AUDIOVESTIBULAR SENSORY PROCESSING IN MIGRAINE

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I, Louisa Jane Murdin, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm this has been indicated in the thesis.

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Abstract

Migraine can be conceptualised as a disorder of sensory processing, manifest by such symptoms as headache (pain), phonophobia and photophobia. Current models of migraine pathophysiology incorporate a significant role for the brainstem. Vestibular migraine (VM) is a subtype of the disorder in which significant brainstem dysfunction has been documented. The condition is known to have a significant effect on mental health. This study was designed to investigate disturbances in audiovestibular brainstem function in vestibular migraine in a four part study:

1. Otoacoustic emission suppression by contralateral noise, a test of auditory efferent pathway function, was measured in a group of 33 VM patients and compared with 31 healthy controls. Regression analysis showed a higher rate of abnormality amongst the VM group ($p=0.03$).
2. Vestibular evoked myogenic potentials were recorded in a group of 30 VM patients and compared with 35 healthy controls. Recordings showed a higher rate of abnormal responses in the VM group than amongst controls ($p=0.008$).
3. The potential for vestibular stimuli to act as migraine triggers was investigated by observing the effect of vestibular testing or a control condition on 148 individuals. Vestibular stimulation was associated with a significant increase in the probability of developing a migraine attack over the following 24 hour period ($p=0.01$).
4. Psychological symptoms of depression and anxiety were assessed using questionnaires 39 patients with VM and compared with a control group of 44 patients with dizziness of other causes. Although the VM group had a significantly higher load of symptoms of depression and anxiety, regression modelling showed that this effect was largely accounted for by an excess of dizziness symptoms.

In conclusion, this study documents a number of audiovestibular sensory processing abnormalities using a variety of techniques. Vestibular migraine has a significant effect on psychological wellbeing, largely via the associated balance symptoms.

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Chapter 1: Introduction

1.1 Migraine and its pathophysiology

1.1.1 Definitions and disease burden

Migraine has been defined as an episodic headache disorder. Diagnosis of migraine is made on clinical grounds, based largely on features of the headache and associated symptoms, according to well-accepted international criteria (Box 1)(International Headache Society Headache Classification Committee 2004). Migraine is a highly prevalent disorder, with peak incidence in the third decade. Its economic importance is illustrated by the fact that it is responsible for average work absenteeism of 2.2 days per month amongst employed sufferers (Osterhaus et al 1992). It is one of the most costly neurological disorders in the European Community at more than €27 billion per year (Berg and Stovner 2005).

Box 1 International Headache Society (2004) definition of migraine without aura

All of criteria A-E must be fulfilled:
A. At least 5 attacks
B. Headache 4 – 72 hours duration
C. At least 2 of:
    -Unilateral;
    -Pulsating;
    -Moderate/severe;
    -Aggravation by routine physical activity
D. During headache at least one of
    -nausea and/or vomiting or
    -photophobia and phonophobia
E. Not attributed to another disorder

There is a considerable body of work related to the pathophysiology of migraine with and without aura that has developed over the last two decades. There still remains discussion as to whether neuronal, vascular or neuro-vascular events are the initiating process, although any pathophysiological theory must clearly account for a significant amount of neurovascular

interaction. There are a number of different mechanisms proposed to have causal pathophysiological roles.

1.1.2 Cortical spreading depression

Cortical spreading depression (CSD), analogous to the waves of Leão, has long been thought to be a key process, especially in the one fifth of migraineurs who experience aura symptoms before an attack. CSD consists of a wave of depolarisation followed by a sustained depression in cortical surface potential. The rate of spread of 2-6mm/min of CSD corresponds to the rate of spread of a visual aura from central to peripheral vision. (Tfelt-Hansen 2010) CSD is still a widely used animal and human model, but the precise mechanism of its relationship to headache in humans remains unclear.

1.1.3 Genetic factors

Familial factors are thought to have a role in the development of migraine, and genetic studies have contributed significantly to understanding of migraine pathophysiology. Migraine is known to be 50% more common among first degree relatives of sufferers than in matched controls. (Stewart et al 1996) The risk is higher for those with more disabling symptoms than for those with less disability, and higher for those with migraine with aura than migraine without aura. Studies have also shown a higher rate of concordance for monozygotic than dizygotic twins, and this effect is greater in females than males. (Larsson et al 1995) Concordance in monozygotic twins is nevertheless under 100%. Migraine is clearly genetically complex, with a non-Mendelian mode of inheritance and mutations likely in multiple genetic loci. Mutations are likely to effect changes in the threshold of susceptibility to migraine attacks.

In familial hemiplegic migraine type 1, a rare autosomal dominant form of migraine with a prolonged hemiplegic aura, various different pathogenic mutations have been documented in *CACNA1A*, a P/Q voltage gated calcium channel gene (see Table 1.I). (Ducros et al 1999) Other mutations in other

genes have also been documented to cause related phenotypes (*ATP1A2* in FHM2 (Vanmolkot et al 2007) and *SCN1A* in FHM3 (Vahedi et al 2009)). *ATP1A2* codes for a Na/K ATPase, and mutations cause changes in the sodium gradient across the cell membrane, with associated changes in synaptic neurotransmitter levels. Similarly, mutations in *SCN1A* affect transmembrane sodium flux.

There is a known association between FHM1 and basilar-type aura symptoms, and between FHM1 and chronic progressive cerebellar ataxia in 50% families.(International Headache Society Headache Classification Committee 2004)

Table 1.I Some single gene mutations have been identified as causal in familial hemiplegic migraine

Gene	**Locus**	**Gene product**	**Migraine subtype**	**Notes**
CACNA1A	19p13	alpha 1 subunit of voltage gated calcium channel	FHM type 1	at least 17 mutations identified; animal models exist
ATP1A2	1q23	loss of function of alpha2 NaKATPase	FHM type 2	at least 11 mutations identified; animal models exist
SCN1A	2q24	alpha1 subunit of voltage gated Na channel	FHM type 3	at least 2 mutations identified

There are also a number of other genetic associations of migraine, including *MTHFR*, *ACE*, *ETA*, and *PGR*, (Lee et al 2007; Rubino et al 2009; Tzourio et al 2001) the latter being an association specific to migraine with vertigo. The relative contribution of each is yet to be verified and quantified in different populations.

1.1.4 Evidence from channelopathies

Ion channel function is critical in the regulation of tissue excitability. Channelopathies are a group of disorders that have been shown to be caused by ion channel dysfunction (Catterall et al 2008). The group includes, for example, hypo- and hyperkalaemic periodic paralysis and also the various forms of episodic ataxia. Migraine shares several clinical features with known channelopathies such as an episodic nature with characteristic triggers. Additionally, many channelopathies exhibit migraine attacks as part of the phenotype. Examples include episodic ataxia type II (Subramony et al 2003) and the CADASIL syndrome (Pantoni et al 2010). These are part of a group of single gene disorders, for which pathogenic genetic mutations are known, that have a strong association with migraine. Recently a potassium channel genetic mutation has been identified in the *TRESK* gene that co-segregated in a large pedigree of individuals with migraine with aura (Lafreniere et al 2010).

1.1.5 Evidence from imaging

Models of migraine pathophysiology acknowledge that the brainstem plays a key role in the genesis of the clinical features of migraine. Rostral brainstem vascular malformation causing chronic migraine is reported (Goadsby 2002; Lafreniere, Cader, Poulin, Andres-Enguix, Simoneau, Gupta, Boisvert, Lafreniere, McLaughlan, Dube, Marcinkiewicz, Ramagopalan, Ansorge, Brais, Sequeiros, Pereira-Monteiro, Griffiths, Tucker, Ebers, and Rouleau 2010). Brainstem activation has been shown on PET scanning in typical spontaneous and induced migraine without aura (Bahra et al 2001; Weiller et al 1995). Furthermore, the activated brainstem areas encroach upon the location of the vestibular nuclei as identified in previous lesion-based structural magnetic resonance imaging (MRI) studies (Afridi et al 2005). Basilar-type migraine strongly suggests a brainstem location in its symptomatology, hence the nomenclature selected.

1.1.6 Evidence from neurophysiology

Trigeminal nerve activation and subsequent changes in the cerebral vasculature are widely acknowledged to be key steps in the pathology of an attack, associated with a neurogenic inflammation with release of CGRP, neurokinin A and 5-HT. These substances, when released, may cause irritation of trigeminal nerve afferents (Iadecola 2002). The role of these neuropeptides such as CGRP has also been explored (Goadsby et al 2009). CGRP is known to be released during migraine attacks (Goadsby et al 1990), and CGRP receptor antagonists are under investigation as migraine treatments (Goadsby 2008). However, it is not only the nociceptive afferent pathways that mediate a migraine attack. Disruption of the natural modulation of other sensory pathways by central structures is also relevant (Goadsby, Charbit, Andreou, Akerman, and Holland 2009). The resultant sensory sensitivity can take many forms. Sensory stimuli may act as migraine triggers (Kelman 2007; Martin et al 2006). Sensory stimuli can also exacerbate a migraine attack once initiated, so that the sufferer will show behavioural responses in the form of avoidance (Noseda et al 2010). In addition some individuals describe symptoms such as ocular discomfort induced by light known as photo-oculodynia. It has been shown that exacerbation of headache by light can occur in individuals suffering with migraine who have preserved non-image forming visual pathways but not in those with no optic nerves or eyes. In addition, the presence of migraine photophobia was associated with the presence of circadian light induced rhythms. The corresponding animal study in this paper used a retrograde immunochemical tracing technique to show that light exposure can modulate trigeminovascular thalamic neurons in the rat (Noseda, Kainz, Jakubowski, Gooley, Saper, Digre, and Burstein 2010). It is therefore suggested that thalamic processing of nociceptive and other inputs could have a role in mediating migrainous symptoms. Further evidence for a role of the thalamus comes from recent work identifying third-order thalamic neurons as a possible site of action for CGRP receptor antagonists, as administration of a CGRP receptor antagonist caused reduction in spontaneous firing rate of cells in the ventroposteromedial nucleus of the thalamus in rats (Summ et al 2010). It is not yet clear how such thalamic

neurons might link to cortical pain processing areas, since higher projections from the thalamus appear rather diffuse.

1.2. The relationships between migraine and the audiovestibular system

1.2.1 Vertigo in basilar-type migraine

Vertigo is thought of as a characteristic symptom of disorder of the vestibular system. It is globally acknowledged to be one possible symptom of the aura of basilar-type migraine (Box 2) (International Headache Society Headache Classification Committee 2004). However, this is but the first of many ways in which migraine and the audiovestibular system interact. The relationship between migraine and the sensory organs of hearing and balance is much more complex and more controversial than this one instance suggests.

Box 2 International Headache Society (2004) definition of basilar-type migraine

A. At least 2 attacks fulfilling criteria B–D
B. Aura consisting of at least two of the following fully reversible symptoms, but no motor weakness:
- -dysarthria
- -vertigo
- -tinnitus
- -hypacusia
- -diplopia
- -visual symptoms simultaneously in both temporal and nasal fields of both eyes
- -ataxia
- -decreased level of consciousness
- -simultaneously bilateral paraesthesias

C. At least one of the following:
- -at least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
- -each aura symptom lasts ≥5 and ≤60 minutes

D. Headache fulfilling criteria for migraine without aura begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder

1.2.2 Childhood periodic syndromes

The IHS classification acknowledges vertigo additionally as the cardinal symptom of benign paroxysmal vertigo of childhood. This condition is referred to the in the IHS system as one of the childhood periodic syndromes which are common migraine precursors. So, the second way in which migraine and vertigo are related is that episodic vertigo can be a childhood migraine precursor (Box 3).

Box 3. International Headache Society (2004) definition of benign paroxysmal vertigo of childhood

This probably heterogeneous disorder is characterised by recurrent brief episodic attacks of vertigo occurring without warning and resolving spontaneously in otherwise healthy children.
Diagnostic criteria:
A. At least 5 attacks fulfilling criterion B
B. Multiple episodes of severe vertigo, occurring without warning and resolving spontaneously after minutes to hours
C. Normal neurological examination, audiometry and vestibular functions between attacks
D. Normal electroencephalogram

1.2.3. "Vestibular" migraine?

Thirdly, audiovestibular symptoms are now thought to arise directly from migrainous processes. Although vestibular disorders and migraine are both common in the general population, it has been shown that they co-incide more frequently than would be expected by chance (Neuhauser et al 2001). Kayan and Hood noted that migraine was more common in patients from a specialist dizziness clinic than was tension headache (Kayan and Hood 1984). Since then various authors have commented on the high prevalence of vestibular symptoms in populations of migraineurs (Vukovic et al 2007), and of migraine in groups of patients with vestibular symptoms (Savundra et al 1997). Estimates of the prevalence of dizziness, a less specific term than vertigo, related to migraine are in the order of one third of those patients with migraine (Bayazit et al 2001). There are numerous studies documenting abnormalities of vestibular tests in migraineurs with vestibular symptoms

including the results of caloric testing and eye movement recording with rotation (Cass et al 1997; Cutrer and Baloh 1992; Dieterich and Brandt 1999; Olsson 1991; Savundra, Carroll, Davies, and Luxon 1997). This group of patients with vestibular symptoms related to migraine have been variously referred to as having migraine-related vestibulopathy, (Cass, Furman, Ankerstjerne, Balaban, Yetiser, and Aydogan 1997) vestibular migraine, (Neuhauser and Lempert 2009) migraine related dizziness, (Johnson 1998) migraine associated vertigo (Brantberg et al 2005) and migraine associated dizziness (Cutrer and Baloh 1992). Research has, in the past, been hampered by a lack of standardised terminology and internationally accepted diagnostic criteria. In terms of clinical management, there are some studies, although generally at lower levels of evidence (retrospective, uncontrolled data) that show an improvement of vertigo symptoms in these patients when treated with migraine prophylactics (Bikhazi et al 1997; Maione 2006; Reploeg and Goebel 2002). Since, however, the mode of action of antimigraine drugs is non-specific, with many of these drugs having numerous indications (e.g. betablockers are used as anxiolytics), these data most be interpreted with some caution.

In 2001 there was a seminal paper proposing clear clinical diagnostic criteria for episodic vestibular symptoms as a migrainous phenomenon outside of the context of basilar-type aura, and putting forward the term *migrainous vertigo* (Neuhauser, Leopold, von Brevern, Arnold, and Lempert 2001). This group however, has recently moved towards a different terminology, preferring the term *vestibular migraine* (Neuhauser and Lempert 2009), without changing the underlying definition. They argue that this term creates less confusion with motion sickness associated dizziness or non –vestibular dizziness. It might also be preferred since many of the vestibular symptoms which patients with migraine encounter are not vertigo *per se*, including as they do head and visual motion intolerance (Cass, Furman, Ankerstjerne, Balaban, Yetiser, and Aydogan 1997). This group also showed that, although vestibular disease and migraine are both common disorders, the co-incidence of migraine and vertigo is three times higher than would be expected by a merely statistical interaction of common disorders. Of course, this observation does not

necessarily imply that migraine is causally responsible for the episodes of vertigo that these individuals experience. It is commonly noted, however, that episodes of vertigo in such patients may or may not be temporally related to typical migraine headaches (Brantberg, Trees, and Baloh 2005; Neuhauser, Leopold, von Brevern, Arnold, and Lempert 2001). Sensitivity to vestibular (Seemungal et al 2006) and auditory stimuli in migrainous vertigo may be analogous to the increased sensitivity to visual stimuli commonly seen in migraine attacks. Motion sickness is long established as a common association of migraine, especially in childhood (Barabas et al 1983; Grunfeld et al 1998). The motion sickness induced by optokinetic stimulation in migraine patients is thought to be related to activation of the vestibular nuclei (Drummond 2002). Alterations in the calibration or gain of vestibular reflexes could account for the chronic imbalance seen in individuals with migrainous vertigo as well as the episodic attacks (Crevits and Bosman 2005). The precise pathological mechanism by which migraine might cause vertigo is unelucidated.

1.2.4 Auditory symptoms in migraine

Phonophobia, arguably an auditory symptom, is of course part of the IHS diagnostic schema for migraine, and is a characteristic symptom in migraineurs. The word “phonophobia” is derived from the Greek roots meaning “sound-fear”, and borrows its structure from behavioural psychology terminology. Originally, then, it referred to the behavioural changes associated with sound during a migraine attack, such as withdrawal from noisy environments. In current usage, especially in the neurological literature, however, it refers to the perception by the sufferer of an aversive effect of sound. This could either manifest as a dislike of the sound *per se*, or it could be manifest as exacerbation of headache pain by sound. This is the usage adopted in this thesis. In the audiological literature, the term hyperacusis is more commonly encountered. The Greek root for this word is “beyond-hearing”, referring to heightened sensitivity to sound. It is used to refer to the symptom of finding uncomfortable sound that would not normally be perceived as such (Baguley 2003). Both phonophobia and hyperacusis should

be distinguished from loudness recruitment. This is a phenomenon associated with cochlear hearing loss, and is a consequence of a reduced dynamic range for sound. Because of this reduced dynamic range, the growth of loudness function is abnormal. Hypacusia (reduced hearing) and tinnitus can also occur as basilar-type aura phenomena, although this is not common in clinical practice.

1.2.5 Epidemiological associations of migraine with vestibular disease

Fourthly, migraine is also statistically associated with a number of different peripheral and central vestibular disorders including benign paroxysmal positional vertigo (BPPV), episodic ataxia type II, and Menière's disease. It has been shown that BPPV is more common in migraineurs than would be expected by chance (Celebisoy et al 2008b; Ishiyama et al 2000; Lempert et al 2000). As an explanation for this observation, it has been speculated that inner ear damage due to vasospasm in migraineurs could predispose to BPPV (Ishiyama, Jacobson, and Baloh 2000). In favour of this idea is the record of case reports of infarction of the inner ear during migraine attacks, suggesting that ischaemic compromise can occur in the inner ear during attacks (Lee et al 2003).

The association between migraine headache and Menière's disease has long been observed (Atkinson 1962). The difficulty in distinguishing between the two disorders in some cases has caused comment, as both disorders are associated with episodic vertigo, and are defined on clinical grounds rather than objective investigations (Boyev 2005; Shepard 2006). In fact, this dilemma makes ascertainment of auditory symptoms in migraine difficult, since many authorities regard the mere presence of auditory symptoms as evidence against migraine as a diagnosis, creating a circular argument. Complex statistical algorithms which are not practical for use in everyday clinical situations have been devised (Dimitri et al 2001). To add to the diagnostic complexity, it seems that there is an association between the two conditions, such that the lifetime prevalence of migraine is increased in

patients with Menière's disease (Ibekwe et al 2008; Radtke et al 2002). In one study 28% of the patients with Menière's disease described typical migrainous headaches as associated always or sometimes with their Menière attacks. Some authors have even gone as far as to suggest an overlapping pathology between the two disorders (Baier and Dieterich 2009), although this is a highly controversial notion. There is a high prevalence of migraine in the population with Menière's disease; and high prevalence of Menière's disease in migraineurs (Radtke, Lempert, Gresty, Brookes, Bronstein, and Neuhauser 2002; Rassekh and Harker 1992). Some cases have been reported to experience migraine aura in the form of the Menière symptom complex (Rassekh and Harker 1992). Again, as for BPPV, it has been suggested that recurrent vasospasm caused by migraine attacks could result in the development of endolymphatic hydrops (Lee et al 2002).

As well as BPPV and Menière's disease, episodic ataxia type II has a strong association with migraine. These disorders are characterized by attacks of vertigo lasting hours. In episodic ataxia type II nystagmus is usually present interictally. Many cases respond to treatment with acetazolamide (Baloh et al 1997).

1.2.6 Migraine as a prognostic factor in neuro-otology

Fifthly, migraine is known to be a poor prognostic factor in recovery from acute vestibular syndromes (Best et al 2009c). This applies both to symptoms of vestibular dysfunction and to associated anxiety and depression. The reasons for this are not elucidated, although speculative pathophysiological mechanisms include involvement of neurotransmitters, especially GABA dependent systems, with a role in generation of migraine, and in psychological symptoms and in mediating central vestibular connections, or a tendency to increased intra-individual fluctuation of central neural excitability.

1.2.7 Vestibular stimuli as migraine triggers

Sixthly, the role of vestibular stimuli as potential migraine triggers should be explored. Migraine triggers are factors which elicit a single attack of migraine. Studying migraine triggers contributes to understanding of the pathophysiology of migraine, as well as contributing to practical aspects of management such as trigger avoidance. Migraine triggers are known to range from the common and well known such as lack of sleep, alcohol and menstrual cycling (Kelman 2007), to the more esoteric such as Chinook winds (Cooke et al 2000) and hair washing in Indian women (Ravishankar 2006). Other sensory stimuli in different modalities including audition (noise)(Martin, Reece, and Forsyth 2006), vision (glare) (Kelman 2007) and olfaction (perfumes) (Kelman 2007) can also act as migraine triggers. The role of purely vestibular stimuli is as yet unexplored.

1.3 Neuro-otological assessment of migraine and vestibular migraine

1.3.1 Evidence from clinical studies

In the majority of patients with vestibular migraine assessed in the interictal state, neuro-otological examination and investigations are normal (Cutrer and Baloh 1992). Audiometry is also generally normal (Battista 2004) in patients with migrainous vertigo, although sudden unilateral hearing loss is reported in a series of case reports (Lee, Whitman, Lim, Yi, Cho, Ying, and Baloh 2003). The evidence that the hearing loss in these cases is due to migraine is somewhat limited, due to the fact that it would be very difficult either to prove or disprove in an individual case. One study of patients with migraine found 14% had latency prolongations on auditory brainstem response testing (Dash et al 2008).

About a quarter of patients with migraine have peripheral vestibular abnormalities interictally, and a smaller number show central abnormalities (Furman et al 2003). For caloric testing and eye movement recording techniques, the proportion of abnormalities is of the order of 20% for a canal paresis and 10% for a directional preponderance (Celebisoy et al 2008a;

Cutrer and Baloh 1992; Dieterich and Brandt 1999). These abnormalities can also be noted in individuals with non-migrainous vestibular disease and in migraineurs with no vestibular symptoms (Harno et al 2003). These abnormalities cannot, therefore, be used to establish a diagnosis of vestibular migraine. The proportion of patients with vestibular migraine who exhibit objective signs of vestibular dysfunction rises when they are assessed during an attack. In a study of ictal eye movements in vestibular migraine, 14/20 showed pathological nystagmus of various types including spontaneous vestibular or central nystagmus, positional nystagmus and various combinations of these (von Brevern et al 2005). These abnormalities suggest significant brainstem dysfunction in this group of patients.

Various electrophysiological techniques have confirmed interictal abnormalities in different groups of migraineurs consisting of lack of habituation of evoked potentials, including cortical auditory evoked potentials. A small study of patients with migraine and vestibular symptoms showed a larger modulation component of the otolith-ocular reflex than normal controls, and increased sway on posturography (Furman et al 2005b).

Neuro-otological investigation of vestibular migraine to date has failed to show any single abnormality which occurs with sufficient frequency to be of diagnostic utility as a biomarker. The overall picture from the literature shows a mixture of central and peripheral findings occurring in a minority of patients interictally, increasing ictally, with no single abnormality of either structure or function being implicated.

1.3.2 The neurophysiological interface between migraine and vestibular disease

Current explanations of the pathophysiological mechanism of vestibular migraine thus remain largely based on what is known about migraine in general and plausible ways in which this could relate to peripheral or central vestibular structures.

There are also neuro-pharmacological interactions between the migraine and the vestibular system. There are animal models which have been developed, involving plasma extravasation in the inner ear after 5-HT administration (Koo and Balaban 2006).
This model showed parallel plasma extravasation in the vestibular periphery and meninges in a murine model of neurogenic migraine. Sites of action of triptans, well established as anti-migraine drugs are present in both the vestibular and trigeminal ganglia and the vestibular and trigeminal nuclei. Areas encroaching on the vestibular nuclear areas have been seen to be activated has during PET scanning of migraine attacks (Afridi, Giffin, Kaube, Friston, Ward, Frackowiak, and Goadsby 2005). Both spontaneous and glyceryl trinitrate induced (Afridi, Giffin, Kaube, Friston, Ward, Frackowiak, and Goadsby 2005; Bahra, Matharu, Buchel, Frackowiak, and Goadsby 2001) migraine headaches are accompanied by increased cerebral blood flow in a region of the dorsal and dorsolateral pons that appears to include portions of the vestibular nuclei, medial parabrachial nucleus, locus coeruleus and raphe nuclei (Moore and Bloom 1979). A large proportion of vestibular ganglia are immunopositive for receptor targets of triptans, such as 5-HT1B, 5HT1D and 5-HT1F (Ahn and Balaban 2010). It is known that there are trigeminal nerve afferent endings within the inner ear which could theoretically be activated in an attack of vestibular migraine (Vass et al 1998a). In addition, the trigeminal ganglion provides sensory innervation to the vertebrobasilar, anterior inferior cerebellar and labyrinthine arteries, providing further neuroanatomical connection between the two systems (Vass et al 2004).

Cortical spreading depression could be relevant in some cases, especially in the minority whose vertigo conforms to the known pattern of aura. It has been noted that trigeminal nerve activation by painful stimulation of the forehead produces or modifies nystagmus in migraineurs but not in healthy controls (Marano et al 2005). This observation shows the potential for a pathophysiological link between vestibular symptoms and headache. In addition, as outlined above, there is evidence of significant brainstem dysfunction in the acute phase of attacks seen in eye movement recordings of

nystagmus. There is therefore a need to investigate pathophysiological sensory processing in individuals with migraine and vestibular disease, and this could reasonably focus on audiovestibular brainstem function. Two potentially useful techniques for executing such an assessment are the recording of vestibular evoked myogenic potentials, and the suppression of otoacoustic emissions by contralateral noise, since both techniques assess pathways travelling through the brainstem.

1.4 Effect of vestibular migraine on individual sufferers.

Vestibular migraine is common, with an estimated lifetime prevalence of 0.98% ascertained by a prospective population based telephone interview study in Germany (Neuhauser et al 2006). Two thirds of those who had VM according to Neuhauser's original criteria (Neuhauser, Leopold, von Brevern, Arnold, and Lempert 2001) had sought medical help, but only one fifth of these had been correctly diagnosed. 37% had seen more than one specialist in the course of the condition. The data from this study also suggest a significant impact of symptoms on quality of life, although the confidence intervals in the patient group are wide due to the small numbers of individuals who had suffered an attack in the study window (previous four weeks). Notably, patients with vestibular migraine scored worst on the mental health and emotional wellbeing domains. This is in keeping with literature noting the effect of both migraine and vestibular disease on mental health (discussed in more detail below). It is known that vestibular migraine has a negative effect on mental health, but it is not known to what extent the different components of the condition (migraine symptoms and vestibular symptoms) contribute to this situation.

Chapter 2. Methodology

2.1 Research hypotheses

2.1.1 Major hypothesis

- Migraine in general, and vestibular migraine (VM) in particular, are characterised by excessive and inappropriate responses to audiovestibular sensory stimuli.

2.1.2 Subsidiary hypotheses

- The effects of altered sensory modulation in individuals with VM can be demonstrated using the following techniques:
    - Assessment of objective audiovestibular function using:
        - vestibular evoked myogenic potentials; and
        - otoacoustic emission recordings including suppression by contralateral noise
    - Clinical responses to vestibular stimuli i.e. a “trigger” effect of sensory stimulation
- The recognised psychological effects of vestibular migraine are due to a synergistic effect between the migraine and vestibular symptoms, so that those with vestibular migraine experience greater psychological symptom load than non-migrainous dizzy controls.

2.2 Setting

The study was divided into four subsections, and more detailed descriptions of participants and methods are given in the chapters describing these subsections below. Chapter 3 of this thesis describes the subsection

concerning otoacoustic emissions and suppression, chapter 4 describes the use of vestibular evoked myogenic potentials, chapter 5 the investigation of vestibular stimuli as a potential migraine trigger and chapter 6 describes the psychological symptoms associated with vestibular migraine. This introductory section describes general principles which apply to the study as a whole.

Patients attending the Neuro-otology and Neurology clinics in a specialist neurological hospital between June 2007 and July 2009 were approached to participate prospectively. The study was conducted with the approval of an institutional ethical standards committee on human experimentation (UCLH Alpha Committee Ref 07/Q0502/30). All participants gave written informed consent to be in the study.

2.3 Definitions

Migraine was defined according to the criteria of the ICHD-II.(International Headache Society Headache Classification Committee 2004) Migrainous vertigo (vestibular migraine) was defined according to the criteria of Neuhauser *et al* (Neuhauser, Leopold, von Brevern, Arnold, and Lempert 2001) for "definite" migrainous vertigo, which incorporate the requirement for a diagnosis of migraine according to IHS (2004) criteria (See Box 4). Diagnosis was confirmed using a semi-structured interview / questionnaire (see appendix 1).

2.4 Participants

Participants were excluded if they had any neurological, medical or orthopaedic problem that could interfere with test procedures. All subjects had normal neurological examination with no fixed signs of brainstem dysfunction.

Box 4: Diagnosis of definite migrainous vertigo (vestibular migraine)

The following criteria must be met

-Episodic vestibular symptoms of at least moderate severity (rotational vertigo, other illusory self or object motion, positional vertigo, head motion intolerance, i.e. sensation of imbalance or illusory self or object motion that is provoked by head motion)

-Migraine according to the ICHD-II criteria

-At least one of the following migrainous symptoms during at least two vertiginous attacks: migrainous headache; photophobia; phonophobia; visual or other auras

-Other causes ruled out by appropriate investigations

Vestibular symptoms were defined as "mild" if they did not interfere with daily activities, "moderate" if they interfered with but did not impede daily activities, and "severe" if patients could not continue daily activities.

41 patients participated in the otoacoustic emission study (chapter 3) and/or the vestibular evoked myogenic potential study (chapter 4). Some patients participated in more than one part of the study (33 participated in both otoacoustic emissions and vestibular evoked myogenic potentials; 6 in only the otoacoustic emission study and 2 in only the vestibular evoked myogenic potential study). All these patients also completed the questionnaires for the psychopathology study (chapter 6). The 123 patients described in chapter 5 comprised an entirely separate population.

Controls were recruited from hospital staff, colleagues and friends. They were required to be well, with no known otological or vestibular problems. All controls were asked about the experience of headache, and excluded if they had ever suffered spontaneous headaches with migrainous features (severe pain or headache associated with nausea or photophobia/phonophobia).

2.5 Sample size estimation

Sample size was calculated prior to data collection to estimate numbers required. It had been previously reported (Murofushi et al 2001) that in

vestibular evoked myogenic potentials with a similar protocol to that used in this thesis, mean p13 latency was 17.3 ms with SD 2.6 ms. In normal controls the equivalent figures were 11.8 ms and 0.86 ms, with the upper limit of the normal range estimated as 13.5 ms. To detect a difference in latencies of 2 ms or more, power required 95% for significance level 0.05 with F = 12.99 (from table). Using $n > 2F\sigma 2/d2$ requires approximately 44 subjects. Hence it was decided to aim for n=40 subjects in the electrophysiology studies.

2.6 Audiovestibular tests

Participants underwent baseline audiovestibular testing according to the following protocols. Tympanometry was carried out to ensure normal middle ear function (GSI 33 Middle Ear analyser). Normal results were a type A trace according to Jerger's classification, with compliance between 0.3 and 1.4ml and pressure between -100 and +100 daPa (Jerger J 1970). Pure tone audiometry was carried out according to British Society of Audiology standard procedures (British Society of Audiology 1981) on a GSI 61 Clinical Audiometer instrument in sound treated booths.

Auditory brainstem response (ABR) tests and/or stapedius reflex thresholds were measured on all patients. ABR was carried out with a Nicolet EP4 system using a 90 dB nHL click at 11.1/s. Stapedius reflex thresholds were measured on the GSI 33 Middle Ear Analyser at 500 Hz and 1,2, and 4 kHz. All patients who were participants in the electrophysiology studies (chapters 3 and 4) had normal ABR (normal waveforms, latencies of I, III and V, and interaural wave V symmetry according to departmental norms) and/or stapedius reflex thresholds (between 80 and 100 dB SPL, difference <10 dB on adjacent frequencies (Katz 1994)).

For vestibular testing, horizontal direct current electro-oculography was carried out according to a standard protocol: gaze testing (+/- 30° searching for nystagmus in the light and darkness), sinusoidal rotation, vestibulo-ocular reflex suppression, impulsive rotation, optokinetic stimulation and smooth pursuit. Sinusoidal rotation was carried out in the dark using a motorised

chair driven at a frequency of 0.2 Hz, peak velocity of +/- 30°/s for a duration of approximately eight cycles. Ability to suppress the vestibulo-ocular was then tested by repeating the sinusoidal stimuli and asking the patient to visually fixate on a target which moves with them (i.e. stationary with respect to the patient), for approximately four cycles. Impulsive rotation comprised velocity steps at +/- 60 °/s until nystagmus subsides (approximately 45 seconds, maximum of 100 seconds; approximate acceleration/deceleration (-140 °/s2). In full field optokinetic testing the subject was stationary whilst the surrounding striped curtain revolved at a speed of 40 °/s, alternating direction every 5-10s for a total of approximately 30s. For smooth pursuit subjects were required to track a laser-projected target moving in a sinusoidal fashion at 0.2, 0.3 and 0.4 Hz. All patients in the vestibular test group underwent bithermal water caloric testing using a 40 second irrigation in each ear at 44°C and 30°C according to the Fitzgerald-Hallpike technique or videonystagmography. Canal paresis was calculated using nystagmus duration according to Jongkees' formula: [(Right 30°C + Right 44°C) - (Left 44°C + left 30°C)]/(Right 30°C + Left 44°C + Right 44°C + Left 30°C). Likewise, directional preponderance was calculated as [(Right 30°C + Left 44°C) - (Right 44°C + left 30°C)]/(Right 30°C + Left 44°C + Right 44°C + Left 30°C). For canal paresis, departmental norms for used (8% for Fitzgerald-Hallpike or 20% for VNG). For directional preponderance, 12% for Fitzgerald-Hallpike or 20% for VNG are the normal values.

