Have you been diagnosed by a doctor with any of the following disorders?
Please check the box to the right for each diagnosis and write the year of the diagnosis

		No	Yes	Year Diagnosed
1	Restless leg syndrome			
2	Chronic fatigue syndrome			
3	Fibromyalgia			
4	Temporomandibular joint disorder (TMJ)			
5	Migraine or tension headaches			
6	Irritable bowel syndrome			
7	Multiple chemical sensitivities			
8	Neck injury (including whiplash)			
9	Anxiety or panic attacks			
10	Depression			

[1]With permission.From Mayer, T.G., Neblett, R., Cohen, H., Howard, K.J., Choi, Y.H., Williams, M.J., Perez, Y., &Gatchel, R.J. (2012).The development and psychometric validation of the Central Sensitization Inventory.*Pain Practice,* **12**(4), 276-285.

3.4 Disability questionnaires

3.4.1 HIT-6™ Headache Impact Test

This questionnaire will be designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please check one box for each question.

1. When you have headaches, how often is the pain severe?

☐ **Never** ☐ **Rarely** ☐ **Sometimes** ☐ **Very Often** ☐ **Always**

2. How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

☐ **Never** ☐ **Rarely** ☐ **Sometimes** ☐ **Very Often** ☐ **Always**

3. When you have a headache, how often do you wish you could lie down?

☐ **Never** ☐ **Rarely** ☐ **Sometimes** ☐ **Very Often** ☐ **Always**

4. In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

☐ **Never** ☐ **Rarely** ☐ **Sometimes** ☐ **Very Often** ☐ **Always**

5. In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

☐ **Never** ☐ **Rarely** ☐ **Sometimes** ☐ **Very Often** ☐ **Always**

6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

☐ **Never** ☐ **Rarely** ☐ **Sometimes** ☐ **Very Often** ☐ **Always**

COLUMN 1	*COLUMN 2*	*COLUMN 3*	*COLUMN 4*	*COLUMN 5*
(6 points each)	*(8 points each)*	*(10 points each)*	*(11 points each)*	*(13 points each)*

To score, add points for answers in each column
Please share your HIT-6 results with your doctor.

Total Score: _____

Higher scores indicate
greater impact on your life.
Score range is 36-78.

HIT-6™ US Original (English) Version 1.0

3.4.2 The Henry Ford Headache Disability Index[2]

Please read carefully: The purpose of the scale is to identify difficulties that you may be experiencing because of your headache. Please check off "YES", "SOMETIMES", or "NO" to each item. Answer each question as it pertains to your headache only.

	YES	SOMETIMES	NO
E1. Because of my headaches I feel handicapped.	□	□	□
F2. Because of my headaches I feel restricted in performing my routine daily activities.	□	□	□
E3. No one understands the effect that my headaches have on my life.	□	□	□
F4. I restrict my recreational activities (eg, sports, hobbies) because of my headaches.	□	□	□
E5. My headaches make me angry.	□	□	□
E6. Sometimes I feel that I am going to lose control because of my headaches.	□	□	□
F7. Because of my headaches I am less likely to socialize.	□	□	□
E8. My spouse (significant other), or family and friends, have no idea what I am going through because of my headaches.	□	□	□
E9. My headaches are so bad that I feel that I am going to go insane.	□	□	□
E10. My outlook on the world is affected by my headaches.	□	□	□
E11. I am afraid to go outside when I feel that a headache is starting.	□	□	□
E12. I feel desperate because of my headaches.	□	□	□
F13. I am concerned that I am paying penalties at work or at home because of my headaches.	□	□	□
E14. My headaches place stress on my relationships with family or friends.	□	□	□
F15. I avoid being around people when I have a headache.	□	□	□
F16. I believe my headaches are making it difficult for me to achieve my goals in life.	□	□	□
F17. I am unable to think clearly because of my headaches.	□	□	□
F18. I get tense (eg, muscle tension) because of my headaches.	□	□	□
F19. I do not enjoy social gatherings because of my headaches.	□	□	□
E20. I feel irritable because of my headaches.	□	□	□
F21. I avoid traveling because of my headaches.	□	□	□
E22. My headaches make me feel confused.	□	□	□
E23. My headaches make me feel frustrated.	□	□	□
F24. I find it difficult to read because of my headaches.	□	□	□
F25. I find it difficult to focus my attention away from my headaches and on other things.	□	□	□

[2]With permission.From Jacobson, G.P., Ramadan, N.M., Aggarwal, S.K., & Newman, C.W. (1994). The Henry Ford Hospital Headache Disability Inventory (HDI). *Neurology,* **44:** 837-842.

3.4.3 Headache Disability Questionnaire

Name:…… Date:……/……./……. Score / 90

Please read each question and circle the response that best applies to you

1. How would you rate the usual pain of your headache on a scale from 0 to 10?

0 NO PAIN	1	2	3	4	5	6	7	8	9	10	WORST PAIN

2. When you have headaches, how often is the pain severe?

NEVER	1-9%	10-19%	20-29%	30-39%	40-49%	50-59%	60-69%	70-79%	80-89%	90-100%	ALWAYS
0	1	2	3	4	5	6	7	8	9	10	

3. On how many days in the last month did you actually lie down for an hour or more because of your headaches?

NONE	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-31	EVERY DAY
0	1	2	3	4	5	6	7	8	9	10	

4. When you have a headache, how often do you miss work or school for all or part of the day?

NEVER	1-9%	10-19%	20-29%	30-39%	40-49%	50-59%	60-69%	70-79%	80-89%	90-100%	ALWAYS
0	1	2	3	4	5	6	7	8	9	10	

5. When you have a headache whilst you work (or school), how much is your ability to work reduced?

NOT	1-9%	10-19%	20-29%	30-39%	40-49%	50-59%	60-69%	70-79%	80-89%	90-100%	UNABLE TO
0 REDUCED	1	2	3	4	5	6	7	8	9	10	WORK

6. How many days in the last month have you been kept from performing housework or chores for at least half of the day because of your headaches?

NONE	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-31	EVERY DAY
0	1	2	3	4	5	6	7	8	9	10	

7. When you have a headache, how much is your ability to perform housework or chores reduced?

NOT	1-9%	10-19%	20-29%	30-39%	40-49%	50-59%	60-69%	70-79%	80-89%	90-100%	UNABLE
0 REDUCED	1	2	3	4	5	6	7	8	9	10	TO PERFORM

8. How many days in the last month have you been kept from non-work activities (family, social or recreational) because of your headaches?

NONE	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-31	EVERY DAY
0	1	2	3	4	5	6	7	8	9	10	

9. When you have a headache, how much is your ability to engage in non-work activities (family, social or recreational) reduced?

NOT	1-9%	10-19%	20-29%	30-39%	40-49%	50-59%	60-69%	70-79%	80-89%	90-100%	UNABLE
0 REDUCED	1	2	3	4	5	6	7	8	9	10	TO PERFORM

3.4.4 Disability Assessment Schedule 2.0

12-item version, self-administered

This questionnaire asks about difficulties due to health conditions. Health conditions include diseases or illnesses, other health problems that may be short or long lasting, injuries, mental or emotional problems, and problems with alcohol or drugs.

Think back over the past 30 days and answer these questions, thinking about how much difficulty you had doing the following activities. For each question, please circle only one response.

.

In the past 30 days, how much difficulty did you have in:						
S1	Standing for long periods such as 30 minutes?	None	Mild	Moderate	Severe	Extreme or cannot do
S2	Taking care of your householdresponsibilities?	None	Mild	Moderate	Severe	Extreme or cannot do
S3	Learning a new task, for example, learning how to get to a new place?	None	Mild	Moderate	Severe	Extreme or cannot do
S4	How much of a problem did you have joining in community activities (for example, festivities, religious or other activities) in the same way as anyoneelse can?	None	Mild	Moderate	Severe	Extreme or cannot do
S5	How much have you been emotionallyaffected by your health problems?	None	Mild	Moderate	Severe	Extreme or cannot do

Please continue to next page...

In the past 30 days, how much difficulty did you have in:						
S6	Concentrating on doing something forten minutes?	None	Mild	Moderate	Severe	Extreme or cannot do\
S7	Walking a long distance such as akilometre [or equivalent]?	None	Mild	Moderate	Severe	Extreme or cannot do
S8	Will behing your whole body?	None	Mild	Moderate	Severe	Extreme or cannot do
S9	Getting dressed?	None	Mild	Moderate	Severe	Extreme or cannot do
S10	Dealing with people you do not know?	None	Mild	Moderate	Severe	Extreme or cannot do
S11	Maintaining a friendship?	None	Mild	Moderate	Severe	Extreme or cannot do
S12	Your day-to-day work?	None	Mild	Moderate	Severe	Extreme or cannot do

H1	Overall, in the past 30 days, how many dayswill be these difficulties present?	***Record number of days*** _____
H2	In the past 30 days, for how many days will be you totally unableto carry out your usual activities or work because of any health condition?	***Record number of days*** _____
H3	In the past 30 days, not counting the days that you will be totally unable, for how many days did you cut back or reduce your usual activities or work because of any health condition?	***Record number of days*** _____

This completes the questionnaire. Thank you.

3.5 Health Questionnaires

3.5.1 The Self-Administered Comorbidity Questionnaire[3]

Instructions:

The following is a list of common problems. Please indicate if you currently have the problem in the first column. If you do not have the problem, skip to the next problem.

If you do have the problem, please indicate in the second column if you receive medications or some other type of treatment for the problem.

In the third column indicate if the problem limits any of your activities.

Finally, indicate all medical conditions that are not listed under "other medical problems" at the end of the page.

	Do you have the problem?		**Do you receive treatment for it?**		**Does it limit your activities?**	
PROBLEM	**No (0)**	**Yes → (1)**	**No (0)**	**Yes (1)**	**No (0)**	**Yes (1)**
Heart disease	N	Y	N	Y	N	Y
High blood pressure	N	Y	N	Y	N	Y
Lung disease	N	Y	N	Y	N	Y
Diabetes	N	Y	N	Y	N	Y
Ulcer or stomach disease	N	Y	N	Y	N	Y
Kidney disease	N	Y	N	Y	N	Y
Liver disease	N	Y	N	Y	N	Y
Anemia or other blood disease	N	Y	N	Y	N	Y
Cancer	N	Y	N	Y	N	Y
Depression	N	Y	N	Y	N	Y
Osteoarthritis, degenerative arthritis	N	Y	N	Y	N	Y
Back pain	N	Y	N	Y	N	Y
Rheumatoid arthritis	N	Y	N	Y	N	Y
Other medical problems (please write in)						
	N	Y	N	Y	N	Y
	N	Y	N	Y	N	Y

[3]With permission.From Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: A new method to assess comorbidity for clinical and health services research. *Arthritis Rheum.* 2003 Apr 15;**49**(2):156-63. PubMed PMID:12687505 .

3.5.2 Depression Anxiety Stress Scales – 21 items

DASS21 *Name:* *Date:*

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

1	I found it hard to wind down	0	1	2	3
2	I will be aware of dryness of my mouth	0	1	2	3
3	I couldn't seem to experience any positive feeling at all	0	1	2	3
4	I experienced breathing difficulty (eg, excessively rapid breathing,breathlessness in the absence of physical exertion)	0	1	2	3
5	I found it difficult to work up the initiative to do things	0	1	2	3
6	I tended to over-react to situations	0	1	2	3
7	I experienced trembling (eg, in the hands)	0	1	2	3
8	I felt that I will be using a lot of nervous energy	0	1	2	3
9	I will be worried about situations in which I might panic and makea fool of myself	0	1	2	3
10	I felt that I had nothing to look forward to	0	1	2	3
11	I found myself getting agitated	0	1	2	3
12	I found it difficult to relax	0	1	2	3
13	I felt down-hearted and blue	0	1	2	3
14	I will be intolerant of anything that kept me from getting on withwhat I will be doing	0	1	2	3
15	I felt I will be close to panic	0	1	2	3
16	I will be unable to become enthusiastic about anything	0	1	2	3
17	I felt I will ben't worth much as a person	0	1	2	3
18	I felt that I will be rather touchy	0	1	2	3
19	I will be aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	0	1	2	3
20	I felt scared without any good reason	0	1	2	3
21	I felt that life will be meaningless	0	1	2	3

Participant's Initials ____ Participant ID _____ Date _____ Time _____ AM PM

3.5.3 Pittsburgh Sleep Quality Index

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1 During the past month, what time have you usually gone to bed at night?

BED TIME _____

2 During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

NUMBER OF MINUTES _____

3 During the past month, what time have you usually gotten up in the morning?

GETTING UP TIME _____

4 During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5 During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the past month____ Less than once a week ____ Once or twice a week ____ Three or more times a week ____

b) Wake up in the middle of the night or early morning

Not during the past month____ Less than once a week ____ Once or twice a week ____ Three or more times a week ____

c) Have to get up to use the bathroom

Not during the past month____ Less than once a week ____ Once or twice a week ____ Three or more times a week ____

d) Cannot breathe comfortably

Not during the past month____ Less than once a week ____ Once or twice a week ____ Three or more times a week ____

e) Cough or snore loudly

Not during the past month____ Less than once a week ____ Once or twice a week ____ Three or more times a week ____

f) Feel too cold

Not during the past month____ Less than once a week ____ Once or twice a week ____ Three or more times a week ____

g) Feel too hot

Not during the past month____ Less than once a week ____ Once or twice a week ____ Three or more times a week ____

h) Had bad dreams

Not during the past month____ Less than once a week ____ Once or twice a week ____ Three or more times a week ____

i) Have pain

Not during the past month____ Less than once a week ____ Once or twice a week ____ Three or more times a week ____

j) Other reason(s), please describe _____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month____ Less than once a week ____ Once or twice a week ____ Three or more times a week ____

6 During the past month, how would you rate your sleep quality overall?

Very good _____

Fairly good _____

Fairly bad _____

Very bad _____

7 During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month____ Less than once a week ____ Once or twice a week ____ Three or more times a week ____

8 During the past month, how often have you had trouble staying awake whilst driving, eating meals, or engaging in social activity?

Not during the past month____ Less than once a week ____ Once or twice a week ____ Three or more times a week ____

9 During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problem _____

A very big problem _____

10 Do you have a bed partner or room mate?

No bed partner or room mate _____

Partner/room mate in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a room mate or bed partner, ask him/her how often in the past month you have had...

a) Loud snoring

Not during the past month____ Less than once a week ____ Once or twice a week ____ Three or more times a week ____

b) Long pauses between breaths whilst asleep

Not during the past month____ Less than once a week ____ Once or twice a week ____ Three or more times a week ____

c) Legs twitching or jerking whilst you sleep

Not during the past month____ Less than once a week ____ Once or twice a week ____ Three or more times a week ____

d) Episodes of disorientation or confusion during sleep

Not during the past month____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

e) Other restlessness whilst you sleep; please describe

_____

_____

Not during the past month____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: Psychiatry Research, 28:193-213, 1989.

3.5.4 International Physical Activity Questionnaire

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spend being physically active in a **usual week**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you do in a **usual week**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you do outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

   ☐ Yes

   ☐ No → ***Skip to PART 2: TRANSPORTATION***

The next questions are about all the physical activity you do on a **usual week**as part of your paid or unpaid work. This does not include traveling to and from work.

2. On a **usual week**, on how many days do you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs**as part of your work**? Think about only those physical activities that you do for at least 10 minutes at a time.

   _____ **days per week**

   ☐ No vigorous job-related physical activity → ***Skip to question 4***

3. How much time do you usually spend on one of those days doing **vigorous** physical activities as part of your work?

   _____ **hours per day**

   _____ **minutes per day**

4. Again, think about only those physical activities that you do for at least 10 minutes at a time. During a**usual week**, on how many days do you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

_____ **days per week**

☐ No moderate job-related physical activity → ***Skip to question 6***

5. How much time do you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ **hours per day**

_____ **minutes per day**

6. On a **usual week**, on how many days do you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you do to travel to or from work.

_____ **days per week**

☐ No job-related walking → ***Skip to PART 2: TRANSPORTATION***

7. How much time do you usually spend on one of those days **walking** as part of your work?

_____ **hours per day**

_____ **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. On a **usual week**, on how many days do you **travel in a motor vehicle** like a train, bus, car, or tram?

_____ **days per week**

☐ No traveling in a motor vehicle → ***Skip to question 10***

9. How much time do you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ **hours per day**

_____ **minutes per day**

Now think only about the **bicycling** and **walking** you might do to travel to and from work, to do errands, or to go from place to place.

10. On a **usual week**, on how many days do you **bicycle** for at least 10 minutes at a time to go **fromplace to place**?