2.7 Overview of Methods

More detailed descriptions of the methods are given in each chapter. A brief overview is given here for orientation to the study as a whole.

2.7.1 Otoacoustic emission suppression study

Patients with vestibular migraine underwent otoacoustic emission suppression testing (for detailed description of technique and protocols see chapter 3). They were compared with healthy non-migrainous controls in a

case-control study design. The principal outcome of interest was the degree of otoacoustic emission suppression.

2.7.2. Vestibular evoked myogenic potential study

Patients with vestibular migraine underwent cervical vestibular evoked myogenic potential testing (for detailed description of technique and protocols see chapter 4). They were compared with healthy non-migrainous controls in a case-control study design. The principal outcomes of interest were the amplitude, latency and threshold of the vestibular evoked myogenic potential response.

2.7.3. Vestibular stimuli as migraine triggers

In this study, patients attending the neurology or neuro-otology clinic were classified as having migraine or not according to standard IHS criteria. They were allocated, prospectively, according to the treating physician's decision, to having a vestibular test protocol (Test group) or not (Control group). All participants were contacted after 24 hours to determine the presence or absence of migrainous symptoms in the 24 hours immediately after testing. The test and control groups were compared to establish whether there was a difference in the frequency of migraine headaches after testing (or hospital visit with no tests). More detailed description of the methods is given in chapter 5.

2.7.4 Psychopathology in vestibular migraine

The patients participating in the otoacoustic emission and vestibular evoked myogenic potential parts of the study also completed questionnaires to determine psychological symptomatology including the Beck Anxiety and Depression Inventories, and the Vertigo Symptom Scales (in Appendices 4, 5 and 6). A group of patients who were consulting for symptoms of dizziness but did not have migraine acted as controls. The scores were analysed using regression modelling to evaluate the factors which had an effect on

determining levels of anxiety and depression symptom load in the two groups. More details are given in Chapter 6.

Chapter 3. Otoacoustic emission suppression by contralateral noise in the assessment of vestibular migraine

3.1 Principles and context.

Otoacoustic emission (OAE) suppression testing is another technique that can be used to assess audiovestibular sensory processing (Murdin and Davies 2008). The technique was developed by Collet (Veuillet et al 1996), Kemp (Kemp 1978) and Berlin (Berlin et al 1993), among others. It is based on the principle that when otoacoustic emissions are recorded with and without the presence of noise, recording in the noise condition shows reduced amplitude in comparison with the quiet condition (Murdin and Davies 2008). The afferent arm of the reflex assessed by OAE suppression travels in the auditory nerve, and the efferent arm along the inferior vestibular nerve. The efferent auditory pathway is postulated to have a role in modifying the gain of cochlear responses, perhaps to protect from excessive noise or aid in selective attention. It could thus be particularly suitable to assess patients with vestibular migraine in whom phonophobia is a common symptom. Indeed, phonophobia is listed as one of the key diagnostic symptoms in the current International Headache Society (2004) definition of migraine (see Chapter 1 Box 1). (International Headache Society Headache Classification Committee 2004)

3.2. Anatomical structures and pathways

There are two olivofugal pathways to the auditory efferent system. The first is the medial olivocochlear bundle (MOC), running from the superior olivary complex to synapse on the outer hair cells of the cochlea (Figure 2.1). Fibres in the MOC, which are mostly large and myelinated, travel predominantly along the contralateral inferior vestibular nerve, having crossed over the midline once in the trapezoid body (de Venecia et al 2005). The second olivofugal path

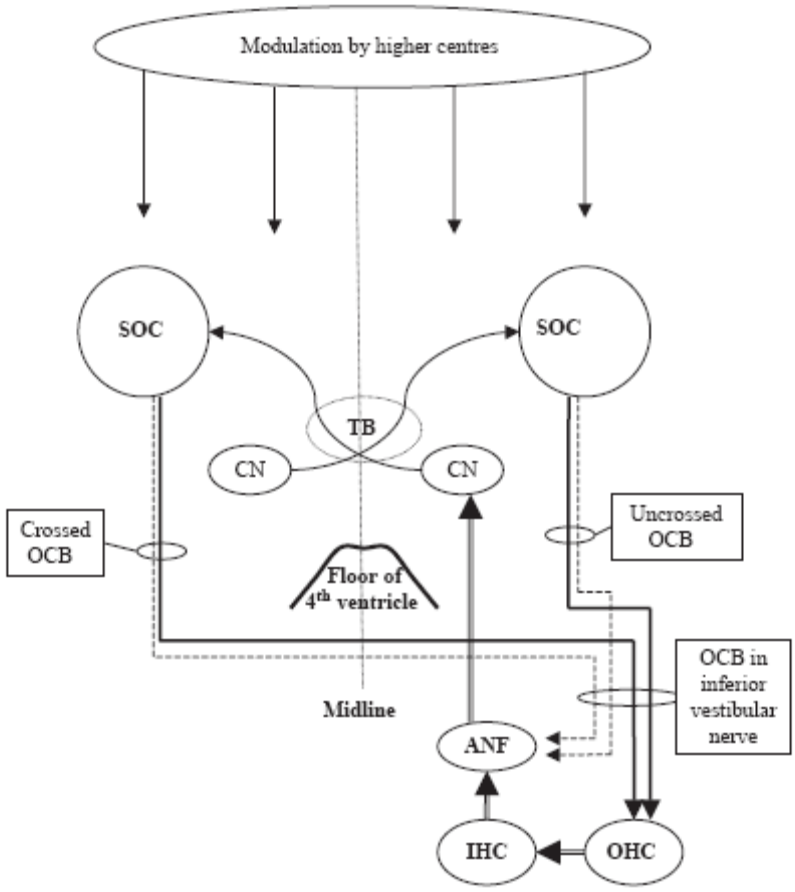
is the lateral olivocochlear (LOC) bundle, consisting mainly of smaller unmyelinated fibres, and it is predominantly ipsilateral. It originates in the superior olivary complex and crossing over once in the trapezoid body and once in the crossed olivocochlear bundle at the floor of the fourth ventricle. MOC neurones synapse directly onto outer hair cells, whereas LOC neurones synapse onto the afferent auditory nerve fibres (Guinan, Jr. 2006). Both pathways are subject to "top down" modulation by the auditory cortex (Xiao and Suga 2002).

Outer hair cell activity modulating cochlear amplifier gain is thought to be the cause of otoacoustic emissions. They are by-products of outer hair cell activity, a consequence of their contractile characteristics (owing to the presence of myosin filaments). Outer hair cells contract in response to sound waves and to passive vibrations of the basilar membrane, with both anterograde and retrograde transmission. The retrograde transmission is measured as otoacoustic emissions. Since MOC neurones synapse directly onto the outer hair cells, it is not surprising that changes in MOC activity influence OAE properties. Noise stimulation activates the efferent pathway and suppresses the OAE amplitude, and additionally causes a phase shift of the OAE response (Ryan et al 1991). This suppressive effect has been demonstrated in spontaneous (Mott et al 1989), transient evoked (Collet et al 1992), stimulus frequency (Guinan, Jr. 2006) and distortion product OAEs. (Wagner et al 2005).

As the auditory efferent system travels along the inferior vestibular nerve, vestibular nerve section presumably disrupts its normal function. OAE suppression is indeed lost in subjects with vestibular deafferentation due to vestibular nerve section (Williams et al 1993). OAE suppression has been observed in patients with Bell's palsy and other conditions with absent middle ear reflexes, suggesting the phenomenon is not mediated via the middle ear reflexes (Giraud et al 1995). The phenomenon is highly frequency specific, which is not a feature of middle ear reflexes, and was shown to be robustly observable at intensities below the acoustic reflex threshold (Veuillet et al 1991). In addition, animal studies have shown+- that crossed olivocochlear

bundle stimulation suppresses OAEs even when middle ear muscles have been severed (Mountain 1980).

Figure 3.1. Lateral olivocochlear pathway (LOC) is shown as dashed lines. Medial olivocochlear pathway (MOC) is shown as bold lines. Lateral olivocochlear axons innervate the dendrites of radial afferent fibres under the inner hair cells. Developed from (Ceranic 2007).



CN: cochlear nucleus
TB: trapezoid body
SOC: superior olivary complex
OCB: olivocochlear bundle
ANF: auditory nerve fibre
IHC: inner hair cell
OHC: outer hair cell

Ascending pathways are shown as double lines. ····➡ .

Lateral olivocochlear path are shown as dashed lines. -·➡ .

Medial olivocochlear path are shown as bold lines. ···➡

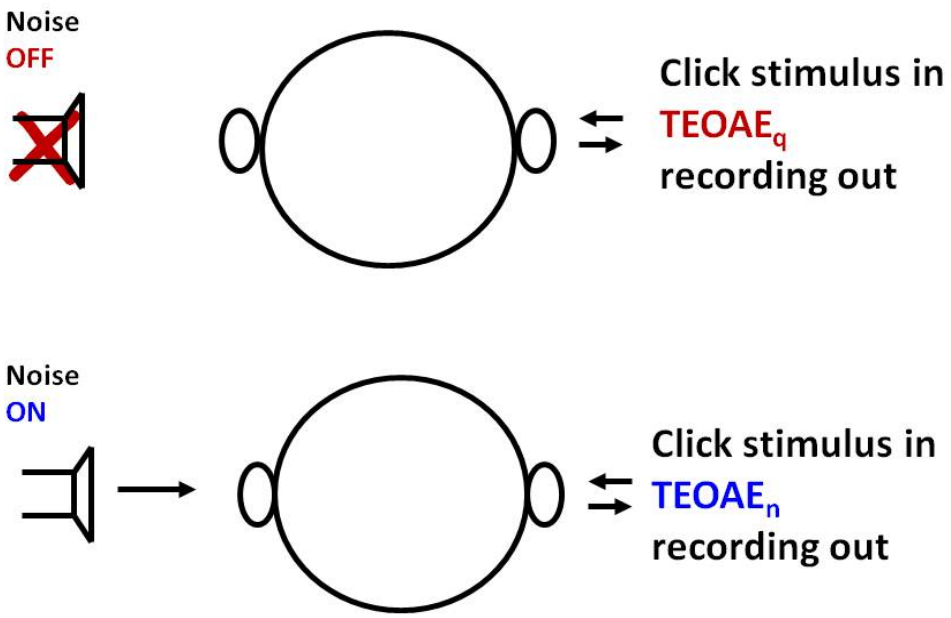
There are many hypotheses as to the physiological role of the MOC system. It has been suggested to shift the dynamic range of hearing to enhance signal detection and frequency selectivity (May et al 2004), to protect from excessive noise (Brown et al 1998; Maison and Liberman 2000) and aid in selective attention (Hill et al 1997).

3.3. Principles of OAE suppression technique

In essence, the OAE is recorded using an evoking click or tone both with and without suppressive noise, and the difference in amplitude of the two responses is calculated (TEOAEq – TEOAEn, Figure 3.2).

Parameters relating to both evocation of the OAE and to the suppressive noise can affect results.

Figure 3. 2 The principle of recording OAE suppression by contralateral noise. The value of suppression is equal to the difference between TEOAEq and TEOAEn.



3.3.1 OAE evoking stimulus parameters

Suppression effects are larger as stimulus level decreases, because cochlear amplifier gain is largest at low evoking stimulus presentation levels (Moulin et al 1993). A low intensity stimulus also avoids the problem of confounding middle ear muscle contraction. However, the stimulus must be big enough to produce a recordable OAE, detectable above the noise floor and for the suppressive effect to be measurable. For transient click evoked OAE suppression in normal hearing individuals, a click stimulus of around 60 dB SPL may be suitable. The uniform click is often selected in favour of the usual reverse-polarity click because the evoked responses will therefore contain a larger proportion of the cochlear responses. Since the outcome of interest is an intra-individual difference, the need for a reverse polarity click to distinguish artefact from response is lessened.

3.3.2. Suppressive noise stimulus parameters

The MOC can be activated by low (just audible) levels of noise, and the suppressive effect increases with higher intensities (Collet et al 1990; Ryan, Kemp, and Hinchcliffe 1991). As is the case for the OAE evoking stimulus, the noise stimulus must use a sound intensity which is too small to elicit middle ear muscle contraction, i.e. less than around 75 dB SPL for broadband noise. Many groups have found that white or broadband noise at 30 to 40 dB SL is adequate (Collet, Veuillet, Bene, and Morgon 1992; De Ceulaer et al 2001; Hood et al 2003). Testing can be done using ipsi-, contra- or bilateral noise, and most centres have used contralateral noise (Attias et al 2005; Ceranic et al 1998; Collet, Veuillet, Bene, and Morgon 1992; Norman and Thornton 1993). It is reported that the suppressive effect is greatest using binaural noise, with a lesser effect from ipsilateral noise and, in fact, contralateral noise results in the weakest suppression (Hurley et al 2002). However, using ipsilateral or binaural noise creates problems in distinguishing signal from noise in the responses, and thus requires more complex analysis or the use of forward masking techniques. Hence, for simplicity, the use of contralateral noise is often preferred.

3.3.3. Which type of OAE?

For greatest frequency specificity, distortion product OAEs may be preferred. The main disadvantage of using distortion product OAEs is that the effect of noise is not always suppressive in normal subjects (Riga et al 2007). The magnitude of the effect is also small. These two factors mean it is difficult to interpret single measurements. Stimulus frequency OAEs are technically more difficult to record, but are perhaps more easily interpretable (Guinan, Jr. 2006). Most clinical work has been done using transient evoked OAEs (TEOAEs).

3.3.4. Interpretation of results

Significant inter- and intra-individual variability of contralateral suppression of TEOAEs has been reported in 6 healthy normals aged 22 – 67 (Graham and Hazell 1994). Giraud *et al* (Giraud, Collet, Chery-Croze, Magnan, and Chays 1995) confirmed the presence of TEOAE suppression in 20 normal subjects, but in some the suppression was weak, and in several cases very asymmetric. This study found no difference between left and right ears and no testing order effect when results were averaged across all individuals. Wagner (Wagner, Heppelmann, Kuehn, Tisch, Vonthein, and Zenner 2005) however found good test-rest reliability in young healthy military service subjects using distortion product OAEs. It seems likely that factors such as repeatability vary considerably depending on the protocol selected, and possibly also on subject factors such as age.

Morand-Villeneuve and colleagues in Lyon reported an asymmetrical effect of benzodiazepines on OAE suppression, with oxazepam having a larger impact on the right than the left ear (Morand-Villeneuve et al 2005). This group has also noted asymmetries in suppression which co-vary with gender and handedness in people under 34 (Khalfa et al 1998). Values of suppression are greater in the right ear in right handed people, but this asymmetry effect is not seen in left handed people, in whom both ears show values similar to the right

ear of right handed people.

Using contralateral noise and TEOAEs, a suppression level below 1.0 dB SPL is often taken as abnormal. This figure gave a false negative rate of about 17% in extrinsic brainstem lesions (n=18) and 0% in intrinsic brainstem lesions (n=11) (Prasher et al 1994).

It has been reported that the suppressive effect is smaller in older subjects than in a younger group (Castor et al 1994). Conflicting reports exist however, showing no effect of age, using a broadly similar protocol (Quaranta et al 2001). A decrease in suppression of distortion product OAEs in middle and older aged groups is reported when compared to younger subjects (Kim et al 2002). It seems likely that there is a gradual fall-off in efferent system function with increasing age. This may be compared with the effect of age on TEOAE amplitude.

At the other end of the age scale, the phenomenon is absent in many premature newborns up to around 34 weeks gestation and becomes increasingly apparent with postnatal maturity (Chabert et al 2006). However, as the afferent arm of the reflex was not assessed independently in this report, it is not possible to tell from these data whether this delay is related to the known maturational effect in the afferent arm, or can be localised to the efferent pathway.

Middle and outer ear factors can have a big effect on recording of OAEs, and suppressive effects may be masked if recording conditions are not optimal. It is considered prudent where possible to make recordings where tympanometry is normal and the external ear is clear of wax and debris; otherwise false positive results may be obtained.

The suppressive effect is observed during sleep but in almost half of cases no suppression is seen at the onset of sleep. Some authors recommend that subjects read during testing to prevent any possible reduction in effect (De

Ceulaer, Yperman, Daemers, Van Driessche, Somers, Offeciers, and Govaerts 2001).

Direct electrical stimulation of MOC fibres is used in animal studies, and MOC effects seem to be larger in these experiments. When OAE suppression is compared with cochlear neural responses as a function of MOC stimulation, cochlear neural responses always show a greater response. In other words, the use of OAE techniques to assess efferent system activity is subject to some idiosyncrasy due to the properties of TEOAEs (Guinan, Jr. 2006). Some patients do not lose suppression completely after vestibular neurotomy (Giraud, Collet, Chery-Croze, Magnan, and Chays 1995), suggesting either that some efferent fibres do not travel in the vestibular nerve, or that middle ear reflexes have a role to play in these circumstances

TEOAE recording, and so also suppression testing, is an imperfect assay of cochlear activity and efferent pathway function. Only a fraction of the acoustic energy emitted by the cochlea can be recorded in clinical scenarios, and the use of suppression testing to assay efferent function is clearly somewhat indirect.

3.4 Clinical applications

3.4.1 Neurological disorders: Cerebello-pontine angle tumours.

Four cases of vestibular schwannoma (acoustic neuroma) are reported in which the amplitude of distortion product OAEs was larger in the affected than the unaffected side, suggesting disinhibition and therefore possible involvement of the MOC system (Gouveris and Mann 2004). Other work is broadly consistent with this hypothesis, although these cases were selected retrospectively from pool of 106 patients, suggesting the effect is not a common one. One study compared TEOAE suppression by contralateral noise in 17 patients with unilateral cerebello-pontine angle tumours with normal controls (Ferguson et al 2001). There was no difference between ears in the patient group. However, there was a difference between control ears and

patient ears (with or without tumour), with normal control subjects showing greater suppressive effects. This suggests that there is impairment of the afferent and efferent pathways on both sides occurring within the tumour group. This may be explained by the diversity of lesion size and precise location.

There are also reports of paradoxical effects of noise on OAE amplitude in patients with acoustic neuroma; that is, an increase in amplitude with noise stimulation (Quaranta et al 2000). The authors speculate that the pathology could impact adaptation occurring at the level of efferent nerve fibre transmitter release, enhancing outer hair cell motion response instead of suppressing it.

In a very useful and clear study of the practical use of OAE suppression as a diagnostic test, OAE suppression was studied in patients with a variety of intrinsic and extrinsic brain lesions (Prasher, Ryan, and Luxon 1994). In those with cerebello-pontine angle tumours, the affected ear showed reduced suppression, and suppression was reduced bilaterally in those with intrinsic brainstem lesions. Similarly, it has been reported that OAE suppression can be affected by cholesterol cysts of the midline petrous apex which are known to affect the efferent pathway (Hurley, Hurley, and Berlin 2002).

3.4.2 Neurological disorders: Multiple sclerosis.

In a comprehensive evaluation of 30 patients with multiple sclerosis, TEOAE suppression was significantly reduced when compared with normal controls (Coelho et al 2007). The results of this study illustrate the fact that suppression testing is a useful addition to the auditory test battery when evaluating such patients. It is worth noting however that most of the ears with abnormal suppression testing also had abnormal auditory brainstem responses, so that the lesion cannot be confidently localised to the efferent pathway.

3.4.3 Neurological disorders: Myasthenia gravis.

In an elegant pharmacological study, suppression of disortion product OAEs in patients with myasthenia gravis was examined before and after acetylcholinesterase inhibitor administration (Di Girolamo et al 2001). In the pre-administration condition there was no significant suppression. After administration however, contralateral noise produced a significant decrease of disortion product OAE amplitudes for middle frequencies (f2 between 1306 and 2600 Hz). The authors suggested that the drug-induced increase in acetylcholine availability could facilitate outer hair cell function, and that contralateral suppression of distortion product OAEs may be useful in monitoring the effectiveness of treatment. These results were independently confirmed by another group, who reported that patients with myasthenia gravis have reduced disortion product OAE suppression, but that such an effect was not seen with TEOAEs (Hamed et al 2006).

3.4.4 Audiological disorders: Tinnitus and hyperacusis

Patients with tinnitus after head injury have been shown to have both larger TEOAE amplitudes and less suppression than either normal subjects or patients with head injury but no tinnitus (Attias, Zwecker-Lazar, Nageris, Keren, and Groswasser 2005; Ceranic, Prasher, Raglan, and Luxon 1998). Patients with acute tinnitus also had less suppression of disortion product OAEs than normal controls (Riga, Papadas, Werner, and Dalchow 2007) although no difference in suppression was shown in this study between symptomatic and asymptomatic ears. It has been reported that OAE suppression can be deficient in some cases of hyperacusis (Collet, Veuillet, Bene, and Morgon 1992). A review of studies of patients who have undergone vestibular nerve section (and therefore presumed de-efferentation) showed that the majority experience no increase in complaints of tinnitus (Baguley et al 2002). Nevertheless, in individual studies up to 60% of this population do experience worsening of symptoms, and it is possible that efferent system dysfunction is relevant to an unidentified subgroup. Effects of vestibular nerve section on symptoms of hyperacusis are less well documented, although one

study reported no effect on various psychoacoustic tests of loudness adaptation in a series of 15 patients (Scharf et al 1997).

3.4.5 Audiological disorders: Hazardous noise exposure

Section of the olivocochlear bundle in chinchillas increases susceptibility to acoustic trauma (Zheng et al 1997). This effect has also been demonstrated in guinea pigs (Maison and Liberman 2000). These results have been taken to suggest that the olivocochlear system may have a role, up to a point, in protecting from noise exposure. OAE suppression is indeed reduced in human subjects exposed to noise (Desai et al 1999), and has even been mooted as a method of early identification for at-risk workers (Sliwinska-Kowalska and Kotylo 2002), although there is currently little evidence that suppression testing would have any advantage over other methods such as TEOAE measurement.

OAE suppression has been examined in military personnel after impulse noise exposure (Veuillet et al 2001). Significant correlations were obtained between audiometric threshold improvement and contralateral TEOAE suppression, with better recovery in subjects with greater MOC suppressive action. The authors suggested that the MOC system could be an underlying mechanism in post-traumatic auditory threshold recovery. However, a similar study which attempted to correlate temporary threshold shift in healthy young men with degree of contralateral suppression of DPOAEs showed no such effect (Wagner, Heppelmann, Kuehn, Tisch, Vonthein, and Zenner 2005). The relevance of this latter observation may be questioned since temporary threshold shift is known not to correlate with permanent threshold shift.

Dysfunction of the MOC may be a factor in susceptibility to the development of tinnitus or hyperacusis, especially in the context of noise induced hearing loss. Indeed, patients with noise-induced tinnitus have less suppression than normal controls or those with tinnitus due to other causes (Attias, Zwecker-Lazar, Nageris, Keren, and Groswasser 2005).

Classical musicians have been shown to have a greater degree of OAE suppression than non-musicians (Brashears et al 2003). This has been postulated to relate to sound conditioning, the phenomenon by which prior exposure to noise protects from further noise damage.

3.4.6 Audiological disorders: Auditory neuropathy/dys-synchrony

Reduced suppression is a common finding in auditory neuropathy/dys-synchrony in patients with absent auditory brainstem responses and robust TEOAEs (Hood, Berlin, Bordelon, and Rose 2003). This effect was demonstrable to an impressive extent even with a small sample of 9 cases. One hypothesis to explain this observation is that afferent dysfunction results in inability to activate the efferent response (Berlin et al 2005; Hood, Berlin, Bordelon, and Rose 2003).

3.4.7 Audiological disorders: Neonatal and paediatric hearing assessment

Neonates with normal TEOAEs but risk factors for hearing loss showed lower levels of suppression than full term neonates without risk factors (Durante and Carvallo 2008). This observation may relate to lower levels of neurological maturity in the high risk group, since, as discussed above, there is a known maturational effect (Gkoritsa et al 2007). The authors emphasise that this is a group effect and might not be detectable in individual cases, but conjecture that reduced OAE suppression might be a risk factor for developing hearing loss or auditory processing disorders. Since the subjects were selected as being at high risk for hearing loss, it remains to be proven that abnormal OAE suppression testing could provide information additional to what is known from the clinical history. Abnormal suppression of TEOAEs by contralateral noise was more common in children with auditory processing disorder than those without (Muchnik et al 2004; Sanches and Carvallo 2006). This effect has also been noted in childhood selective mutism (Bar-Haim et al 2004). If the MOC has a role in selective attention or noise suppression, it may be, perhaps rather speculatively, hypothesised that MOC

dysfunction could have a role in the development of specific language impairment by disrupting language access. However, when this hypothesis was investigated using TEOAE suppression by contralateral noise in a fairly small sample of 20 diverse children with specific language impairment, no evidence of such an effect was found (Clarke et al 2006).

3.4.8 Audiological disorders: Monitoring ototoxicity

Can OAE suppression predict susceptibility to ototoxicity from drugs such as aminoglycosides or other ototoxic drugs? The clinical studies are not yet there to answer this question, but one animal study suggested it may be possible (Halsey et al 2005). In guinea pigs, rapid efferent adaptation of DPOAE to noise predicted both number of days before onset of deafness and final threshold shift.

3.4.9 Otoacoustic emission suppression testing for migraine?

Phonophobia, heightened sensitivity to sounds or noise which would not normally cause distress, is listed as one of the key diagnostic symptoms in the current International Headache Society (2004) definition of migraine(International Headache Society Headache Classification Committee 2004). Similarly, the association of phonophobia with vestibular symptoms such as head motion intolerance is one key criterion in Neuhauser's diagnostic schema for vestibular migraine(Neuhauser, Leopold, von Brevern, Arnold, and Lempert 2001). The auditory efferent pathway assessed by otoacoustic emission suppression is thought to have a role in modulating the gain of auditory responses, and travels via the brainstem as outlined above (Figure 2.1). Otoacoustic emission suppression could therefore be hypothesised to be particularly suitable to assess patients with vestibular migraine, in whom significant brainstem dysfunction is known to occur (see Chapter 1.3), and in whom the subjective experience of heightened sensitivity to auditory and vestibular stimuli are a cardinal feature according to the standard diagnostic criteria referred to above.

This part of the study was therefore conceived to seek evidence of sensory dysmodulation as a physiological correlate of the subjective experience of heightened sensory sensitivity in vestibular migraine. The primary hypothesis was that the patients with vestibular migraine would show more extreme responses to auditory sensory stimuli than healthy controls, measurable using OAE suppression.

3.5 Methods

3.5.1 Otoacoustic emissions protocol

The underlying methods for assessing OAE suppression were developed from a published protocol developed in the same laboratory and with identical systems to that to be used in this study (Ceranic, Prasher, Raglan, and Luxon 1998). This basic protocol will now be described.

External ears were required to be clean and free of wax and external debris. Tympanometry was carried out to ensure normal middle ear function (GSI 33 Middle Ear analyser). Normal results were a type A trace according to Jerger's classification, with compliance between 0.3 and 1.4ml and pressure between -100 and +100 daPa (Jerger J 1970). Pure tone audiometry was carried out according to British Society of Audiology standard procedures on a GSI 61 Clinical Audiometer instrument. If the average pure tone threshold at 0.5, 1, 2 and 4 kHz was above 35 dB HL in either ear, or tympanometry was abnormal patients and controls were excluded from OAE measurements (Kemp et al 1990). The procedure was carried out with subjects seated in a comfortable chair.

Transient evoked otoacoustic emissions (TEOAEs) were recorded using the non-uniform click at 80 dB SPL with 260 averages on an ILO92 system (Otodynamics, UK (Kemp, Ryan, and Bray 1990)). The non-uniform click consists of three similar stimuli followed by one three times larger and of opposite polarity. The effect of this reversal of polarity is to facilitate the software in distinguishing artefact from genuine cochlear responses, since the

former will show linear growth while the latter will saturate. The response amplitude is calculated by the ILO92 hardware system over the frequency range 500Hz to 6 kHz with a time window from 2.5 to 20.5 ms. The criteria for defining presence of the TEOAE were that reproducibility should be greater than 70% and the total response should exceed the noise floor level. If TEOAEs were present with an overall amplitude of greater than 3.5 dB SPL, testing proceeded to include suppression by contralateral noise.

The ILO88 software was set to Difference B on/off function. A uniform click was presented at 60 +/-3dB SPL via the ipsilateral probe. The threshold for white noise detection was ascertained in the contralateral ear via a second insert probe. During testing, white noise was presented contralaterally at 40dB SL. The software then presents a series of runs, each of which comprises 60 responses below the noise floor, set at 48dB SPL. The time taken to obtain 60 responses therefore varied between subjects according to the background noise level generated by that individual. The runs of 60 sweeps alternated between the quiet condition (no contralateral noise) and noise condition (white noise presented contralaterally according to parameters defined above). This pattern of interleaving responses evens out any subject noise across the quiet and noise conditions. The OAE suppression response was taken as the difference between the amplitude of the response with contralateral noise and the amplitude of the response without contralateral noise. This was calculated for right and left ear for each individual.

3.5.2 The concept of total suppression

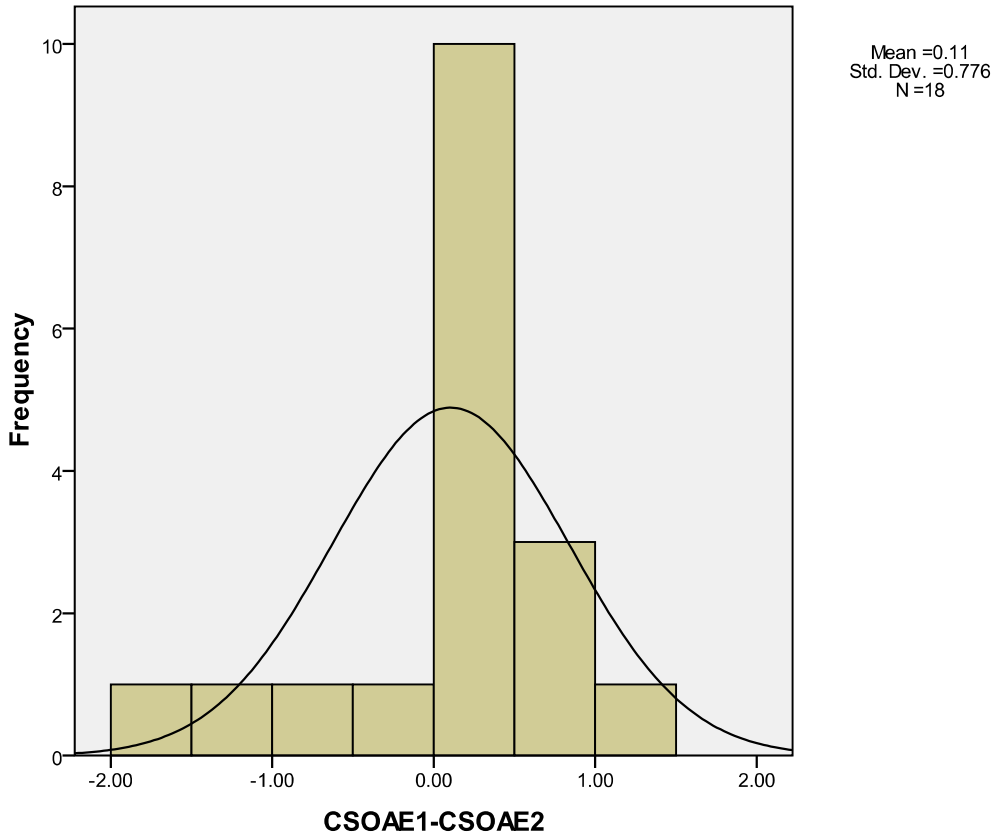
The technique as described above generates a measure of suppression for each ear, i.e. two outcomes (right and left ear) for each individual. In other studies, results have been analysed on the basis of each ear providing an independent output (Coelho, Ceranic, Prasher, Miller, and Luxon 2007). There are two reasons why this technique is not ideal for the purposes of this study. The first is mathematical: statistical tests attach more weight to findings with an increased number of measurements based on the assumption that the readings are *independent*. However the two ears in an individual are clearly

not independent measurements. In other words, mathematically speaking, it might be possible, given the value of suppression in one ear, to make predictions about suppression in the other. The second reason relates to the nature of migraine as a condition. It is, essentially, a brain disorder, and there is no reason to think that right ears should be affected any more or less than left ears. In other studies, the right and left ears are analysed separately (Hood, Berlin, Bordelon, and Rose 2003). This is also unsatisfactory for the purposes of this present study, since it discards the information available from the pairing between right and left ears in an individual. Therefore the concept of *total suppression, Ts,* was devised. Ts is defined as the sum of suppression values of the two ears in an individual, i.e. right ear (OAEq – OAEn) + left ear (OAEq – OAEn). This analysis technique was designed incorporate all data without erroneously claiming to have double the number of independent recordings.