    _____ **days per week**

    ☐ No bicycling from place to place → ***Skip to question 12***

11. How much time do you usually spend on one of those days to **bicycle** from place to place?

    _____ **hours per day**

    _____ **minutes per day**

12. During a **usual week**, on how many days do you **walk** for at least 10 minutes at a time to go **from place to place**?

    _____ **days per week**

    ☐ No walking from place to place → ***Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY***

13. How much time do you usually spend on one of those days **walking** from place to place?

    _____ **hours per day**

    _____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might do in a **usual week** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you do for at least 10 minutes at a time. On a **usual week**, on how many days do you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

    _____ **days per week**

    ☐ No vigorous activity in garden or yard → ***Skip to question 16***

15. How much time do you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ **hours per day**

_____ **minutes per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. On a **usual week**, on how many days do you do **moderate** activities like carrying light loads, sweeping, will behing windows, and raking **in the garden or yard**?

_____ **days per week**

☐ No moderate activity in garden or yard → ***Skip to question 18***

17. How much time do you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ **hours per day**

_____ **minutes per day**

18. Once again, think about only those physical activities that you do for at least 10 minutes at a time. On a **usual week**, on how many days do you do **moderate** activities like carrying light loads, will behing windows, scrubbing floors and sweeping **inside your home**?

_____ **days per week**

☐ No moderate activity inside home → ***Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY***

19. How much time do you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ **hours per day**

_____ **minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you do in a **usual week** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, on a **usual week**, on how many days do you **walk** for at least 10 minutes at a time in your **leisure time**?

_____ **days per week**

☐ No walking in leisure time → ***Skip to question 22***

21. How much time do you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day**

_____ **minutes per day**

22. Think about only those physical activities that you do for at least 10 minutes at a time. On a **usual week**, on how many days do you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ **days per week**

☐ No vigorous activity in leisure time → ***Skip to question 24***

23. How much time do you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day**

_____ **minutes per day**

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. On a **usual week**, on how many days do you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ **days per week**

☐ No moderate activity in leisure time → ***Skip to PART 5: TIME SPENT SITTING***

25. How much time do you usually spend on one of those days doing **moderate** physical activities in your leisure time?

_____ **hours per day**

_____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting whilst at work, at home, whilst doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. On a **usual week**, how much time do you usually spend **sitting** on a **weekday**?

_____ **hours per day**

_____ **minutes per day**

27. On a **usual week**, how much time do you usually spend **sitting** on a **weekend day**?

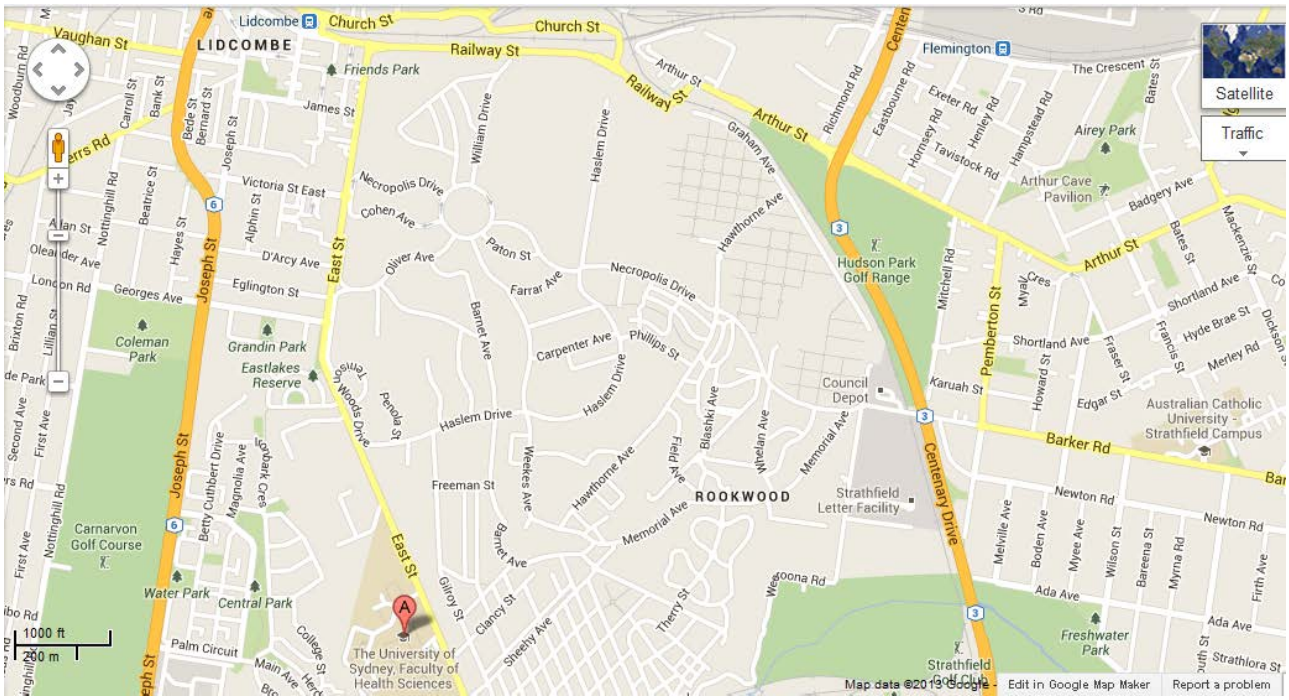
_____ **hours per day**

_____ **minutes per day**

This is the end of the questionnaire, thank you for participating.

4.0 Where do I go for clinical assessment?

Please come to the Arthritis and Musculoskeletal Research Group Laboratory (AMRG Lab) on the second floor of S Block, Room 218 of the University of Sydney (Cumberland Campus) in Lidcombe. The address of University of Sydney (Cumberland Campus) is 75 East Street, Lidcombe NSW 2141.



A member of the research team (Ms. Marilie Aguila, Dr Andrew Leaver or Dr Trudy Rebbeck) will meet you at the receiving area of the AMRG Lab which you will find as soon as you enter S218.

Here are some suggestions to get to the Cumberland campus by public transport:

By train

The nearest railway station to the Cumberland campus is Lidcombe station. It takes approximately 20-30 minutes to walk to campus from the station. We recommend using the available bus services.

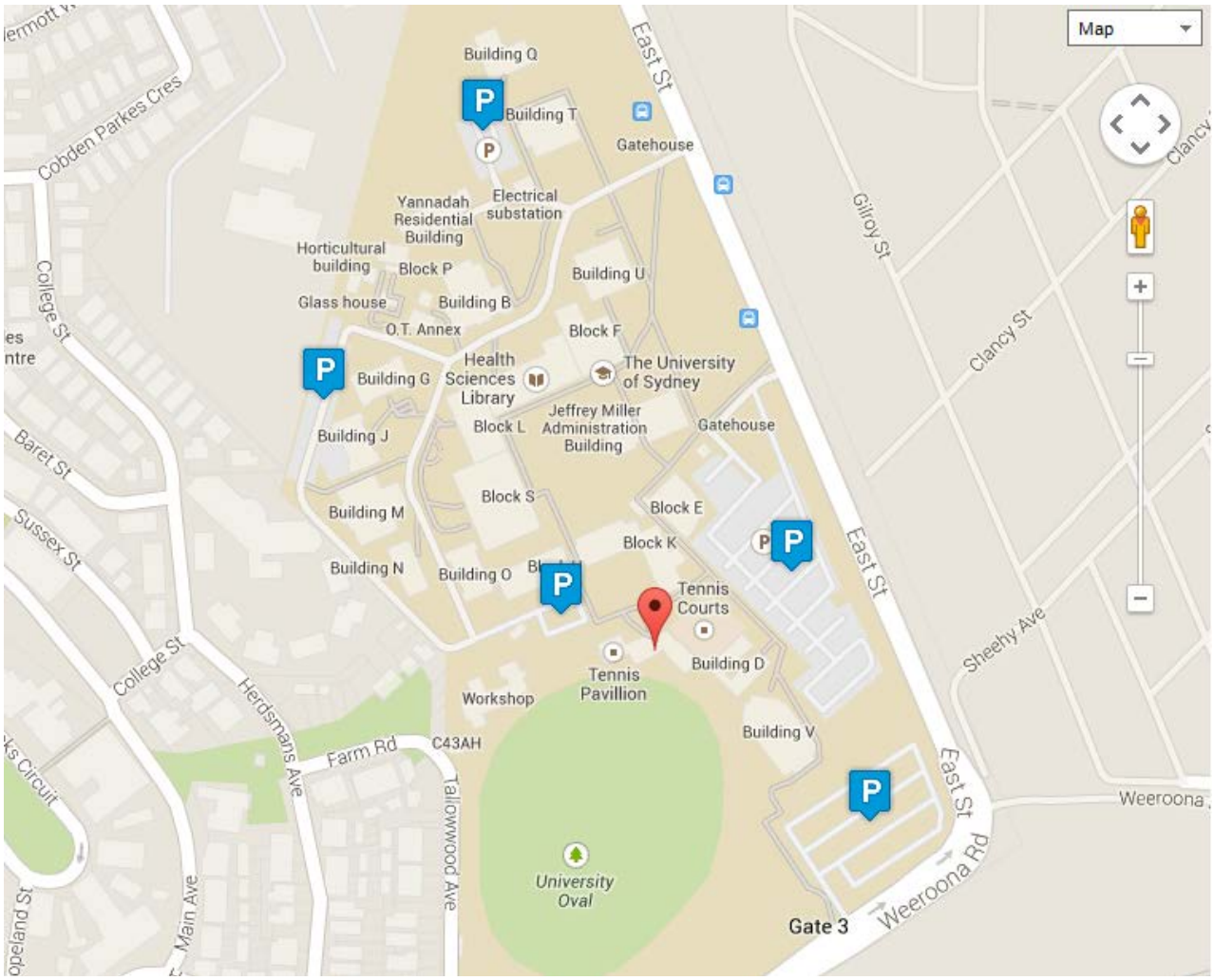
By bus

- The Metrobus M92 service (Parramatta to Sutherland via Cumberland Campus)
- The 915 bus (Lidcombe/TAFE/University) service.

Bus stop locations

- **From Lidcombe Station:** On the eastern Commonwealth Bank side
- **From Cumberland Campus:** Going to Lidcombe, the bus stop is located outside Gate 1. Travelling from Lidcombe station or towards Bankstown the bus stop is on East Street, located on the opposite side of road from the campus between Gates 1 & 2.

If you are driving, there are a number of parking spots inside the campus.



Current visitor parking fees are $5.00 per entry for Gate 2 & $4.00 per day for Gate 3.

Contact: Ms Marilie Aguila T 02 9351 9010 M 0405-756675

Alternative clinical assessment venue:

Sydney Specialist Physiotherapy Centre
Level 1, 50 York Street, Sydney 2000

Please refer to http://www.transportnsw.info/ for trip planning and public transportation timetables**.**

5.0 Clinical assessment

5.1 Subjective Examination

5.1.1 Check information on baseline questionnaire for completeness and confirm details for accuracy

5.1.2 Other questions: general health etc.:

1. Do you have headache today? ☐ Yes ☐ No

   If yes:

   When did it start? How long has this episode been going on? _____

   How would you describe the headache? _____

   How would you rate the intensity of the headache on a scale of 0 to 10, 0 being no pain and 10 being the worst possible pain? _____

2. When will be your last headache episode?
   _____

3. How long does a headache episode last if it is untreated or if it is not successfully treated?

   Minimum _____ hours _____ minutes

   Maximum _____ hours _____ minutes

4. Does your headache go away between episodes? ☐ Yes ☐ No

5. What symptoms accompany your headaches?

   Does it always come with your headache?

   How would you rate the intensity of that symptom?(Mild? Moderate? Severe?)

Accompanying symptoms	How often			Intensity		
	Never	Occasionally	Often	Mild	Moderate	Severe
Nausea						
Vomiting						
Light sensitivity						
Noise sensitivity						
Lightheaded/dizzy						
Unsteadiness						
Blurred vision						
Eye swelling						
Loss of appetite						
Yawning						
Fatigue						
Confused thinking						
Other._____						

6. Do you have neck pain or stiffness ☐ Yes ☐ No

with your headache

7. Do you feel any sensation for a period of minutes to an hour before the onset of your headache?

   a. visual aura (e.g. blind spots, flashing or zigzag lights) □ Yes□ No

   b. feeling of pins/needles or numbness □ Yes□ No

   c. feeling of weakness □ Yes□ No

   d. feeling of difficulty speaking □ Yes□ No

   If you have any of these aura symptoms, can you describe how long each symptom lasts? _____

8. What do you think causes your headache or makes it worse?

   a. Certain foods (e.g. chocolate, cheeses) ❒
   b. Alcohol (e.g. red wine, beer, spirits) ❒
   c. Awkward head or neck postures or neck movement ❒
   d. Sustained neck postures (e.g. reading) ❒
   e. Pressure over the neck or base of skull on the headache side ❒
   f. Medication ❒
   g. Routine physical activity or walking stairs ❒
   h. Lifestyle factors (e.g. excessive sleep, fasting or dieting) ❒
   i. Exercises/sports ❒
   j. Environmental factors (e.g. strong odours, smoke, weather changes) ❒
   k. Stress or anxiety ❒
   l. Fatigue ❒
   m. Hormonal changes ❒
   n. Other. Please describe_____ ❒
   o. Does not know what brings on headache / Does not see any pattern ❒

9. Do you know what started your headache?

   What do you think started your headache?

   Does not know ❒

   Knows what started headache (Please describe below) ❒

   _____

10. What relieves your headache?

a. Medication*(Are these the same ones you listed on the baseline questionnaire?)* ❒
b. Heat/ice applications ❒
c. Physical activity ❒
d. Neck exercise or change of position ❒
e. Alcohol ❒
f. Relaxation ❒
g. Massage ❒
h. Sleeping/rest ❒
i. Unknown ❒
j. Other. Please describe _____ ❒

11. Have you received physical treatment for your headache? ☐ Yes ☐ No

If yes, what are these? _____

12. Have you received alternative treatment for your headache? ☐ Yes ☐ No

If yes, what are these? _____

13. Have you been diagnosed with any other condition that may be related to your headache? ☐ Yes ☐ No

14. Have you had any imaging or laboratory test done on your neck? ☐ Yes ☐ No

If *yes,* what will be the test and what will be the result?

_____

15. Do other members of your family suffer from similar headaches?

☐ Yes (please specify relation) ☐ No ☐ Unsure

_____

16. Are you comfortable to go through clinical tests typically done forneck pain? ☐ Yes ☐ No

17. Are you comfortable to go through ultrasound imaging? ☐ Yes ☐ No

18. Are you willing to fill out an online headache diary for 6 months? ☐ Yes ☐ No

5.2 Clinical Examination

5.2.1 Cervical ROM

Procedure for Measuring Neck Motion with the CROM (Reproduced from CROM Procedure Manual)

"The CROM Instrument is aligned on the nose bridge and ears and is fastened to the head by a Velcro strap (see Figure 1).The **rotation meter** is magnetic and responds quickly to the shoulder-mounted **magnetic yoke**, accurately measuring cervical rotation. Because the rotation meter is controlled by the magnetic yoke, shoulder substitution is eliminated.

Figure 1. CROM with rotation arm and magnetic yoke

Three dial angle meters are used to take most of the measurements. The **sagittal plane meter** and the **lateral flexion meter** are gravity meters. The **rotation meter** is magnetic and responds quickly to the shoulder-mounted **magnetic yoke**, accurately measuring cervical rotation. Because the rotation meter is controlled by the magnetic yoke, shoulder substitution is eliminated.

Cervical Flexion and Extension

Instruct the participant to sit erect in astraight-back chair sitting upright with the sacrum against the back of the chair, the thoracic spine away from the back of the chair, arms hanging at sides and feet flat on the floor. Next, instruct the participant to position the CROM instrument as if putting on a pair of glasses. Ensure the CROM sitting on ears. Fasten the Velcro straps snuggly in line with the bows. You will not need the magnetic yoke, rotation armforward head arm or vertebra locator for these measurements.

To assure full flexion in this multi-joint area, the participant should start in neutral posture.First,instruct the participant to "bring your chin to your chest as far as you can comfortably go" (suboccipital flexion). Then ask "Can you go any further?" in order toobtain full cervical flexion(see Figure 2). To take the reading on the sagittal plane meter, read through the meter's beveled edge; from this angle the pointer will be magnified to the dial edge. Record this measurement in the appropriate space on the recording sheet.

Figure 2: Cervical flexion

To measure cervical extension, first instruct the participant to

“Look up to the ceiling as far as you comfortably can. Then have the participant extend further until full extension is achieved. “Can you go any further?” Record this measurement also.