2.5.3 Establishing repeatability (intra-individual)

To assess repeatability of the OAE suppression measures, measurements were repeated on 9 healthy subjects (18 ears). The second measure was taken at least 24 hours after the first (range 24 hours – 4 months). The differences between the value of suppression for each ear on the two occasions were measured and the frequency distribution of the difference was plotted (Figure 2.3). The distribution of differences had a mean of 0.11, with a standard deviation of 0.78. Since this analysis was concerned with the repeatability of a particular measurement, regardless of the ear it was obtained from, ear measurements from an individual were counted as distinct events.
The paired t test statistic is 0.577 (df 17), p=0.572, suggesting there is no evidence of a systematic difference between the two occasions. The British Standards Institution repeatability coefficient is 2SD = 2 x 0.776 = 1.552, giving limits of agreement of 0.11 ± 1.552 i.e. -1.4 to 1.7. This gives an intraclass correlation coefficient of 0.818, p=0.001.

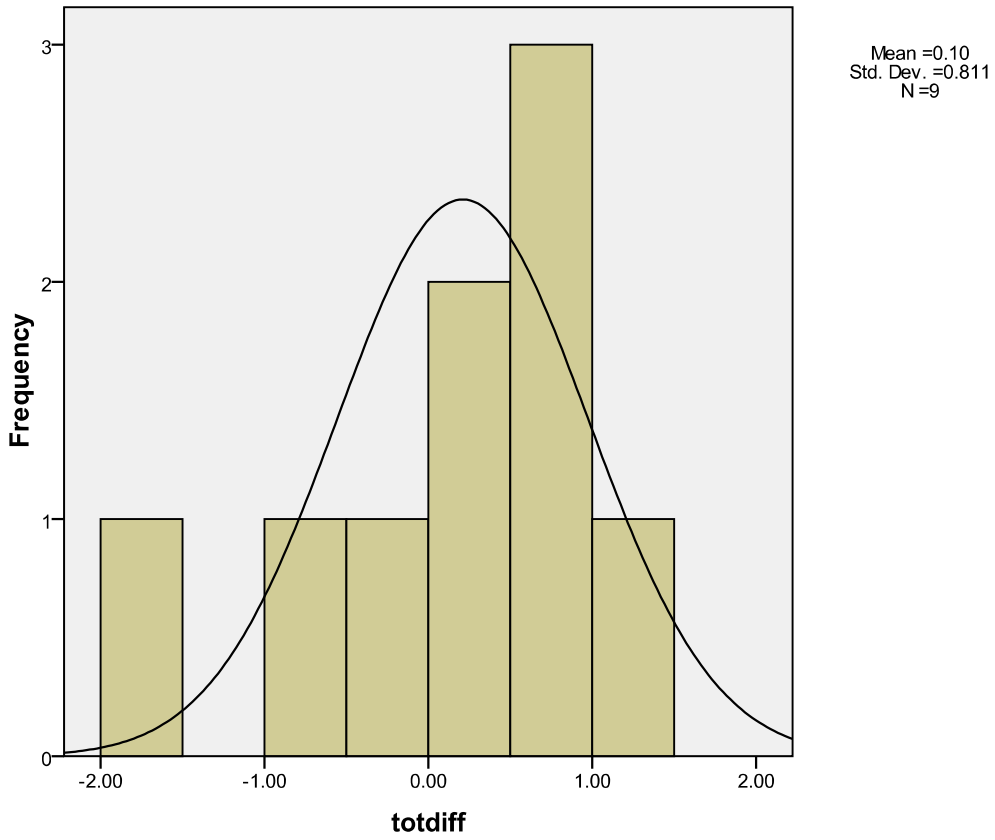
Figure 3.3 Distribution of the differences between first and second measures of OAE suppression in separate ears



An identical procedure was carried out for total suppression Ts, with the results plotted in figure 2.4. The paired t test statistic is 0.37 (df 8), p=0.752, suggesting there is no evidence of a systematic difference between the two occasions. The British Standards Institution repeatability coefficient is 2SD = 2 x 0.811 = 1.622, giving limits of agreement of -1.5 to 1.7. This gives an intraclass correlation coefficient of 0.946, p=0.000.

These results suggest that the measurement of OAE suppression using this technique is highly repeatable, both for separate ears and for total suppression Ts.

Figure 3.4 Distribution of the differences between first and second measures of OAE suppression using total suppression Ts



3.5.4 Optimisation of technique: Is "dB thr" a useful concept?

De Ceulaer and colleagues reported that the optimal stimulus level is determined by relation to the threshold of stimulus at which an OAE is just recordable, termed "dB thr" (De Ceulaer, Yperman, Daemers, Van Driessche, Somers, Offeciers, and Govaerts 2001). They record that the optimal stimulus for presentation is at 12dB thr, the level at which suppression is largest. This technique, whilst intuitively appealing, has not been adopted or replicated by other groups. Therefore an exploratory study to evaluate the hypothesis that larger values of suppression could be obtained by adoption of the dB thr method was devised.

External ears were required to be clean and free of wax and external debris. Tympanometry was carried out to ensure normal middle ear function (GSI 33 Middle Ear analyser). Normal results were a type A trace according to Jerger's classification, with compliance between 0.3 and 1.4ml and pressure between -100 and +100 daPa (Jerger J 1970). All ears had pure tone auudiometry thresholds <20dB HL from 500 Hz to 8 kHz inclusive. The procedure was carried out with subjects seated in a comfortable chair in a sound treated room.

For each ear, a two part protocol was followed:

Part 1: Establishing dB thr

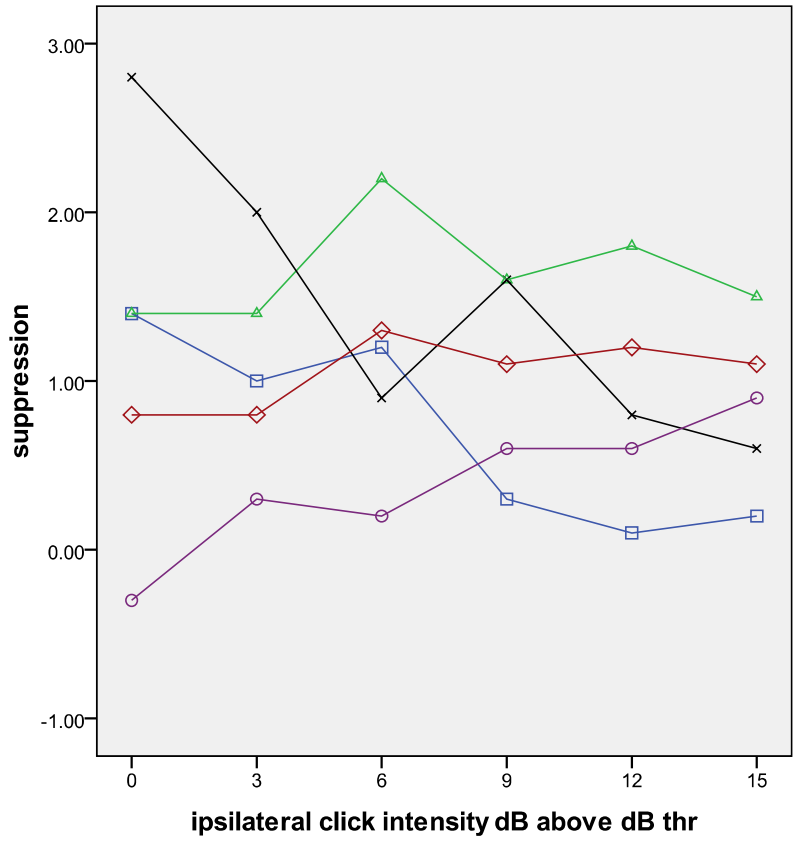
The stimulus and recording probe was sited in the ipsilateral ear. The noise probe was sited contralaterally. Threshold for perception of white noise presented contralaterally was ascertained, and then presented at 40 dB SL. dB *thr* was then determined by the following technique. The uniform click stimulus was presented at 60 dB SPL and then increased or decreased by 3dB according to the presence or absence of an OAE recording with reproducibility of >70% and amplitude just visibly above the noise floor. The number of accepted responses was set at 260. dB *thr* was defined as the minimum stimulus presentation level required to produce an OAE recording with reproducibility of >70% and amplitude just visibly above the noise floor.

Part 2: Establishing optimal suppression relative to dB thr

The OAE was recorded with 260 accepted responses using a stimulus of 0 *dB thr*, first with and then without contralateral white noise at 40dB SL. This process was repeated with the ipsilateral click stimulus presented at 0, +3, +6, +9, +12 and +15 dB above dB *thr*.

For each of the five ears in the study, the value of suppression was plotted against ipsilateral click intensity *re* dB *thr*. Values are shown below (Figure 2.5), with each line representing one series of recordings on one ear.

Figure 3.5 dBthr against level of suppression in five ears



There was no consistent pattern with respect to the optimum level for suppression, with two ears having maximum suppression at 0 dB *thr*, two ears having maximum suppression at 6 dB *thr*, and one ear having maximum suppression at 15 dB *thr*.

The preliminary data from detailed study of five ears did not support the hypothesis that using the dB *thr* technique would maximise suppression values. Therefore this potential modification of the technique was rejected.

3.6 Otoacoustic emission suppression results

3.6.1 General descriptors of participants

39 patients and 33 controls were assessed. TEOAEs were present bilaterally in all controls. Of the patients, they were absent bilaterally in one 49 year old woman with basilar migraine. TEOAE amplitudes were too small to record verifiable suppression in at least one ear in five patients, who were thus excluded from further analysis. Thus there were therefore 33 patients in the main analysis. General descriptors of these patients and controls are shown in **Table 3.I**.

Table 3.I. General descriptors of participants in OAE study

	Controls	**Migraine group**
n	31	33
Age (yrs) mean ±SD	36.1 ± 8.4	36.2 ± 9.2
% female	61	82
Aura symptoms according to IHS definition	-	13 (39%)
Basilar type migraine	-	9 (27%)
Years since onset of migraine attacks	-	mean 12, SD 11 range 0-41
Phonophobia	-	29 (88%)
Other auditory symptoms with attacks	-	17 (52%)
On migraine prophylaxis	-	17 (52%)
Canal paresis in caloric testing	-	13 (39%)
Directional preponderance on ENG	-	8 (24%)

3.6.3 Otoacoustic emission suppression outcomes

To validate the suppression paradigm, a paired t – test was used to seek evidence of a difference in amplitude. In both the vestibular migraine and

control groups, a paired t test between the quiet (OAEq) and noise (OAEn) conditions confirmed that significant suppression has occurred using this protocol (Table 3.II). There was no significant difference between mean values of suppression for right (mean 1.9 dB; SD 1.4 dB) and left (1.8 dB; SD 1.1 dB) sided recordings for (p=0.7, t test).

Table 3.II OAE suppression results

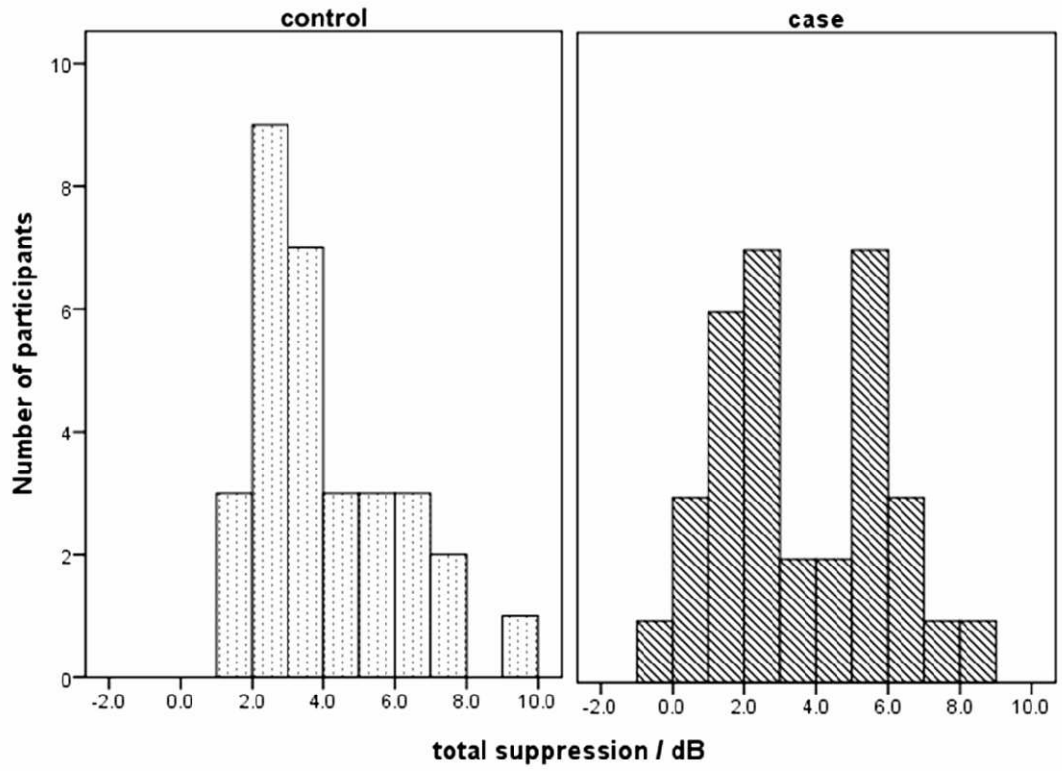
	Controls n=31	**Migraine group n=33**	**Migraine vs. Controls Mann Whitney U**
OAEq-OAEn right ear / dB (median and IQR)	1.7 (1.3-2.6) paired t test p =0.000	1.4 (0.6-1.4) paired t test p =0.000	p =0.42
OAEq-OAEn left ear / dB (median and IQR)	2.0 (1.2-2.4) paired t test p =0.000	1.7 (0.6-2.7) paired t test p =0.000	p =0.38
Total suppression /dB (median and IQR)	3.3 (2.5-5.3)	2.8 (1.5-5.5)	p=0.27

The vestibular migraine and control groups were compared to seek a difference in mean values of suppression. Since the data were not convincingly normal in distribution, non parametric tests were selected. Mann Whitney U testing showed no difference in the mean value of suppression between vestibular migraine patients and controls for either right or left ears, or for the total value of suppression (Ts) in each individual. The frequency distributions for total suppression are given in Figure 3.6.

Participants were also classified into those with normal suppression, where total suppression was ≥2 dB, and those with abnormal suppression where the total suppression was <2dB. 3/31 controls had low total suppression (Ts) compared with 11/33 cases (p=0.022, Chi squared test). Phonophobia was

present in 10/11 (91%) cases with low total suppression and 19/22 (86%) cases with normal total suppression (Ts) (p=1), Fisher's exact probability test).

Figure 3.6. Total suppression frequency distributions for controls *vs*. migraine group



To account for the effect of multiple potential confounders, binary logistic regression analysis was carried out to identify factors which had an effect on the probability of being in the control or vestibular migraine groups. Age, sex, and abnormal total suppression (Ts) were examined. Age and sex were not significant predictors, and there were no significant interactions between factors. Abnormal total suppression (Ts) was a significant predictor of vestibular migraine (*vs* control) status (Table 3.III). This implies that abnormal total suppression (Ts) is associated with vestibular migraine.

Table 3.III. Binary logistic regression analysis to predict case-control status

	Regression coefficient B	**Exp (B) Odds ratio estimate (95% confidence interval)**	**Significance level (p value)**
Age	-0.013	0.987 (0.944-1.033)	0.573
Sex	0.506	1.659 (0.626-4.396)	0.308
Low total suppression Ts	-1.540	0.214 (0.053-0.863)	**0.030***

To look for factors which identify the subgroup of vestibular migraine patients with abnormal total suppression (Ts), a separate binary logistic regression analysis was carried out. In this analysis, use of migraine prophylaxis, duration of symptoms, cand presence of phonophobia were assessed as predictors of low total suppression (Ts) (Table 3.IV). None was significant.

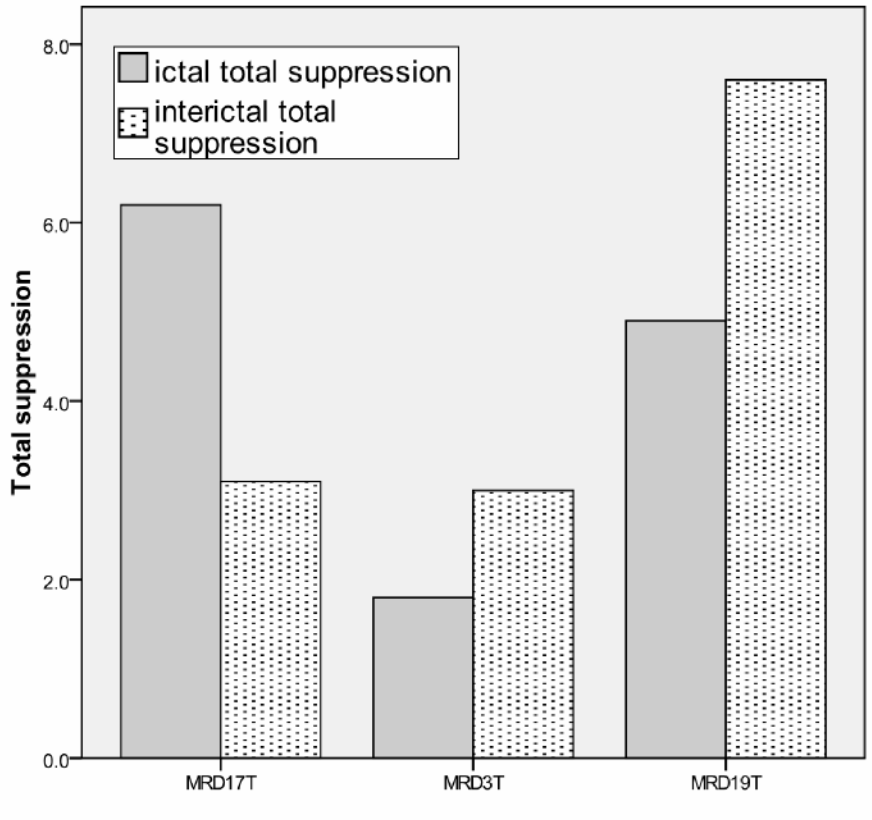
Table 3.IV. Binary logistic regression analysis to predict low total suppression in participants with vestibular migraine

	Regression coefficient B	**Exp (B) Odds ratio estimate (95% confidence interval)**	**Significance level (p value)**
disease duration	0.023	1.024 (0.956-1.096)	0.528
phonophobia	-0.129	0.879 (0.068-11.380)	0.921
migraine prophylactics	-0.218	0.770 (0.186-3.470)	0.770
canal paresis	-0.685	1.112 (0.093-2.725)	0.426

3.6.3 Ictal and interictal comparison

In three patients, OAE suppression recordings were obtained both during an attack of vestibular migraine (ictal condition) and when well (interictal condition), illustrated in **Figure 3.7**.

Figure 3.7 Ictal and interictal measures for total OAE suppression. In normals, the maximum amplitude of change between two recordings was 1.7 dB.



In the repeatability study, the 95% confidence interval for the difference (mean±2SD) for Ts_1 - Ts_2 was -1.5 to 1.7 dB (see section 3.5.3 above). For two of the cases, the change in total suppression was considerably outside of the normal range (3.1dB and 2.7dB). It is noted that these changes are in opposite directions so that in one patient suppression reduced with recovery from an attack of vestibular migraine and in the second it increased. In the third case the change in total suppression was within the normal range (Ts_1 - Ts_2 = 1.2).

3.7 Discussion

Otoacoustic emission suppression testing was established as a repeatable test, and significant suppression was confirmed in a healthy, non-migrainous population. Modification to the standard OAE suppression technique in the form of dB *thr* was rejected after pilot data failed to support the hypothesis that this would increase the amplitude of the response.

This study then evaluated the auditory efferent pathway in individuals with vestibular migraine, looking for evidence of impaired sensory modulation in the auditory modality.

OAE suppression was clearly demonstrated in both the vestibular migraine group and in the control group, with no significant difference in amplitude between left and right ears. However, total OAE suppression by contralateral noise assumed a low value in patients with vestibular migraine (33%) more frequently than in controls (10%) ($p=0.022$). Abnormally low values of total suppression were associated in the binary logistic regression analysis with presence of vestibular migraine. Symptoms of phonophobia were not shown to relate to low suppression.

Reduced OAE suppression could occur due to problems anywhere along the reflex arc from the outer hair cells through the auditory nerve, central pathways via the cochlear nucleus, trapezoid body and superior olivary complex, through the crossed and uncrossed olivocochlear bundles and the efferent pathway via the inferior vestibular nerve; or, indeed, by affecting top-down modulation via corticofugal pathways from the auditory cortex (Perrot et al 2006). It is known that audiometry is usually normal in migraineurs with dizziness symptoms (Battista 2004). Given current understanding about the pathophysiology of migraine, and the fact that sensory dysmodulation occurs across different modalities it seems likely that the source of the dysfunction in this case is at the level of processing in the brainstem or higher structures, rather than occurring in the peripheral labyrinth or cochlea.

These patients might perhaps be expected to have a higher rate of vestibular dysfunction, since they have, by definition, significant vestibular symptom load. This could be a potential confounder, since a high rate of (inferior) vestibular nerve dysfunction could be associated with abnormal total suppression. However, there was no relationship between canal paresis (indicative of superior vestibular nerve function) and OAE suppression. Results and analysis discussed later in this thesis also show there was no relationship between OAE suppression and VEMP abnormalities (see chapter 4.9.5).

During the execution of this study, some data on OAEs in individuals with migraine were published (Bolay et al 2008). The authors of this study record that there is a statistically significant difference between TEOAE amplitude in quiet and contralateral noise conditions in healthy controls, but not in migraineurs. This result is of interest, but there are methodological limitations. The analysis depends on pooled data for noise and quiet conditions, rather than making use of paired data for each individual. Additionally the eliciting stimulus was set at 83 dB SPL, and a role of middle ear reflexes cannot be excluded at this high level of sound intensity, so it is difficult to localise the lesion. The methodological differences may account for the fact that, although the work presented in this thesis did find abnormalities in suppression, it does not replicate the primary observation made in this previous study.

There was no demonstrable relationship between abnormal OAE suppression and either clinical symptoms heightened auditory sensitivity (phonophobia) or other factors such as age, gender or time since onset of first migraine symptoms. Therefore although it is clear that there is a subgroup of patients with vestibular migraine who have abnormal OAE suppression, it has not been possible to identify a common factor amongst this subgroup.

The mechanism of phonophobia is not well understood. One quantitative study showed that migraineurs had lower sound aversion thresholds than controls interictally, with even lower thresholds ictally (Ashkenazi et al 2009).

The observation that hearing thresholds often reduce with an associated increase in dynamic range during migraine attacks suggests that cochlear recruitment is not likely to be cause of phonophobia (Woodhouse and Drummond 1993). Loss of efferent suppression is a plausible alternative hypothesis. However, there was no demonstrable relationship between abnormal OAE suppression and phonophobia in our study. The mechanism of phonophobia may not relate directly to auditory efferent function as measured by OAE suppression. There may be a dissociation between the subjective experience and the objective measurement. It is known that there is considerable variability in patients' responses to questions about sound sensitivity which is an essentially subjective experience (Evans et al 2008). This may make it difficult to demonstrate a difference between "phonophobic" and "non-phonophobic" individuals. The intensity of phonophobia also varies in an individual over time, both between the ictal and interictal conditions, but also from attack to attack. Comparing OAE suppression recorded ictally and interictally in three patients however still showed no clear pattern of abnormality. There are variations in the degree of phonophobia, it being very marked in some patients but only mild in others (Woodhouse and Drummond 1993), and it may also be that loss of suppression is only a relevant mechanism in an as yet unidentified subgroup of those with phonophobia.

It is noted that in two out of three cases, there is a high degree of change between the ictal and interictal conditions. This was in opposite directions, so that in one case the suppression reduced with recovery and in one it increased. This is a small sample and as such it may be difficult to generalise from this observation, but it is certainly in keeping with dysregulation of the pathways serving OAE suppression, with variable direction of dysregulation.

3.8 Conclusion

OAE suppression is reduced in a third of individuals with vestibular migraine. This objective phenomenon does not have a simple relationship to the subjective experience of phonophobia. When comparing ictal and interictal recordings, the responses show a high amplitude of change, but with variable

direction. These observations can be construed as evidence in support of auditory efferent pathway dysfunction in vestibular migraine.

Chapter 4. Use of vestibular evoked myogenic potentials in the assessment of vestibular migraine

4.1 Overview of vestibular evoked myogenic potentials

Vestibular evoked myogenic potential recordings (VEMPs) have become established as a test of a neuro-otological (sacculo-collic) reflex (Welgampola and Colebatch 2005). Surface electromyographic (EMG) activity is recorded from the sternocleidomastoid (SCM) muscle in response to sound stimuli. The reflex is carried from the saccule through the inferior vestibular nerve, vestibular nuclei and the medial vestibulospinal tract via the medial longitudinal fasciculus, and thence to the sternocleidomastoid in the eleventh cranial nerve (Figure 4.1). The response measured is a biphasic, inhibitory, short latency potential. The initial positive peak occurs at around 13 ms followed by a negative peak at around 23ms (Figure 4.2). Later responses are frequently seen but are not reliably present in normal subjects (Colebatch et al 1994) .

Figure 4.1 VEMP assesses the sacculo-collic reflex.

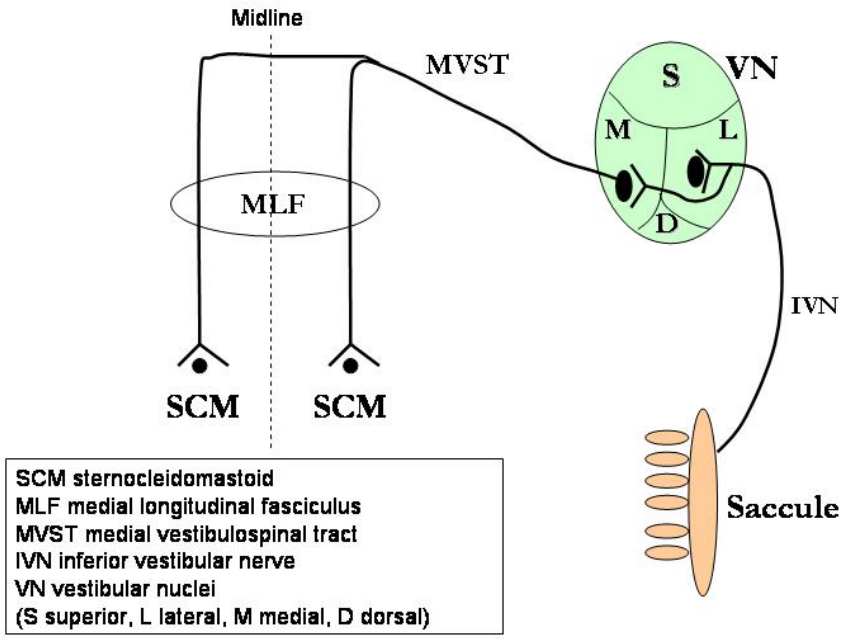
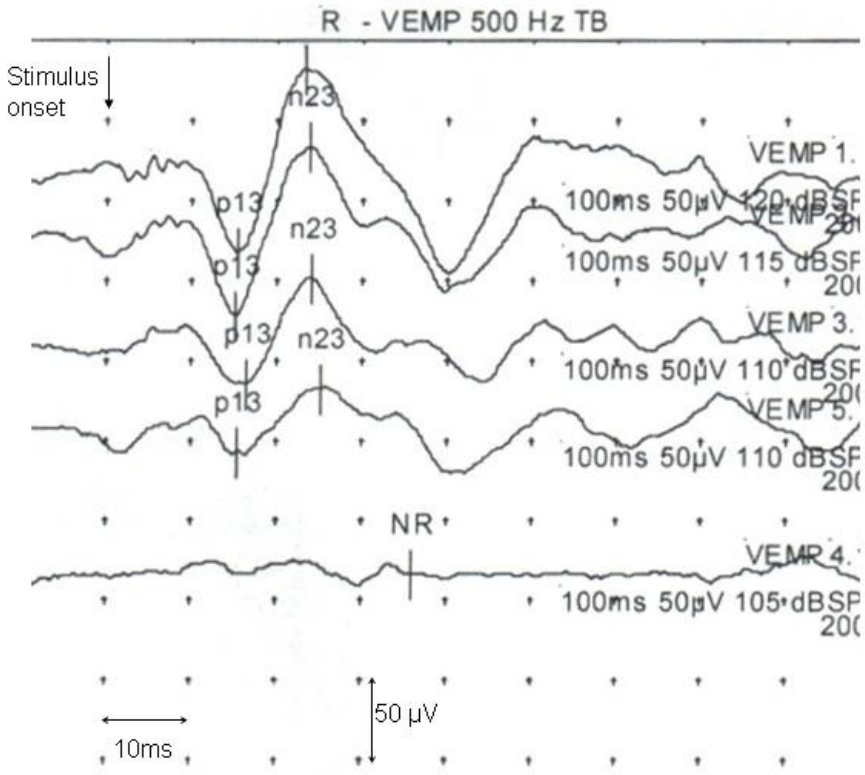


Figure 4.2 VEMPs are a biphasic inhibitory short latency response



It has long been known that the vestibular system in humans responds to sound stimuli. Bekesy observed in 1935 that a sense of motion and involuntary head movements occur towards an ear stimulated by sound. The technique as it is now recognised was pioneered by Bickford *et al* in 1964 (Bickford et al 1964), and then developed into that used today by Colebatch and colleagues in 1994 (Colebatch, Halmagyi, and Skuse 1994). Bickford was in fact investigating the reliability of using computer averaging to record cortical evoked auditory responses, but noted that there were "unexpected observations which suggested that the phenomenon should receive additional study", namely "large and invariant early waves". This group also correctly identified that the response was myogenic rather than neural in origin. They noted that it was absent in an anaesthetised and "partially curarized" subject and a patient with absent labyrinthine function but present symmetrically in patients with complete unilateral or bilateral sensorineural hearing loss and preserved caloric responses. Later, Colebatch *et al* recorded responses from the anterior neck muscles rather than the inion (which Bickford was using),

and showed that the response is present in patients with profound unilateral or bilateral sensorineural hearing loss with apparently normal vestibular function. This group also noted that the early responses (named p13-n23) were abolished in the operated ear of patients who had undergone vestibular nerve section, but present on the intact side.

4.2 Stimulus factors

Clicks and tone bursts are both used as sound stimuli, with tone burst evoked VEMPS showing similar properties to click evoked VEMPs (Murofushi et al 1999). The dependence of amplitude on stimulus frequency of tone burst VEMPS can be plotted, and shows a pattern akin to the tuning curves of auditory nerve fibres, with maximal response at 500Hz to 1kHz (Rauch et al 2004). In general, a lower stimulus intensity is required for tone bursts as opposed to clicks. VEMPs have also been recorded using galvanic stimulation and through bone conduction via skull taps with a tendon hammer or bone conducted tones. The stimulus can be delivered either monaurally or binaurally. Although there are apparently no significant differences between the monaural and binaural response conditions (Wang and Young 2003), most investigators prefer for research purposes to use a monaural stimulus and response to reduce the risk of contamination by crossover effects. The threshold for recording robust and repeatable responses is around 85-100dB nHL for clicks (Colebatch, Halmagyi, and Skuse 1994). The amplitude of the response depends directly on sound stimulus intensity. 100dBnHL clicks produced normal responses in 75% normals in another study (Robertson and Ireland 1995). This sound intensity is at the upper limit of what is considered safe, but most subjects tolerate the sound stimulus well. The optimal click repetition rate, balancing competing factors of variance, test comfort for patients and duration of testing time, is reported to be 5/s (Wu and Murofushi 1999).

VEMP responses as described above are sometimes referred to as cervical VEMPs (c-VEMPs) to distinguish them from the more recently developed ocular VEMP (o-VEMP). The bone conductor stimulated o-VEMP response is

quite distinct from the air conducted c-VEMP response, being an excitatory response thought to be primarily utricular in origin (Nguyen et al 2010). The work described in this thesis relates purely to air conduction stimulated c-VEMP recordings.

4.3 Other factors affecting properties of the response

It has been recognised that, unsurprisingly, outer and middle ear factors which impede sound transmission (conductive hearing loss of any aetiology) can abolish or attenuate the response where air conducted stimuli are used (Bath et al 1999). The amplitude of the response also depends on the level of tonic EMG activation in a linear fashion (Colebatch and Halmagyi 1992). Raw amplitude is a highly variable parameter between individuals (Ochi et al 2001). Maintaining muscle activation in a controlled fashion around 50 μV minimises amplitude variability, and using a visual feedback technique improves reliability (Vanspauwen et al 2006). Electrode placement also affects response amplitude, with the optimal placing identified as on the middle third of the sternocleidomastoid muscle (Sheykholeslami et al 2001). The response to clicks is almost invariably present in individuals under 60 years old (Welgampola and Colebatch 2005) but amplitude is known to decrease with increasing age (Brantberg et al 2007). The reference electrode can be sited on the mid-clavicle, sternum or forehead (Welgampola and Colebatch 2001). The method used to activate SCM is very variable between institutions, but is presumably irrelevant if target tension is measured and maintained using visual biofeedback.

4.4 Anatomical correlates

Otololith afferents are known to respond to intense sound stimulation (McCue and Guinan, Jr. 1994; McCue and Guinan, Jr. 1995; Murofushi and Curthoys 1997). In monkeys, saccular afferents have the lowest thresholds to sound stimulation (Young et al 1977). In other animal studies, stimulation of the saccular nerve results in a similar inhibitory response in about two thirds of sternocleidomastoid neurons. Utricular nerve stimulation, by contrast, evoked

excitatory responses (Uchino 1997). There is also evidence from studies in patients with inner ear anomalies suggesting that the response is primarily saccular (Sheykholeslami and Kaga 2002).

Acoustic startle reflexes are characterised by longer latencies, prolonged refractory periods and rapid habituation (Brown et al 1991). Although VEMPs are known to habituate in normal subjects (Roceanu et al 2008), they are not seen to have prolonged refractory qualities. The short latencies of the VEMP suggest a disynaptic pathway is responsible for generation (Colebatch and Halmagyi 1992). The response is thought to be mostly ipsilateral via the medial vestibulospinal tract with only weak contralateral effects. However, VEMPs have been recorded in some subjects after vestibular nerve section with intact cochlea and cochlear nerves (Ferber-Viart et al 1998). The response is generated by the surface EMG of the sternocleidomastoid muscle.

4.5 Clinical applications

The most striking clinical application of the VEMP has been in the evaluation of the Tullio phenomenon, in which individuals experience symptoms of dizziness or imbalance in response to loud sounds (Colebatch et al 1998). It is caused by presence of a “third mobile window” allowing undampened transmission of sound energy into the labyrinth. These disorders include superior semicircular canal dehiscence and perilymph fistula. It has been shown that patients with superior semicircular canal dehiscence diagnosed by high resolution CT scans have abnormally low VEMP thresholds and associated high amplitudes.

VEMPs have also been shown to be abnormal in eighth nerve pathologies such as cerebellopontine angle tumours including vestibular schwannomas (Matsuzaki et al 1999). Multiple sclerosis patients can have prolongation of latency (Murofushi, Shimizu, Takegoshi, and Cheng 2001). As might be expected, there are variable findings in clinical studies of brainstem strokes, with VEMP absence, latency prolongation and reduction of amplitude all seen as well as normal responses in some cases (Pollak et al 2006). Low VEMP

amplitude and high threshold are seen in seasickness susceptible individuals (Tal et al 2006).

4.6 Limitations of technique

Tinnitus is a relative contra-indication, and subjects must endure sounds of high intensity (120 dB SPL) which some find difficult to tolerate. Subjects must maintain SCM activation by head flexion and/or lateral head turn, with or without resistance. Subjects with back or neck pain may find this difficult. The technique also has limited clinical applicability thus far, with superior semicircular canal dehiscence being the only application where VEMPs show a high degree of diagnostic sensitivity.

4.7 VEMPs in migraine

Patients with vestibular migraine are known to have evidence of significant vestibular brainstem dysfunction ictally (von Brevern, Zeise, Neuhauser, Clarke, and Lempert 2005), and variable reports of peripheral and central vestibular dysfunction in the interictal period (Furman, Marcus, and Balaban 2003). It might therefore be expected that study of a technique that assesses vestibular brainstem function could yield insights into the pathogenesis of VM. In a study of benign paroxysmal vertigo of childhood (Chang and Young 2007), thought to be a migraine precursor, 30% cases had absent VEMPs, and this study also reports that latency abnormalities were fairly common. At the time of conception of this study, however, there was but a single report of VEMPs in migraine (Liao and Young 2004). This was a study of 20 basilar-type migraine patients, and showed abnormalities of presence, latency or threshold in 10 (50%). These patients have a very distinct presentation from vestibular migraine. The observed abnormalities resolved in 9/10 with three months treatment with flunarizine 10mg. During the execution of this present study further reports have evolved. Two groups have reported a reduction in mean amplitudes (Allena et al 2007; Baier et al 2009), one has reported reduced habituation of the VEMP response (Allena, Magis, De Pasqua, and Schoenen 2007), and reported that migraineurs with and without vertigo have

similar results (Roceanu, Allena, De, V, Bisdorff, and Schoenen 2008). On the other hand it is also reported that the majority of individuals with VM have normal VEMPs (Vitkovic et al 2008), albeit in a study where the VEMPs were not the principal outcome of interest and the technique and results are not reported in detail. Review of these studies suggests some heterogeneity of findings (summarised in Table 3.I), and the need for further confirmatory study is thus apparent.

Table 4.I VEMP findings in previous studies of migraine

Study	**Subjects**	**Principal VEMP findings**
Liao (2004)	basilar migraine	prolonged latency 15%, absent VEMPs in 35% abnormalities resolved with treatment
Allena (2008)	migraine and migrainous vertigo	reduced habituation and reduced raw and normalised amplitude in both groups
Vitkovic (2008)	migrainous vertigo	normal in 80%, rest inconclusive
Murofushi (2009)	migraine associated vertigo	Absence unilaterally in 1/11 at 1000Hz Reduced 500Hz-1000Hz slope in 3/11 Prolonged p13 latency in 4/11
Baier (2009)	definite or probable vestibular migraine	reduced amplitude in 68%

4.8 Methods

4.8.1 Participants

Exclusion criteria were a history of middle ear disease, otologic surgery, conductive hearing loss, high-risk noise exposure, abnormal otoscopy or tympanometry, or any other medical, neurological or orthopaedic disorder likely to interfere with testing. Participants on drugs known to affect the nervous system were excluded, with the exception of those on anti-migraine treatments. All participants were between 16 and 60 years of age, as VEMP data are less reliable in people over 60 (Welgampola and Colebatch 2005).

Normal controls were recruited from hospital staff, friends and colleagues. Potential controls were excluded if they had a history of headaches with migrainous features, a history of otologic disease or clinically significant audiovestibular symptoms, or any medical, neurological or orthopaedic disorder likely to interfere with testing. They were selected as a group to match the age and sex distributions of the patients.

4.8.2 Vestibular evoked myogenic potentials protocol

Vestibular evoked myogenic potentials were recorded using a Medelec Synergy system (Oxford Instruments, Surrey, UK). A 500 Hz tone burst monaural stimulus was used via headphone with a repetition rate of 4.7/s, 2-4-2 ms rise-plateau-fall time and Blackman filter. 200 sweeps were averaged for each run. The 500Hz tone burst had been selected as a stimulus rather than clicks due to lower sound intensity required and larger amplitudes in preliminary recordings. Recordings were made with electrodes placed at the midpoint of the ipsilateral sternocleidomastoid, using the midpoint of the clavicle as a reference and the forehead as the ground. Subjects reclined on a couch and activated sternocleidomastoid through neck flexion and lateral head turn, in whatever combination the subject was able to maintain adequate activation comfortably. EMG activation was maintained at 60-80 μV throughout recording using a visual biofeedback technique. If VEMPs were

absent at the first recording session, participants were invited back for repeat testing on a subsequent occasion, several weeks later.

Measurements were made of threshold, amplitude and latency of the waveforms. Amplitude was measured as the peak-to-peak difference between the p13 and n23 components of the response. Raw amplitudes were corrected for underlying EMG activity by dividing the raw amplitude (A_{RAW}) by the pre-stimulus mean EMG (A_{EMG}) i.e. normalised amplitude ratio = A_{RAW} / A_{EMG}. Amplitude and latency measurements were made at 120 dB SPL, or 125 dB SPL if the response threshold was 120 dB SPL. Maximum stimulus intensity was 125 dB SPL, and responses were said to be absent if not recordable at this level. An asymmetry ratio was computed for normalised amplitude ($100 * ((A_L - A_R)/ (A_L + A_R)$) where A_L is the normalised amplitude ratio on the left, and A_R the normalised amplitude ratio on the right (Welgampola and Colebatch 2005). A response was said to be present if waveforms were consistently and repeatably present above the noise floor.

Since determination of response absence or presence could be perceived to be subject to individual investigator bias, 22 traces were randomly selected and presented to an independent reporter blinded to case-control status and to previous reporting. For each of these ears, the reporter only had access to the two traces with the highest stimulus presentation levels, but the intensity of these stimuli was withheld (as this could give clues about the original report).

In addition, a small study was carried out to determine the repeatability of VEMPs in a small sample of healthy subjects normalised amplitude, threshold and p13 latency were measured on two occasions at least two weeks apart by different investigators. The repeatability was assessed using the intraclass correlation coefficient (ICC), and the distribution of differences between the two measurements, using a two-way mixed effects model where people effects are random and measures effects are fixed.

4.9 Results

4.9.1. Repeatability

11 controls underwent VEMP repeatability studies. In one subject data were only available on one ear due to time constraints, hence n=21.

Figure 4.3 is the frequency distribution for the difference between the first measurement of normalised amplitude ratio and the second measurement . ICC was -0.281 (95% confidence interval -4.159 to 0.682; F test with true value=0 p=0.641). It shows wide variation with a poor ICC, suggesting poor repeatability. Limits of agreement are calculated as -1.4 to + 1.5.

Figure 4.3.Frequency distribution of the difference between two measures of normalised amplitude ratio ("allampdiff")

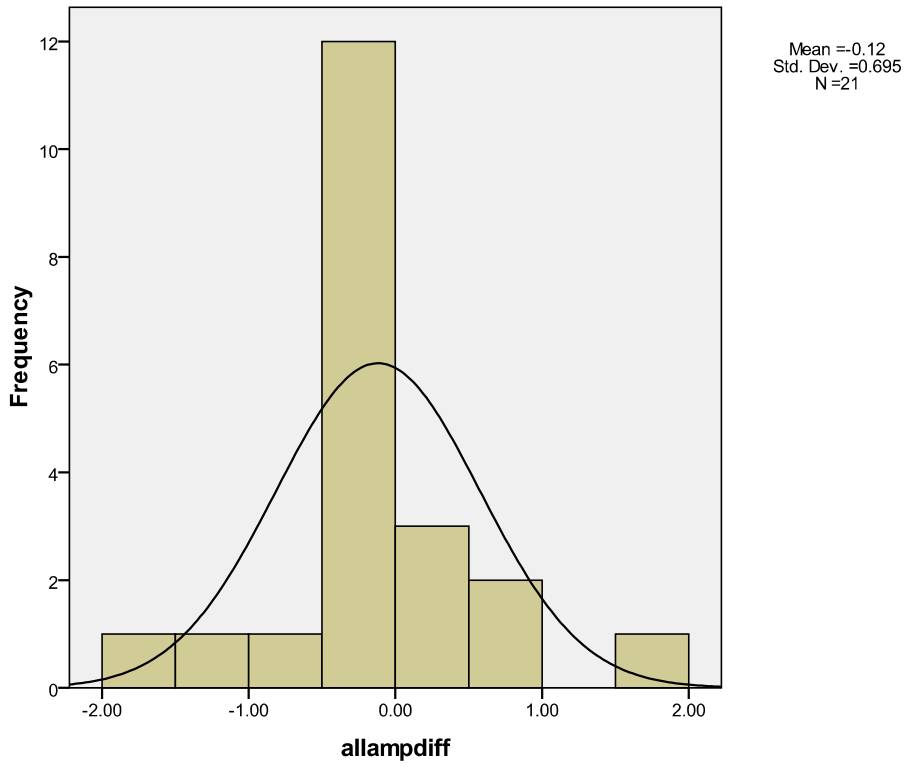


Figure 4.4 shows the frequency distribution for the difference between the first and second measurements of threshold. ICC was 0.815 (95% confidence interval 0.545 to 0.925; F test with true value 0 p=0.000). It shows a maximum difference of ± 10 dB with a high ICC, suggesting good repeatability. Limits of agreement for threshold are -11 to + 12 dB.

Figure 4.4 Frequency distribution of the difference between two measures of threshold ("allthreshdiff")

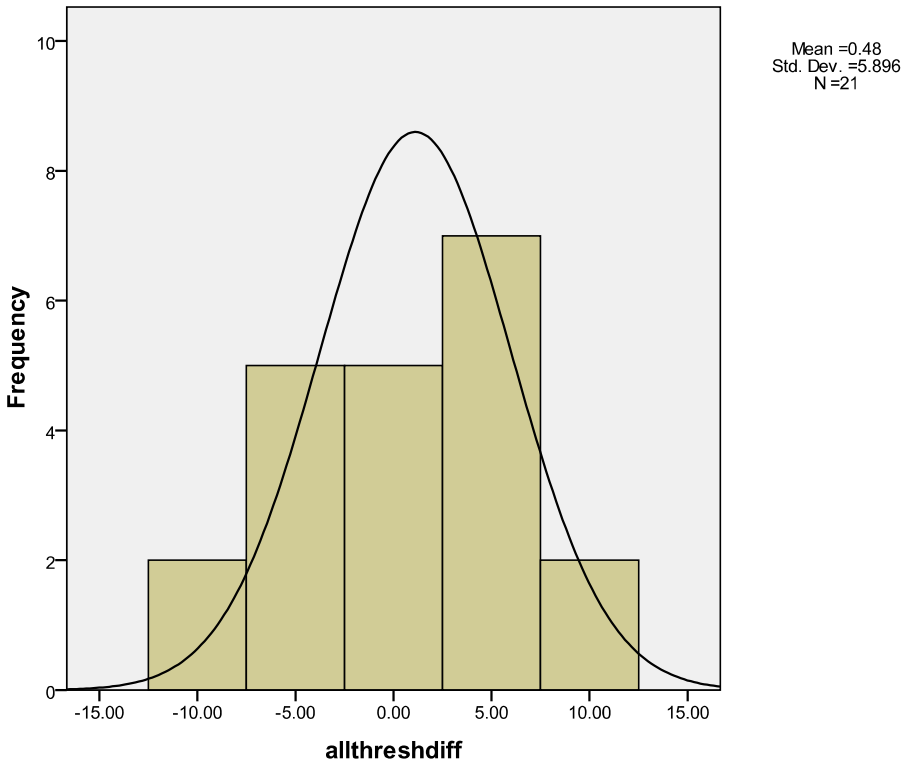
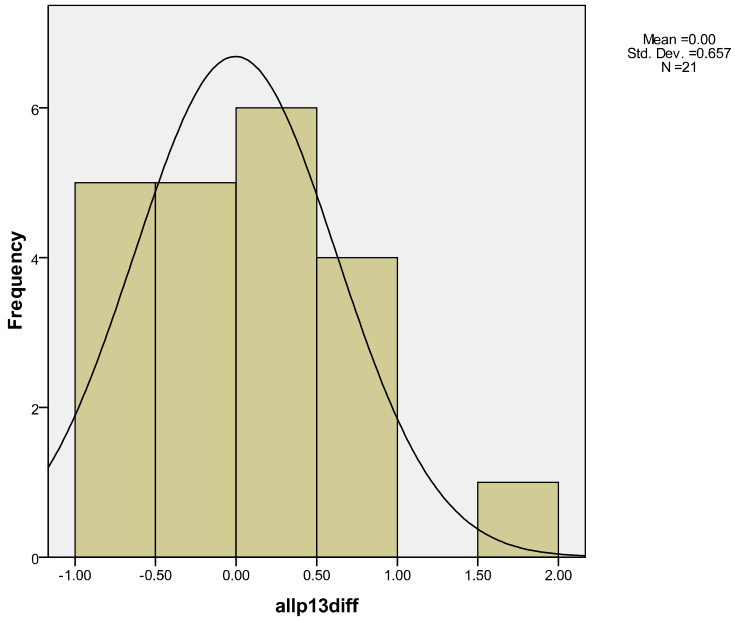


Figure 4.5 shows the frequency distribution for the difference between measurement 1 of p13 latency and measurement 2. ICC was 0.796 (95% confidence interval 0.497 to 0.917; F test with true value 0 p=0.000). It shows a maximum difference of with a high ICC, suggesting good repeatability. Limits of agreement are -1.3 to + 1.3 ms.

Figure 4.5. Frequency distribution of the difference between two measures of p13 latency ("allp13diff")



In summary, these data, in keeping with previous findings in the literature, show good repeatability for latency and threshold but poor repeatability for amplitude.

4.9.2 Basic descriptors of participants

35 patients with definite migrainous vertigo (Neuhauser, Leopold, von Brevern, Arnold, and Lempert 2001) and 30 controls were recruited, with characteristics as set out in table 4.II.

Table 4.II Characteristics of patients and controls

	Patients	**Controls**
Mean age	37 yrs (SD 11)	38 yrs (SD 9)
% female	74%	70%
Duration of migraine attacks	Range 0-47 yrs (mean 15)	-
Aura symptoms	37% (20% basilar)	-
Auditory symptoms with attacks	51%	-
Phonophobia	71%	-
On migraine prophylaxis	49%	-
Canal paresis on caloric testing	33%	-
Directional preponderance on ENG impulsive rotation >25%	27%	-
Central signs on ENG recordings	9%	-

4.9.3 VEMP results

To examine the potential for investigator bias in reporting "absent" traces, the reporting of responses as "present" or "absent" was investigated further using a blind reporter technique. All identifying information including case-control status was removed from a random sample of 22 traces, including 5 traces originally reported as "absent" and 17 originally reported as "present". The blinded investigator reported the traces with a 100% concordance for both "absence" and "presence", suggesting minimal investigator bias in reporting of absence of repeatable response.

VEMPs were demonstrably present in all control ears on the first recording session (Figure 4.6). On first assessment, they were absent in three VM patients bilaterally and in four patients unilaterally. In three of these ears with absent waveforms, recordable waveforms were present at the second session. One participant with a unilaterally absent VEMP declined repeat testing. Therefore there were six ears in which VEMPS were consistently absent, in addition to one in which the recording could not be repeated. VEMP absence was unilateral in four cases and bilateral in one case. The proportion of cases

with persistent VEMP absence in at least one ear is therefore 5/35 cases (14%), compared with 0/30 in the control group (p=0.06, Fisher's exact test).

Considering only the VM group, there was no relationship between VEMP absence and age, disease duration, presence of canal paresis on caloric testing, aura, tinnitus, hearing loss or symptoms of phonophobia.

The relationship between subjective clinical state and fluctuations in VEMP presence was examined (Figure 4.7). There were too few measurements to attempt statistical analysis, but half the six patients fell on the line of complete correlation between VEMP improvement and subjective clinical improvement.

Figure 4.6. Presence of VEMP waveform at 125 dB SPL or below on recording over two sessions

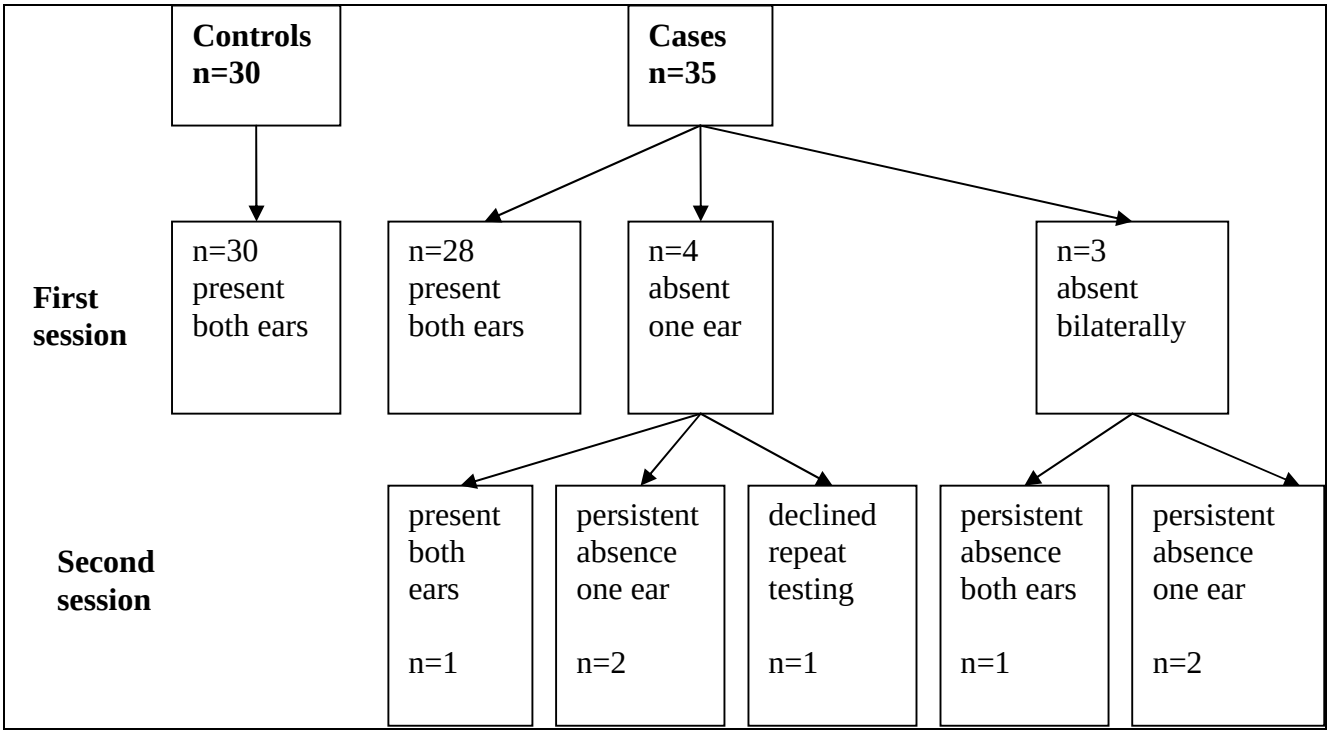
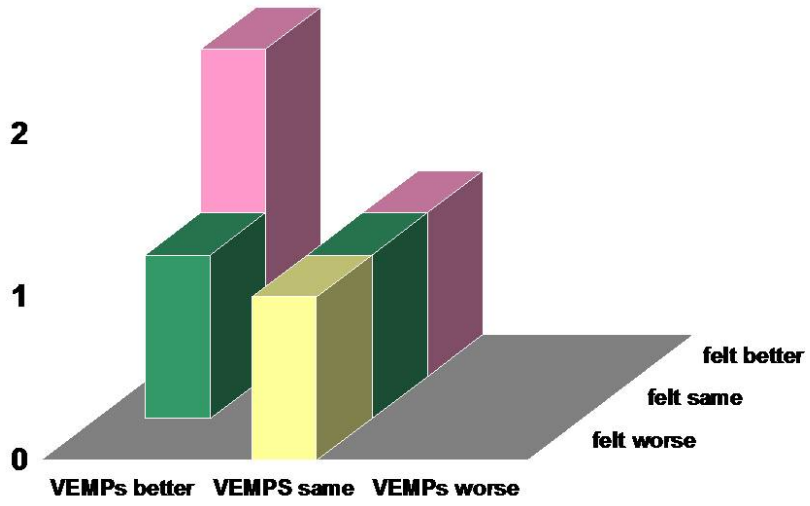


Figure 4.7. Change of clinical state shown with respect to VEMP absence and presence where "VEMP better" indicates a VEMP presence which had previously been absent, and "VEMP worse" indicates VEMP absence where a response had previously been present. The vertical (z) axis represents number of individuals.



Student's t-test was used to compare means in VM patients with recordable VEMPs and controls for amplitude, threshold and latency where distributions were approximately normal, and the Mann-Whitney U test for other distributions (Table 4.III). There was no significant difference between patients and controls for the mean values of p13 latency, normalised amplitude ratio or threshold.

Table 4.III. VEMP results. Variables are reported as mean ± standard deviation unless stated otherwise**.**

VEMP parameter	**Ear**	**VM group (n=31 right ears; n=32 left ears)**	**Controls n=30**	**p value**
Threshold /dB SPL	right	112±8.6	113±6.5	0.93 t test
Threshold /dB SPL	left	111±7.3	112±7.3	0.41 t test
Interaural threshold difference / dB SPL	interaural	5.2±4.0	4.7±4.3	0.64 t test
Normalised amplitude ratio	right	0.97±0.5	1.1±0.6	0.28 t test
Normalised amplitude ratio	left	1.0±0.6	1.3± 0.7	0.07 t test
Interaural amplitude difference (Asymmetry ratio)	interaural	22.4±17	22.2±15.0	0.97 t test
p13 latency /ms	right	15.6±1.4	15.3±1.0	0.26 t test
p13 latency /ms	left	16.0±1.4	15.7±1.3	0.16 t test
Interaural p13 difference / ms (median and IQR)	interaural	1.5 (0.4-2.4)	1.0 (0.6-1.4)	0.23 Mann Whitney U

Using an identical protocol, previous independent work using the same equipment on a set of 40 unrelated healthy volunteers, had defined normal ranges for threshold, amplitude, latency and presence of response. Individual patients or controls were then classed as either having normal responses, if all data were within the normal range, or abnormal responses, if any parameter fell outside the normal range. Study data were compared with these normal

ranges to define the proportion of patients and controls that had abnormal VEMP responses (Table 4.IV).

Table 4.IV. For patients, VEMP results outside departmental normal range

	VM Patients	**Controls**	**p value**
Abnormal VEMP	11/35	3/30 (10%)	p=0.036
VEMP absence	5/35 1 bilateral 4 unilateral	0/30	p=0.057
p13 latency (normal range	3/35	1/30	p=0.2
Threshold (normal	1/35	0/30	p=1
Amplitude (normal	5/29	3/30	p=0.37

Binary logistic regression analysis showed that, taking into account age and gender effects, the presence of a history of vestibular migraine was a significant determinant of VEMP abnormalities, i.e. the patients with VM had a higher rate of VEMP abnormalities than the controls (Table 4.V; p=0.008).

There was no relationship between the presence of canal paresis and the absence of VEMP response. On the right side, two ears with absent VEMPs also had canal paresis and two did not. Six ears also had canal paresis and normal VEMP (Fisher's exact test p=0.241). On the left side neither of the two ears with absent VEMPs had canal paresis. Three ears with canal paresis had normal VEMP (Fisher's exact test p=1.00).

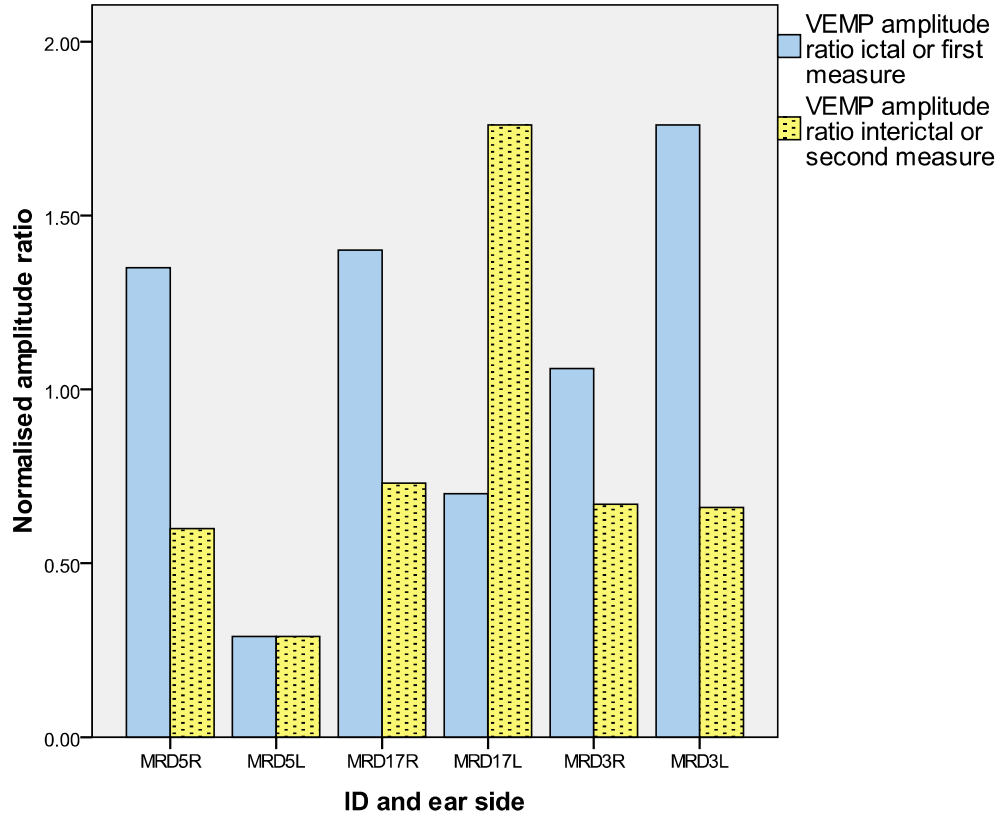
Table 4.V Binary logistic regression analysis to predict case (VM)-control status

	B	Sig.	Exp(B) Odds ratio estimate	95% C.I.for Exp(B)	
				Lower limit	Upper limit
Any parameter outside departmental norms	1.642	0.008	5.167	1.527	17.481
age	-0.020	0.467	0.980	0.928	1.035
sex	0.597	0.335	1.817	0.540	6.113

4.9.4 VEMP recordings in the ictal condition

In three individuals, VEMPs were recorded in the ictal and interictal conditions. Normalised amplitude ratio, latency, and threshold were compared according to known repeatability parameters (see section 4.9.1 above). These data are illustrated in Figure 4.8, 4.9 and 4.10 respectively. There were no changes outside the normal range with respect to threshold or amplitude. Two individuals had one ear in which the difference in latency was outside the normal range of ±1.3 ms (described in 4.9.1 above), with the actual differences being -3.2 and +1.6 ms.