Lateral Flexion

Instruct the participant to sit erect on a straight-back chairwith the sacrum against the back of the chair, thethoracic spine away from the back of the chair, arms hanging at sides and feet flat on the floor. To eliminate rotation during lateral flexion, the participant should focus on a point on a wall straight ahead. The sagittal plane meter will read zero if the participant is looking straight ahead. The lateral flexion meter will also read zero if the head is not laterally flexed. If the lateral flexion meter does not read zero, record the reading as lateral flexion at rest. You will not need the magnetic yoke, rotation arm, forward head arm nor vertebra locator for these measurements.

Instruct the participant to flex the head laterally to the left, keeping the shoulders level and without rotating the head (see Figure 3). Monitor for shoulder elevation by lightly placing your hand on the right shoulder, and correct manually any head motion outside the coronal plane. Note and record the measurement from the lateral flexion meter.

Now instruct the participant to flex the head laterally to the right, again keeping the shoulders level without rotating the head (see Figure 4). As before, monitor for left shoulder elevation and correct head motion. Note and record the measurement from the lateral flexion meter.

Figure 3: Left lateral flexion

Figure 4: Right lateral flexion

WARNING: The magnetic yoke should not be used if the participant has an implanted pacer or defibrillator.

Rotation

You will need to use the CROM instrument plus the magnetic yoke and rotation arm for these measurements. To obtain an accurate rotation measurement, first determine which direction is north. (You can find magnetic (map) north by noting the direction of the red needle on the rotation meter when it is at least four feet from the magnetic yoke.)

Next, place the magnetic yoke on the participant's shoulders with the arrow pointing north.(See Figure 5.)

Figure 5: Magnetic yoke pointing north

Instruct the participant to sit erect on a straight-back chair with the sacrum against the back of the chair, the thoracic spine away from the back of the chair, arms hanging at sides and feet flat on the floor. The lateral flexion and sagittal plane meters must read zero for the rotation meter to be level; if necessary, assist the participant into the correct position. As the participant faces straight ahead, grasp the rotation meter between your thumb and index finger and turn the meter until one of the pointers is at zero.

Instruct the participant to focus on a horizontal line on the wall so the head is not tipped during rotation. Ask participant to straighten up if required. Have the participant turn the head as far to the left as possible (see Figure 6), and to ensure that no shoulder rotation occurs, lightly stabilize the right shoulder with your hand. (Note: if the head and shoulders are rotated together the pointer will not move because the magnetic yoke positioned on the shoulders eliminates shoulder substitution). Record this measurement in the appropriate place on the recording sheet.

Whilst you lightly stabilize the left shoulder, instruct the participant to turn the head as far as possible to the right (see Figure 7). Record this measurement also."

Figure 6: Left rotation

Figure 7: Right rotation

Movement	Range (degrees)	Comment
Flexion		
Extension		
Left lateral flexion		
Right lateral flexion		
Left rotation		
Right rotation		

5.2.2 Cervical flexion rotation test

NOTE: Do the flexion rotation test using the CROM device.

Cervical flexion rotation test will be done following the protocol described in Hall T, Robinson K (2004)[4].

The cervical flexion rotation test assesses dysfunction at the C1-C2 segment (Hall & Robinson, 2004)[4]. This test will be done following the protocol of Stratton and Bryan (1994) as described by Hall and Robinson (2004)[4] and using the CROM to measure the range of passive cervical rotation.

The participant is asked to wear the CROM device and lies supine and relaxed. The patient's head is pre-positioned so that the cervical spine is in end range of flexion. Keeping the

[4] Hall T, Robinson K (2004) The flexion-rotation test and active cervical mobility—A comparative measurement study in cervicogenic headache. Man Ther 9:197–202.

cervical spine maximally flexed, the head is then passively rotated to the left and the right. The assessor then instructs the participant as follows: “Let me do all the work. You just have to relax and let me know if the movement produces or increases pain or headache”. End of range is at that point when a firm resistance is felt by the assessor or when the participant complains of pain or headache, whichever comes first. It is important to do this test with the least provocation of headache or other related symptoms. The examinerthen measures of the range of rotation to determinewhether the FRT is positive or negative.

A positive test is defined where the range of movement at which restriction, pain or headache sets in is $\leq 32^{o.5}$.

☐ Positive Left: _____ degrees ☐ Negative

Right: _____ degrees

5.2.3 Cranio-cervical flexion test (CCFT)

Cranio-cervical flexion test will be done following the protocol of Jull et at., 2008[6]

This will be done in two stages.

Stage 1: Analysis of performance of the craniocervical flexion (CCF) action.

The participant is positioned in supine, crook lying with theirears aligned with the shoulder or parallel with the plinth. Initially, check that participant has the range passively—hence the examiner performs passive CCF first. The dial should increase to at least 30mmHg. Ensure the movement is NOT provocative of headache symptoms to proceed. If provocative of symptoms, DO NOT proceedwith the test. Note that sometimes if you adjust the participant position to slightly elevate shoulders, the test may become asymptomatic (presumably because reducing stretch on sensitive neural tissue).

Instruct the participant to “*Slowly slide the back of your head up the bed to nod your chin.*”The examiner analyses the movement to ensure that it is head rotation with negligible activity in the sternocleidomastoid or anterior scalene muscles. This movement is analysed by observing and/or palpating the activity in the superficial flexors during the flexion.

[5]Ogince M, Hall T, Robinson K (2007) The diagnostic validity of the cervical flexion-rotation test in C1/2-related cervicogenic headache. Man Ther 12:256–262.

[6] Jull GA, O'Leary SP, Falla DL (2008) Clinical assessment of the deep cervical flexor muscles: The craniocervical flexion test. J Manipulative PhysiolTher 31:525–533.

Then ask the participant to do this movement using the pressure biofeedback unit (PBU). The PBU is partially inflated and positioned such that its top is on the back of the head (Figure 8). With the participant in starting position, inflate the PBU to 20mmHg. Ask the participant to do the nodding movement to elevate the target pressure from 20 to 22 mmHg (top of red/pink band).

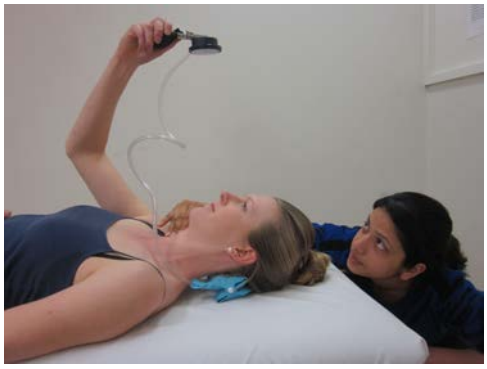


Figure 8. Participant starting position for CCFT

Signs of abnormal muscle behaviour or activation patterns of the deep cervical flexors are as indicated below, and the corrective strategies in the adjacent column.

Abnormal Action	Corrective Cues
Retraction strategy: Head rotation does not increase with increases in pressure targets and the movement becomes more a head retraction action than craniocervical flexion	Passively correct the movement pattern by moving the participant's head through craniocervical flexion.
Early activation of SCM: Superficial cervical flexors are overly active especially at the early stage of the movement	Use the following verbal cues: "eye look down", "Look at the ceiling and slowly look down to just above your knees"
Compensation with hyoid muscles.	Inhibit activity of the hyoid muscles using this verbal cue: "Put your tongue on the roof of your mouth, lips together and teeth apart)"
The head does not return to the starting position. This is indicated on the dial by being less than or greater than 20mmHg.	First, check the cuff position and inflation of the PBU. Make sure the top edge of the cuff is just under the occiput. Make sure that the cuff is inflated adequately. Second, check head position. Is this due to a lack of proprioception? Passively move the participant's head to neutral or to the starting position and then check the cuff reading again

Record the reason for ‘failure of the test’ and verbally or manually correct the action. Allow the participant 1-2 repetitions to correct the action then proceed to stage 2.

Stage 2: Testing isometric endurance of the deep cervicalflexors at test stages that the participant is able to achieve withthe correct craniocervical flexion action.

Proceed with this stage when the participant can correctly perform the craniocervical flexion movement. Otherwise, provide corrective cues to address the abnormal action.

The participantdoes the head nod action to 22mmHg and holds the head nod for 5 seconds. If the participant canperform at least 3 repetitions of 5-second holds withoutsubstitution strategies, the test is progressed to the nextpressure target.Repeat the process in 2 mmHg increments, until 30 mmHg. Use “top of green band” as cue for 24 mmHg, top of yellow band for 26 mmHg, top of blue band for 28 mmHg, and black line next to blue band for 30 mmHg. At each stage, make sure that the correct head nod action is done for all pressure increments and that no substitutions are occurring, and the SCM or AS are not overly active.

Once a level is reached when the participant cannot hold the head nod for 5 seconds for repetitions (eg 26mmHg), go back to the previous level (eg 24mmHg). Ask the participant to do 10- second hold at this pressure increment for 3 repetitions.If the participant can perform as many repetitions of 10-second holds of the head nod without substitution strategies.

The examiner should watch out for signs of reduced endurance of the deep cervical flexors during the head nod: the superficial flexor muscles are overly active, the head is jerky despite holding the neck in flexion, the pressure of the PBU is not held steady and/or decreases.

Record the pressurelevel(s) that the participant can hold steady for 10 seconds and the number of repetitions at that level, with minimal superficial muscle activity and without substitution strategies.If the test will be not performed because of provocation of headache, record accordingly.

22 mmHg:	Number of repetitions of 10 sec-hold[a]: _____
24 mmHg:	Number of repetitions of 10 sec-hold: _____
26 mmHg:	Number of repetitions of 10 sec-hold: _____
28 mmHg:	Number of repetitions of 10 sec-hold: _____
30 mmHg:	Number of repetitions of 10 sec-hold: _____
☐ Unable to do test	

[a] Must be able to do at least 3 good repetitions to progress to the next pressure target

5.2.4 Strength test: Cervical flexors

Maximal isometric force in the neck flexor and extensor muscles will be measured using the Lafayette Manual Muscle Tester (Model 01163) handheld dynamometer using a protocol by Silvermann et al 1991[7], also described in Dumas et al., 2001[8].This technique has been shown to have good reliability (ICC>0.74). Two trials will be done and the highest score will be used for statistical analysis.

The participant will be positioned supine, with the chin nodded (that is, maintaining craniocervical neutral). The examiner places his/her hand under the participant's occiput at the beginning of the test. The participant is instructed to lift the head just off the examiner's hand by gently pushing against the dynamometer then pushing progressively harder whilst the examiner holds the device still (isometric hold, make test). Contraction is held for about 3–5 seconds (or until the dynamometer beeps twice). Two trials will be done with adequate rests between trials.

The mean of both repetitions will be used for statistical analysis.

Strength Test	**Force (kg)**			**Comment**
	Trial 1	Trial 2	Highest Score	
Neck flexors				

[7]Silverman JL, Rodriquez AA, Agre JC (1991) Quantitative cervical flexor strength in healthy subjects and in subjects with mechanical neck pain. Arch Phys Med Rehabil 72:679–681.

[8] Dumas JP, Arsenault AB, Boudreau G, Magnoux E, Lepage Y, Bellavance A, Loisel P. (2001) Physical impairments in cervicogenic headache: traumatic vs. nontraumatic onset. Cephalalgia 21:884–893.

5.2.5 Endurance test: Cervical flexors

Cervical flexor endurance will be measured following the protocol of Harris et al., 2005[9]; also cited in Edmonston et al., 2008[10].

This technique will be appropriate for participants with headaches showed excellent test-retest reliability (ICC = 0 93) when used with individuals with postural neck pain [9].

The test will be performed with the participant in crook-lying on a plinth, with hands on the abdomen (Figure 9).

Figure 9. Starting position for endurance test of the neck flexors

Guide the participant's head through slight upper neck flexion (head nod). The amount of flexion is just enough so that the head lifts about 2.5 cm above the plinth. After two trials and with the participant able to do the correct movement, the participant is ready to do the test. The examiner then places his/her hand on the plinth just below the occiput. The participantslowly flexes his or her upper neck and lifts his or her head just off the examiner's handwhilst retaining the upper neck flexion (Figure 10).

Figure 10. Head position for endurance test of the neck flexors

[9]Harris KD, Heer DM, Roy TC, Santos DM, Whitman JM, Wainner RS (2005) Reliability of a measurement of neck flexor muscle endurance. Physical therapy 85:1349–1355.

[10]Edmondston SJ, Wallumrød ME, Macléid F, Kvamme LS, Joebges S, Brabham GC (2008) Reliability of isometric muscle endurance tests in subjects with postural neck pain. J Manipulative PhysiolTher 31:348–354.

Verbal feedback to maintain the head in slight flexion is provided ("tuck your chin in" or "hold your head up"). The test will be terminated if the participant is unable to maintain the flexed position, or is limited by exacerbation of pain or headache or discomfort,or at 1 minute, whichever comes first. The holding time will be measured in minutes and seconds.

Endurance Test	Time (mins:secs)	Comment
Neck flexors		

5.2.6 Palpation

Manual examination of the upper cervical joints will be done following the protocol of Maitland, 1982[11] and Zito, Jull & Story, 2006[12].

Participant position: Participant is in prone with forehead resting on one palm (hands overlapped) and neck positioned in neutral mid-flexion-extension position.

Examiner position: Standing at the head of the treatment table.

Palpate the suboccipital area overlying and superior to the atlas with the tips of the middle three fingers. To do this, the pressure of the finger tips should be directed towards the participant's eyes and the tissue should be palpated by both a medial-lateral movement and a postero-anterior movement (Figure 11).

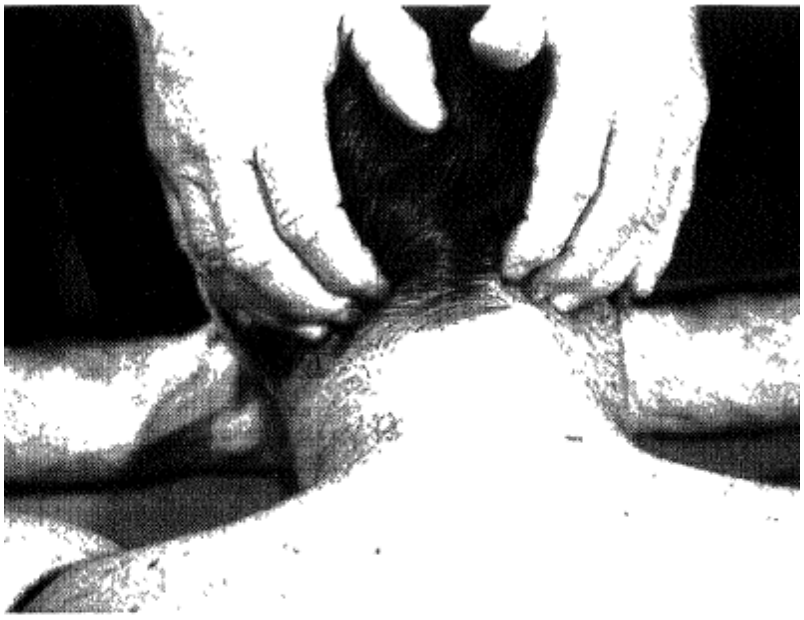


Figure 11. Palpation of the suboccipital area

Continue palpation by using the full length of the pads of the middle and ring fingers of each hand in the laminar-trough area (that is from the lateral surface of spinous process to the lateral margin of the articular pillar), from C1 to C4. The technique involves moving both

[11]Maitland GD (1982) Palpation examination of the posterior cervical spine: The ideal, average and abnormal.Aust J Physiother 28:3–12.

[12]Zito G, Jull G, Story I (2006) Clinical tests of musculoskeletal dysfunction in the diagnosis of cervicogenic headache. Man Ther 11:118–129.

hands in rhythm with each other, moving the skin up and down with the pads of the fingers as far as the skin allows, whilst gently sinking into the muscle bellies and other soft tissue. The purpose is to feel for areas of thickness, swelling and tightness in the soft tissue and also for abnormalities of the general bony contour. Perform two or three up and down movements in the upper cervical area, then slide the fingers caudally 2 or 3 centimetres and the process is repeated until the level of C4 is reached.

Once the general andmore gross impression has been gained through the full pads of the fingers, the procedure should be repeated but this time using the tip of the pad of only one finger of each hand.

Ask the participant if any of the movements provoke or relieve the headache. Then ask the participant to rate any local or referred pain provoked during the manual examinationat any joint. The participant then rates the pain using a 0–10 verbal analogue scale, where 0 is no pain and 10 is the worst pain possible.