Figure 4.8 a). Raw data for change in normalised amplitude ratio in the ictal and interictal condition in three individuals (six ears, marked by study ID number and then R or L indicating right or left respectively). b) Frequency distribution for the difference between ictal and interictal recordings for these data



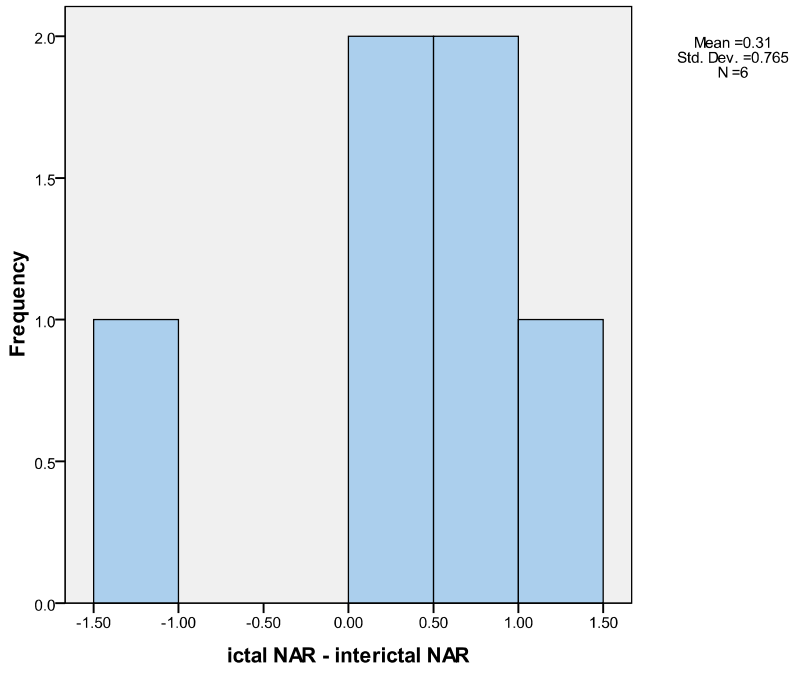
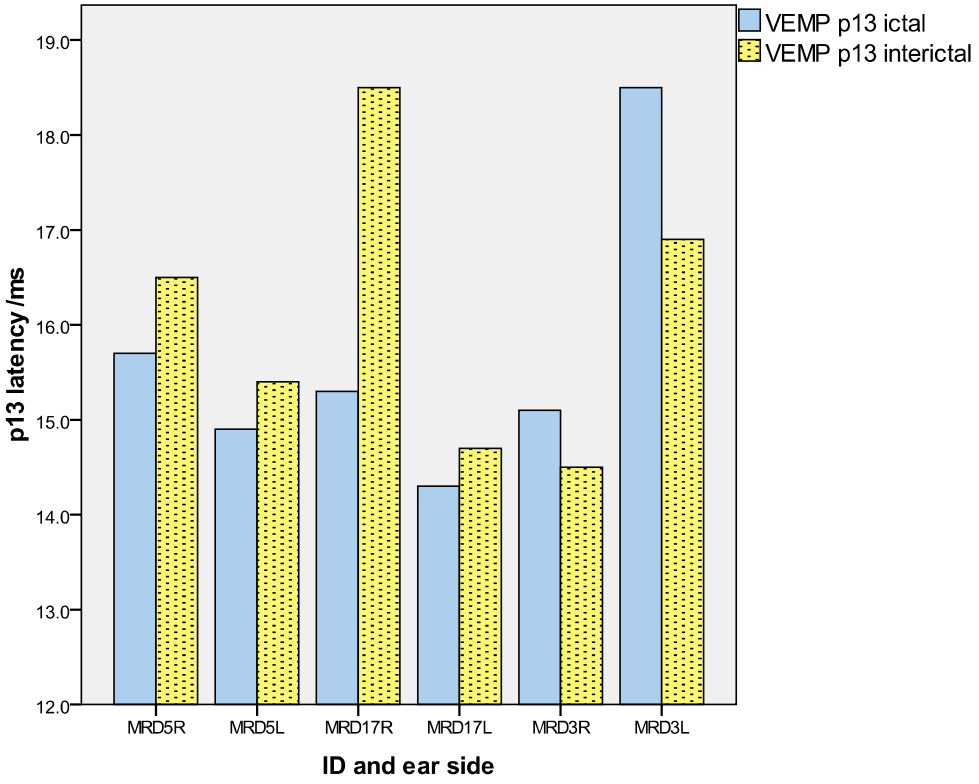


Figure 4.9 a). Raw data for change in latency in the ictal and interictal condition in three individuals (six ears, marked by study ID number and then R or L indicating right or left respectively). b) Frequency distribution for the difference between ictal and interictal recordings for these data



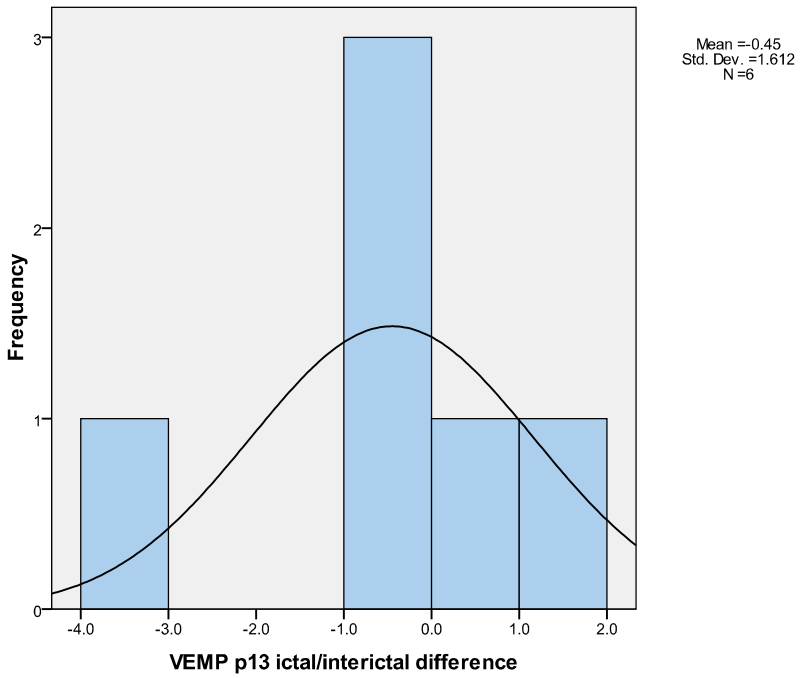
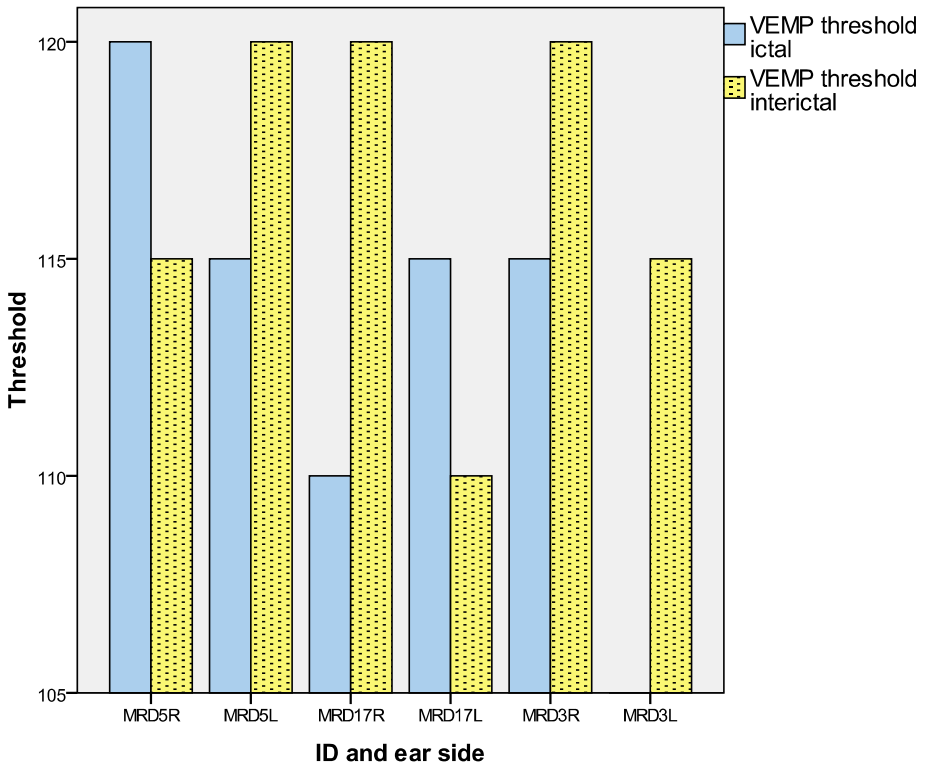
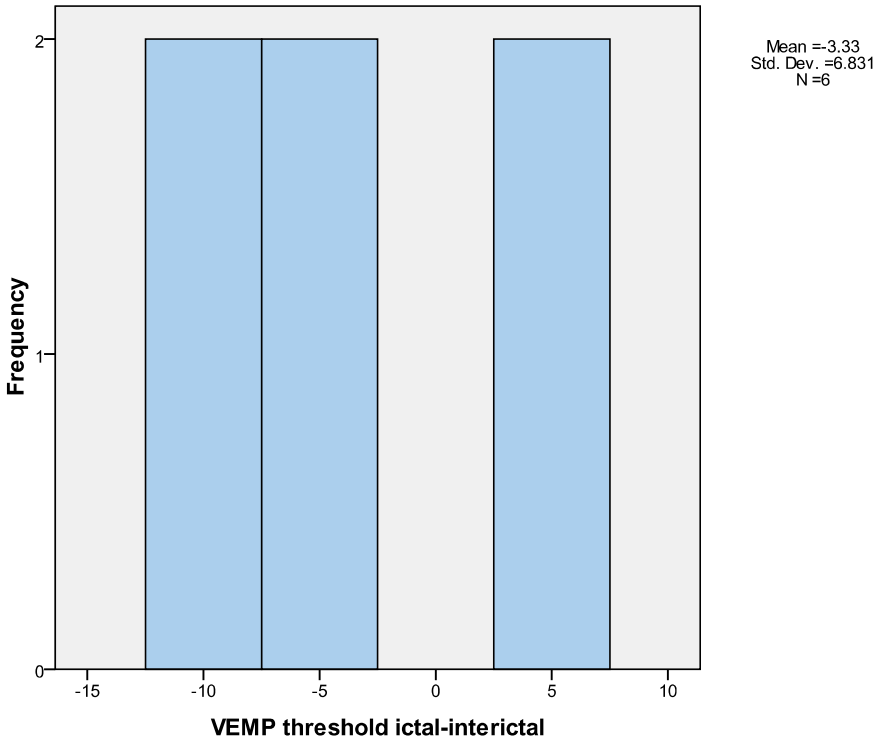


Figure 4.10 a). Raw data for change in threshold in the ictal and interictal condition in three individuals (six ears). b) Frequency distribution for the difference between ictal and interictal recordings for these data





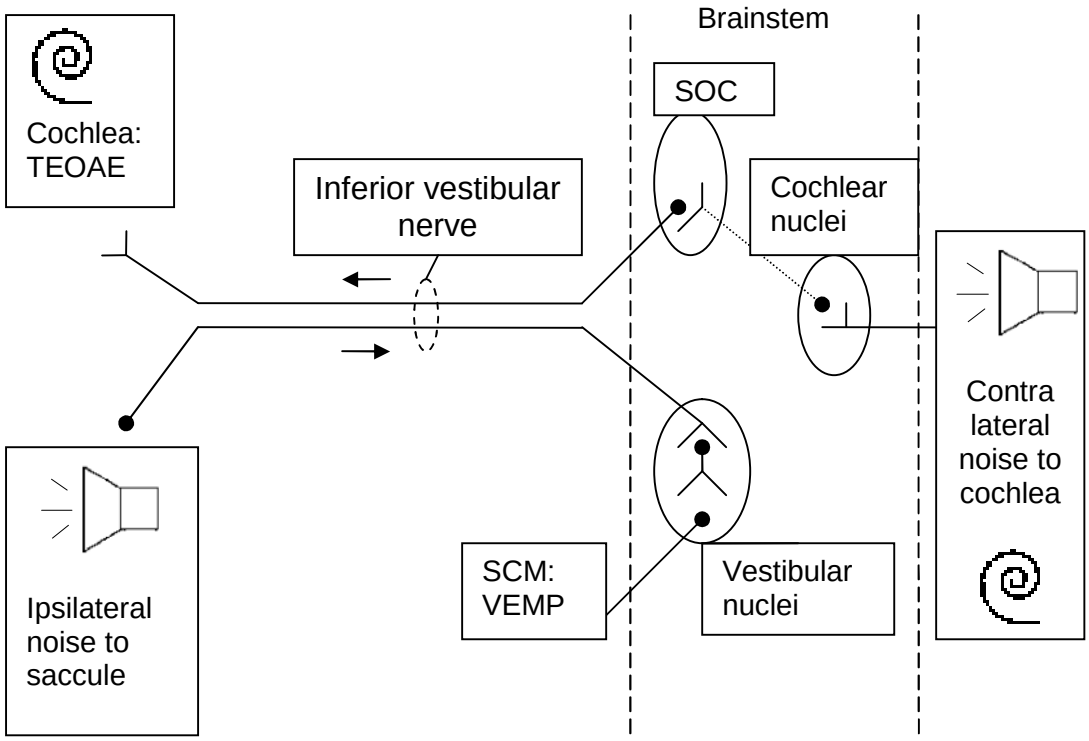
4.9.5 Comparing VEMP findings and OAE suppression findings

The pathways for VEMP and OAE suppression have some common components (figure 4.11), and the majority of VM participants (33/41) had both VEMP and OAE recordings. The data were thus examined to seek evidence of a relationship between VEMP and OAE results. There was no correlation between VEMP amplitude and OAE suppression. The mean value of suppression for those VM ears with absent VEMPS was 1.0 dB (n=5, SD 0.75), whereas for those with VEMP present it was 1.9 dB (n=52, SD 1.4) generating p= 0.09 using the Mann Whitney U test. There was no significant difference in the proportions of those with absent VEMPs amongst those with low total suppression Ts (2/9) or with normal total suppression Ts (3/16; p=0.5 Fisher's exact test). The ictal-interictal results can also be compared with OAE results (section 3.6.3 in the preceding chapter), since two out of the three individuals in whom VEMPs were recorded ictally also had OAE recordings on the same occasion (Table 4.VI).

Table 4.VI OAE recordings compared with VEMP recordings in the ictal and interictal phases

Study ID number	**OAE ictal-interictal comparison**	**VEMP ictal-interictal comparison**
MRD5	no recordings made	normal
MRD17	abnormally large shift in Ts	right ear showed large increase in latency
MRD3	normal	left ear showed large reduction in latency
MRD19	abnormally large shift in Ts	no recordings made

Figure 4.11 Principal neural pathways for VEMP and OAE suppression showing overlap via the inferior vestibular nerve (SCM sternocleidomastoid; SOC superior olivary complex)



4.10 Discussion

The results from this study show a high rate of absent responses in the cases of vestibular migraine (5/35 cases (14%)), compared with 0/30 in the healthy control group (p=0.06). Regression analysis also shows that the VM group had a higher overall rate of abnormal VEMPs when compared to the controls. In addition, data from ictal and interictal recordings show latency shifts outside the normal range in two out of three individuals.

This present study replicates Liao's finding of absent VEMPs in a high proportion of cases (Liao and Young 2004). This was also found by Murofushi's group to a lesser extent (Murofushi et al 2009). The stimulus intensity in the VEMP protocol used in the present study is restricted to a maximum of 125dB SPL, and it could be that VEMP absence in our study is a representation of raised thresholds above this level. The finding of reduced mean amplitude (Allena, Magis, De Pasqua, and Schoenen 2007; Baier, Stieber, and Dieterich 2009) is not replicated.

What could be the possible reasons for the VEMP absence? Repeat assessment by a blinded investigator showed a 100% concordance for interpretation of the traces as present or absent suggesting that investigator bias is not a likely explanation. Colebatch wrote in 2001: "The usual reasons for failing to record robust responses are inadequate tonic activation of the sternocleidomastoid muscles, confusion about the intensity of clicks required, or the presence of conductive hearing loss …responses can be obtained in nearly all normal individuals less than 65 years old." In this study, the tonic activation of EMG was recorded, measured and sustained using a visual biofeedback mechanism. Presence or absence of response was determined at 125 dB SPL, the highest level if output deliverable from the system. This is higher than the normal upper limit in most studies. Conductive hearing loss or middle ear dysfunction were excluded by tympanometry and audiometry prior to testing, and all individuals participating were under 60 years of age.

VEMP absence is reported in the literature to occur in some pathological states, and only very occasionally in normals (Table 4.VI). To summarise the information in this table, in 33 papers reporting VEMPs in various populations, absence is reported in multiple sclerosis, benign paroxysmal vertigo of childhood, brainstem strokes, dizzy clinic patients, HTLV with cervical myelopathy, Meniere's disease, sudden sensorineural hearing loss with vertigo. Only two reported absence in normals.

Table 4.VII. VEMP absence in normals and patients

Study	VEMP stimulus	Number of normals	Any absent recordings in normals?	Absent VEMPs in patients?
Allena 2007	Click 95dBnHL	20	no	No (in 25 migraineurs)
Aw 2006	Click 110dB nHL	11	no	0/19 with superior semicircular canal dehiscence
Bandini 2004	100 dBnHL click	21	no	0/36 with MS
Brantberg 2007	500Hz tone burst 129 dB SPL peak	0	0	1000 neuro-otology patients (no conductive hearing loss or bilateral vestibular failure) ?11 absences
Chang 2007	500Hz tone burst at 95dBHL	20 children	no	6/20 children with benign paroxysmal vertigo of childhood
Chen 2003	Click and 500Hz tone burst at 95 dB (reference not specified)	"lab norms"	not reported	5/7 with brainstem stroke
Colebatch 1994	95dB nHL clicks	10	no	Absent unilaterally in 5 after vestibular nerve section
Heide 1999	110 dB nHL click	39	no	11/40 mostly peripheral vestibular disorder (0/6 with "psychogenic vertigo")
Itoh 2001	Click 105 dB nHL	21	no	1/13 brainstem lesions
Felipe 2008	1kHz tone burst 118 dBHL	30	no	10/72 HTLV patients
Ito 2007	500Hz TB	14	?no	-
Iwasaki and Murofushi 2005	Click 95 dB nHL	0	-	17/22 on affected side idiopathic sudden hearing loss with

				vertigo
Iwasaki and Murofushi 2005	Click 95 dB nHL	18	no	811 NO clinic patients: identified 40 with absent VEMP and present caloric unilaterally
Kuo and Young 2005	500Hz tone burst 95 dB	"lab norms"	?no	7/12 with Menières
Liao and Young 2004	500Hz TB 95 dB	"lab norms"	?no	7/20 with basilar type migraine
Lee 2008	Click 95nHL	97	no	-
Lim 1995	Click 95nHL	10	?no	-
Lin 2006	250, 500, 1000 Hz tone burst at 90dBHL	12	no	-
Murofushi 1998	Click 95dBnHL	8	no	15/21 vestibular schwannoma
Murofushi 2001	Click 95dBnHL	18	no	15/43 MD affected ear; 9/23 vestibular neuritis; 39/62 vestibular schwannoma; 3/12 MS
Ochi 2001	Click 95dBnHL	18	no	-
Osei Lah 2007	500Hz TB	18	no	-
Pollak 2006	Click 110dBnHL	53	no	0/34 cerebellar/brainstem strokes
Rauch 2004	Click and 250,500,1,2,4	14	1 normal ear no response to click. 3 normal ears no response to 4kHz TB.	1/34 unaffected Menière's ears; 6/34 affected Menière's ears for clicks
Robertson and Ireland 1995	Click ?maximum stimulus	7	absent 25%	-
Roceneau 2008	Click 95 dB nHL	20	?no	?0/17 migrainous vertigo, 0/25 vertigo free migraineurs
Sartucci 2002	Click 140 dB SPL	15	no	0/15 with multiple sclerosis
Seo 2008	Click 95dBnHL	10	no	0/18 "dizzy patients"
Takegoshi and Murofushi 2000	Click 95dBnHL	9	no	0/10 olivopontine cerebellar atrophy; 2/3 Machado Joseph
Vanspauwen 2006	500Hz tone burst	15	no	-
Versino 2007	145dB SPL click	18	no	70 with multiple sclerosis

Is the observation merely a statistical aberration, given a p value of only a small amount below 0.05? Other groups do not publish reports of high levels

of VEMP absence in normals, and so it seems likely that Colebatch is correct to assert that, with correct technique, VEMPs are almost universally recordable in normal individuals under 60.

Another possible explanation is the heterogeneous nature of vestibular migraine. It is a clinical diagnosis, but is still fairly broad, and the community of international experts on vestibular migraine are refining Neuhauser's original definition in a working party via the Barany Society. Is there a synergistic mechanism at work with another pathology? For example, Menière's disease, which is known to affect VEMPs, can interact in a complex way with migraine (Radtke, Lempert, Gresty, Brookes, Bronstein, and Neuhauser 2002), as can vestibular neuritis (Best et al 2009b), and it is conceivable that the predominantly migrainous presentation of some patients masks an underlying alternative pathology.

Ultimately, then, we can consider the possibility that VEMP absence is actually a feature of vestibular migraine due to underlying migrainous pathology. This would suggest an abnormality of sensory processing or response along the sacculocollic reflex arc, though the observation is not specifically localising. Since some participants also had OAE suppression recordings, which were largely normal, however, it can be seen that the problem does not lie in complete malfunction of the inferior vestibular nerve. Given what is known about migraine pathophysiology, thought of as a brain disorder rather than one of peripheral or cranial nerves, this is perhaps unsurprising. In the two individuals with both abnormal OAE suppression and absent VEMPs, this could either be a chance finding (and there is no evidence in this study to conclude otherwise). Alternatively, one might speculate that an event such as an inferior nerve vestibular neuritis has been the triggering event in these individuals. This could be investigated further using video head impulse testing to delineate whether the posterior semicircular canal was functional, but this facility was not available during this investigation.

Although VEMP abnormalities might be expected in migraine, in the context of its current conception as disorder of sensory dysmodulation, one might expect abnormalities such as disinhibition, lack of habituation or hyperexcitability rather than absence of response. It should nonetheless be acknowledged that there are other groups which have independently reported similar findings (Liao and Young 2004). Reduction in amplitude is the other principal finding in VEMPs in vestibular migraine (Baier, Stieber, and Dieterich 2009). However, it is known that amplitude is a weak parameter in VEMP recordings, with high variability (as shown in this study, Figure 4.3 above and elsewhere.

The ictal and interictal recordings obtained, albeit in a small number of individuals, also show results of interest. Threshold and amplitude differences between the ictal and interictal conditions were within normal limits. However, there were large latency shifts unilaterally in two individuals, one becoming shorter in the interictal condition and one becoming longer. It is important to be wary of attaching too much importance to such a small number of readings, but, for practical reasons related to testing an acutely ill patient, it is difficult to obtain large quantities of data. These observations need further independent verification.

4.11 Conclusion

VEMP abnormalities, including absence of response, are seen more frequently than expected in cases of MV. This does not seem to be a result of technical, experimental or statistical factors. The observed absence of VEMPs could be due to the heterogeneous nature of VM and its interaction with other conditions.

Chapter 5. Vertigo as a migraine trigger

5.1 Introduction

Understanding migraine triggers is one key to understanding the pathophysiology, and, potentially, the management of migraine. Triggers are known to be diverse, ranging from phase of menstrual cycle, to sensory stimuli such as noise (Martin, Reece, and Forsyth 2006), smells (Sjostrand et al 2010) and glare (Kelman 2007), and even the more esoteric such as hair washing in Indian women (Ravishankar 2006) and the Chinook winds of Canada (Cooke, Rose, and Becker 2000). It has been reported that caloric testing, a potent vestibular sensory stimulus, appeared to trigger migraine attacks in three individuals (Seemungal, Rudge, Davies, Gresty, and Bronstein 2006). It is also known that visual-vestibular stimuli such as optokinetic stimulation (Granston and Drummond 2005) and motion sickness (Grunfeld and Gresty 1998) can trigger or exacerbate migraine symptoms. Migraineurs are also reported to experience more nausea in response to vestibular stimulation in the form of caloric testing (Vitkovic, Paine, and Rance 2008).

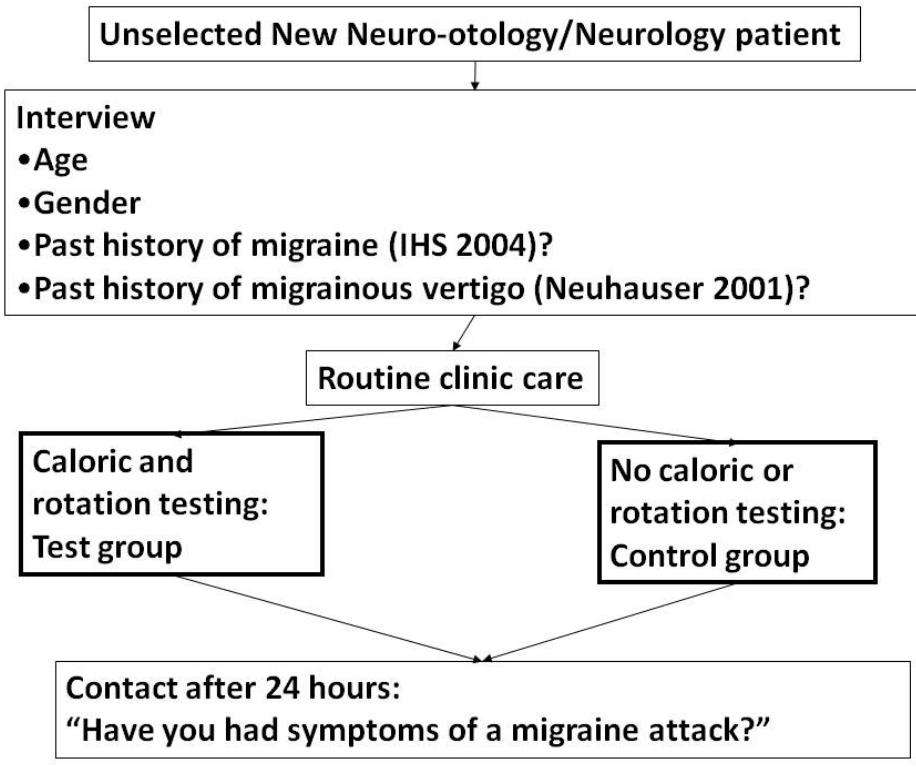
This combination of observations raises the possibility that vestibular stimulation and the associated vertigo could be acting as migraine triggers, although as yet there is a lack of systematic evidence for or against this hypothesis. This section of the study was therefore conceived to examine the hypothesis that vestibular stimulation, in the form of caloric testing, could act as a migraine trigger.

5.2 Methods

Patients attending the Neuro-otology or Neurology clinics for the first time were approached. Data were collected on age, gender, presenting complaint and medication status. Participating subjects were classified, regardless of the presenting complaint, as having a history concordant with International

Headache Society (IHS) (2004) criteria for migraine (International Headache Society Headache Classification Committee 2004) (migraineurs) or not (non-migraineurs) based on a structured interview/questionnaire (appendix 4). They were also assessed for conformity to the diagnosis of definite migrainous vertigo according to Neuhauser (Neuhauser, Leopold, von Brevern, Arnold, and Lempert 2001). Participants then underwent their standard clinic care as determined by the treating physician. This either involved vestibular testing (vestibular test group) or did not (control group). The protocol of the study is illustrated in figure 5.1. This aspect of design was intended to control for the stress of a hospital appointment and associated investigations as a new patient, which could of itself act as a potential migraine trigger. Patients were excluded if they experienced daily headaches of any kind, as it would be difficult to identify a clear relationship between the stimulus and any headache outcome in such cases.

Figure 5.1. Trigger study protocol



All patients had horizontal direct current electro-oculography according to a standard protocol: gaze testing (+/- 30° searching for nystagmus in the light and darkness), sinusoidal rotation, vestibulo-ocular reflex suppression, impulsive rotation, optokinetic stimulation and smooth pursuit. Sinusoidal rotation was carried out in the dark during with a motorised chair at a frequency of 0.2 Hz, peak velocity of +/- 30°/s for a duration of approximately eight cycles. Ability to suppress the vestibulo-ocular was then tested by repeating the sinusoidal stimuli and asking the patient to visually fixate on a target which moves with them (i.e. stationary with respect to the patient), for approximately four cycles. Impulsive rotation comprised velocity steps at +/- 60 °/s until nystagmus subsides (approximately 45 seconds, maximum of 100 seconds; approximate acceleration/deceleration (-140 °/s2). In full field optokinetic testing the subject was stationary whilst the surrounding striped curtain revolved at a speed of 40 °/s, alternating direction every 5-10s for a total of approximately 30s. For smooth pursuit subjects were required to track a laser-projected target moving in a sinusoidal fashion at 0.2, 0.3 and 0.4 Hz. All patients in the vestibular test group underwent bithermal water caloric testing using a 40 second irrigation in each ear at 44°C and 30°C.

Any patient who had rotation testing without calorics was excluded, since rotational testing was deemed to be of insufficient potency as a vestibular stimulus for the purposes of this study. To be eligible for the vestibular test group patients were required to be naive to vestibular testing, since a previous negative experience (including triggered migraine attacks) could be a reason for refusal to undergo repeat testing, and this would bias results. Patients who had vestibular testing were excluded from analysis if results showed bilateral vestibular failure or if there was no subjective response to vestibular testing, since the adequacy of vestibular stimulation in such subjects was in doubt. Patients in the control group did not have induced vertigo (caloric/rotational testing or positive response to positional testing) during their visit. All the patients in the vestibular test group were recruited from the Neuro-otology clinics, and those in the control group were predominantly from the Neurology clinics.

Participants were contacted after 24 hours by telephone or email to determine any symptoms brought on during or after the hospital visit. If initial attempts at contact were unsuccessful, further attempts were made up to a maximum of two weeks after the initial visit. The principal outcome measure was the occurrence of post visit migraine. The definition for post visit migraine was derived from the IHS (2004) definition of migraine (International Headache Society Headache Classification Committee 2004). Post visit migraines met two out of three of criteria B, C and D in the IHS definition where criterion B requires that the headache lasts 4–72 hours untreated or unsuccessfully treated, C requires that the headache has at least two out of a set of characteristic features (unilateral location, pulsating quality, moderate/severe intensity and aggravation by routine physical activity) and D requires that the headache is associated with one of either (i) nausea/vomiting or (ii) photo- and phonophobia. This definition using two out of three criteria was selected to overcome the difficulty that most patients took abortive medication so that criterion B was not normally fulfilled. A post visit migraine was defined as occurring within 24 hours of the hospital appointment, and patients were asked to define if possible the time of onset of premonitory symptoms or headache. Data were also collected on the presence of other types of headache, other migraine symptoms, and whether vestibular symptoms (dizziness, vertigo, imbalance) were present during a triggered migraine attack.

To account for the effects on outcome of multiple variables (age, gender, past history of migraine or migrainous vertigo), binary logistic regression analysis was used. Statistical testing was carried out using SPSS Statistics software version 17.0 (www.spss.com).

5.3 Results

5.3.1. General descriptors

One hundred and forty eight (148) people were approached; five declined to participate and 20 were excluded (five for daily headache, 12 were not contactable within two weeks, three had bilateral vestibular failure or no

subjective response to vestibular testing). There were therefore 123 participants in the study, comprising 79 in the vestibular test group (39 migraineurs and 40 non-migraineurs) and 44 in the control group (21 migraineurs and 23 non-migraineurs). The mean age was 43 in the vestibular test group (SD 15, range 17-78) and 50 in the control group (SD 15, range 17-75). The control group was 34 % male (15/44) and the test group was 30% male (24/79); 8/44 (18%) controls were consulting for a form of migraine, compared with 25/79 (32%) of the case group ($p=0.11$, $\chi 2 = 2.61$).

Participants were consulting for a range of neurological and neuro-otological disorders including migraine (30%), incompletely compensated vestibular neuritis (17%), Menière's disease (7%), central neuro-otological disorders (15%), benign paroxysmal positional vertigo (3%), auditory disorders (11%) and other neurological disorders (16%). Of the 60 migraineurs in the study, 23 (38%) met the Neuhauser criteria for migrainous vertigo (Neuhauser, Leopold, von Brevern, Arnold, and Lempert 2001). All patients who had vertigo as part of a positive response to positional testing were in the vestibular test group. Four of the migraineurs were taking migraine prophylactic agents at the time of assessment (three in the test group and one control subject). Nine patients in the vestibular test group were taking prescribed vestibular suppressant medications, but all had been advised not to take them in the forty-eight hours preceding their assessment.

5.3.2 Headache outcome

The headache outcome for all four groups is shown in Table 5.I.

Table 5.I. Headache outcome for all participants according to test group and migraine history

Vestibular test status	Past history of migraine (according to IHS criteria)	n	No post visit headache	Post visit headache (other than migraine)	Post Visit Migraine within 24 hours
Vestibular tests	Migraineurs	39	15 (38%)	5 (13%)	19 (49%)
Controls	Migraineurs	21	16 (76%)	4 (19%)	1 (5%)
Vestibular tests	Non-migraineurs	40	28 (70%)	7 (18%)	5 (12%)
Controls	Non-migraineurs	23	19 (83%)	4 (17%)	0

Figure 5.2 illustrates the difference in headache outcomes for those with a background history of migraine (migraineurs). Among the migraineurs, 19/39 (49%; 95% confidence interval 41 to 57%) of those in the test group experienced a migraine within 24 hours, compared with 1/21 (5%; 95% confidence interval 0 to 10%) of the control group who did not have vestibular tests ($\chi 2 = 11.868$, $p=0.001$). Two participants from the test group who experienced migraines within 24 hours of the visit attributed the symptoms to a specific alternative trigger (one to a difficult journey home, the other to the phase of her menstrual cycle) and these cases were counted as negative responses (“no headache”).

Figure 5.2 Headache outcome for migraineurs in vestibular test and control groups

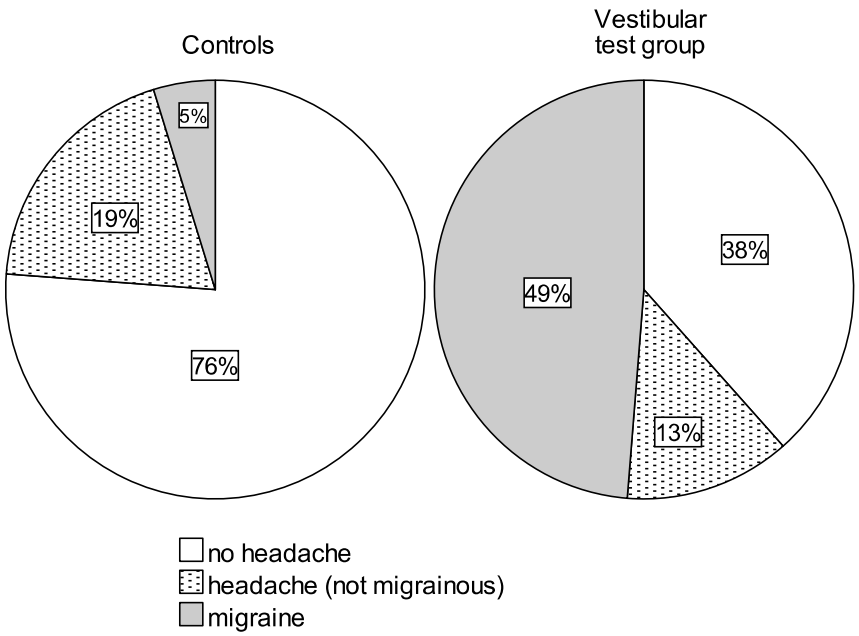


Table 5.II shows the significance levels achieved for the variables entered into the binary logistic regression model, which was designed to identity predictive factors for post visit migraine. Vestibular testing, history of definite migraine and history of migrainous vertigo were all significant factors. Of those migraineurs who had vestibular testing, 14/21 (67%) of those with established migrainous vertigo had post visit migraines, whereas only 5/18 (28%) of those without established migrainous vertigo did so ($\chi 2 = 5.867$, $p=0.015$).

Age and gender were not shown to have independent effects in this model, and therefore these factors were not subject to further analysis.

Table 5.II Binary logistic regression analysis of factors associated with post visit migraine. P values less than 0.05 are marked with an asterisk *.

Factor	P value	Odds ratio estimate (95% confidence interval)
Vestibular testing (i.e. status within the test group)	**0.01***	14.6 (1.8-120.6)
History of migraine	**0.05***	3.5 (1.0-12.8)
History of migrainous vertigo	**0.04***	3.6 (1.0-12.5)
Female gender	0.47	1.6 (0.5-5.5)
Age	0.89	1.0 (0.96-1.04)

5.3.3 Associated features of triggered attack

There were 24 vestibular test group participants in whom post visit migraine occurred. Symptoms of dizziness, imbalance or vertigo were experienced with 11 (46%) of these attacks. In the single control patient who experienced a post visit migraine, no dizziness, vertigo or imbalance were reported. For 15 vestibular test group participants with post visit migraine, data were available regarding the timing of the migraine attack. For seven of these 15 (47%), the onset of migraine (premonitory symptoms or headache) was reported as occurring during the induced vertigo i.e. the vestibular stimulus was time-locked to the migraine response. One of these seven reported migraine onset during rotation testing (which always occurred prior to caloric testing) with the other six citing onset during caloric testing.

5.4 Discussion

These results show that 49% of migraineurs experience a migraine headache within 24 hours of a hospital assessment that included vestibular testing, in contrast to only 5% of those migraineurs who had a hospital assessment without vestibular tests. These results are in keeping with the hypothesis that vestibular stimulation can be a migraine trigger (Seemungal, Rudge, Davies, Gresty, and Bronstein 2006), since the probability of experiencing a migraine in the study time window was significantly higher in the vestibular test group than in the control group. As expected, a past history of migraine was also a significant determinant of whether an attack was triggered. Although in this study data were not collected on the frequency or severity of migraine attacks, which could have introduced a bias between the test and control groups, the proportions consulting for a migraine-related condition in the two groups were not significantly different.