Headache provoked?	☐ Yes	☐ No
If yes, at which level?	☐ 0/C1	VAS:
	☐ C1/C2	VAS:
	☐ C2/C3	VAS:
	☐ C3/C4	VAS:

5.2.7 Cervical extensor test

Cervical extensor test will be performed as described on page 213 of Jull G, Sterling M, Falla D, Treleaven J, O'Leary S. (2008)[13].

Background

Cervical muscle behaviour is commonly assessed in people with neck pain. Reliable protocols for cervical flexor motor performance have been established and there is increasing body of evidence supporting the coexistence of neck pain and cervical flexor muscle behaviour[e.g. 14]. Whilst protocols for measuring cervical extensor muscle endurance and

[13]Jull G, Sterling M, Falla D, Treleaven J, O'Leary S. (2008). *Whiplash, headache, and neck pain: research-based directions for physical therapies.* Churchill Livingstone/Elsevier, Edinburgh.

[14]O'Leary S, Falla D, Jull G (2011)The relationship between superficial muscle activity during the cranio-cervical flexion test and clinical features in participants with chronic neck pain. Manual Therapy 16:452-455.

strength have been established [e.g. 15], to date, reliable protocols for assessing cervical extensor motor control have not.

Associations between deep extensor (multifidus) muscle cross sectional area and motor activation of the lumbar multifidus and pain have been demonstrated in participants with lower back pain[16]. This same association is believed by some clinicians to be a feature of neck pain, but has yet to be demonstrated.

Deep Extensor Muscle Behaviour

Cervical Extensor Test

The cervical extensor test will be performed as described by Jull et al (2008)[17]. This test is understood to bias activation of the deep cervical extensors (namely the semispinalis cervicis and multifidus groups) with some validity obtained under fMRI[18]. The cervical extensor test will be scored through video analysis of the performance of the participant according to maintenance of the start position, eccentric phase and concentric phase. The following scores will be reported: Overall score, Phase 1 (Maintenance of start position) score,Phase 2 (Eccentric phase) score, Phase 3 (Concentric phase) score, and aggregate score which is the total of the phase scores. The participant is required to expose the neck, upper back and shoulder. A singlet top will provide sufficient exposure.

Start position

The participant will be instructed on adopting a prone position on the plinth with their head over the edge of the bed (see Figure 12).The participant is instructed on holding this position for 10 seconds then performing a slow neck flexion (see Figure 13) and extension procedure without involving head extension beyond neutral.

Instruction (Video filming commences)

Participant instructions

One standard instruction will be issued to the participant: *"I will place your head in a position called the start position. Look at a point directly below your head on the floor. Can you hold this position for 10 seconds first then perform the movement. The movement to perform is to curl your neck slowly downwards so that you are looking underneath the plinth, then slowly curl your neck back up to the start position without lifting your chin. Ensure you*

[15]Edmondston SJ, Wallumrød ME, Macléid F, Kvamme LS, Joebges S, Brabham GC (2008) Reliability of isometric muscle endurance tests in subjects with postural neck pain. J Manipulative PhysiolTher 31:348–354.

[16]Hides JA, Stokes MJ, Saide MJ, Jull GA, Cooper DH (1994) Evidence of lumbar multifidus muscle wasting ipsilateral to symptoms in patients with acute/subacute low back pain. Spine 19:165.–172.

[17] Jull G, Sterling M, Falla D, Treleaven J, O'Leary S. (2008). Whiplash, headache, and neck pain: research-based directions for physical therapies. Churchill Livingstone/Elsevier, Edinburgh (beginning page. 213).

[18]O'Leary S, Cagnie B, Reeve A, Jull G, Elliott JM (2011) Is there altered activity of the extensor muscles in chronic mechanical neck pain? A functional magnetic resonance imaging study.Archives of physical medicine and rehabilitation 92:929–934.

finish so that your eyes are looking at the ground where they started." The participant will be given verbal feedback and manual correction for two test movements.

The participant will be asked to repeat this 10 times.

Testing
The participant assumes the "Start Position" with manual and verbal correction by the examiner as required.

The participant will be asked to hold the starting position for 10 seconds. The "hold time" will be recorded by the assessor using a stopwatch. The assessor will count each second of this period aloud. At the conclusion of the "hold time", the assessor will repeat the instructions through each stage of the test movement.

"Look at a point directly below your head on the floor.

Now slowly curl your neck downwards so that you are looking underneath the plinth.

Now slowly curl your neck back up to the start position without lifting your chin.

Your eyes should be looking at the same point on the ground as where they started.

Now repeat 10 times."

The assessor then counts each repetition that the participant performs.*(Video filming concludes.)*

Figure 12: Start position (Phase 1)

.

Figure 13: Neck flexion during Phase 2 (eccentric phase)

<u>Video Analysis</u>
Concurrent video analysis will be conducted. The video camera will be positioned on a tripod perpendicular to the participant to obtain a lateral view. The distance between the camera and the participant, tripod height, camera inclination and zoom setting will be standardised. Ensure that the legs of the plinth (at the head of the plinth) and the tripod are on their designated markers on the floor.

Optimal settings to be determined

Camera distance	Position the head at start position in centre grid of camera screen
Tripod height	(As set)
Camera inclination	Position the head at start position in centre grid of camera screen
Zoom	100%

Rate overall performance using the following scale:

Normal	9-10 repetitions of correct pattern
Mostly normal:	5-8 repetitions of correct pattern
Mostly abnormal	1-4 repetitions of correct pattern
Abnormal	Unable to perform 1 repetition correctly

Number of repetitions until failure (loss of optimal motor performance) _____out of 10

Overall performance ☐ Normal ☐ Mostly normal ☐ Mostly abnormal ☐ Abnormal

Assessment Notes:
Rating of each phase: Encircle the cell that describes the performance at each phase.

Phase 1: Maintenance of start position

0	1	2	3	Comment
Maintains start position	Mostly maintains start position	Mostly does not maintain position	Definitely does not maintain start position	Drifts into Flexion Drifts into UCE

Phase 2: Eccentric phase

0	1	2	3	Comment
Normal control	Mostly normal	Mostly abnormal	Abnormal	Forward translation of head Dominant CCF motion Movement is jerky or quick Full range of neck flexion not achieved

Phase 3: Concentric phase

0	1	2	3	Comment
Normal control	Mostly normal	Mostly abnormal	Abnormal	Head not returned to starting position Low cervical spine not returned to the starting position Dominant CCE motion Movement is jerky or quick

Cause of failure, if any (Tick all that apply, based on video.)

- ☐ Lower cervical spine drifts into flexion at starting position
- ☐ Forward translation of the head during eccentric phase
- ☐ Movement is jerky during eccentric phase
- ☐ Participant does not lift head back up to start position during concentric phase
- ☐ The head returns to the starting position by the low cervical spine remains in flexion (sags) during concentric phase
- ☐ Inability to maintain a neutral craniocervical flexion/extension position
- ☐ Participant in a position of craniocervical extension through or at the end of repetition
- ☐ Visually prominent semispinalis capitis muscle
- ☐ Other: (Please describe.) _____

Failure of optimal motor performance of this task is understood to occur for many reasons. Some of the reasons suggested are outlined in the following table with description of how this will appear visually.

Table. Common reasons for failure of the CET

Reason for failure	Description
1. Starting Position	
Lower cervical spine drifts into flexion	An inability to maintain a neutral cervical spine posture against gravity i.e., the lower cervical spine will sag into flexion
2. Eccentric Phase	
Forward translation of the head	Participant cannot control flexion of the lower cervical spine against gravity (eccentric extensor action). Instead the head translates downward rather than curling downward.
Movement is jerky	
3. Concentric Phase	
Return of head position	Participant does not lift head back up to start position as they fatigue. A difference of 5 degrees is considered not returning to the start position.
Return of low cervical spine position	The head returns to the starting position but the low cervical spine remains in flexion (sags)
4. Overall Performance	
Dominance of craniocervical extension action	Inability to maintain a neutral craniocervical flexion/extension position, participant in a position of craniocervical extension through or at the end of repetition. Visually prominent semispinalis capitus muscle
Number of repetitions of accurate performance	

5.2.8 Strength test: Cervical extensors

Cervical extensor strength will be measured using a Lafayette Manual Muscle Tester (Model 01163) handheld dynamometer using a protocol similar to that used by Silvermann et al 1991[19] also described in Dumas et al., 2001[20]. This technique has been shown to have good reliability (ICC>0.74).

The participant lies in prone. The dynamometer is placed on the back of the head. The participant will be asked to lift his or her head off the bed. The examiner will place his or her hand under the participant's forehead to ensure the head remains off the bed for the test. The participant will be asked to first gently push against the dynamometer then to push progressively harder whilst the examiner holds the device still (isometric hold, make test). Contraction will be performed against the dynamometer for about 3-5s (until dynamometer beeps twice). Two trials will be done.

The mean of both repetitions will be used for statistical analysis.

Strength Test	Force (kg)			Comment
	Trial 1	Trial 2	Highest Score	
Neck extensors				

[19]Silverman JL, Rodriquez AA, Agre JC (1991) Quantitative cervical flexor strength in healthy subjects and in subjects with mechanical neck pain. Arch Phys Med Rehabil 72:679–681.

[20] Dumas JP, Arsenault AB, Boudreau G, Magnoux E, Lepage Y, Bellavance A, Loisel P. (2001) Physical impairments in cervicogenic headache: traumatic vs. nontraumatic onset. Cephalalgia 21:884–893.

5.2.9 Endurance test: Cervical extensors

Cervical extensor endurance will be measured following the protocol of Edmonston et al 2008[21].

The endurance test for the cervical extensors is a modification of a test described byLjungquist et al (1999)[22], also adapted from the Biering-Sorensen lumbar extensor test. The participantwill lie in prone with the head over the edge of the plinth. Arms are kept to the side. The examiner supports the participant's head A strap will be placed at the level of T6 to support theupper thoracic spine. A band will be fixed aroundthe head with a fluid inclinometer attached to the band overthe occiput. A 2-kg weight will be suspended from theheadband so that the weight will be located just short of thefloor. The participant's head will be positioned in neutral position and the test begins when the examiner removes the support of the participant's head. (see Figure 14).

Figure 14. Starting position for endurance test for the cervical extensors

The participantholds the cervical spine horizontal with the chinretracted. The test is terminated if the neck position changes by more than 5° from the horizontalas measured by the inclinometer, or if the participant could no longer hold the position due to pain or discomfort, or at 3 minutes and 20 seconds, whichever comes first. Theholding time will be measured in minutes and seconds.

Endurance Test	Time (mins:secs)	Comment
Neck extensors		

[21]Edmondston SJ, Wallumrød ME, Macléid F, Kvamme LS, Joebges S, Brabham GC (2008) Reliability of isometric muscle endurance tests in subjects with postural neck pain. J Manipulative PhysiolTher 31:348–354.

[22]Ljungquist T, Fransson B, Harms-Ringdahl K, Björnham Å, Nygren Å (1999) A physiotherapy test package for assessing back and neck dysfunction—Discriminative ability for patients versus healthy control subjects. Physiotherapy Research International 4:123–140.

5.2.10 Real-time ultrasound imaging

Measurement of cervical multifidus using real time ultrasound

Configuration of the ultrasound machine

For the measurement of cervical multifidus, a 5-10MHz transducer (adjusted to 5MHz for big build, 7.5 MHz for medium build, and 10MHz for small build) transducer is used to make measurements of muscle size and shape (VF 8- 3 +); depth is set at 4cm (may need to adjust for a larger neck size i.e. 5 cm) and focus adjusted to the level of the midpoint of the muscle. Gain, dynamic range, TGC and contrast is adjusted to optimise visualisation of the fascial planes.

Participant positioning

A standardised position of the participant is to be ensured for reproducibility of measurements across participants. The participant is seated in a chair with the feet flat on the floor facing the bed. The participant's head is rested on pillows.

Identification of the cervical multifidus

The spinous process of the C4level is identified by palpation and marked with a pen.

Imaging of the neck

Imaging of the neck is carried out by placing the transducer perpendicular to the long axis of the posterior neck at the C4 level. The left and right side of the neck is imaged separately by sliding the transducer left/right until an image is obtained where the spinous process is horizontally level with the uppermost part of the articular pillar. Multifidus is identified by the following landmarks: inferiorly the bony outline of the lamina, laterally by the facet joint, superiorly by the fascial plane, medially by the spinous process. The clearest image is ensured by maintaining the transducer 90 degrees to the fascia of the underlying muscle or varying the tilt of the transducer until the clearest fascial plane is present. In the presence of two facial planes, measurements are taken from the facial plane closest in level to the spinous process.

Measurements

- Lateral dimension

The lateral dimension is measured as the distance between the echogenic spinous process/highest point of the spinous process and the point where the two fascial planes meet adjacent to the supero/medial border of the facet.

- Antero-posterior dimension

The anterior-posterior dimension is measured by bisecting the lateral distance, measuring from leading edge to leading edge-top edge of fascial plane superiorly (lower of the two when two present), to the top edge of the lamina (brightest part).

- How to use the equipment: Siemens RTUS machine
    1. Press power button
    2. Allow a few minutes for machine to start
    3. Press New participant
    4. To choose “neck” protocol, go to exam and double click “NECK”
    5. Enter participant data
    6. Press ok
    7. This will take you to “Live image”
    8. Apply a liberal amount of gel on the transducer head
    9. Place transducer over spinous process at C4 level
    10. When ready, press “Freeze” and then “Print store” to capture the image
    11. Then place the transducer over the cervical multifidus at C4 level on the left side
    12. When ready, press “Freeze” and then “Print store” to capture the image
    13. Turn menu button (central) x1 to left
    14. Choose “clip capture”
    15. Scroll down far left toggle to “time capture”
    16. Choose 8 secs by scrolling toggle up
    17. Adjust clip speed if necessary on left button corner of screen
    18. Keep the transducer on the cervical multifidus and ask the participant to lift his/her head off the pillow, and capture this image by pressing “Freeze” and then “Clip store”.
    19. Then place the transducer over the cervical multifidus at C4 level on the right side
    20. When ready, press “Freeze” and then “Print store” to capture the image
    21. Keep the transducer on the cervical multifidus and ask the participant to lift his/her head off the pillow, and capture this image by pressing “Freeze” and then “Clip store”.
    22. To create new participant data, press “live screen” and repeat steps 3-5

23. To retrieve clip, go to participant data (2nd button top left on key board) and click on latest entry
24. To save image on USB, plug in USB (port is located at the back of machine on right), USB will appear on screen under "export/import"

Neck Protocol Pre-set Parameters:

VF 8 3+	Persist 4
Neck	R/S 3
36 dB	Map 3
7.3 MHz	Tint 1
DR 55dB	DTCE Med
Edge 2	32 fps

- Instructions for measuring
  - *Measuring D1: Lateral dimension*

1. Press calliper first, then move the mouse to place on the ***echogenic spinous process/highest point of the spinous process***, ***not past the convexity of the spinous process.*** Note, at times the best frame may not display the spinous process on the screen, with it being on the edge or just off the screen. If this is the case, choose the highest point of the spinous process at the point it leaves the screen or follow the lamina up.
2. Press set.
3. Move calliper using the mouse to the second point***where the two fascial planes meet adjacent to the supero/medial border of the facet, medial to the convex curve of the facet joint.*** Note, you may follow the lamina up to the facet joint to reach this same point.
4. Press set.
5. This will display as D1 on the screen. Record this in the table provided.

  - *Measuring D2: Bisecting point of D1*

6. Calculate (D1)/2 (i.e. ½ the D1 distance)
7. Press calliper and place on one of the lateral dimension points
8. Press set.
9. Follow the lateral dimension line across by the distance measured in step 6.
10. Press set.
11. This will display as D2 on the screen. Record this in the table provided.

  - *Measuring D3: Perpendicular bisector of D1*

12. Press calliper and place on the D2 point which halves the D1 line (the point from step 9).
13. Press set.
14. Move the mouse down to the ***top edge of the lamina (highest brightest part).*** This will be close to the fascial layer for rotatores.
15. Press set.

16. This will display at D3. Record this in the table provided.

- *Measuring D4: 'Shortest' AP dimension (closest to multifidus AP dimension)*

17. Press calliper then move the mouse to the ***top edge of the lamina (highest brightest part)*** at the point perpendicularly below your D2 point (the bottom of the D3 line).
18. Press set
19. Move the calliper using the mouse along the D3 line until you meet the***leading edge (top edge) of the first facial plane that you can see, usually situated close to the D1 line or in line with the facet joint and spinous process.*** This first facial plane will not be present on all video clips. If this is the case, simply record N/A or comment in the table provided.
20. Press set.
21. This will display as D4. Record this in the table provided. If the first facial plane is not present in the clip, simply record N/A or comment in the table provided.