In 47% of those who had post visit migraine, the onset of migraine occurred during the vertigo induced by vestibular tests. This is further evidence indicating that it is the vestibular stimulus rather than the stress of a hospital visit which has triggered the attack. This observation is in keeping with the clinical observation that sensory stimuli in other modalities (audition, olfaction, vision) are known to be migraine triggers. Patients not uncommonly cite sensory stimuli as triggers (e.g. perfumes, fluorescent lighting (Kelman 2007)), and experimental paradigms using stimuli such as noise have validated these reports (Martin, Reece, and Forsyth 2006).

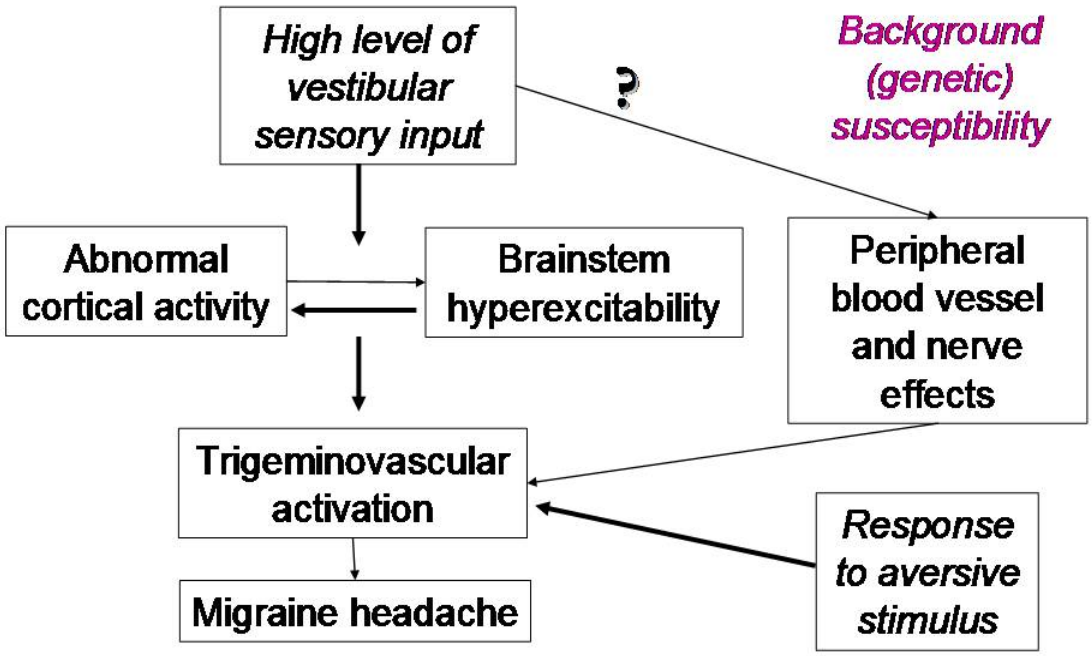
A history of vestibular migraine also has a significant effect on the outcome. Patients who have a diagnosis of definite vestibular migraine are more likely to experience a migraine after vestibular testing than those with other forms of migraine. Indeed, all the participants who underwent vestibular testing had a history suggestive of vestibular disturbance, and it could be the case that such subjects are particularly sensitive to vestibular stimuli as a migraine trigger. The difference in outcome between the two groups might be somewhat less marked if those in the test group had no such history. It is of note,

however, that, despite using a vestibular stimulus to provoke an attack, fewer than half the induced migraine attacks were associated with dizziness, vertigo or imbalance which might suggest an attack of migrainous vertigo. This figure is not dissimilar to the frequency of such symptoms in migraine attacks in general (54.5% in one study (Kayan and Hood 1984)). Therefore it seems that the vestibular stimulus is triggering migraine attacks through a final common headache pathway which does not necessarily trigger the vestibular system.

Current understanding of the pathophysiology of migraine suggests a role for both cortical and subcortical structures, and incorporates the concept of sensory dysmodulation (Goadsby, Charbit, Andreou, Akerman, and Holland 2009). It is thought that the pain of migraine derives from activation of trigeminovascular input to meningeal vessels, which is presumed to be the final common pathway for initiation of migraine headache (Bolay et al 2002). Migrainous aura is believed to be the result of a cortical process equivalent to the animal model known as Leão's spreading depression (Lauritzen 2001). It is a matter of some debate whether attacks of migraine without aura originate in the cortex or the brainstem. One hypothesis is that cortical activation is the primary event, with descending pathways converging on brainstem nuclei which regulate responses to sensory stimuli, such as the periaqueductal grey and nucleus raphe magnus (Lambert and Zagami 2009).

There are therefore a number of putative mechanisms by which vestibular stimuli could trigger migraines (Figure 5.3).

Figure 5.3. Putative mechanisms for triggering of migraine headaches



Firstly, vestibular stimuli such as caloric testing cause activation of the vestibular nuclei and thereby cortical structures, especially in the temporo-parieto-insular areas (Dieterich and Brandt 2008). The vestibular nuclei have connections to the dorsal raphe nucleus (Cuccurazzu and Halberstadt 2008) and locus coeruleus (Nishiike et al 2001). Imaging studies show activation of areas encroaching on the vestibular nuclei during an attack of migraine without aura (Afridi, Giffin, Kaube, Friston, Ward, Frackowiak, and Goadsby 2005). The trigeminovascular reflex could thus be activated through these cortical or subcortical pathways. Alternatively, it is theoretically possible that trigeminovascular activation could occur as a direct consequence of peripheral stimulation, by local release of neuroactive substances such as CGRP or substance P. In support of this hypothesis, it is known that there is direct innervation of vestibulocochlear structures by afferent trigeminal nerve endings (Vass et al 1998b).This explanation is less likely given that the triggered attacks do not specifically incorporate vestibular symptoms. Thirdly,

there is the possibility that the migraines triggered in this study are occurring due to a general stress or anxiety effect. It is well known that patients with vestibular disorders find the experience of vertigo distressing and anxiety provoking, and this is discussed elsewhere in this thesis (chapter 6, (Balaban and Thayer 2001). In this part of the study, those undergoing vestibular testing had a history of symptoms of dizziness, vertigo or imbalance. In such patients, the concern that their symptoms would be reproduced by caloric stimulation could be expected to produce some anxiety. The resulting physiological stress response could be the trigger factor for the migraine attack. However, many of the control patients also had potentially stressful or aversive procedures such as blood tests or imaging on the day of their appointment. This would tend to argue against the notion that the migraine triggering effect of vestibular tests relates purely to stress responses. Other sensory stimuli which act as migraine triggers are generally aversive (e.g. noise, glare) although this is not exclusively the case (e.g. perfumes).

Whatever the mechanism, it is clear that induced vertigo from vestibular stimulation is associated with the development of migraine attacks in around half the migraineurs attending a Neuro-otology clinic. This observation can be considered in the context of the known relationships between established migraine and some disorders which cause episodic vertigo. It is reported that the lifetime prevalence of migraine is increased in patients with Menière's disease (Radtke, Lempert, Gresty, Brookes, Bronstein, and Neuhauser 2002). In this study 28% of the patients with Menière's disease described typical migrainous headaches as associated always or sometimes with their Menière attacks. Our data suggest that this observation could be at least partly explained by a trigger effect of the vertigo experienced as part of an attack of Menière's disease. Episodic ataxia type 2 is another disorder in which attacks of vertigo have been reported to trigger migraine headaches (Baloh, Yue, Furman, and Nelson 1997). Interestingly, attacks of ataxia (but not migraine) can also be triggered by caloric stimulation in episodic ataxia type 1 (Vandyke et al 1975). It is also reported in the literature that migraine is more common than expected in cases of benign paroxysmal positional vertigo (BPPV) ((von Brevern et al 2007). It has been speculated that inner ear damage due to

vasospasm in migraineurs could predispose to BPPV, explaining this association. The data from this study suggest another possible contributory mechanism: there could theoretically be an unmasking effect of BPPV on migraine whereby episodes of BPPV act as triggers in susceptible individuals, thus apparently increasing the frequency of attacks of migraine headache.

5.5 Conclusions

These data therefore have implications for clinical practice. Where a patient gives a history of vertigo followed closely by a migraine headache, the diagnosis will commonly be migrainous vertigo or basilar-type migraine. However, some other disorder which causes episodic vertigo could be acting as a migraine trigger in this individual. In order to reduce the migraine attack frequency in such a patient, such a disorder would need to be identified and appropriately treated. Such attacks could be thought of as a "secondary" form of vestibular migraine, to distinguish it from a "primary", intrinsic vestibular migraine. The study suggests further avenues for research to characterise and quantify the relative prevalences of primary and secondary vestibular migraines.

Chapter 6. Psychopathology of vestibular migraine: what is the mechanism?

6.1 Introduction

It is well known that there is a higher prevalence of psychopathological symptomatology, especially symptoms seen in depressive and anxiety disorders, in both individuals with migraine (Jelinski et al 2007) and in individuals with vestibular disease (Eagger et al 1992). It is also known that, among psychiatric outpatient populations, there is an exacerbation of depressive symptoms associated with migraine attacks (Hung et al 2006). It may be suspected therefore that those with vestibular migraine are subject to an additive effect of vestibular disease and migraine, showing particular vulnerability to symptoms of anxiety and depression.

Depression and anxiety are common psychiatric diagnoses, affecting around 13% and 10% of the UK population at one time. (King et al 2008). The standard diagnostic criteria for these disorders are derived from DSM-IV-TR (American Psychiatric Association 2000).

6.2 Definition of Depressive and Anxiety Symptoms

A major depressive episode is defined in DSM-IV-TR (American Psychiatric Association 2000) as the presence of a severely depressed mood that persists for at least two weeks (see Appendix 2 for fuller definition). This is manifest by the experience of five or more symptoms from a list relating to low mood, anhedonia, appetite or sleep disturbance, psychomotor agitation/retardation, low self-worth, poor concentration and suicidal ideation.

Generalised anxiety disorder is also defined in DSM-IV-TR, within the broad and varied family of anxiety disorders including panic disorder, agoraphobia and anxiety disorder due to a general medical condition (American Psychiatric Association 2000). Generalised anxiety disorder (GAD) is defined as characterised by excessive, uncontrollable and disproportionate worry ("apprehensive expectation") for at least six months (see Appendix 3 for fuller definition). DSM-IV specifically acknowledges

an aspect of the relationship between vestibular disease and anxiety under the heading “Anxiety disorder due to a general medical condition”. For this diagnosis, the manual writes that “there must be evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.” To determine this, the clinician must look for a temporal relationship between anxiety symptoms and those of the physical condition, and features atypical of the primary anxiety disorders.

6.3 Anxiety and depression in patients with vestibular disorders.

The relationship between vestibular symptoms and psychopathology, especially in relation to anxiety disorders, has been well explored over the last twenty years. It has long been recognised that the symptoms of vestibular disorders, in particular episodic dizziness and loss of balance, are also manifest in psychological disorders such as panic disorder and generalised anxiety disorder (Monzani et al 2001; Yardley and Redfern 2001). This raises the issue of distinguishing the two, since the presentations can be similar as well as present concurrently (Staab and Ruckenstein 2003). There is less symptomatic overlap with depression, although fatigue and lack of concentration are, in clinical practice, common complaints in balance clinics.

The relationship is more complex however than simply making a distinction between two separate conditions with overlapping clinical presentations. Psychological disorders are commonly associated with vestibular disorders, and may in fact be co-morbid. There could be pathophysiological overlap between pathways or transmitters involved in development of anxiety or depression and the perception of dizziness. There could be a causal relationship, for example the experience of vestibular disorder could engender reactive depression or anxiety in predisposed individuals. Alternatively, the persistence of dizziness symptoms may relate to pre-existing personality or psychological factors. These ideas have been called “somatopsychic”, where the psychological symptoms are thought of as a consequence of the physical disorder, and “psychosomatic”, where the persistence of physical symptoms is thought to be due to either pre-existing psychological factors, or a classical conditioning explanation of autonomic symptoms and disorientation. Another possibility is that psychological symptoms act as a trigger for attacks of dizziness

through a generalised "stress" response, or *vice versa,* that dizziness acts as a non-specific trigger for psychological disorder through a similar mechanism.

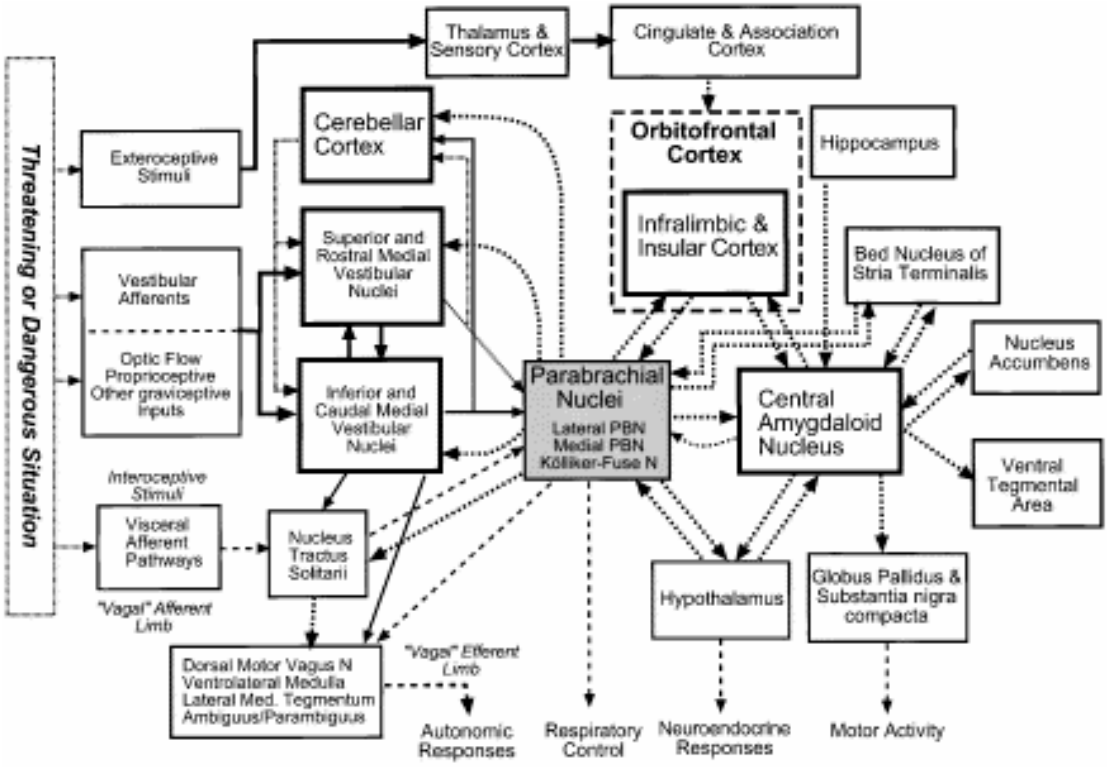
One study has reported that, amongst a group of 54 patients with objectively diagnosed vestibular disorder, 50% had evidence of psychiatric disturbance when interviewed three to five years later (Eagger, Luxon, Davies, Coelho, and Ron 1992). This included anxiety (GAD, phobias) and depressive disorders (major depression). It is also known that development of depressive or anxiety-based symptoms after vestibular neuritis or other acute vestibular syndrome is associated with for poor recovery (Best et al 2009d). BDI results have also been reported in a community sample in Finland, showing a prevalence of 19% of mild-severe depression amongst those who had vertiginous symptoms, twice the general population rate (Ketola et al 2007; Yardley et al 1999a). Other studies have also noted that depression can occur in those with confirmed peripheral vestibular dysfunction (Eagger, Luxon, Davies, Coelho, and Ron 1992; Honrubia et al 1996; Yardley et al 1992a). In a study of patients from a balance clinic in Mexico, patients had a mean BAI score in the mild range and a mean BDI score in the mild-moderate range (Yardley et al 1999b).

Certainly, by definition, experiencing intrusive incapacitating dizziness or vertigo is associated with feelings of disorientation, and thereby associated with confusion, fear, and a "precariousness of self" (Yardley L 1994). There is a sense of social handicap, as a consequence of having a condition which is invisible to others. This invisibility can result in a lack of empathy: "But you look fine to me." There is some evidence that intolerance of uncertainty is a significant factor in anxiety in Menière's disease (Kirby and Yardley 2009).

Lucy Yardley has written: "the links between dizziness and anxiety are complex and bidirectional, and appear to be mediated not only by a variety of cognitive-behavioural mechanisms, but also by multiple central connections between the vestibular and autonomic systems" (Yardley, Medina, Jurado, Morales, Martinez, and Villegas 1999a). For example, one factor at the neurophysiological interface between anxiety and balance disorders is visual processing. It is reported that patients with the least degree of retinal slip felt the most handicapped by oscillopsia, which at first sounds paradoxical (Grunfeld et al 2000). However, the authors of this study suggest that part of the mechanism for tolerance of oscillopsia is adaptation to retinal image movement during self motion, more likely to occur with larger slips. Also, patients with anxiety disorders also appear to be more visually dependent than controls in

posturography studies (Redfern et al 2007). Other bases for the neuroanatomical links include the strong links between the vestibular and autonomic systems (Furman et al 1998), activation of the latter widely recognised as an intrinsic part of an acute anxiety response. There are also distinct anatomical links between fear, anxiety, emotion, autonomic control and vestibular information processing, via a network centring on the parabrachial nucleus, as laid out by Balaban and Thayer (Balaban and Thayer 2001). This schema shows the functional connections between the parabrachial nucleus and areas which control the somatic, neuroendocrine and visceral motor components of emotional responses, known to be associated with anxiety and panic disorders. These areas include those which mediate autonomic responses such as the nucleus tractus solitarius, and those which mediate fear responses such as the central nucleus of the amygdala, the infralimbic cortex and parts of the hypothalamus (Figure 6.1).

Figure 6.1. Scheme of central connections between balance and anxiety as devised by Balaban and Thayer (Balaban and Thayer 2001). ((Balaban and Thayer 2001. Copyright 2001. Reprinted with permission from Elsevier)).



Indeed, tests of the vestibulo-ocular reflex are abnormal (unilateral caloric hypofunction, earth vertical rotation asymmetries) more frequently in patients with anxiety disorders than in healthy controls, although this study did not account for confounders such as age and sex in this comparison (Jacob et al 2009). Animal models exploring the link between balance and anxiety have been developed (Kalueff et al 2008; Shefer et al 2010). Meniere's disease, which is associated with episodic vertigo, is also associated with anxiety (Kirby and Yardley 2008). However, patients with Meniere's disease have a constellation of difficulties distinct from other episodic vertigo disorders, in that the condition is associated with acquired hearing loss and also tinnitus, both of which are known of themselves to be associated with psychological symptoms, especially anxiety and depression (Hallam et al 2006; Krog et al 2010).

There are also pharmacological links between depression/anxiety and balance, with noradrenergic, serotonergic and dopaminergic brainstem nuclei all having direct connections with the vestibular nuclei. All these neurotransmitter systems are thought to have a role in development or maintenance of depression or anxiety, and pharmacological modification of these transmitter systems are key modes of action of many anxiolytic or antidepressant drugs.

6.4 Anxiety and depression in patients with migraine.

As is the case for balance disorders, there are ample data showing an association between migraine headache and both mood and anxiety disorders (Baskin et al 2006). This has been documented in a variety of ways. In population based studies, migraineurs are more likely to suffer with depression than non-migraineurs (Hamelsky and Lipton 2006). In one such study, carried out over two years, those who had depression at the beginning of the study had a higher risk of developing migraine (and not other severe headaches) over the study interval, and those who had migraine (and not other severe headaches) at the beginning of the study had a higher risk of developing depression (Breslau et al 2003). The simplest interpretation of these results is that the relationship between migraine and depression is specific and bi-directional, and may be supportive of the view that the association is due to a common pathological mechanism, rather than a psychological consequence of suffering unpredictable and unavoidable episodes of severe pain.

Migraine and anxiety have also been shown to be related in population based studies, (McWilliams et al 2004; Merikangas et al 1990). In one study general anxiety disorder (OR 5.3, 95%CI 1.8 to 15.8) had the strongest association with migraine of the all the anxiety disorder subtypes. This study also carried out logistic regression analysis to determine the strength of association between psychiatric disorders (major depression, general anxiety disorder, bipolar spectrum and social phobia) and migraine. The best model incorporated general anxiety disorder alone (Merikangas, Angst, and Isler 1990).

The temporal relationship documented for migraine and anxiety has not been explored in detail, in contrast to migraine and depression. Additionally, it is less clear that the relationship between migraine and generalised anxiety is specific to migraine rather than being general to all types of severe headache (Hamelsky and Lipton 2006). The picture is different for data relating specifically to panic disorder where specificity to migraine and bi-directionality are maintained (Baskin, Lipchik, and Smitherman 2006).

There are a number of biological explanations for the relationship between migraine and anxiety disorders. It is known that migraine and depression have a bidirectional association at least partly explained by genetic factors (Schur et al 2009; Stam et al 2010). Also, the aminergic neurotransmitters which are modified by anxiolytic and antidepressant drugs are present in brainstem areas such as the periaqueductal grey thought to be important in the modulation of the trigeminovascular reflex (Holland 2009).

6.5 Migraine, vestibular disease and psychological disorders

Given the evidence of links between migraine and psychological disorders, and between balance and psychological disorders, it might be hypothesised that individuals with both migraine and a balance disorder could be particularly susceptible. Some work has been done investigating this proposition.

In one series of 100 patients with “migraine related vestibulopathy” seen in a specialist centre, anxiety or panic disorder were reported as comorbidities in 14 (Cass, Furman, Ankerstjerne, Balaban, Yetiser, and Aydogan 1997). 53% of patients

in one study of vestibular migraine cited stress or emotional upset as a trigger for attacks (Brantberg, Trees, and Baloh 2005).
It is also known that migraine is a risk factor for impaired recovery after vestibular neuritis (Best, Tschan, Eckhardt-Henn, and Dieterich 2009c). In addition, when compared to other vestibular vertigo syndromes such as BPPV, vestibular neuritis and Meniere's disease, individuals with vestibular migraine are at higher risk of developing a somatoform disorder (Best et al 2009a). However, none of the studies which report this observation account for the variation in vertigo severity or frequency which could conceivably account for at least some of these observed differences.

A German population based study screening for individuals with dizziness found that those who also had anxiety were more likely to have migraine than those who did not have anxiety symptoms (OR 2.57 (95%CI 0.05–7.21)) (Wiltink et al 2009). This was also true for skin and pulmonary complaints i.e. this relationship was not specific to migraine.

In a prospective balance clinic based study, chronic (non-episodic) non vertiginous subjective dizziness was associated with migraine in 17% cases. 47/57 of these cases (82%) also had at least one of panic disorder, GAD, minor anxiety and major depression (Staab and Ruckenstein 2007). This is much higher than would be expected in the general population. The authors report that this suggests that "anxiety related mechanisms may play a more significant role in sustaining chronic symptoms than headache", although perhaps this conclusion is not wholly justified by the data, since it could just as easily be hypothesised that the headache is the cause of the anxiety symptoms.

A recent study examining the interrelation of migraine, vestibular symptoms and psychological disorder examined a psychiatric clinic population underwent neuro-otological assessment (Teggi et al 2009). Migraine was equally common in those with panic disorder without agoraphobia, those with panic disorder with agoraphobia and those with depressive disorders. However, the panic disorder group had a higher prevalence of migrainous vertigo as defined by Neuhauser (Neuhauser, Leopold, von Brevern, Arnold, and Lempert 2001). In fact, almost all the patients in this study with abnormal vestibular function on caloric testing met criteria for migrainous vertigo. Having dizziness with migraine headaches is known to increase handicap as

measured by MIDAS score and degree of depression (PHQ9 score) (Bisdorff et al 2010).

The links between migraine, anxiety and balance disorders have also been synthesised as "Migraine anxiety related dizziness", proposed as a new entity (Furman et al 2005a). This idea is based on an amalgamation of pathophysiological concepts relating to psychogenic and organic dizziness, and vestibular migraine. The authors state that "MARD is unlikely to be the chance combination of a balance disorder, migraine headache and anxiety". They cite the high prevalence of panic disorder in migraine, and the poorer prognosis of patients with anxiety and migraine than migraine alone as supportive of this view. They then outline a schema for a putative pathophysiological connection, linking the parabrachial nucleus network with the trigeminovascular reflex via the vestibular nuclei. Although interesting in theory, this concept has yet to be validated in clinical terms, either in diagnostics or therapeutics.

So, it is accepted that migraine is associated with vestibular disorders, migraine is associated with anxiety and depression, and vestibular disorders are associated with anxiety and depression. There is also some evidence interlinking all three conditions. It might be thus hypothesised that individuals who suffer from migraine and vestibular disorders have a higher susceptibility to psychological symptoms than those who suffer vestibular disorders alone. However, it is important in any such study to control for frequency or severity of the vertigo symptoms which are suspected to have an independent effect on the presence of psychopathology as described above. No study has yet addressed this question specifically.

6.6 Rating Scales for Anxiety, Depression and Vertigo

What, then, would be suitable outcome measures to assess anxiety, depression and vestibular symptom load for such a study?

Various screening instruments for GAD and depression have been developed. The two most commonly cited depression rating scales are the Hamilton Rating Scale for Depression (Hamilton 1960) and the Beck Depression Inventory, BDI (Beck and Beamesderfer 1974). The BDI is a checklist of 21 items which the respondent rates on a four point scale, scored 0 – 3, see Appendix 5. The sum is calculated to give an overall index of the severity of depression. The BDI has well established content,

construct and concurrent validity and correlates well with other measures of depression (Beck et al 1988b). It was originally intended to be administered by a clinician, but is now established as a self-report screening instrument, assessing symptoms as reported over the past week.

The BDI, like all rating scales, has limitations. It was developed on a psychiatric patient population, and gives considerable weight to the somatic symptoms of depression. Relying as it does on self-report, it can be faked to suggest the responder is depressed or otherwise (Beck and Beamesderfer 1974). Since the original version was published, various revisions have been proposed including BDI-II (Steer et al 1998) (incorporating some text changes to the items and symptom duration record) and BDI-PC (Steer et al 1999) (designed for use in primary care situations), but the original BDI is still in common usage in many clinical settings and it still has an international currency.

The Beck Anxiety Inventory was developed later than the BDI (Beck et al 1988a). With a similar structure to the BDI, the BAI consists of 13 self report items which the respondent rates on a four point scale scored 0-3, see Appendix 4. The BDI and BAI have both been used to screen for psychological symptoms in patients with medical disorders (Huffman et al 2008; Waisbren and White 2010).

There is clear overlap between symptoms of episodic vestibular disease and symptoms of anxiety. In assessing anxiety symptoms in individuals with vestibular disease, it is desirable to assess vertigo severity since this is one factor which is could conceivably affect anxiety scores. A suitable measure of vertigo severity and frequency is the Vertigo Symptom Scale, VSS, which was designed to measure vertigo severity and distinguish it from anxiety based symptoms (Yardley et al 1992b). This instrument has subscales to quantify autonomic sensations and arousal as distinct from vertigo severity, and was developed in order to address some of the difficulties with distinguishing episodic vertigo from panic disorder. 36 symptoms frequently observed in patients with vertigo were included in a questionnaire answered by 127 vertiginous patients. The 36 symptoms were then rearranged to produce 24 questions. Later, a question on “bowel sensations’” was then removed because it embarrassed respondents, and an item on “feeling spaced out” was omitted because it did not discriminate well between vertigo and anxiety (Yardley, Medina, Jurado, Morales, Martinez, and Villegas 1999a). With these changes, the final 22 questions of VSS long form were selected, see Appendix 6.

There are two sets of sub-scales used for grouping the responses of the VSS.
One set consists of two long scales (2 scale):
a. Vertigo severity (VER) – 19 questions
b. Somatic anxiety (or anxiety/autonomic symptom scale) (AA) - 15 questions.

The second set consists of four short sub-scales (4 scale):
a. severe vertigo(VSS-SV)/acute vertigo of vertigo scale (VACU) - 13 questions.
b. brief vertigo (VSS-BV)/vertigo of short duration (VSH) - 6 questions.
c. Autonomic symptoms (VSS-AS)/Autonomic symptom scale (AU) - 6 questions.
d. Somatisation (VSS-SOM)/ (SOM) - 5 questions.

The 4 sub-scale version was used in earlier work and now only the two long sub-scales are recommended for use (L Yardley, personal communication). There have also been various versions of the scale with scores from 0-4 (Yardley L et al 1994) or 0-5 (Yardley, Masson, Verschuur, Haacke, and Luxon 1992b) or 1-5 (Yardley, Medina, Jurado, Morales, Martinez, and Villegas 1999a), making direct numerical comparisons between studies difficult.

6.7 Hypothesis

Individuals with vestibular migraine have higher levels of depressive and anxiety-related symptoms than other patients with other vestibular vertigo symptoms, even when severity and frequency of vestibular symptoms are accounted for.

6.8 Methods

Unselected patients attending the Neuro-otology department with a primary complaint of dizziness were invited to participate if they had an adequate standard of reading and writing English to complete questionnaires. Those who gave informed consent were required to undergo a structured physician-administered interview/questionnaire to determine history of migraine and vestibular migraine according to standard criteria (International Headache Society Headache Classification Committee 2004; Neuhauser, Leopold, von Brevern, Arnold, and Lempert 2001). All participants also completed the Vertigo Symptom Scale, Beck Anxiety Inventory and Beck Depression Inventory (Appendices 4, 5 and 6). Where

questionnaires were completed in the waiting area, the investigator receiving questionnaires checked them for completeness. If items were unanswered, this was verbally indicated to respondents who were offered another chance to complete these unanswered items if they wished. For comparison and to validate the questionnaires, a control sample was obtained from staff at the hospital. Potential controls were excluded if they had a history of severe headaches, ear disease (other than infrequent otitis media or externa) or a history of episodic dizziness.

BAI and BDI questionnaire responses were excluded from analysis if there were more than 10% of questions either unanswered or with multiple selections for a single item i.e. where there were three or more uninterpretable items for these 21 item questionnaires. If patients had an index (questionnaire score) with missing data for one or two responses, the median for the index was taken for that (those) question(s) and added to the original total to obtain the modified total.

The items on the VSS are:

1. *A feeling that things are moving*
2. Chest pains
3. Hot/cold spells
4. *unsteadiness*
5. *nausea*
6. muscle tension/soreness
7. *lightheadedness*
8. trembling
9. aural pressure
10. heart pounding
11. *vomiting*
12. limb heaviness
13. visual disturbance
14. headache
15. *unable to walk or stand without support*
16. breathlessness
17. poor concentration
18. unsteadiness
19. tingling/prickling/numbness
20. low back pain
21. sweating
22. faintness

Questions 1, 7 and 18 are broken down into 5 stems based on duration of symptoms (less than two minutes, up to 20 minutes, 20 minutes to 1 hour, several hours and more than 12 hours).
The VSS was divided into two subscales: vertigo (questions 1,4,5,7,11 and 15, italicised in above list) and autonomic anxiety (other questions). Data were excluded if patients left >10% questions unanswered. For the three "stem" questions, responses were scored zero if left unscored. (L Yardley, personal correspondence). For other questions, the median for that subscale was used.

The BAI items are:

1. numbness
2. feeling hot
3. wobbly legs
4. unable to relax
5. fear of the worst
6. dizziness
7. heart pounding
8. unsteadiness
9. terror
10. nervousness
11. choking feeling
12. hands trembling
13. shaking
14. fear of losing control
15. difficulty breathing
16. fear of dying
17. scared
18. indigestion
19. faint/lightheadedness
20. face flushed
21. hot/cold sweats

There is some overlap between these two scales, with VSS item 3 corresponding closely to BAI 21, VSS 4 to BAI8, VSS 7 to BAI 6, VSS 10 to BAI 7 and VSS 16 to BAI 15 and VSS 19 to BAI 1. No anxiety is classed as 0-7; 8-15 is mild, 16-25 is moderate, and 26-63 is severe.

The Beck indices were also calculated leaving out items which referred to symptoms that are typical of vestibular disease (wobbliness, dizziness and unsteadiness from BAI, health preoccupation from BDI).

The BDI items are:

1. sadness
2. future hopelessness
3. sense of failure
4. dissatisfaction
5. sense of guilt
6. sense of being punished
7. sense of disappointment
8. self criticism
9. suicidal ideation
10. crying
11. irritability
12. interest in other people
13. making decisions
14. unattractiveness
15. work
16. sleep
17. fatigue
18. appetite
19. weight loss
20. health preoccupation
21. interest in sex

0–9 is a normal score, 10–18 suggests mild-moderate symptoms, 19–29 is regarded as moderate-severe and 30–63 indicates severe depression. For statistical testing, the Mann-Whitney U was used to compare means in distributions not normally distributed. To evaluate the effect of multiple potentially significant factors, multiple linear regression analysis was carried out, to examine the effects of gender, age, and VSS-V scores on VSS-AA, BAI and BDI scores. Analysis was carried out using SPSS version 17.0.

6.9 Results

6.9.1. Basic descriptors and raw BAI, BDI and VSS scores

Table 6. I records the number of participant and age and sex data.