- *Measuring D5: "Longest" AP dimension (closest to multifidus plus semi-spinalis)*

22. Press calliper and move the mouse to ***the top edge of the lamina (highest brightest part),*** the same point as in step 17.
23. Press set.
24. Move the calliper using the mouse to ***the leading edge (top edge) of the first fascial plane that you see above the facet joint or spinous process.*** Note, in some video clips, there may be two fascial planes (quite close together) present above the facet joint or spinous process.
25. Press set.
26. This will display as D5. Record this using the table provided.

- *Measuring contracted dimensions:*

27. Click patient browser again. This should display the original clip.

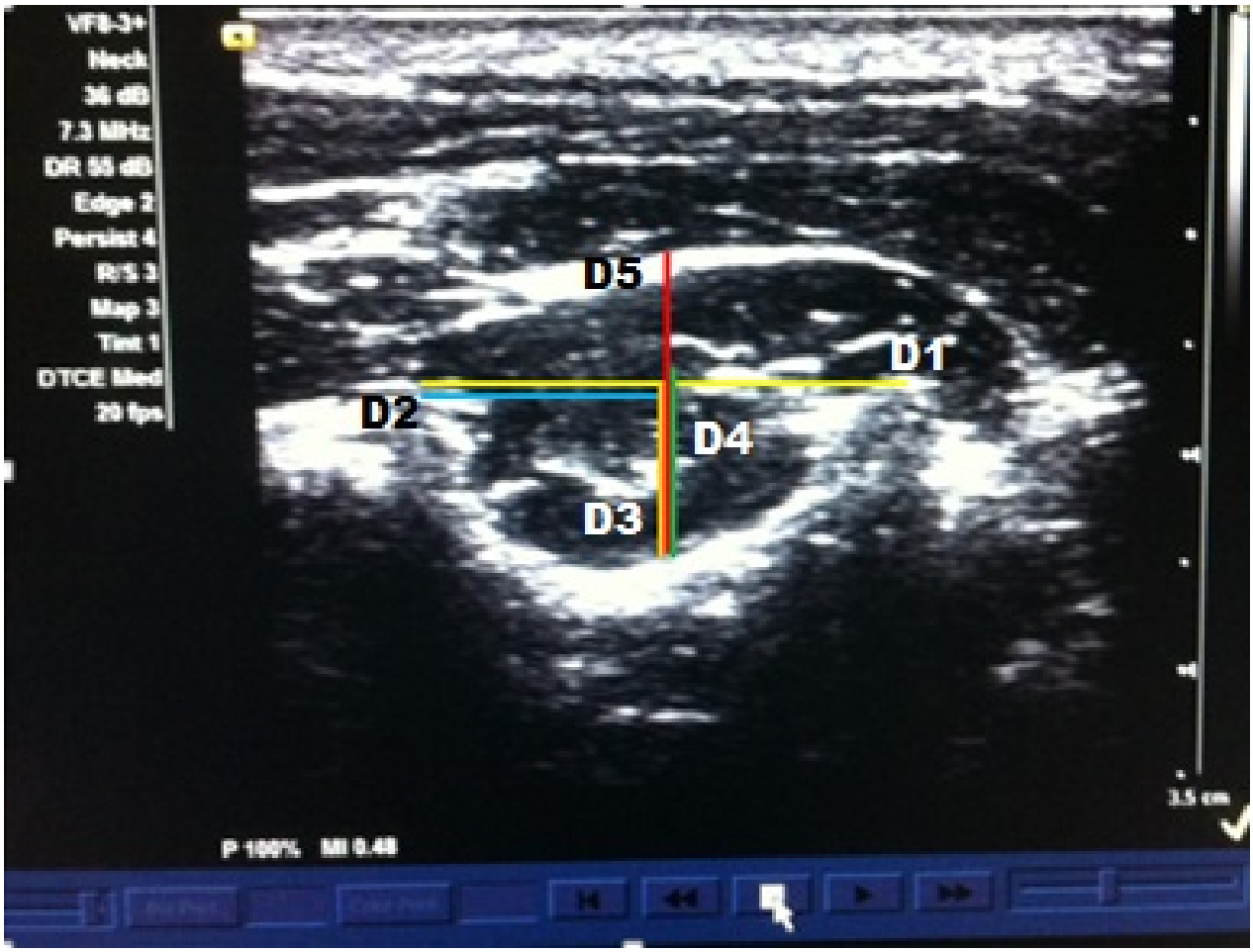
  - *Choosing the frame: Muscle contracted*

28. Watch the clip once more to determine when multifidus is contracting.
29. Move the clip to the time given in the table. The time is located at the top of the screen, next to the date.

  - *Measuring D1–D5 FOR CONTRACTED STATE*

30. Repeat steps 1–26.

- Data collection_RTUS cervical multifidus EXAMPLE:



	Left		Right	
	Relaxed	Contracted	Relaxed	Contracted
Lateral dimension				
Antero-posterior dimension (D4)				
Antero-posterior dimension (D5)				
Muscle shape (Lat / AP)				
Multiplied linear dimension (Lat x AP)				

- How to use the equipment: GE Logiq Portable Ultrasound Machine
    1. Press power button (top centre of keyboard)
    2. Allow a few minutes for machine to start
    3. Press “New Patient” (left side of control panel).
    4. A login window will appear. Leave the password blank and move the trackball to “log on”. Press “Set /B Pause” button (lower right off centre of control panel) to select “log on” on screen.
    5. Enter participant data: Patient ID, Last Name, First Name. If these cells are not blank, move trackball to “New Patient” on screen and then press “Set /B Pause” button (lower right off centre of control panel)
    6. Check that Category on left side of screen has “Small Parts” depressed.
    7. Press “New Patient” button on control panel again. This will take you to the live image screen.
    8. Check that the following parameters are correct:
        - Neck (protocol)
        - B mode
        - Fq 8.0Hz
        - Gn 62
        - E/A 3/2
        - Map N/0
        - D 3.0cm
        - DR 66
        - FR 65Hz
        - AO 100%
    9. Apply a liberal amount of gel on the transducer head.
    10. Place transducer over spinous process at C4 level.
    11. When ready, press “Freeze” and then “P1” to capture the image.
    12. Then place the transducer over the cervical multifidus at C4 level on the left side.
    13. When ready, press “Freeze” and then “P1” to capture the image.
    14. Keep the transducer on the cervical multifidus and ask the participant to lift his/her head off the pillow, and capture this image by pressing “Freeze” and then “P1”.
    15. Then place the transducer over the cervical multifidus at C4 level on the right side.
    16. When ready, press “Freeze” and then “P1” to capture the image
    17. Keep the transducer on the cervical multifidus and ask the participant to lift his/her head off the pillow, and capture this image by pressing “Freeze” and then “P1”.
    18. To retrieve clips from live image screen:
        a. Press “Freeze” button (lower right of control panel) so that it is lit up.

b. Press unmarked button (lower left off centre of control panel). This will make the cursor appear.
c. Move trackball to desired image.
d. Press “Set /B Pause” button (lower right off centre of control panel).

19. To retrieve clips from home screen:
    a. Press “New Patient” (left side of control panel).
    b. Choose the participant name or ID of interest from the list at the bottom of the screen.
    c. Press “Set /B Pause” button (lower right off centre of control panel).
    d. Move trackball to “Image History” on upper left of screen. Press “Set /B Pause” button to select image.
20. To measure:
    a. Press “Measure” button above trackball.
    b. Move the trackball to position the active caliper at the point of interest.
    c. Press “Set /B Pause” button to fix caliper at start point.
    d. Move the trackball along the distance or depth.
    e. Press “Set /B Pause” button to fix first caliper at end point.
21. To save image on hard disk:
    a. Press unmarked button (lower left off centre of control panel). This will make the cursor appear.
    b. Move cursor using trackball to image of interest then click “Set /B Pause” button.
    c. Move trackball to Menu on right bottom corner of screen then click “Set /B Pause” button.
    d. Select “Save as”.
    e. In “Save in” box, choose “HD (E:\export)” from dropdown choices.
    f. Write file name as “(Participant ID_left/right_resting/contracting”) e.g. IS-000_left_resting
    g. Use the following parameters for the rest of the details:
        i. Image only
        ii. Compression: None
        iii. Quality: 100
        iv. Save as type: Jpeg (*.jpg)
22. To save image on removable disk:
    a. Plug in removable disk (USB port at the back)
    b. Follow instructions for saving to hard disk but choose to save in removal disk.

5.3 Classification to Headache Groups

5.3.1 Checklist for *Migraine Group*

ICHD-3 beta criteria 2.3.1. Migraine without aura	**Participant response**
A. At least 5 attacks fulfilling criteria B-D	
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)	
C. Headache has at least two of the following characteristics: ☐ Unilateral location ☐ Pulsating quality ☐ Moderate or severe pain intensity ☐ Aggravation by or causing avoidance of routine physical activity (eg walking or climbing stairs)	
D. During headache at least one of the following ☐ Nausea and/or vomiting ☐ Photophobia ☐ Phonophobia	
E. Not better accounted for by another ICHD-3 diagnosis	

ICHD-3 beta criteria 2.3.2. Migraine with aura	**Participant response**
A. At least 2 attacks fulfilling criteria B and C	
B. One or more of the following fully reversible aura symptoms: ☐ Visual *(e.g. flickering lights, spots or lines, loss of vision)* ☐ Sensory *(e.g. pins and needles, numbness)* ☐ Speech and/or language ☐ Motor ☐ Brainstem ☐ Retinal	
C. At least two of the following: ☐ At least one aura symptom develops gradually over ≥ 5minutes, and/or two or more symptoms occur in succession	

ICHD-3 beta criteria 2.3.2. Migraine with aura	Participant response
☐ Each individual aura symptom lasts 5-60 minutes ☐ At least one aura symptom is unilateral ☐ The aura is accompanied, or followed within 60 minutes, by headache	
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded	

ICHD-3 beta criteria 2.3.3. Chronic migraine	Participant response
A. Headache (tension-type like and/or migraine-like) on ≥ 15 days per month for > 3 months and fulfilling criteria B and C	
B. At least 5 attacks fulfilling criteria B-D for migraine without aura and/or criteria B and C for migraine with aura	
C. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)	
D. Headache has at least two of the following characteristics: ☐ Unilateral location ☐ Pulsating quality ☐ Moderate or severe pain intensity ☐ Aggravation by or causing avoidance of routine physical activity (eg walking or climbing stairs)	
E. During headache at least one of the following ☐ Nausea and/or vomiting ☐ Photophobia ☐ Phonophobia	
F. One or more of the following fully	

ICHD-3 beta criteria 2.3.3. Chronic migraine	Participant response
reversible aura symptoms: ☐ Visual (e.g. flickering lights, spots or lines, loss of vision) ☐ Sensory (e.g. pins and needles, numbness) ☐ Speech and/or language ☐ Motor ☐ Brainstem ☐ Retinal	
G. At least two of the following: ☐ At least one aura symptom develops gradually over > 5minutes, and/or two or more symptoms occur in succession ☐ Each individual aura symptom lasts 5-60 minutes ☐ At least one aura symptom is unilateral ☐ The aura is accompanied, or followed within 60 minutes, by headache	
H. On > 8 days per month for > 3 months, fulfilling any of the following: ☐ Criteria C and D for migraine without aura ☐ Criteria B and C for migraine with aura ☐ Believed by the participant to be migraine at onset and relieved by a triptan or ergot derivative	
I. Not better accounted for by another ICHD-3 diagnosis	

Fulfilled criteria for migraine?

- ☐ **Yes: Included in *Migraine Group***
- ☐ **No: Consider inclusion in *Other Non-Migrainous Headaches Group***

5.3.2 Checklist for *Other Non-Migrainous Headaches Group*

5.3.2.1 Tension-type headache

ICHD-3 beta criteria 2.4.1.1. Infrequent episodic tension-type headache	**Participant response**
A. At least 10 episodes of headache occurring on <1 day per month on average (<12 days per year) and fulfilling criteria B-D	
B. Lasting from 30 minutes to 7 days	
C. At least two of the following: ☐ Bilateral location ☐ Pressing or tightening (non-pulsating) quality ☐ Mild or moderate intensity ☐ Not aggravated by routine physical activity such as walking or climbing stairs	
D. Both of the following: ☐ No nausea or vomiting ☐ No more than one of photophobia or phonophobia	
E. Not better accounted for by another ICHD-3 diagnosis	

ICHD-3 beta criteria 2.4.1.2. Frequent chronic tension-type headache	**Participant response**
A. At least 10 episodes of headache occurring on 1-14 days per month on average for > 30 months ($\geq$ 12 days and $\leq$ 180 days per year) and fulfilling criteria B-D	
B. Lasting from 30 minutes to 7 days	
C. At least two of the following: ☐ Bilateral location ☐ Pressing or tightening (non-pulsating) quality ☐ Mild or moderate intensity ☐ Not aggravated by routine physical activity such as walking or climbing stairs	
D. Both of the following: ☐ No nausea or vomiting ☐ No more than one of photophobia or phonophobia	
E. Not better accounted for by another ICHD-3 diagnosis	

ICHD-3 beta criteria 2.4.1.3. Chronic tension-type headache	Participant response
A. ≥ 15 days per month on average for >3 months (≥ 180 days per year), fulfilling criteria B-D	
B. Lasting hours to days or unremitting	
C. At least two of the following: ☐ Bilateral location ☐ Pressing or tightening (non-pulsating) quality ☐ Mild or moderate intensity ☐ Not aggravated by routine physical activity such as walking or climbing stairs	
D. Both of the following: ☐ No more than one of photophobia, phonophobia or mild nausea ☐ Neither moderate or severe nausea or vomiting	
E. Not better accounted for by another ICHD-3 diagnosis	

5.3.2.2 Cervicogenic headache

ICHD-3 beta criteria 2.4.2. Cervicogenic headache	Participant response
A. Any headache fulfilling criterion C	
B. Clinical, laboratory and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck, known to be able to cause headache	
C. Evidence of causation demonstrated by at least two of the following: ☐ Headache has developed in temporal relation to the onset of the cervical disorder or appearance of the lesion ☐ Headache has significantly improved or resolved in parallel with improvement in or resolution of the cervical disorder or lesion ☐ Cervical range of motion is reduced and headache is made significantly worse by provocative manoeuvres ☐ Headache is abolished following	

ICHD-3 beta criteria 2.4.2. Cervicogenic headache	Participant response
diagnostic blockade of a cervical structure or its nerve supply	
D. Not better accounted for by another ICHD-3 diagnosis	

☐ **Yes: Included in *Other Non-Migrainous Headaches Group***
☐ No: Consider inclusion as mixed type or unclassifiable

6.0 REDCap headache diary for 6 months

7.0 Follow up at 1 month, 3 months and 6 months after enrolment

7.1 REDCap headache diary
7.2 McGill Pain Questionnaire
7.3 Central Sensitization Inventory
7.4 Headache Impact Test-6
7.5 The Henry Ford Headache Disability Index
7.6 Headache Disability Questionnaire
7.7 WHO Disability Assessment Schedule 2.0

APPENDIX 6

Summary of Media Coverage for the Study

Presented in Chapter 3

This summary was provided by The University of Sydney Media Office.

WED 17 FEBRUARY 2016

Media coverage on migraine and GABA study

Executive summary

The following is a summary of the media coverage gained on the study 'Elevated levels of GABA+ in migraine detected using 1H-MRS' *NMR in Biomedicine,* May 2015.

The study was released to the media in October 2015 with Maria Aguila as the media spokesperon.

The media coverage gained reached an estimated audience of 2,028,208, with the biggest audience share from TV.

*Note: This report may not capture all online articles.

A cure for debilitating migraines could be a step closer thanks to a world-first ...

Channel 7, Perth, Seven News, Rick Ardon and Susannah Carr — 13 Oct 2015 6:20 PM

Duration: 1 min 32 secs • ASR AUD 14,523 • WA • Australia • Radio & TV • ID: M00063542601

A cure for debilitating migraines could be a step closer thanks to a world-first breakthrough by University of Sydney researchers. They've discovered a chemical imbalance of a substance called GABA in the brain of sufferers, and are now looking to develop new ways to treat the condition.

Audience

191,000 ALL, 80,000 MALE 16+, 94,000 FEMALE 16+

Interviewees

Maria Aguila, University of Sydney|Marnee McKay, Migraine Sufferer

Also broadcast from the following 1 station

GWN7 (Perth)

A cure for migraine could be one step closer thanks to a breakthrough by researchers at ...

Channel 7, Melbourne, Seven News, Jennifer Keyte 13 Oct 2015 6:28 PM

Duration: 2 mins 0 sec • ASR AUD 50,286 • VIC • Australia • Radio & TV • ID: M00063540742

A cure for migraine could be one step closer thanks to a breakthrough by researchers at the University of Sydney.

Audience

327,000 ALL, 128,000 MALE 16+, 179,000 FEMALE 16+

Interviewees

Maria Aguila, University of Sydney|Marnee McKay, Migraine Sufferer

Also broadcast from the following 9 stations

Prime7 Albury (Albury), Prime7 Ballarat (Ballarat), Prime7 Bendigo (Bendigo), Prime7 Gippsland (Sale), Prime7 Mildura (Mildura), Prime7 Shepparton (Shepparton), Prime7 Swan Hill (Swan Hill), Prime7 Warrnambool (Warrnambool), Southern Cross Darwin (Darwin)

A cure for debilitating migraines could be a step closer thanks to a world-first ...

Channel 7, Brisbane, Seven News, Sharyn Ghidella and Bill McDonald 13 Oct 2015 6:30 PM

Duration: 1 min 51 secs • ASR AUD 37,070 • QLD • Australia • Radio & TV • ID: M00063541425

A cure for debilitating migraines could be a step closer thanks to a world-first breakthrough by University of Sydney researchers. They've discovered a chemical imbalance of a substance called GABA in the brain of sufferers, and are now looking to develop new ways to treat the condition.

Audience

405,000 ALL, 133,000 MALE 16+, 224,000 FEMALE 16+

Interviewees

Maria Aguila, University of Sydney|Marnee McKay, Migraine Sufferer

Also broadcast from the following 9 stations

Seven Bundaberg (Bundaberg), Seven Cairns (Cairns), Seven Central (Alice Springs), Seven Mackay (Mackay), Seven Mt Isa (Mt Isa), Seven Rockhampton (Rockhampton), Seven Sunshine Coast (Sunshine Coast), Seven Toowoomba (Toowoomba), Seven Townsville (Townsville)

Research at the University of Sydney into migraines has found a chemical called Gamma ...

Channel 7, Sydney, Seven News, Mark Fergusson — 13 Oct 2015 6:47 PM

Duration: 2 mins 0 sec • ASR AUD 87,548 • NSW • Australia • Radio & TV • ID: M00063541157

Research at the University of Sydney into migraines has found a chemical called Gamma which causes them. Migraines cost the economy $7b a year.

Audience

406,000 ALL, 133,000 MALE 16+, 232,000 FEMALE 16+

Interviewees

Maria Aguila, University of Sydney|Marnee McKay, Migraine Sufferer

Also broadcast from the following 15 stations

Prime7 ACT (Canberra), Prime7 Armidale (Armidale), Prime7 Coffs Harbour (Coffs Harbour), Prime7 Cooma (Cooma), Prime7 Dubbo (Dubbo), Prime7 Gold Coast (Gold Coast), Prime7 Griffith (Griffith), Prime7 Moree (Moree), Prime7 Newcastle (Newcastle), Prime7 North Coast (Lismore), Prime7 Orange (Orange), Prime7 Tamworth (Tamworth), Prime7 Taree (Manning River), Prime7 Wagga Wagga (Wagga Wagga), Prime7 Wollongong (Wollongong)

Migraine breakthrough: One step closer to solving the painful puzzle

Countryman by Dr Andrew Rochford, 7 News — 13 Oct 2015 7:14 PM

332 words • ASR AUD 4,710 • University of Sydney Internet • ID: 480273767

Read on source website

Audience

N/A UNIQUE DAILY VISITORS, N/A AV. STORY AUDIENCE

Australian researchers at the University of Sydney have made a breakthrough in ...

Southern Cross Tasmania, Hobart, Southern Cross Nightly News, Jo Palmer — 14 Oct 2015 6:35 PM

Duration: 1 min 54 secs • ASR AUD 4,477 • TAS • Australia • Radio & TV • ID: M00063557029

Australian researchers at the University of Sydney have made a breakthrough in understanding migraines.

Audience

63,000 ALL, 22,000 MALE 16+, 32,000 FEMALE 16+

Interviewees

Maria Aguila, University of Sydney|vox pops

FED:CheckUp medicaL column for October 16

AAP Newswire, Australia, National, AAP — 16 Oct 2015

669 words • ASR N/A • Photo: No • Type: AAP NewswireClassification: • National • Australia • Press • ID: 481958842

View original - Full text: 669 word(s), ~2 mins

Audience

N/A CIRCULATION

Researching the baffling migraine

District Reporter Camden, Camden, General News — 19 Oct 2015

Page 7 • 475 words • ASR AUD 189 • Photo: No • Type: News ItemClassification: • Size: 230.00 cm² • NSW • Australia • Press • ID: 484405048

View original - Full text: 475 word(s), ~1 min

Audience

16,900 CIRCULATION

Chemical imbalance linked to migraines

lifehealthinsuranceNEWS.com.au by lifehealthinsurancenews.com.au editor — 21 Oct 2015 3:00 AM

324 words • ASR N/A • University of Sydney Internet • ID: 484419993

Read on source website

Audience

N/A UNIQUE DAILY VISITORS, N/A AV. STORY AUDIENCE

What I Live With: The Untold Toll Of Migraines Experienced By 1 In 10 Australians

huffingtonpost.com.au by huffingtonpost.com.au editor 22 Oct 2015 10:37 AM

939 words • ASR AUD 7,004 • University of Sydney Internet • ID: 484893677

Read on source website

Audience

N/A UNIQUE DAILY VISITORS, N/A AV. STORY AUDIENCE

Headache over for migraine researchers?

Newcastle Herald, Newcastle NSW, General News 26 Oct 2015

Page 21 • 121 words • ASR AUD 471 • Photo: No • Type: News ItemClassification: • Size: 45.00 cm² • NSW • Australia • Press • ID: 486621869

View original - Full text: 121 word(s), <1 min

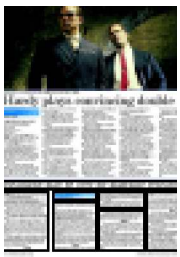
Audience

32,731 CIRCULATION

Headache may be over for migraine researchers

Western Advocate, Bathurst NSW, General News, Margaret Scheikowski 31 Oct 2015

Page 13 • 537 words • ASR AUD 1,146 • Photo: No • Type: News ItemClassification: • Size: 264.00 cm² • NSW • Australia • Press • ID: 489790935



View original - Full text: 537 word(s), ~2 mins

Audience

2,707 CIRCULATION

Brain is linked to the pain

Inner West Courier, Sydney, General News 03 Nov 2015

Page 24 • 366 words • ASR AUD 1,186 • Photo: Yes • Type: News ItemClassification: • Size: 248.00 cm² • NSW • Australia • Press • ID: 490631265

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Audience

82,285 CIRCULATION

16 Oct 2015
AAP Newswire, Australia
Author: AAP • Section: National • Article type : AAP Newswire • Classification : National
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FED:CheckUp medicaL column for October 16

A weekly round-up of news affecting your health
By Margaret Scheikowski and Angelo Risso
WALK UNNATURALLY TO BURN MORE KILOJOULES
If you want to burn more kilojoules when you're walking, just do "weird" things.
That's the advice of the co-author of an engineering study which found that varying your walking speed can burn up more energy than maintaining a steady pace.
The very act of changing speeds burns energy, says Professor Manoj Srinivasan from The Ohio State University.
"Walking at any speed costs some energy but when you're changing the speed, you're pressing the gas pedal, so to speak.
"Changing the kinetic energy of the person requires more work from the legs and that process certainly burns more energy."
Other ways for walkers to burn more kilojoules involve doing it in a way that feels unnatural.
"Just do weird things," he says.
"Walk with a backpack, walk with weights on your legs. Walk for a while, then stop and repeat that.
"Walk in a curve as opposed to a straight line."
SLEEPY DRIVERS AS DANGEROUS AS DRUNK ONES
Tired? Behind the wheel? You might as well be drink-driving.
A Queensland University of Technology study found young drivers were more likely to drive drowsy than drunk, despite the act being equally as dangerous.
The study examined 114 drivers under 30 and 177 drivers over 30, finding young drivers were both more likely to 'sleepy drive' and to disapprove of enforcement practices for sleepy driving.
"What this shows is that drivers, in particular young drivers, don't view equally the dangers of drink driving and sleepy driving despite the crash risks being similar," researcher Chris Watling said.
"Given younger drivers are over-represented in crash statistics and more likely to be impaired by sleepiness, it is vital we look to increase their perception of the dangers of driving while sleepy."
Research shows a blood alcohol content of 0.05 is the same as 17 consecutive hours awake, while 20 hours awake is the equivalent of a 0.1.
NDIS GUIDE FOR MENTAL HEALTH CARERS
Navigating Australia's new National Disability Insurance Scheme isn't easy.
But people who provide unpaid care and support to a family member or friend with a psychosocial disability related to a mental condition can now be helped by a new guide.
Psychosocial disability describes the experience of people with impairments and participation restrictions related to mental health conditions.
The guide, developed by Mental Health Australia and Carers Australia, can be accessed at http://mhaustralia.org/ and http://www.carersaustralia.com.au/
HEADACHE OVER FOR MIGRAINE RESEARCHERS?
Migraines have been puzzled over for years but the code may finally have been cracked.
University of Sydney researchers have found higher levels of the gamma-aminobutyric acid (GABA) chemical are present in the brains of migraine sufferers.
GABA is the brain's most abundant inhibitory brain chemical and plays a major role in a person's pain threshold.
This lends support to the idea migraines are caused by chemical imbalances in the brain.
"For such a debilitating condition, very little is known about migraine so this is a big step forward and could lead to better diagnosis and treatment of the disease in the future," lead researcher Maria Aguila said.
"GABA could be used to help us identify migraine sufferers and track responses to drug trials and measuring GABA levels over a period of time could well reveal what's causing attacks."
GROW MEDICINES IN YOUR BACKYARD?
Two scientists seeking to re-engineer plant proteins to tackle diabetes, obesity and cancer could be a step closer to their goal.
David Craik from the University of Queensland and Marilyn Anderson from La Trobe University have taken out the prestigious $1 million Ramaciotti Biomedical Research Award to produce "next generation" biodrugs incorporated into plant products such as seeds and teas.
This could enable patients to cheaply grow medicines in their own backyard, saving millions of lives across the developing world.
"This type of blue-sky research falls outside the realm of work typically funded by government or industry so we are particularly grateful," Professor Craik said.
AAP mss/mmr

19 Oct 2015
District Reporter Camden, Camden

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Country: Australia • ASR: AUD 189 • Words: 475 • Item ID: 484405048

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Researching the baffling migraine

Migraines have baffled scientists for years - no-one knows why they come or how they go - but researchers at the University of Sydney have taken a significant step forward in understanding the debilitating condition.

A new study, reveals higher levels of the chemical gamma-aminobutyric acid in the brain of migraine sufferers, supporting the theory that migraines are linked to a chemical imbalance in the brain.

"The finding paves the way for the discovery of new, effective treatments for migraines," said lead researcher Maria Aguila, PhD candidate in the Faculty of Health Sciences.

"For such a debilitating condition, very little is known about migraine so this is a big step forward and could lead to better diagnosis and treatment of the disease in the future," she said.

Gamma-aminobutyric acid or GABA as it is commonly known, is the most abundant inhibitory brain chemical and has long been suspected to play a role in migraines because of its ability to influence pain. This study is the first to accurately measure GABA levels in the living brain.

While the expert are still at a loss to understand "what causes migraine, how it starts and ends, or why the triggers appear to differ from one person to the next" the latest finding can assist with more specific research, Ms Aguila said.

"For example, GABA could be used to help us identify migraine sufferers and track responses to drug trials, and measuring GABA levels over a period of time could well reveal what's causing attacks."

The study compared the levels of GABA in twenty chronic migraine sufferers to an age and gender matched control group who did not experience any form of regular headaches. Brain scans were conducted when the participants were not having a migraine.

Associate Professor in Neuroimaging, Jim Lagopoulos said the ability to directly measure these chemicals in the brain would not have been possible several years ago.

"These advances not only allow us to study fundamental changes in brain chemistry that are associated with migraine, but they also open a whole new world with respect to monitoring a patient's response to treatment and compliance," he said.

The researchers were unable to tell if the increase in GABA is related to a recent migraine attack or signalling a new one as the scanning process is currently too complex to carry out during a migraine attack.

Fast facts on migraine -

- Migraine is the third most common disease in the world;
- It is estimated to affect 1 in 7 adults;
- It is up to three times more common in women than men;
- Often starting at puberty, migraine most affects those aged between 35 and 45 years;
- Current diagnosis is based on a complex checklist of signs and symptoms, and;
- Migraine is believed to be under-reported and under diagnosed globally.

26 Oct 2015
Newcastle Herald, Newcastle NSW

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Country: Australia • ASR: AUD 471 • Words: 121 • Item ID: 486621869

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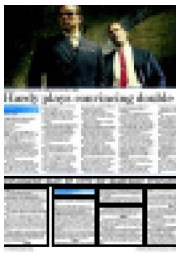
Headache over for migraine researchers?

MIGRAINES have been puzzled over for years but the code may finally have been cracked. University of Sydney researchers have found higher levels of the gamma-aminobutyric acid (GABA) chemical in the brains of migraine sufferers. GABA is the brain's most abundant inhibitory brain chemical and plays a major role in a person's pain threshold. This lends support to the idea that migraines are caused by chemical imbalances in the brain. The finding could lead to better diagnosis and treatment. "GABA could be used to help us identify migraine sufferers and track responses to drug trials and measuring GABA levels over a period of time could well reveal what's causing attacks," lead researcher Maria Aguila said.



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Headache may be over for migraine researchers

Checkup

Margaret Scheikowski

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GABA is the brain's most abundant inhibitory brain chemical and plays a major role in a person's pain threshold.

This lends support to the idea migraines are caused by chemical imbalances in the brain.

"For such a debilitating condition, very little is known about migraine, so this is a big step forward and could lead to better diagnosis and treatment of the disease in the future," lead researcher Maria Aguila said.

"GABA could be used to help us identify migraine sufferers and track responses to drug trials and measuring GABA levels over a period of time could well reveal what's causing attacks."

■■■

TWO scientists seeking to re-engineer plant proteins to tackle diabetes, obesity and cancer could be a step closer to their goal.

David Craik from the University of Queensland and Marilyn Anderson from La Trobe University have taken out the prestigious $1 million Ramaciotti Biomedical Research Award to produce "next generation" biodrugs incorporated into plant products such as seeds and teas.

This could enable patients to cheaply grow medicines in their own backyard, saving millions of lives across the developing world.

"This type of blue-sky research falls outside the realm of work typically funded by government or industry so we are particularly grateful," Professor Craik said.

■■■

NAVIGATING Australia's new National Disability Insurance Scheme isn't easy.

But people who provide unpaid care and support to a family member or friend with a psychosocial disability related to a mental condition can now be helped by a new guide.

Psychosocial disability describes the experience of people with impairments and participation restrictions related to mental health conditions.

The guide, developed by Mental Health Australia and Carers Australia, can be accessed at http://mhaustralia.org/ and http://www.carersaustralia.com.au/

■■■

LOGIE-WINNING actor John Wood is fronting a new campaign to raise awareness about shingles, which will affect one in three adults.

The condition, involving the painful outbreak of rash or blisters, is estimated to have doubled among the over-60s in recent years, says Chronic Pain Australia.

Half will go on to experience longer-term nerve pain, lasting 3.5 years on average.

Wood was bedridden for 13 weeks when he first had shingles as a teenager and had it again while filming *Blue Heelers* in his 50s.

"I want to make sure that those at highest risk, people over 60, know about the potential pain and suffering that shingles can cause and have a conversation with their doctor about their risk," he said.

■■■

SHINGLES often has vague symptoms such as mild to severe pain in a particular area, or a rash, leading people to dismiss the possibility until it's too late to treat the nerve damage.

People with gut problems are taking part in a world-first trial of an Australian seaweed extract.

University of Wollongong researchers are investigating whether the extract can help prevent the onset of chronic disorders such as Type 2 Diabetes.

Seaweed dietary fibres are known to improve the gut and digestive condition of animals and reduce metabolic stress such as experienced in the pre-diabetic condition.

03 Nov 2015
Inner West Courier, Sydney

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CAMPERDOWN

Brain is linked to the pain

MIGRAINE STUDY'S FINDINGS

IT'S A disease that has baffled health professionals for years, but University of Sydney research has findings that support the theory that migraines are linked to a chemical imbalance in the brain.