Table 6.I Participant and age and sex data

	Normal controls	**Vestibular migraine**	**Dizzy controls**	**Significance testing between VM and dizzy control group**
Number recruited	51	39	44	-
F:M	34:15(67%F)	30:9 (77%F)	28:16 (67%F)	p=0.188, χ^2
Age mean±SD	37.6±11	38.2±12	46±12	p=0.004, t test

Of the dizzy controls, 14 had a peripheral vestibular disorder confirmed on caloric testing (including bilateral vestibular failure), 7 had a condition being managed as a peripheral vestibular disorder although objective tests were normal, 7 had benign paroxysmal positional vertigo, 7 had Meniere's disease, 4 had central vestibular disorder, 1 had idiopathic intracranial hypertension, 2 had postural hypotension and 2 had other causes of dizziness.

6.9.2 BAI and BDI scores

There were three VM patients with incomplete data for the BAI and one VM patient with incomplete data for the BDI. One normal control was incomplete for the BDI. All dizzy controls had complete data sets. Frequency distributions for cases and controls are shown in figure 6.2, and noted not to conform well to the normal distribution.

Figure 6.2 BAI scores in VM patients and dizzy controls

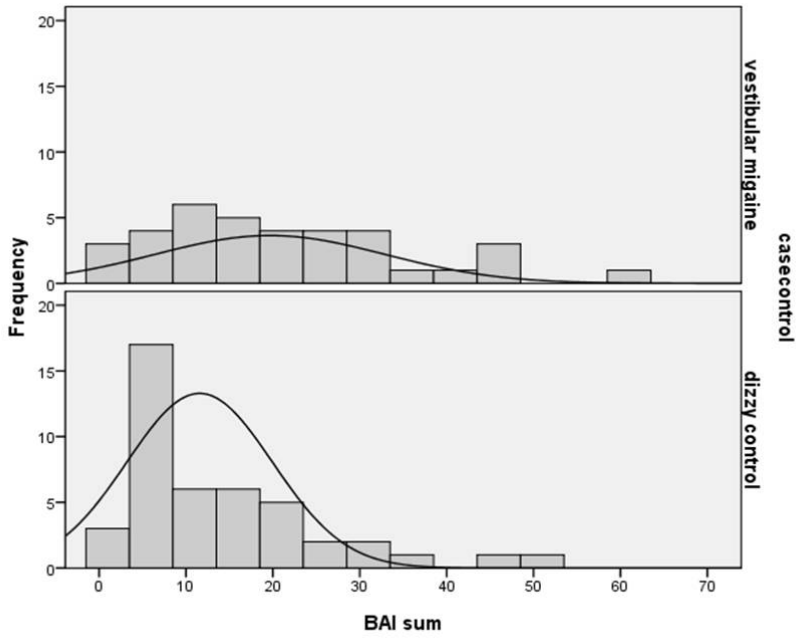


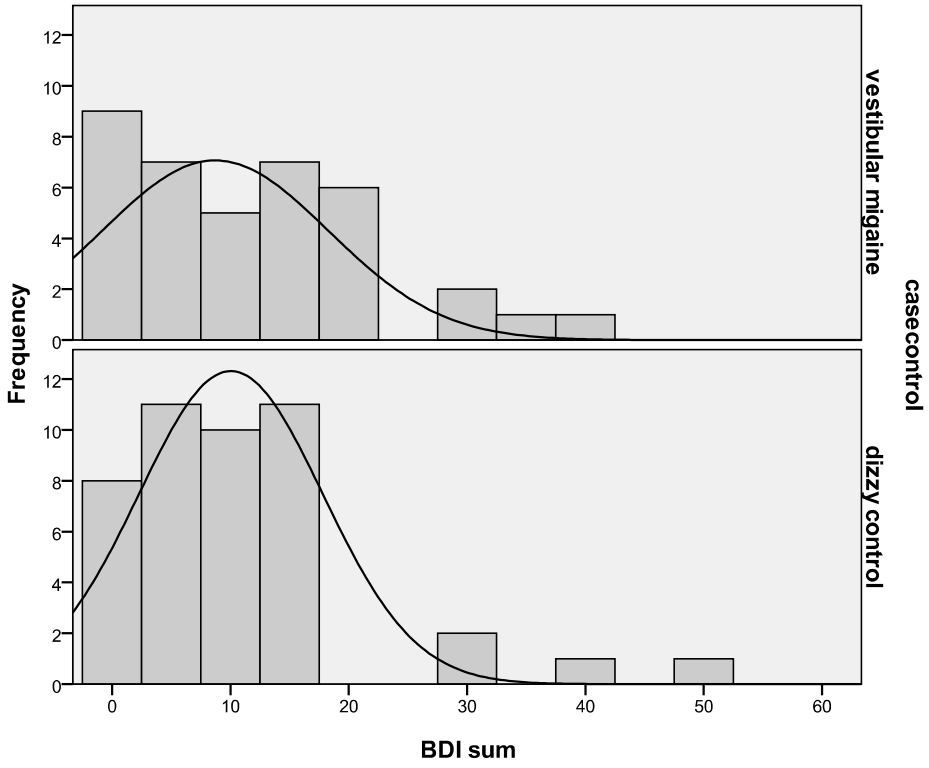
Table 6.II shows the median BAI and BDI scores for the VM group and controls. Kruskal Wallis testing confirms a highly significant difference between the normal controls and patients (p=0.000) for VSS-AA and VSS-V. Since differences between normals and patients were not the primary focus of the study, the normal controls were not subject to further analysis.

Table 6.II BAI and BDI scores for the VM group and controls

	VM group	**Dizzy controls**	**Normal controls**
BAI score total median (IQR)	19 (10-29)	11 (6-21)	2 (0-6)
BAI without vestibular symptoms (IQR)	13 (5-23)	5 (4-14)	-
BDI score total median (IQR)	10 (3-19)	8 (4-16)	2(0-4)
BDI without vestibular symptoms (IQR)	9.5 (3-18)	8 (3-15)	-
BAI score in normal range	7/36 (19%)	14/44 (32%)	44/51 (86%)
BAI in the mild range	8/36 (22%)	17/44 (39%)	6/51 (12%)
BAI in the moderate range	9/36 (25%)	7/44 (16%)	1/51 (2%)
BAI in the severe range	12/36 (33%)	6/44 (14%)	0/51 (0%)
BDI in the normal range	18/38 (47%)	26/44 (59%)	46/50 (92%)
BDI in the mild-moderate range	11/38 (29%)	14/44 (32%)	4/50 (8%)
BDI in the moderate-severe range	9/38 (24%)	4/44 (9%)	0/50 (0%)

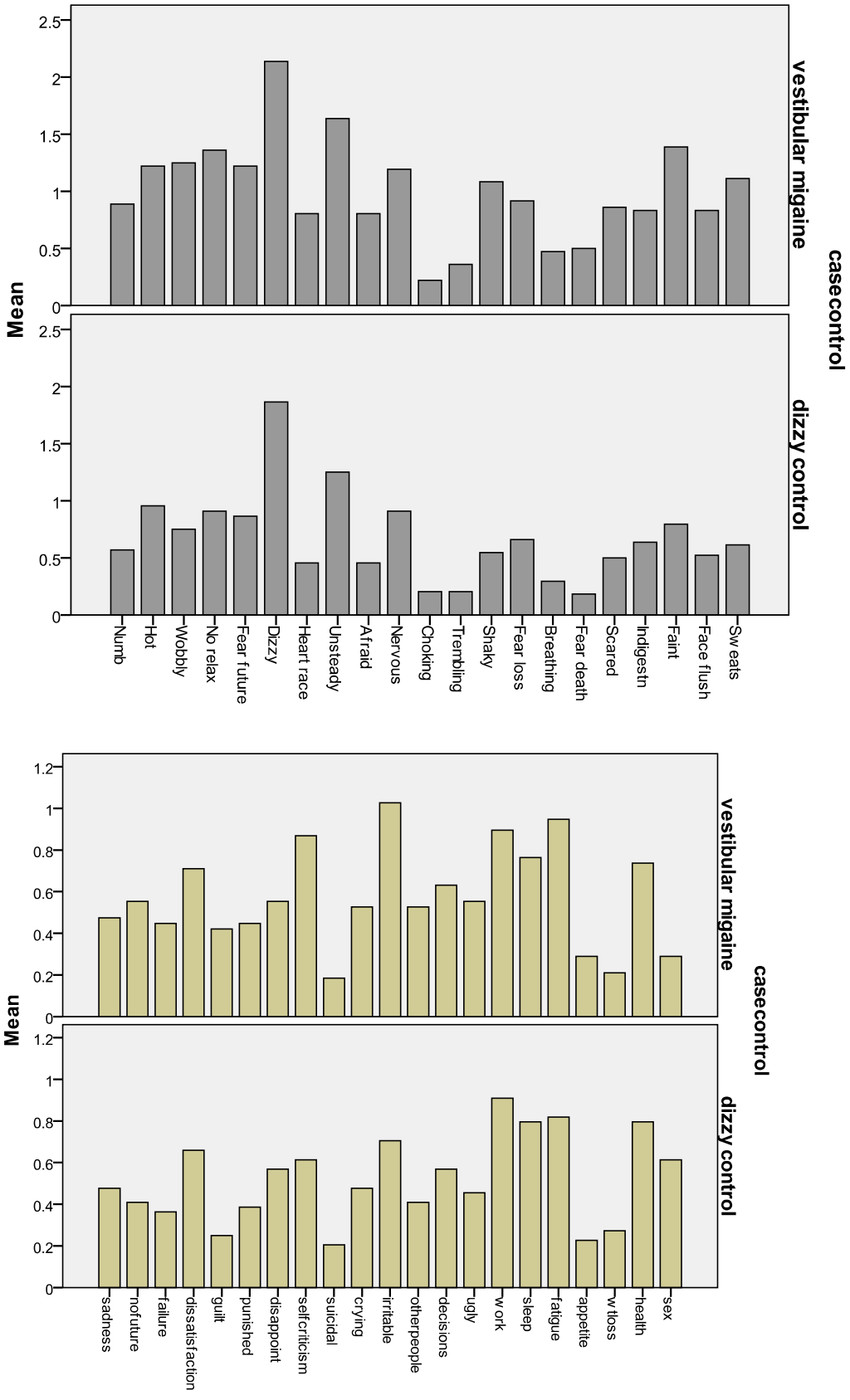
Using a non parametric testing (Mann Whitney U), the vestibular migraine patients have significantly higher BAI scores (median 19) than the dizzy controls (median 11)($p=0.03$). There was no such relationship for the BDI scores ($p=0.57$, figure 5.3). Similar figures applied when the BAI without vestibular symptoms ($p=0.03$) and BDI without vestibular symptoms ($p=0.61$) were computed.

Figure 6.3 BDI scores in VM patients and dizzy controls



On the BAI, the highest scoring item was, unsurprisingly, dizziness, followed by unsteadiness, in both VM and dizzy control groups (Figure 6.4a). However, even when vestibular symptom items from the BAI (items 3, 6, 8) were excluded, the VM group still had a higher mean total than the dizzy control group (p=0.028, Mann Whitney U). For the BDI the two groups showed similar scores across all items (Figure 6.4b).

Figure 6.4a and b: Mean scores per item in the BAI and BDI for VM patients and dizzy controls



6.9.3 VSS scores

Table 5.III shows the VSS scores for VM and dizzy and normal control groups, broken down into VSS-AA and VSS-V subscales. VSS data were incomplete on three responses in the normal controls who were excluded.

Table 6.III VSS scores for VM and dizzy and normal control groups

	VM group	**Dizzy controls**	**Normal controls**
VSS-V median (IQR)	30 (20-41)	16 (9-25)	1(0-3)
VSS-AA median (IQR)	25 (14-36)	14 (10-22)	5 (2-13)
VSS-total median (IQR)	58 (14-36)	30 (19-54)	6(2-16)
VSS-AA without headache item (IQR)	22 (11-33)	14 (9-20)	-

Kruskal Wallis testing confirms a highly significant difference between the normal controls and patients (p=0.000) for VSS-AA and VSS-V. Since differences between normals and patients were not the primary focus of the study, the normal controls were not subject to further analysis.

The vestibular migraine group had significantly higher scores than controls in terms of total scores (p=0.001), and both the VSS-V (p=0.003, Mann Whitney U) and VSS-AA (p=0.002) subscales than the dizzy controls. The difference persisted even when the headache item was removed from VSS-AA (p=0.01). This is illustrated in Figures 6.5a and 5b.On the VSS-V subscale, both groups scored most strongly for vertigo lasting less than two minutes, nausea, and lightheadedness / giddiness lasting less than two minutes. On the VSS-AA subscale, highest scoring items for the VM group were headache, ear pressure and muscle tension, and for the dizzy controls were ear pressure, visual disturbance and loss of concentration (figures 6.6a and 6b).

Figure 6.5a and 5b VSS scores in VM and dizzy control groups in VSS-V subscale (top) and VSS-AA subscale (bottom)

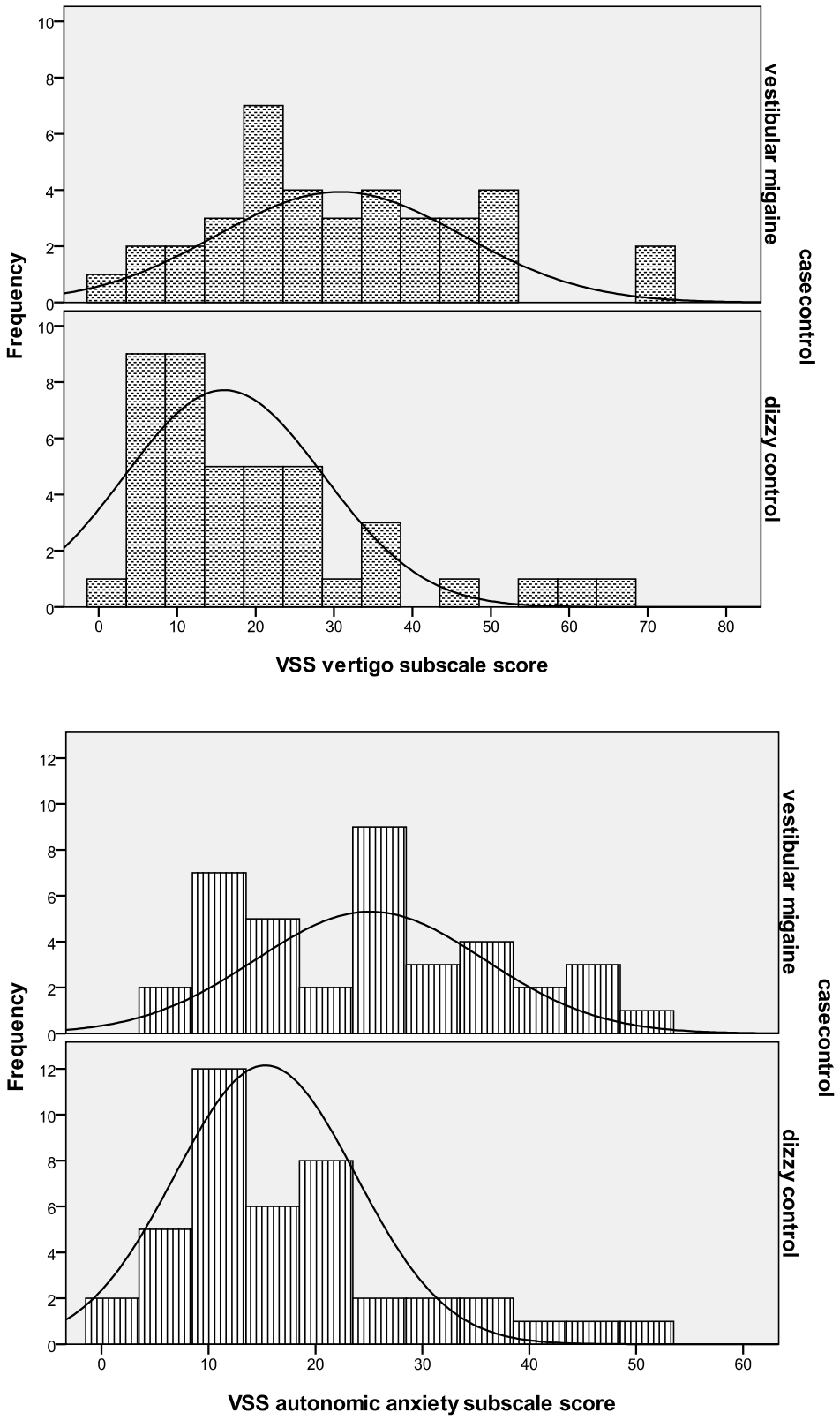
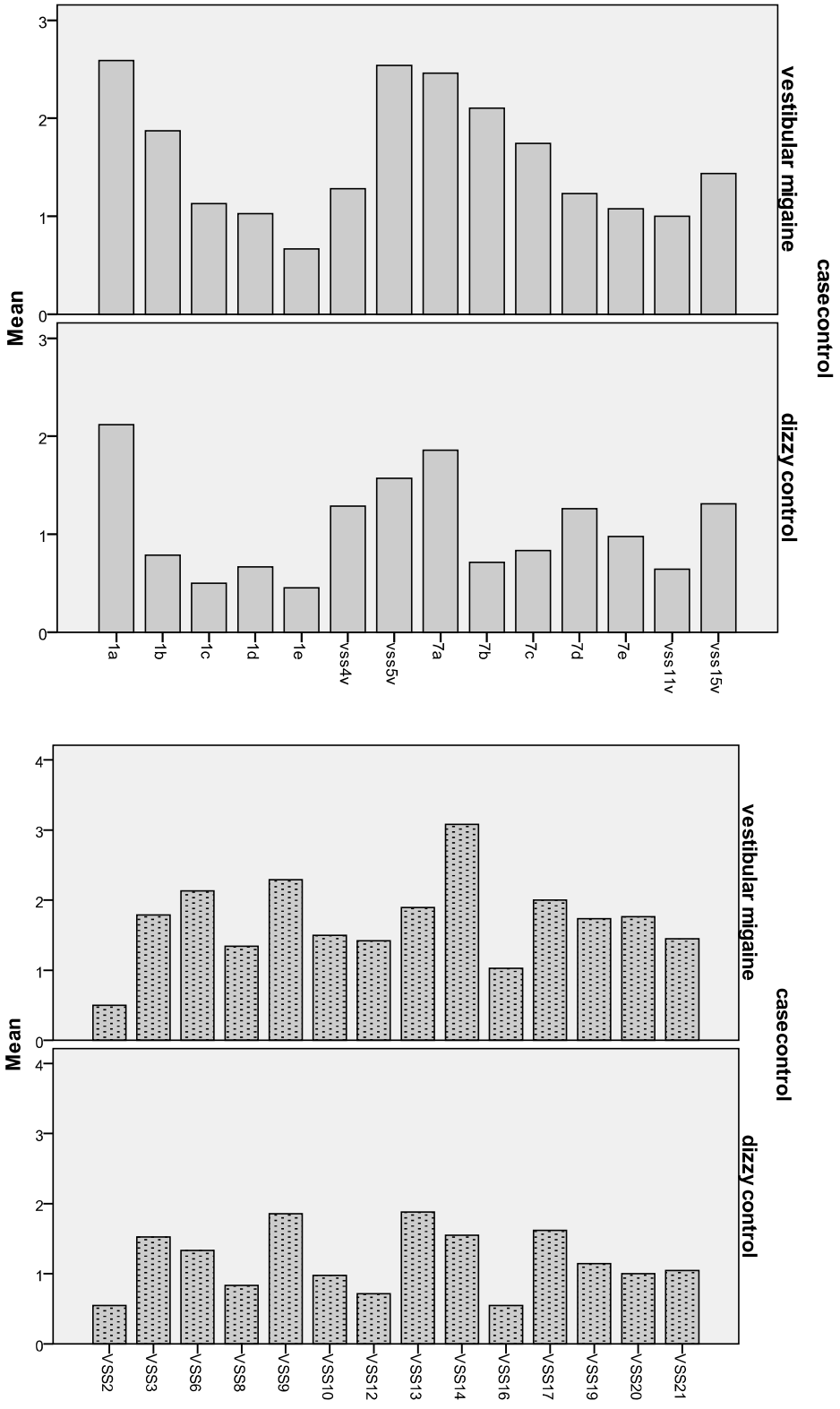


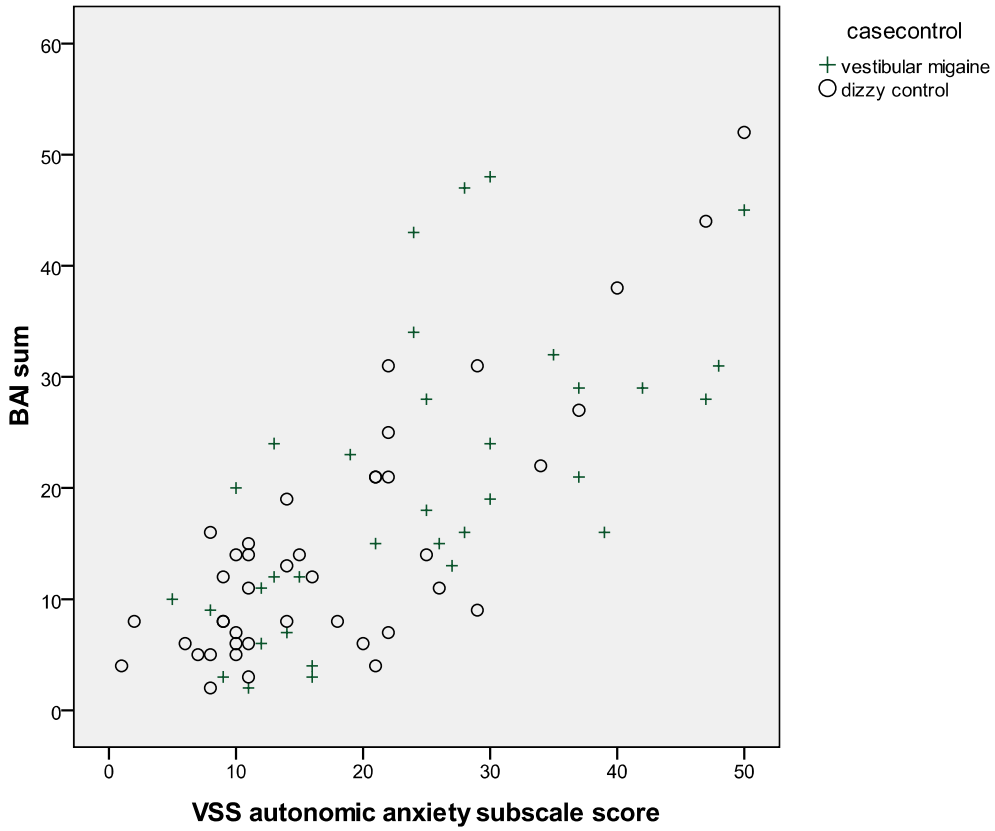
Figure 6.6a and 6b: VSS scores for VM patients and dizzy controls by item for VSS-V subscale (figure 5a) and for VSS-AA subscale (figure 5b)



6.9.4 Relationship between anxiety scales

As an internal consistency assessment, the relationship between the BAI and VSS-AA scores was examined. As expected, there was a significant positive linear correlation between BAI scores and VSS-AA scores (Pearson r=0.743, p=0.000, figure 6.7). This relationship was preserved in both the VM and dizzy control groups considered separately. This correlation is expected since both the BAI and VSS-AA scores are designed as indices of anxiety.

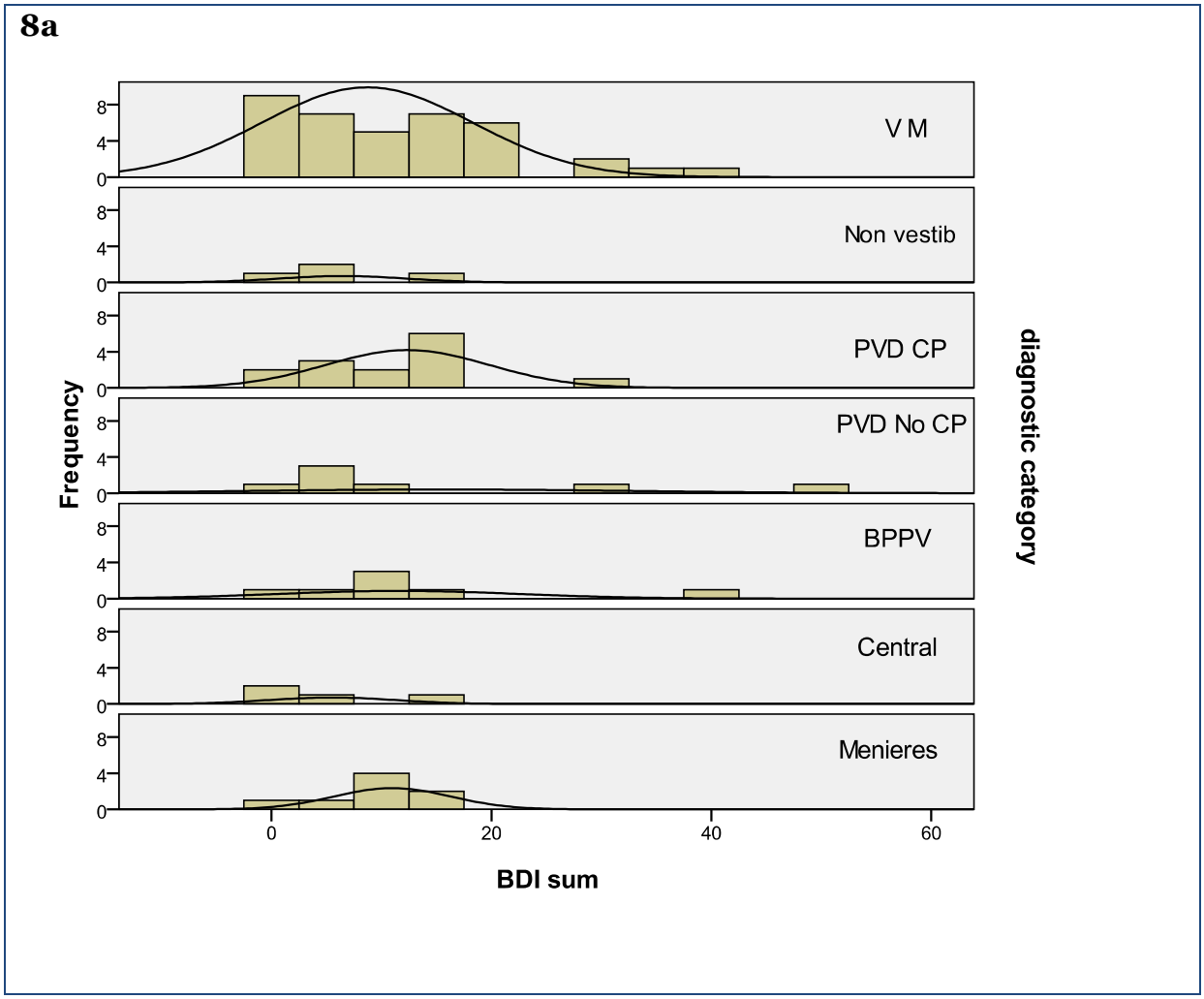
Figure 6.7 BAI scores against VSS-AA subscales showing correlation



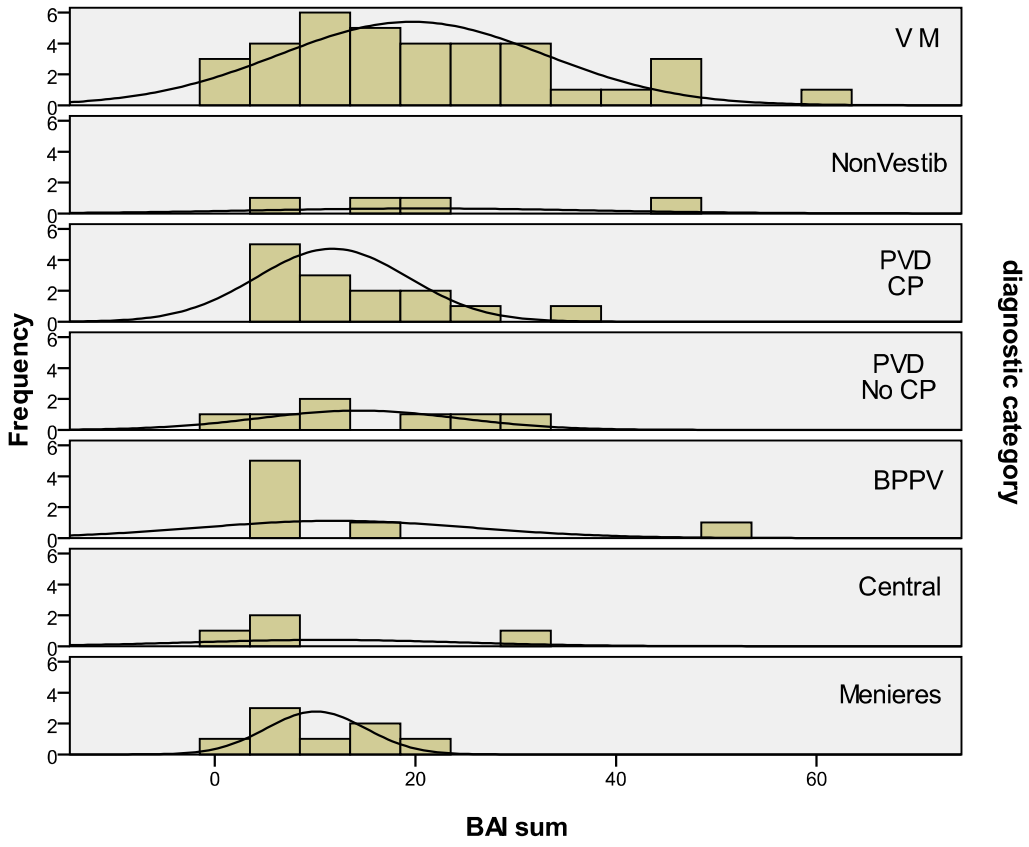
6.9.5 Results by diagnostic grouping

Data were plotted according to diagnostic grouping to compare BAI, BDI, VSS-V and VSS-AA scores across different pathologies. Distributions were broadly similar in all groups other than vestibular migraine (figure 6.8). Kruskal Wallis one-way of analysis of variance showed no difference in median scores between the five diagnostic groups (Table 6.IV).

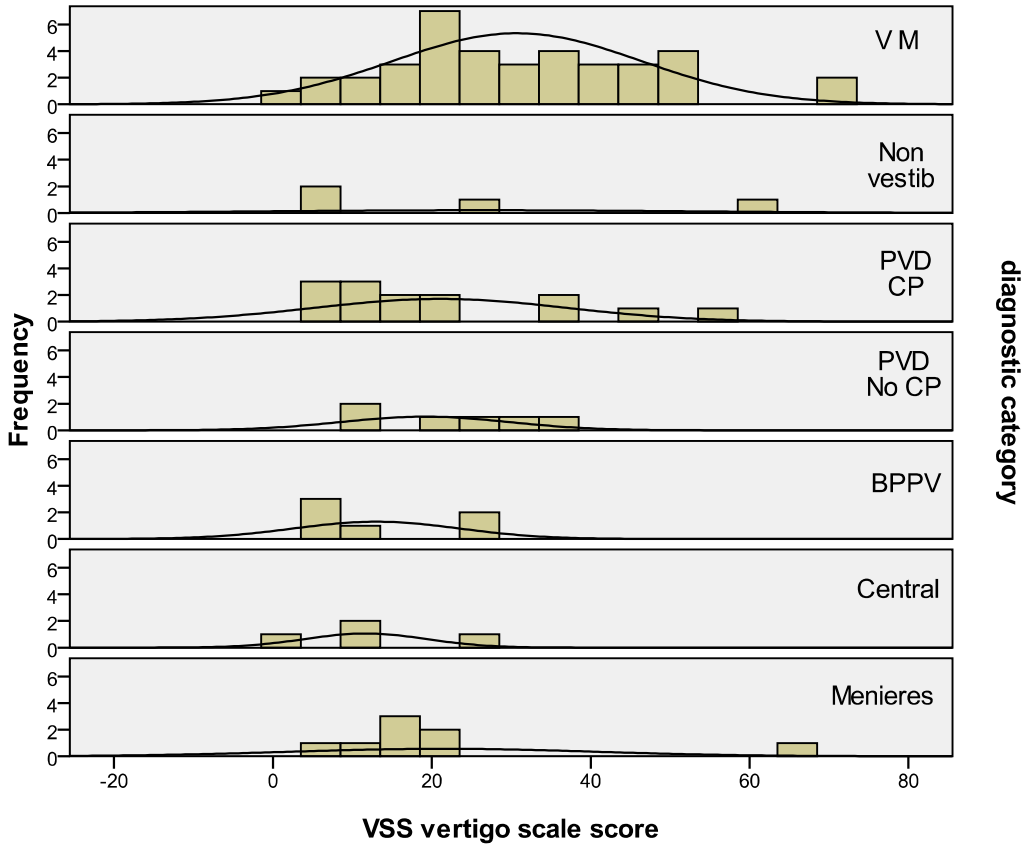
Figure 6.8. BDI (**8a)**, BDI **(8b)**, VSS-V **(8c)** and VSS-AA **(8d)** scores broken down by diagnostic group. VM=vestibular migraine; Non vestib= non vestibular dizziness; PVD CP= peripheral vestibular disorder confirmed on caloric testing; PVD no CP= managed as peripheral vestibular disorder but normal caloric test; BPPV=benign paroxysmal positional vertigo; central=central vestibular disorders; Menieres=Menière's disease.