A new study reveals higher levels of the chemical gamma-aminobutyric acid in the brain of migraine sufferers and paves the way for the discovery of new, effective treatments, said lead researcher Maria Aguila, PhD candidate in the Faculty of Health Sciences.

"For such a debilitating condition, very little is known about migraine so this is a big step forward and could lead to better diagnosis and treatment of the disease in the future."

Gamma-aminobutyric acid, or GABA as it is commonly known, has long been suspected to play a role in migraines due to its ability to influence pain.

"We still don't know what causes migraine, how it starts and ends ... but this discovery means that we can now be much more specific with our research going forward," said Ms Aguila.

"For example, GABA could be used to help us identify migraine sufferers and track responses to drug trials, and measuring GABA levels over a period of time could well reveal what's causing attacks."

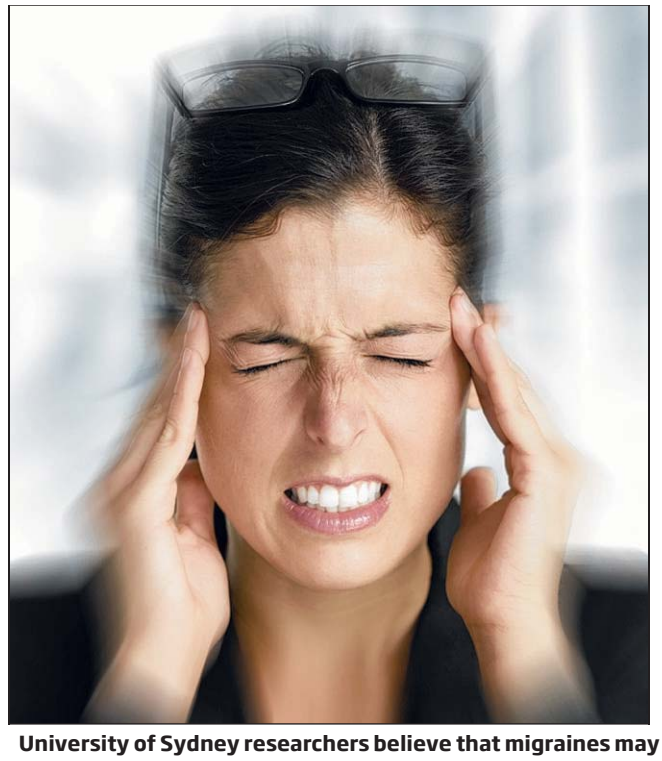
The study compared the levels of GABA in 20 chronic migraine sufferers to an age- and gender-matched control group who did not experience any form of regular headache.

Brain scans were conducted when the participants were not having a migraine.

The researchers were unable to tell if the increase in GABA is related to a recent migraine attack or signalling a new one, as the scanning process is currently too complex to carry out during a migraine attack.

ONE IN SEVEN HIT

- Migraine is the third most common disease in the world
- It is estimated to affect one in seven adults
- It is up to three times more common in women than men
- Often starting at puberty, migraine most affects those aged between 35 and 45
- Current diagnosis is based on a complex checklist of signs and symptoms
- Migraine is believed to be under-reported and under diagnosed globally



University of Sydney researchers believe that migraines may be linked to a chemical imbalance in the brain.

APPENDIX 7

Cover Art Published in Journal of Pain

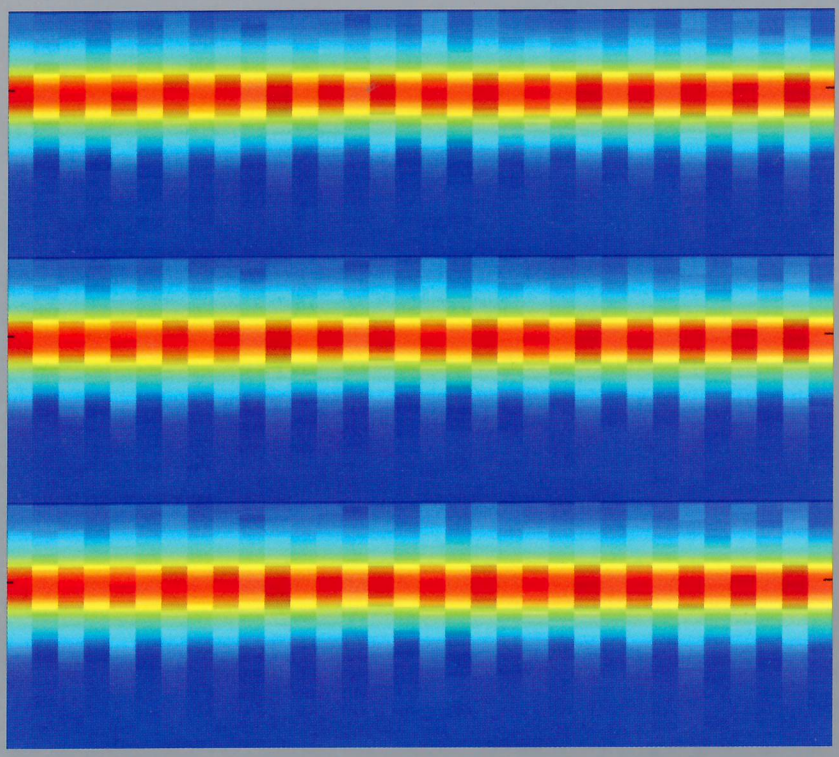
Appendix 7 presents the cover art published in The Journal of Pain Volume 17, Issue 10 (October 2016) (http://www.jpain.org/issue/S1526-5900(16)X0011-9). The cover illustration was a stylised image from an output of the editing process of GABA from the study in Chapter Four published in the same issue: [Aguila ME, Rebbeck T, Leaver AM, Lagopoulos J, Brennan PC, HübscherM,Refshauge KM. The association between clinical characteristics of migraine and brain GABA levels: An exploratory study. *J Pain* 2016; 17:1058–67. doi:10.1016/j.jpain.2016.06.008]

ELSEVIER

Volume 17, Number 10
October 2016

The Journal of Pain

OFFICIAL JOURNAL OF THE AMERICAN PAIN SOCIETY



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The Journal of Pain

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Volume 17, Number 10, October 2016

Original Reports

The Journal of Pain will publish appropriate images on the journal cover. Selected figures may accompany a submitted manuscript (authors should make a note in the covering letter), or images may be submitted individually. Please present your art for consideration. Visit http://ees.elsevier.com/jpain to upload your materials.

ON THE COVER

Migraine is prevalent and disabling yet is poorly understood. One way to better understand migraine is to examine clinical characteristics and potential biomarkers such as gamma-aminobutyric acid (GABA). This work explored whether relevant disease characteristics of migraine are associated with brain GABA levels. This illustration, provided by the authors, was stylized from an output of the editing process of GABA, particularly of the creatine signal after frequency correction. See Aguila et al, page 1058.

The Journal of Pain (ISSN 1526-5900) is published monthly by Elsevier Inc., 230 Park Avenue, Suite 800, New York, NY 10169. POSTMASTER: Send address changes to Journal of Pain, Elsevier Health Sciences Division, Subscription Customer Service, 3251 Riverport Lane, Maryland Heights, MO 63043.

APPENDIX 8

The Clinical Significance of Immediate Symptom Responses to Manual Therapy Treatment for Neck Pain: Observational Secondary Data Analysis of a Randomized Trial

Appendix 8 is the peer reviewed version of the following article: Trott, CA, Aguila, MER, Leaver, AM, The clinical significance of immediate symptom responses to manual therapy treatment for neck pain: Observational secondary data analysis of a randomized trial. *Man Ther.* 2014; 19:549–554.doi: 10.1016/j.math.2014.05.011, which has been published in final form athttp://www.mskscienceandpractice.com/article/S1356-689X(14)00113-1/fulltext; with permission from Elsevier.

Authorship Statement

As co-authors ofthe paper “The clinical significance of immediate symptom responses to manual therapy treatment for neck pain: Observational secondary data analysis of a randomized trial”, we confirm that Maria Eliza Ruiz Aguila has madethe following contributions:

- Analysis and interpretation of data
- Drafting and revising of the manuscript and critical appraisal of its content

Signed:  Caelum A Trott Date: 31 March 2017

Signed:  Andrew M Leaver Date: 31 March 2017

The clinical significance of immediate symptom responses to manual therapy treatment for neck pain: an observational study

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Word Count:	251 words (Abstract) 3685 words (Introduction, Method, Results, Discussion)
References:	27
Tables:	2
Figures:	1

ABSTRACT

Objective

Toexplore aspects of symptom responses to manual therapy treatment for neck pain.

Methods

An observational study based on data collected in a randomized trial.181 participants seeking care from a physiotherapist or chiropractor for a new episode of neck pain were included. Outcome variables included recovery timeand participant-perceived effect of treatment (GPE) at 3-months.

Results

There was a significant reduction of ≥1.4points (95%CI 1.2 to 1.5) in pre- and post-treatment pain scores at each occasion of treatment. There was also small but significant increases in pain of ≤0.7points (95%CI 0.4 to 1.0) between each treatment session, without regression to the preceding pre-treatment level. The relationships between immediate post-treatment effects and longer-term outcomes were explored using multivariate regression analyses. There was significant univariate association between recovery time and cumulative post-treatment changes in pain from the second, third and fourth (Exp(B)=1.2) treatment sessions, as well as the presence of post-treatment headache (Exp(B)=0.7) and other minor adverse symptoms (Exp(B)=0.6). There was significant univariate association between GPE at 3-months and cumulative pain responses from first (B=0.2), second (B=0.3), third (B=0.3) and fourth (B=0.4) treatment sessions. The change in pain after session 1 was independently associated with GPE (B=0.2). There was a consistently significant

difference of ≥0.7points (95%CI 0.43 to 0.89) in the different methods of reporting pain.

Conclusions

Our results show that manual therapy for neck pain involves a “two-steps forward, one-step back” recovery pattern. Whilst minor adverse events are undesirable, they do not seem to be significantly associated with long-term recovery.

KEY WORDS

Manual Therapy, Neck Pain, Manipulation Spinal, Pain Measurement

INTRODUCTION

Neck pain is a common musculoskeletal condition experienced by up to 15% of people at any given time, and afflicting most people at some stage of their lives (Haldeman et al., 2008; Hoy et al., 2010). Manual therapy is one of the few effective treatments for neck pain, with demonstrated benefits in improving pain and function, at least in the short term (Korthals-de Bos et al., 2003; Hurwitz et al., 2008; Driessen et al., 2012). The clinical course of neck pain appears to have fluctuating periods of aggravation and remission, with recurrence a common feature of the condition (Cote et al., 2004; Haldeman et al., 2008; Hush et al., 2011). Based on current evidence, it would appear that manual therapy is of most value in reducing symptoms, restoring function and hastening recovery during an episode of acute neck pain.

Although acknowledged as an effective treatment, the therapeutic mechanisms underpinning manual therapy are not fully understood, and many different theoretical and philosophical approaches exist amongst and between the disciplines that practice manual therapy. One of the most widely recognized approaches to manual therapy practice is the approach developed by Australian physiotherapist Geoffrey Maitland. One of the key features of Maitland's approach was the emphasis on monitoring and reassessing symptoms during and after application of a technique, as a means guiding choice of technique, dosage and treatment progression (Maitland, 1970; Maitland, 1986). This approach differed from the approaches of many of Maitland's contemporaries who tended to focus more on biomechanical principles to guide treatment decisions (Larson, 2005).

The use of patient-reported numerical ratings of current pain intensity to guide treatment selection and to monitor treatment outcomes is now widespread in modern manual therapy practice. Numerical rating scales for pain are also widely used as primary outcome measures in clinical trials of manual therapy, as a means of determining recovery from an episode of neck pain.The construct of recovery, howver, is complex and multidimensional, encompassing many different elements that are not necessarily captured by a single number. Focus group interviews of people with back pain for example, have shown that people with pain scores of zero do not necessarily consider themselves recovered, and some who consider themselves recovered can still register pain scores above zero (Hush et al., 2009).Inconsistencies have been demonstrated between verbal reports of pain and the standardized questionnaires that measure pain and disability in people with low back pain (Ong et al., 2006; De Souza and Frank, 2007).Better understanding of the relationship between pain scores and patient-relevant indices of recovery, and the ability to identify possible biases in patient reports of sympotms might improve monitoring of clinical and research outcomes in people with neck pain.

Several studies have previously investigated the relevance of within-session changes in symptoms in patients undergoing manual therapy treatment. There is some evidence that symptom changes that occur within a treatment session are maintained between treatment sessions (Hahne et al., 2004; Tuttle, 2005; Tuttle et al., 2006; Tuttle, 2009), and tend to continue throughout the duration of care (Cook et al., 2012). There is also some evidence to suggest that changes in pain and disability scores during treatment correlate with self-reported rate of recovery(O'Halloran et al., 2013). This suggests a relationship between positive treatment responses and recovery in the

very short term. The relationship between positive within-session treatment responses and longer-term recovery, however, is lacking. Further, the previous studies into the within- session responses to manual therapy concentrated primarily on the positive effects of manual therapy, such as improvement in pain and range of motion. Manual therapy can also result in a range of minor adverse effects (Hurwitz et al., 2005) most commonly increased neck pain and headache. Less is known about the effect of these adverse effects on recovery.

The aim of this study was to explore aspects of the immediate symptom responses to manual therapy treatment, in people with neck pain. Specifically, this study aimed to investigate

1. The typical clinical course of reported symptoms during a short episode of manual therapy care
2. The relationship between the immediate changes in reported pain following manual therapy and longer-term outcomes
3. The influence of minor adverse effects of manual therapy on longer-term outcomes
4. The consistency between pain scores reported by patients to practitioners and those recorded by patients in diaries.

METHODS

Design

This study involved observational secondary data analysis from a randomized controlled trial (Leaver et al., 2010) that compared high-velocity thrust manipulation with non-thrust mobilization in people with a new episode of neck pain. The original randomized controlled trial demonstrated no difference in outcomes between the manipulation and mobilization groups. We were therefore able to combine both treatment groups for an observation study.

Participants in the randomized controlled trial kept a daily diary of pain scores and the participating practitioners recorded pre- and post-treatment pain scores at each treatment session. This provided an opportunity to explore the relationship between the short-term effects of manual therapy treatments and longer-term patient relevant outcomes, as well as other features of manual therapy care. The study was approved by the University of Sydney Human Research Ethics Committee and all participants provided written informed consent.

Participants

The study was conducted in 11 physiotherapy and chiropractic clinics in Sydney, Australia, between October 2006 and April 2008. Participants aged 18-70 years who were seeking care from a physiotherapist or chiropractor for a new episode of non-specific neck pain were recruited by their treating practitioner. Eligible participants had neck pain of less than three months duration that was preceded by at least one month without neck pain. Participants were excluded if they had whiplash-associated disorder, history of neck surgery, serious pathology (e.g. malignancy, infection, inflammatory disorder, fracture, radiculopathy or myelopathy), primary complaint

other than neck pain, mild neck pain (<2/10 on a 0-10 point scale) or were unable to communicate in English. For the purpose of the associated randomized controlled trial, participants were also excluded if the treating practitioner deemed them unsuitable for neck manipulation. Participants from both groups (i.e. manipulation and mobilization) were included in the observational study.

Procedures

Baseline data were collected using participant questionnaires and practitioner assessment forms (Leaver et al., 2010). All participants were treated with up to four sessions of multimodal physical therapy that included manual therapy. The manual therapy that was provided to participants was either high velocity thrust manipulation or non-thrust mobilization according to the randomization schedule of the associated randomized controlled trial. Participants were followed for a period of three months after baseline assessment. The manual therapy treatments were applied pragmatically with the treating manual therapists selecting the target spinal segment, manual therapy technique and grade according to their clinical judgment. The treating practitioners were physiotherapists and chiropractors with post-graduate training and qualifications in spinal manipulative therapy, with at least two years of post-graduate experience. Participants completed a pain diary for three months. Diary entries were collected by telephone and transcribed weekly to minimize loss of data. An exit interview was conducted by telephone at three months to obtain participant's pain, activity and global perceived effect scores. The sample size was determined by the original trial and was powered to explore the differences between mobilization and manipulation in terms of speed of recovery.

Variables/outcomes

Demographic variables collected at baseline included age, sex, smoking habit, self-rated general health (5-point categorical scale) and compensation status. Clinical variables collected at baseline included pain intensity (numerical rating scale 0-10), duration of the current episode of neck pain in days, neck-related disability (Neck Disability Index 0-50), past history of neck pain, use of analgesic medications and the presence of associated symptoms including arm pain, headache, upper back pain, lower back pain, dizziness and/or nausea.

Pre-treatment and immediate post-treatment pain scores were recorded by the treating practitioner using a 0-10 numerical rating scale (NRS). '*Within-session*' changes in pain were calculated as the difference between pre-treatment and post-treatment scores at each treatment session. '*Cumulative change in pain*' relative to baseline was also calculated as the difference between the baseline pain score and the post-treatment score at each treatment session. Variables recorded in the participant diary included average 24-hour pain scores on a daily basis for three months as well as Neck Disability Index (NDI) (Vernon and Mior, 1991) and Global Perceived Effect (GPE) (Kamper et al., 2010) at three-month follow-up. Adverse effects of treatment were recorded in the participant diary during the treatment period. A checklist of common minor adverse effects including additional neck pain, additional headache, dizziness, nausea, fatigue and other was used as well as open-ended questioning.

The outcome variables were the recovery time for the episode of neck pain and the participants' perception of treatment effects. Recovery time for the episode of neck pain was defined as the number of days it took from the day of enrolment in the study for a participant to report a pain score of <1 (NRS 0-10) for the first of seven

consecutive days. The participants' perception of the effects of treatment was measured with the Global Perceived Effect scale (GPE). The GPE scale rates perception of recovery on a scale from -5 (Much worse) to +5 (Much better) and is a reliable and patient-focused indicator of recovery (Kamper et al., 2010).

Statistical analysis

All data were analyzed using Statistical Package for Social Sciences (SPSS)® statistical software, version 21 (SPSS Inc., Chicago, Illinois, USA) for Windows. Baseline demographic and clinical characteristics were reported as frequencies (%) or using descriptive statistics.The clinical course of neck pain during the two-week episode of care was reported by plotting pre- and post-treatment pain scores for each treatment session during the episode of care. Repeated measures *t*-test was used to compare pre- and post-treatment scores within and between sessions.

The relationships between immediate positive and adverse post-treatment effects and longer-term outcomes were explored using multivariate regression. Specifically, the relationship between post-treatment effects and recovery time was explored using Cox regression. The relationship between post-treatment effects and the perceived effects of treatment at three-month follow-up was explored using linear regression. For both regression models, the univariate relationships between the within-session changes in pain (including the cumulative changes in pain scores from baseline at each treatment session) and adverse events were calculated. In the multivariate analysis, all variables associated ($p<0.1$) with faster recovery or better-perceived treatment outcomes were included in the regression models. Variables that no longer

associated with recovery were removed in a stepwise manner. Where there was strong correlation (Pearson r>0.4) between the predictor variables, the earliest associated post-treatment response and the adverse effect with the strongest association were included in the multivariate model. Clinical and demographic variables, previously shown (Leaver et al., 2013) to be associated with either faster recovery (better self-rated general health, shorter duration of symptoms, being a smoker, and absence of concomitant upper back pain or headache) or higher disability (concomitant upper or lower back pain, older age, and previous sick leave for neck pain) were also included in the multivariate models. Data and residuals were explored to ensure that all assumptions for the use of linear regression analysis were met (Zuur et al., 2010).

The consistency between post-treatment pain scores recorded by the treating therapist and those recorded by the patients in their diaries 24-hours after a treatment session was tested using paired-samples *t*-tests.

RESULTS

Participant characteristics

One hundred and eighty-one participants were recruited. Of the 237 patients screened, 56 were excluded due to either not meeting the eligibility criteria (n = 46) or declining to participate (n = 10). Five participants withdrew from the study before the three-month follow-up point. These participants were included in the survival analysis and were censored at the date of last data collection. Two of the participants who were lost to follow-up completed their course of treatment and were included in all analyses that were related to the two-week treatment period. Three participants withdrew from the study without completing the course of treatment and were

excluded from all analyses. Baseline participant characteristics are presented in Table 1. The cohort had an average age of 39 years, with two-thirds of participants being female. Participants had moderate neck pain (NRS 6.2), moderate disability (NDI 16/50) and were seeking treatment on average three weeks into the episode of neck pain. Concomitant symptoms occurred frequently, particularly pain affecting the upper limb (79.6%), head (64.6%) and upper back (63.5%).

Clinical course of neck pain during a episode of manual therapy care

The clinical course of neck pain over the two-week treatment period, determined by serial pre- and post-treatment pain scores featured a 'descending saw-tooth' pattern of recovery (Figure 1). On each occasion of treatment there was a statistically significant improvement in pain within the session, resulting in a trajectory of cumulative improvement across the treatment period. There was also a consistent pattern of small but statistically significant increases in neck pain between each treatment session. These small relapses did not, on any occasion reach the level of the preceding pre-treatment score.

Relationship between within session changes in symptoms and outcome

There was significant (p<0.1) univariate association between time taken to recover from the episode of neck pain and several of the response to treatment variables including; cumulative post-treatment change in pain from baseline after the second (Exp (B)=1.2, 95% CI 1.1 to 1.3), third (Exp (B)=1.2, 95% CI 1.1 to 1.3) and fourth (Exp (B)=1.2, 95% CI 1.1 to 1.4) treatment sessions, as well as post-treatment headache (Exp (B)=0.7) and other minor adverse symptoms (Exp (B)=0.6). There was moderate correlation between the cumulative post-treatment change in pain

scores from baseline at each of the treatment sessions (Pearson's *r* 0.49, $p<0.01$). The score from the earliest treatment session with univariate association, Session 2, was included in the multivariate analysis. There was strong correlation between reports of post-treatment headache and other minor adverse effects (Pearson's *r* 1.0, $p<0.01$). The presence of post-treatment headache was used in the multivariate analysis because it had the strongest univariate association. None of the response to treatment variables remained independently associated with recovery time after controlling for duration of symptoms, self-rated general health, and baseline headache.

There was significant ($p<0.1$) univariate association between the perceived effects of treatment at three months and cumulative post-treatment change in pain from baseline after the first (*B*=0.2, 95% CI 0.0 to 0.4), second (*B*=0.3, 95% CI 0.1 to 0.4), third (*B*=0.3, 95% CI 0.1 to 0.4) and fourth (*B*=0.4, 95% CI 0.2 to 0.5) treatment sessions. The association between the perceived effects of treatment at three months and reported adverse effects was not statistically significant. The earliest cumulative change in post-treatment pain score with univariate association to GPE, Session 1, was included in the multivariate analysis. The post-treatment change in pain from Session 1 remained independently associated (*B*=0.2, 95% CI 0.01 to 0.4) with the perceived effects of treatment at three months after controlling for concomitant upper back pain, lower back pain, older age, and previous sick leave for neck pain.

Consistency of patient-reported pain scores

There was a significant difference ($p<0.05$) between the pain scores reported to the treating practitioners and the scores recorded by participants in their diaries. On each

occasion of treatment, the average 24-hour pain scores recorded in the diaries was on average approximately one point (0-10 NRS) higher than the scores reported to the treating practitioner (Table 2).

DISCUSSION

A detailed investigation of the change in symptoms reported by patients and practitioners in response to manual therapy for neck pain has provided clinically relevant findings and has raised further clinical questions. These findings include new information about the clinical course during an episode of manual therapy care, as well as new information about the consistency between patient and practitioner reports of changes in pain. This study also provides further confirmation of the value of within-treatment changes in symptom levels and a means of predicting longer-term outcomes.

Unlike previous studies that describe a rather pessimistic outlook for patients with neck pain (Carroll et al., 2008; Hush et al., 2011), these results suggest that the prognosis is quite favorable for those with a new episode of neck pain who are identified by experienced manual therapists as suitable for manual treatments. These participants experienced large and rapid improvement in neck symptoms over the course of manual therapy treatment. The significant improvements in pain between treatment sessions were consistent with previous research exploring manual therapy in musculoskeletal pain (Cook et al., 2012), however by tracking changes in reported symptoms from treatment to treatment rather than using strict time-contingent review

points, we also saw a pattern of recovery that would have otherwise not been evident. There was a distinct pattern of a large improvement in reported pain scores within a treatment session, followed by a slight relapse between sessions and this pattern was consistent across the entire course of treatment. It is tempting to attribute the observed pattern of recovery entirely to the beneficial effects of the treatment provided. However our study did not include a no-treatment or placebo control and is therefore limited in its ability to account for the non-specific interaction effects of the treatment. A placebo-controlled trial with a similar review schedule would help to identify whether natural recovery or regression to the mean play a role in the identified pattern. Another limitation is the use of pain as the sole indicator of short-term treatment success. The findings would have been strengthened by periodically exploring other short-term outcomes measures like range of motion or function.

There is also reason for caution in interpreting the observed pattern of recovery due a possible systematic bias in reporting of symptoms. The pain scores reported by treating therapists were on average one point lower on the numerical rating scale than scores independently recorded by patients over the following day. There are several possible explanations for this finding. This discrepancy might represent the same tendency for slight relapse following treatment suggested by the between-session changes recorded by the practitioners. Alternatively, it is possible that patients under-reported their post-treatment pain to the therapist out of a desire to please or seem grateful. The use of blinded assessors for collection of pre- and post-treatment outcomes might have yielded different results. It is also possible that the mode of reporting, verbal versus written, has a systematic influence on the levels of pain reported by the participants. Despite being a simple and apparently one-dimensional

scale, the relationship between a numeral rating of pain and perceptions of recovery is complex (Hush et al., 2009). A qualitative research model could possibly be employed to further explore some of the questions raised by our observations of the difference in patient and therapists reports of pain.

Despite the differences in symptoms reported by the patients to the practitioners and those recorded by the patients, both sets of pain scores demonstrated significant and progressive improvements with each treatment session. This is important information for patients who are being treated with manual therapy for neck pain. Evidence-based guidelines for neck and low back pain and (van Tulder et al., 2006; Childs et al., 2008) emphasize the importance of providing accurate and assuring information to patients and setting expectations of recovery. For a patient, information that a brief course of treatment is likely to be effective and that their recovery will probably involve "two-steps forward, one-step back" is potentially helpful. Improving a patient's understanding of the context of a slight relapse between treatment sessions might help provide additional reassurance and decrease negative affective interpretations of relapses.

The other important finding for manual therapists and their patients was the association between the immediate responses to manual therapy treatment and longer-term outcomes. This is consistent with other studies that have demonstrated the predictive value of within-session responses on treatment outcomes (Hahne et al., 2004; Tuttle, 2005; Tuttle, 2009; O'Halloran et al., 2013), but adds information about the broader value of treatment responses beyond the treatment period. There was an independent association between within-session improvements in pain and the

perceived effects of treatment at three months after controlling for clinical and demographic variables previously found (Leaver et al., 2013) to be associated with neck-related disability. There was also a univariate association between the rate of recovery and the cumulative improvement in pain scores at the second, third and fourth treatment sessions. Whilst a progressive improvement in symptoms during a course of treatment does not predict the rate of recovery independent of the duration of pain, general health or absence of headache, it can still be a useful guide for clinicians about expected progress. There is an intuitive link between short-term and longer-term improvement, which can be incorporated into discussions with patients about their expected course of recovery.

Minor adverse events such as headache during the treatment period are of course undesirable, however our results suggest that the occurrence of such events does not necessarily affect longer-term recovery. There was no independent association between experiencing minor adverse events during the treatment period and recovery time or the perceived effects of treatment at three months. A recent randomized controlled trial(Walker et al., 2013) has shown that adverse events are common in both manual therapy treatment groups and placebo controls, suggesting that these events may be a feature of the condition rather than due to the effects of treatment. The reporting of minor increases in pain or concomitant symptoms after manual therapy might even relate to the tendency for minor regression of improvement between treatments that our results demonstrate. This information can be used to shape patients' understanding that experiencing minor adverse events may be a part of the recovery process and does not reflect impeded recovery.

Our results demonstrate than an episode of manual therapy care for patients with non-specific neck pain results in rapid resolution of symptoms and a positive prognostic outlook. By communicating the normality and relatively benign nature of minor relapses and minor adverse events during treatment, therapists can assist in shaping realistic patient expectations about recovery from the episode of neck pain. Although discrepancies and imperfections exist in the reporting styles of pain, treatment responses contain valuable information about longer-term outcomes and play a role in predicting overall treatment perception and recovery.

Conclusion

Our results demonstrate that recovery from an episode of neck pain features a pattern of significant improvements in pain coinciding with manual treatments, with small relapses in pain scores between treatments. There is a relationship between immediate improvements in pain during manual therapy treatment and speed of recovery, as well as longer-term perceived benefits of treatment.Our findings also indicate that minor adverse events or relapses during treatment are not associated with delayed recovery.

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Table 1. Baseline characteristics (*n*=181)

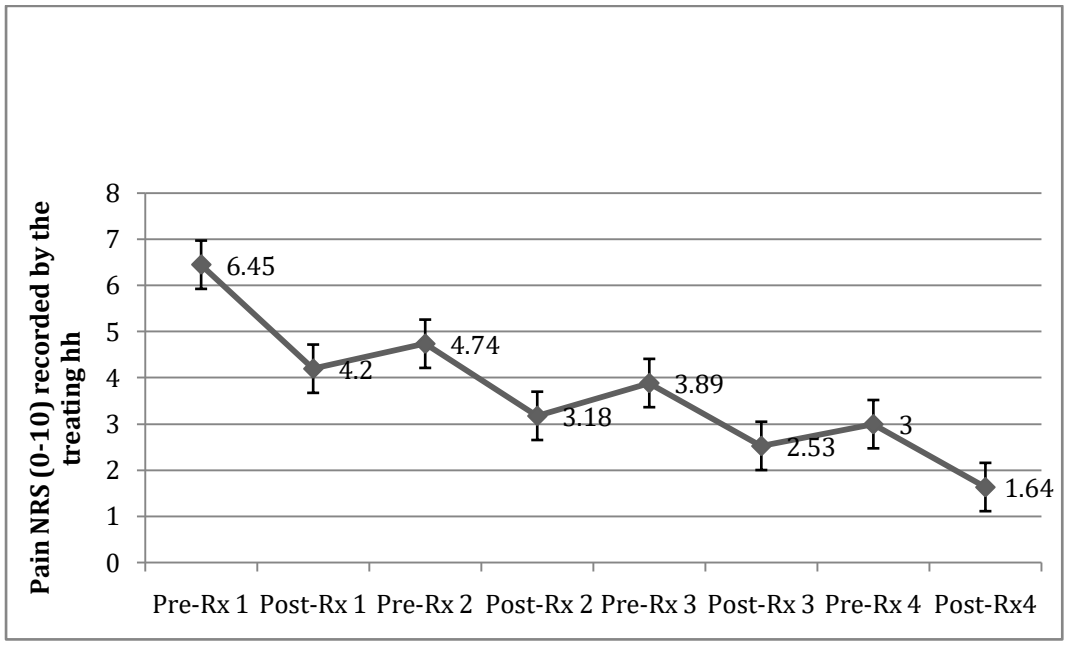
Age (years)	38.8 ±10.7
Sex-Female	117 (64.6%)
Current smoker	17 (9.4)
Neck pain duration (days)	19.5 ± 20.1
Neck-related disability (NDI)	15.5 ± 7.4
Past history of neck pain	114 (63.0%)
Past sick leave for neck pain	57 (31.5%)
Upper limb pain	144 (79.6%)
Upper back pain	115 (63.5%)
Lower back pain	71 (39.2%)
Headache	117 (64.6%)
Dizziness	56 (30.9%)
Nausea	41 (22.7%)

Data are Mean ± SD or *N*(%);NDI=Neck Disability Index (0-50)

Table 2. Differences between pain scores immediately reported to practitioner and pain scores entered in participant diary the following day

Treatment session	**Immediate post-treatment pain recorded by practitioner. NRS** Mean (SD)	**Average 24-hour pain recorder by patient the following day. NRS** Mean (SD)	**Mean difference NRS between practitioner and patient score. (95%CI)**
Treatment 1	4.2 (1.8)	5.4 (2.0)	1.2* (0.86 to 1.48)
Treatment 2	3.2 (1.8)	4.2 (2.2)	1.0* (0.70 to 1.31)
Treatment 3	2.5 (1.8)	3.2 (2.0)	0.7* (0.43 to 0.89)
Treatment 4	1.6 (1.6)	2.6 (2.1)	1.0* (0.71 to 1.26)

*p<0.1; NRS=Numerical rating scale (0-no pain, 10-worst possible pain)



NRS = Numerical rating scale; Rx = treatment number

Figure 1. Clinical course of neck pain (Numerical Rating Score 0–10) during an episode of manual therapy treatment demonstrating the "descending saw-tooth" pattern of immediate improvement followed by slight relapse.