8b


V M
NonVestib
PVD
CP
PVD
No CP
BPPV
Central
Menieres
Frequency
diagnostic category
0
20
40
60
BAI sum

8c


V M
Non vestib
PVD CP
PVD No CP
BPPV
Central
Menieres
Frequency
diagnostic category
VSS vertigo scale score
-20
0
20
40
60
80

8d

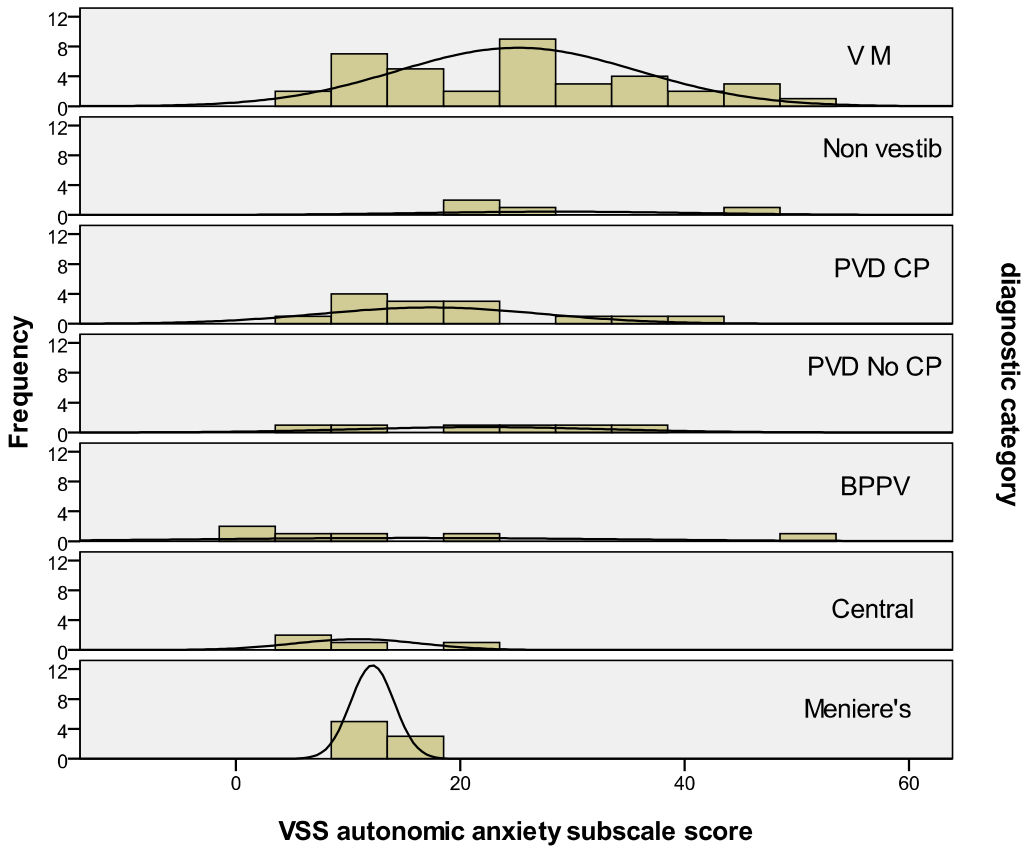


Table 6.IV Means and medians for BAI, BDI, VSS-AA and VSS-V across subgroups

	BAI		**BDI**		**VSS-AA**		**VSS-V**	
	Mean	Med	Mean	Med	Mean	Med	Mean	Med
VM	21	19	12	10	25	25	31	30
nonvestibular dizziness	21	18	7	5	29	24	26	18
PVD-CP	14	12	11	12	19	17	22	17
PVD-no CP	15	11	22	7	22	24	22	23
BPPV	15	8	13	8	16	9	12	7
central	11	6	6	5	12	10	12	11
Meniere's	11	11	10	10	12	11	22	17
Kruskal-Wallis p value (Df 4)		0.660		0.710		0.316		0.496

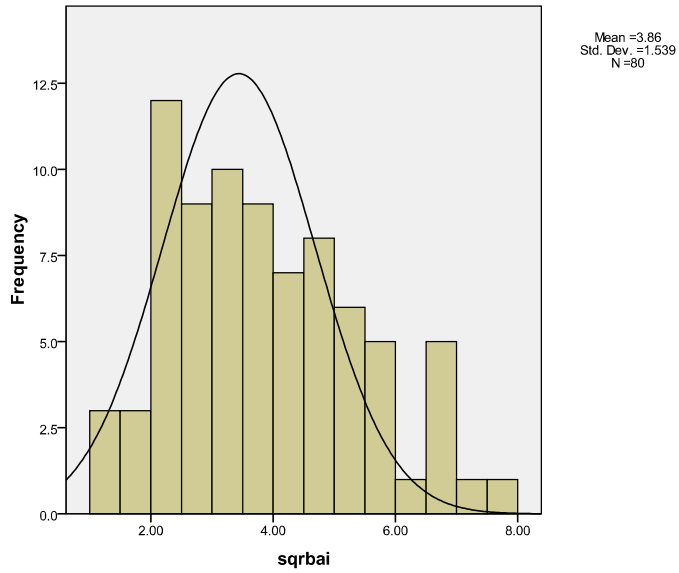
6.9.6 Regression modelling

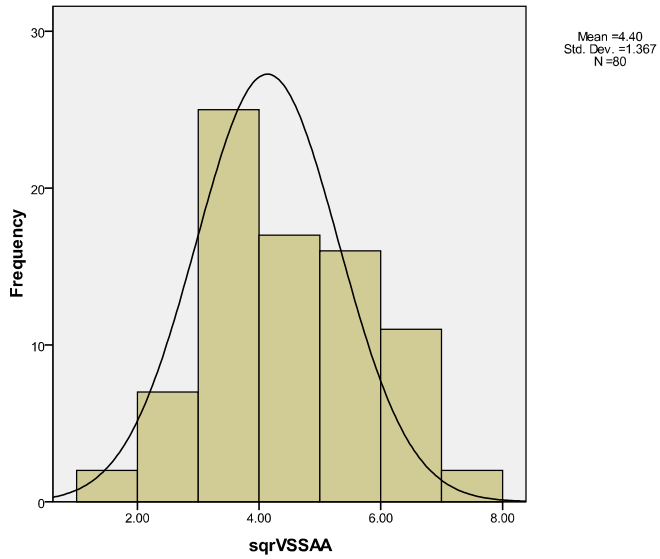
Superficial inspection of data therefore suggests that the VM group has higher levels of anxiety symptoms (BAI and VSS-AA), but may also have a higher balance symptom load. In addition there are potential confounders in the form of age and gender. Regression analysis was therefore carried out to deal with these variables. Since this requires normality as an assumption, data for dependent variables were transformed using a square root function $y=x^{1/2}$ and also log (x). The transformation $y= x^{1/2}$ gave better results in minimising kurtosis and skew. Normality assumptions were then met (Table 6.V, figures 5.9a, b and c). The transformation $y=x^{1/2}$ was thus adopted for the purposes of regression, with the nomenclature sqrt (x). In this section male gender was assigned the value 0, and female gender was assigned the value 1.

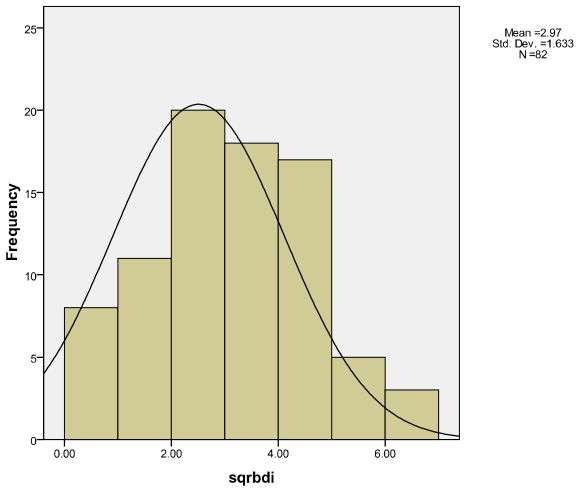
Table 6.V Log and square root transformations

	N	Minimum	Maximum	Mean		Std. Deviation	Skewness		Kurtosis	
		Statistic	Statistic	Statistic	Std. Error	Statistic	Statistic	Std. Error	Statistic	Std. Error
logBAI	80	0.30	1.78	1.1468	.03708	.33168	-0.235	.269	-0.519	.532
logBDII	82	0.00	1.69	0.9184	.04930	.44645	-0.670	.266	-0.320	.526
logVSS-V	80	0.30	1.85	1.3093	.03697	.33064	-0.595	.269	-0.025	.532
logVSS-AA	80	0.30	1.71	1.2711	.03074	.27494	-0.721	.269	1.130	.532
sqrtBAI	80	1.00	7.68	3.8648	.17206	1.53892	0.446	.269	-0.449	.532
sqrtBDI	82	0.00	6.93	2.9737	.18028	1.63250	-0.028	.266	-0.303	.526
sqrtVSS-AA	80	1.00	7.07	4.3994	.15283	1.36691	0.099	.269	-0.511	.532
sqrtVSS-V	80	1.00	8.31	4.7013	.19277	1.72415	0.133	.269	-0.654	.532

Figure 6.9. Transformed data using sqrt(x)=$x^{1/2}$. The medians for sqrtBAI, sqrtVSS-AA, sqrtBDI are 3.74, 4.42, and 3.00 respectively.







Sqrt BAI: simple linear regression

First, age, gender, case-control (VM status vs control status) were each analysed using simple linear regression. The results are shown in Table 6.VI. These results suggest that vestibular migraine and VSS-V scores may be significant determinants of BAI scores.

Table 6.VI Simple linear regression for sqrt BAI

	estimated R^2	**Adjusted R^2**	**ANOVA F value**	**ANOVA p value**	**standardised Beta**	**t statistic**	**t test p value**
Age	0	-0.13	0.000	0.997	0.000	-0.004	0.997
Gender	0.008	-0.004	0.657	0.420	0.091	0.811	0.420
case-control	0.069	0.57	5.783	0.019	-0.263	-2.405	0.019
VSS-V	0.187	0.176	170225	0.000	0.432	0.746	0.000

Sqrt BAI: multiple linear regression

Using age, gender, case control status and VSS-V as independent variables and sqrt BAI as the dependent variable gives the following regression equation:

sqrtBAI=0.034(VSS-V) + 0.01(age) + 0.156(gender)-0.523(casecontrol)+3.408

Standardised beta coefficient value is highest for VSS-V (0.378), compared with 0.082 for age, 0.048 for gender and -0.173 for case-control status. R^2 was 0.217 with adjusted R^2 0.174. Maximum R^2 was not increased by removing regressors from the equation to form alternative models.

The regression analysis was not a good fit, describing only 22% of the variance in sqrtBAI, but the overall relationship was statistically significant (F=5.001, p =0.001). With other variables held constant, sqrtBAI scores were positively correlated to age, increasing by 0.01 for every year of age, and positively related to VSS-V score, increasing the sqrtBAI by 0.034 for every unit rise in VSS-V. Women tended to have higher sqrtBAI scores than men by 0.156 points. However, the effect of VSS-V was the only significant effect (t=3.452, p=0.001). Residual plots were satisfactory.

The multiple linear regression analysis therefore suggests that the difference in VM when compared to dizzy controls in terms of BAI scores can largely be attributed to VSS-V scores.

Sqrt BDI: Simple linear regression

Age, gender, case-control status and VSS-V scores were compared to sqrt BDI scores using simple linear regression (Table 6.VII). No significant relationships were seen.

Table 6.VII Simple linear regression for sqrt BDI

	estimated R^2	**Adjusted R^2**	**ANOVA F value**	**ANOVA p value**	**standardised Beta**	**t statistic**	**t test p value**
Age	0.006	-0.006	0.512	0.476	0.080	0.715	0.476
Gender	0.000	-0.012	0.039	0.845	0.022	0.196	0.845
case-control	0.000	-0.012	0.010	0.921	-0.011	-0.099	0.921
VSS-V	0.035	0.023	2.815	0.097	0.188	1.678	0.097

Sqrt BDI: Multiple linear regression

Using age, gender, case control status and VSS-V as independent variables and sqrt BDI as the dependent variable gives the following regression equation:

sqrtBDI=0.019(VSS-V) + 0.01(age) -0.043(gender)+0.097 (casecontrol)+1.908

Standardised beta coefficient value is highest for VSS-V (0.198), compared with 0.101 for age, -0.012 for gender and 0.030 for case-control status. R^2 was 0.048with adjusted R^2 -0.004.

This regression analysis was therefore a poor fit, describing only 5% of the variance in BAI, and the overall relationship was not statistically significant (F=0.932, p=0.450), in keeping with the preliminary finding of no relationship between BDI and these variables.

Sqrt VSS-AA:Simple linear regression

Age, gender, case-control status and VSS-V scores were compared to sqrt VSS-AA scores using simple linear regression (Table 6.VIII).

Table 6.VIII Simple linear regressopm for Sqrt VSS-AA

	estimated R^2	**Adjusted R^2**	**ANOVA F value**	**ANOVA p value**	**standardised Beta**	**t statistic**	**t test p value**
Age	0.009	-0.004	0.724	0.397	0.096	0.851	0.397
Gender	0.084	0.072	7.158	0.009	0.290	2.675	0.009
casecontrol	0.100	0.089	8.703	0.004	-0.317	-2.950	0.004
VSS-V	0.508	0.258	27.173	0.000	0.508	5.213	0.000

SqrtVSS-AA: Multiple linear regression

Using age, gender, case control status and VSSV as independent variables and sqrt VSS-AA as the dependent variable gives the following regression equation with maximum efficiency:

sqrtVSS-AA = 0.008(VSSV) + 0.398(gender)+2.938

Other models did not increase the value of R^2. Standardised beta coefficient value is highest for VSS-V (0.378), compared with 0.082 for age, 0.048 for gender and -0.173 for case-control status. R^2 was 0.217 with adjusted R^2 0.174.

The regression analysis was a reasonable fit, describing 31% of the variance in VSS-AA, and the overall relationship was statistically highly significant (F=17.544, p =0.000). With other variables held constant, sqrt VSS-AA scores were positively related to VSS-V score, increasing the sqrt VSS-AA by 0.039 for every unit rise in VSS-V. Women tended to have sqrt VSS-AA higher scores than men by 0.698 points. Both VSS-V (t= 5.066, p=0.000) and gender (t=2.476, p=0.015) effects were significant. Residual plots were satisfactory.

6.9.7. Age and anxiety nonlinearity problem

If age affects anxiety in a nonlinear way, then regression analysis will not pick up such a relationship. Therefore, data were re-analysed with dizzy controls selected to match the age of VM participants to within 3 years. In this sample the means for VM group were 40 yrs with SD 11 and for the dizzy control group 40 with SD 10. This did not affect the outcome of the regression analysis significantly.

6.9.8. Summary of results

As expected, normal controls had significantly lower scores than both patient groups across all measures. The vestibular migraine group had significantly higher levels of anxiety than the dizzy control group, assessed using either the BAI or the VSS-AA. This group also had higher levels of vertigo symptom load (VSS-V score). However, using multiple linear regression analysis it can be seen that the significant difference in anxiety scores between the groups in terms of BAI scores disappears when the difference in VSS-V scores is taken into account. Similarly, multiple linear regression analysis suggests that the differences in VSS-AA scores between VM cases and controls are largely accounted for by differences in VSS-V and in gender. There was no significant difference between the groups in terms of BDI score.

6.10 Discussion

These data show a burden of psychological symptomatology carried by patients recruited from a specialist neuro-otology clinic with vestibular migraine and with other forms of dizziness, but especially with the former. Both groups had significantly worse scores than normal controls. A third of the patients with VM scored in the severe range on the BAI, as did 14% of the control group of dizzy patients. This is in keeping with previous reports that vestibular disorders, and migraine, are both potentially associated with psychopathology. This sample, taken from a tertiary neuro-otology clinic, is likely to represent the severe end of the spectrum of disease. It is interesting to note that the VM group have significantly higher BAI scores than the dizzy control group, even when items which correspond directly to typical vestibular symptoms are excluded. Similarly, they score more highly on the VSS-V and VSS-AA subscales. Unsurprisingly, the VM group are more troubled by headache than the other dizzy controls.

The picture is however, more complex than this superficial initial inspection of the data would suggest. The VM group scored more highly on the VSS-V, and there is a correlation between VSS-V and BAI scores, could the difference in anxiety scores be accounted for by a difference in vertigo symptom load? Also, could there be any effect of confounders such as age and gender?

Regression analysis confirms that this is so. The interaction of gender and VSS-V scores renders case-control status insignificant as a predictor of VSS-AA scores. For the other index of anxiety used in this study, the BAI, VSS-V is the only significant factor.

One possible explanation for the difference in anxiety scores in the raw data is the difference in age distribution between the two groups. A previous study which examined psychiatric symptoms in different vestibular syndromes found no effect of age (Eckhardt-Henn et al 2008). On the other hand, it is known from primary care based studies that anxiety prevalence is highest in women aged 20-29, and declines at older ages (Martin-Merino et al 2010). It is possible that at least some of the high anxiety levels reported elsewhere are related to the age and sex distribution of VM. One large population based epidemiological study showed a median age of onset of 23 years with 82% female preponderance (Lempert and Neuhauser 2009). However, in the regression model, age is not significant as a predictor of either VSS-AA or BAI. This model cannot however account for a nonlinear relationship with age, which might occur if anxiety symptoms peak in early adult life. For this reason, the data were re-analysed using individuals selected from the larger sample to match for age. The outcomes were essentially unchanged. This suggests that the increased anxiety symptom load seen in the VM sample may be largely due to a higher vertigo symptom load.

Are the observed effects the result of the design of the rating scales selected? It was noted earlier that the rating scales for anxiety and depression all contain items which would be expected to score highly in individuals with physical disorders of balance and headache. Indeed, headache is the item scored most highly by the VM group on the VSS-AA subscale. However, even when vestibular symptom items from the BAI (items 3, 6, 8) were excluded, the VM group still had a higher mean total than the dizzy control group ($p=0.028$, Mann Whitney U). The same applies to the VSS-AA scores when headache is excluded**.** This suggests that the scores and analyses have not been excessively influenced by these items.

Depression scores were similar in the two groups. Both groups had a high proportion of individuals scoring outside the normal range. Migraine is known to be associated with depressive symptoms, and there is evidence suggesting that those with vestibular symptoms may also be more susceptible. This study however found no evidence in support of a synergistic or additive effect of the two disorders on depressive symptom scores, since the levels were similar in the VM and dizzy control groups.

Why do the VM patients appear to have more severe vertigo, and, associated higher anxiety levels? One possibility is that this is a chance consequence of sampling. Another possibility is that patients with VM are referred to the clinic later at a later stage in the condition, perhaps due to the under-recognition of the condition previously reported elsewhere (Neuhauser, Radtke, von Brevern, Feldmann, Lezius, Ziese, and Lempert 2006). One might also speculate

that VM patients could have a higher tendency to report symptoms, i.e. a higher degree of somatic focus, perhaps, as a result of contending with a headache disorder as well as a vestibular disorder. These data do not answer these questions, and further research could address these issues. It is known from other work that patients with migraine and dizziness achieve worse scores across a range of mental and physical health and quality of life measures (Bisdorff, Andree, Vaillant, and Sandor 2010). Since migraine is known to be an adverse prognostic factor for recover in some vestibular syndromes (Best, Tschan, Eckhardt-Henn, and Dieterich 2009c), perhaps due to impeded central compensation, there may be a physiological explanation why migraineurs appear to have more severe symptoms.

However, other reports do suggest that individuals with VM do have a more "severe" presentation, as discussed above. For example, those with vestibular migraine are known to have a higher risk of developing somatoform dizziness (Best, Eckhardt-Henn, Tschan, and Dieterich 2009a). This same study reported on the other hand that there was no correlation with the degree of vestibular dysfunction as measured by objective neuro-otological assessment including caloric test, ocular torsion and subjective visual vertical measures. However, it is recognised that none of these objective measures has been shown to correlate with the experience of vertigo or reported symptom severity, so these observations do not negate the idea that VM individuals may experience symptoms more severely. This notion is also in keeping with concepts of migraine in general as a disorder of heightened sensitivity to sensory stimuli. Vestibular symptoms such as head and visual motion intolerance may have much lower thresholds in such predisposed individuals.

Other studies have reported a difference in the prevalence of psychiatric disorder between different vestibular disorders, with VM scoring more highly than other conditions such as BPPV. To some extent this is replicated in this study since we do find that the vestibular migraine group have significantly more anxiety than other groups.

It must be remembered when interpreting these data that, given the sample source in a tertiary Neuro-otology clinic, the degree to which these observations generalise to other populations may be limited. Also, the scales used are merely screening instruments which can give an approximate indication of severity of symptoms, but should not be confused with a formal psychiatric diagnosis which can only be made by interview.

6.11 Conclusions

In this tertiary level specialist clinic population, patients with vestibular migraine have higher anxiety scores than patients with dizziness due to other conditions. This appears to be largely accounted for by the higher levels of vertigo severity reported by this group. Whatever the underlying explanation, individuals with VM seen in a clinic setting can be regarded as at high risk for developing symptoms of anxiety, and clinicians should be aware of this.

Chapter 7. Overall conclusions

7.1 Aim and initial hypotheses revisited

The work presented in this thesis has examined audiovestibular sensory processing in migraine using varied and complementary techniques, and made novel observations contributing to the understanding of sensory processing in migraine.

The original hypothesis for this study was that migraine in general, and vestibular migraine (VM) in particular, are characterised by abnormalities in audiovestibular processing in the brainstem. Sensory processing via the brainstem in individuals with VM was examined using the recently developed translational techniques of vestibular evoked myogenic potentials and otoacoustic emission recordings including suppression by contralateral noise.

As well as examining interictal processing of audiovestibular stimuli, the study considered the hypothesis that such stimuli could act as triggers for an attack of migraine, since in the past this had been noted in a small number of individuals and this observation required further systematic evaluation. This is another dimension of sensory processing in migraine, the capacity of stimuli to cause an individual to reach the threshold at which attacks occur.

In addition it was hypothesised that the recognised psychological effects associated with vestibular migraine are due to a synergistic effect between the migraine and vestibular symptoms, so that those with vestibular migraine experience greater psychological symptom load than non-migrainous dizzy controls. Studies were constructed to examine each of these hypotheses in turn, and each has been systematically addressed in the preceding chapters.

7.2 Summary of principal findings

- The use of vestibular stimulation appeared to act as a migraine trigger in a high proportion (49%) of individuals with a history of migraine when compared with 5% of a control population (p=0.001).
- Otoacoustic emission study using contralateral suppression in patients with VM showed that a higher than expected proportion of subjects with vestibular migraine have low total OAE suppression (11/33 cases *vs* 3/31 controls, p=0.02).
- There is a high rate of absence of responses amongst those with vestibular migraine (5/35), a finding conspicuous by its absence (0/30) amongst the healthy control population (p=0.06). There is a higher overall rate of all abnormalities amongst the VM population than the controls (p=0.036).
- Individuals with vestibular migraine have a high rate of psychological symptom load (median BAI score 19) suggestive of anxiety disorder, when compared to dizzy controls without a history of migraine (median BAI score 11, p=0.3).
- The rates of depressive symptoms are similar in patients with VM and dizzy controls (median BDI scores 10 and 8 respectively, p=0.57).
- Multiple logistic regression modelling showed that the difference in psychological symptom burden was largely explicable by the much higher vestibular symptom load carried by these patients.

7.3 Summary of secondary findings

- There was no demonstrable relationship between the subjective experience of phonophobia and reduced OAE suppression, with phonophobia present in 91% cases of low suppression and 86% cases of normal suppression. In a focussed study, there was higher variability in suppression during attacks of vestibular migraine in two out of three individuals.

- Similarly, there was higher variability in VEMP recordings, with large latency shifts unilaterally in two individuals, one becoming shorter in the interictal condition and one becoming longer.
- When migraines were triggered by vestibular stimuli, the resulting migraine attack involved vestibular symptoms in only 46% cases.

7.4 General interpretation of findings

This work has outlined disruption in auditory efferent function in a group of individuals. The defining characteristics of this group are yet to be elucidated. The objective phenomenon of OAE suppression by contralateral noise did not, however, relate to the subjective experience of phonophobia. However, since 88% of VM patients had phonophobia, there was limited power to detect such an effect. The VEMP study parallels previous work using objective vestibular tests in migraine, in that the findings show great heterogeneity that can only partly be explained by technical differences.

It is interesting to compare the results obtained in the VEMP and OAE suppression mechanism parts of this thesis. The types of abnormality documented vary, as would be expected given that these two techniques are quite different. One clear parallel, however, is the ictal and interictal comparisons made. Using both techniques, the key observation was of excessive magnitude of change between the two recording conditions, with variable direction of change. One might speculate that this is a characteristic of the migraineur's state, that normal mechanisms of sensory gain modulation are impaired in a variable way. Against this notion it could be argued that the migraineur in the ictal state is always more responsive than in the interictal state: the threshold for response does not increase during an attack. Patients do not report feeling less sensitive to sound or light during attacks. Still, as observed in the otoacoustic emission suppression study, a simple relationship between perceived experience and reported symptoms, and the objective physiological measures is often elusive. Since the numbers of ictal-interictal comparisons made were small, it is important not to place excessive weight on these observations, but it is interesting that the VEMP and OAE suppression data give a similar picture in this respect.

The work on induced vertigo as migraine triggers suggests a new concept of primary and secondary vestibular migraine. In primary vestibular migraine the vestibular

symptoms arise directly from the migraine itself, and in secondary vestibular migraine, the vestibular symptoms arise secondary to an alternative aetiology which is provoking migraine headache. This notion could contribute to refinement of the concept of vestibular migraine, and account for some of the observed clinical heterogeneity of the condition, especially in terms of vestibular test findings (discussed in Introduction, section 1.3). The findings of the VEMP and OAE suppression work contained in this thesis emphasise this heterogeneity. The findings presented in this thesis show that neither of these two techniques will be sensitive or specific enough to be of diagnostic utility for VM.

While definitions are dependent on clinical description, and while there continues to be phenotypic overlap with other vestibular disorders such as Menière's disease, this is likely to remain the case. Much has advanced since Neuhauser *et al* published their landmark paper nearly 10 years ago (Neuhauser, Leopold, von Brevern, Arnold, and Lempert 2001). Revision of diagnostic criteria is underway among the international balance disorders community, starting with standardised definitions of vestibular symptom terms, (Bisdorff et al 2009) and the search for an improved definition to aid clinicians, researchers and sufferers continues.

7.5 Limitations of study

The study was set in the neurology and neuro-otology departments of a tertiary level specialist hospital and the findings presented may have limited generalisability outside this setting. This is especially relevant in the interpretation of the psychological symptoms, since the patient population seen in this setting is likely to be biased towards more severe cases of VM. There were methodological limitation associated with each subsection of the study and discussed in the relevant chapters (3, 4, 5 and 6).

7.6 Future directions – where next?

The work highlights the need for a systematic study of phonophobia and heightened auditory sensitivity in migraine attacks. A validated instrument would be of use,

since patients vary considerably in their responses to questions about phonophobia (Evans, Seifert, Kailasam, and Mathew 2008). It would also potentially be of interest to consider the phenomenon of phonophobia during migraine attacks in groups with specific auditory deficits, such as profound hearing loss, low and high frequency loss, auditory neuropathy and central auditory processing disorders. Patients with profound hearing losses could conceivably experience phonophobia in the form of exacerbation of headache by sound, as long as they have some means of sound detection. This could be through the high sound intensities that profoundly deaf patients may still perceive, or via vestibular detection of sound (*cf* the observation that profoundly deaf patients show VEMP responses to sound stimuli (Welgampola and Colebatch 2005)).

Technical advances in VEMP techniques (e.g. ocular VEMP recordings, assessment of habituation) may yield further understanding of the pathways affected in migraine in general and VM in particular, although on the basis of the literature so far seems unlikely to provide the definitive answer to the elusive question of the pathophysiological mechanism of vestibular migraine.

At least in the study setting, individuals with vestibular migraine are greatly burdened by their condition. The question of why this patient group is so much more disabled than others is relevant. Is vestibular migraine an intrinsically more disabling condition than other vestibular disorders commonly seen in a balance clinic? Are those with vestibular migraine referred late for specialist help? Is the management of this disorder more complex than for other conditions?

In conclusion, this work contributes to the body of knowledge on migraine in general and vestibular migraine in particular, and suggests plentiful further fruitful lines of enquiry to understand this important problem.

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Appendix 1 Vestibular migraine anamnesis

1) Are you or have you been subject to headaches?

No Yes

If 'No' please answer the questions 14b to 17 of the questionnaire.

2) Do your headaches come in more or less identical attacks?

No Yes

3) Are your headaches

A. at the front ?.....No Yes

B. on both sides of your head ?.....No Yes

C. at the back of your head ?.....No Yes

D. In your neck?.....No Yes

4) How old were you when your headache started? (in years) ----------

5) When was your last headache?

A. 0-7 days ago

B. 1 week to 4 weeks ago

C. 1 month to 6 months ago

6) How long does your headache last on average?

A. 1 to 60 minutes

B. 1 to 2 hours

C. 2 to 24 hours

D. 1 to 7 days

E. longer than 1 week

7) How often do you get headaches?

A. several times a day

B. daily

C. once or twice a week

D. once or twice a month

E. several times a year

F. once every few years

G. in association with menstrual cycle

8) Do your headaches have a throb at any time during the attack?

No Yes

9) How severe is your headache?

A. Mild

B. Moderate

C. Severe (interferes with daily activity)

10) When was the last time you had a typical headache?

---------- (hours / days / months ago)

11) Do you have dizzy spells at other times than with your headaches?

No Yes

If No, go to question 12.

11a) Do the dizzy spells occur more than once between spells of headache?

No Yes

11b) How long do these dizzy spells last?

A. Few seconds

B. 1 to 60 minutes

C. 1 to 24 hours

D. 1 to 7 days

E. longer than 1 week

11c) Are your dizzy spells related to head movements?

No Yes

12) Are your headaches relieved by any of the following?

a. Aspirin	No	Yes
b. Cafergot	No	Yes
c. Migraleve	No	Yes

d. Neurofen / ibuprofen No Yes
e. Coproxamol No Yes
f. Cocodamol No Yes
g. Imigran No Yes
h. maxalt No Yes
i. migraine prophylaxis (preventives) No Yes
eg propranolol, pizotifen, amitryptiline
(specify name .....)

j. other medicine No Yes
(specify name .....)

13) Have you ever had motion sickness? No Yes
If no, go to question 14.

13a) If 'Yes'

A. during childhood only
B. in childhood and adulthood
C. adult only

13b.) If you ever had motion sickness does it occur when travelling by
A. car? No Yes
B. bus? No Yes
C .train? No Yes

14a) During or within an hour before your attack of headache, do you have any of the following complaints? If Yes, please circle to show whether it is before or during the attack, for each of the choices given.
a) spots/shimmering lights/ zigzag lights in your field of vision?
No Yes (before /during)
b) Dark areas at the centre of your vision?
No Yes (before /during)
c) Darkness in one half of your vision?
No Yes (before / during)
d) Numbness or tingling around your mouth?
No Yes (before / during)
e) Numbness or tingling over one half of your face or body?

No Yes (before / during)

f) Weakness on one side /both sides of your face or body?

No Yes (before / during)

g) Difficulty with finding the right words or understanding words?

No Yes (before / during)

h) Dizziness No Yes (before / during)

i) Unsteadiness No Yes (before / during)

j) Double vision No Yes (before / during)

k) Slurred speech No Yes (before / during)

l) Noises in your ear/s No Yes (before / during)

m) Hearing loss No Yes (before /during)

n) Decreased level of consciousness No Yes (before / during)

o) Blackouts No Yes (before / during)

14b) During or within an hour before your attack of vertigo or dizziness, do you have any of the following complaints? If Yes, please circle to show whether it is before or during the attack, for each of the choices given.

a) spots/shimmering lights/ zigzag lights in your field of vision?

No Yes (before /during)

b) Dark areas at the centre of your vision?

No Yes (before /during)

c) Darkness in one half of your vision?

No Yes (before / during)

d) Numbness or tingling around your mouth?

No Yes (before / during)

e) Numbness or tingling over one half of your face or body?

No Yes (before / during)

f) Weakness on one side /both sides of your face or body?

No Yes (before / during)

g) Difficulty with finding the right words or understanding words?

No Yes (before / during)

h) Dizziness No Yes (before / during)

i) Unsteadiness No Yes (before / during)

j) Double vision No Yes (before / during)

k) Slurred speech No Yes (before / during)

l) Noises in your ear/s	No	Yes (before / during)
m) Hearing loss	No	Yes (before /during)
n) Decreased level of consciousness	No	Yes (before / during)
o) Blackouts	No	Yes (before / during)

15) Do you have any of the following complaints during your attacks (headaches/vertigo/dizziness)?

a. Nausea	No	Yes
b. Nausea and vomiting	No	Yes
c. Increased sensitivity to bright lights	No	Yes
d. Increased sensitivity to loud sounds	No	Yes
e. Disturbance by smells	No	Yes
f. Nervousness and irritability	No	Yes
g. Aggravated by walking stairs or similar routine physical activities	No	Yes

16) Are your dizzy spells accompanied by noise in your ears or change in your hearing?

No Yes

17) Have any of your relatives complained of headaches or have they been diagnosed as having migraine/or have attack like the ones you have? No Yes

(if yes who?

E.g. brother / mother .....)

Thank you for filling in the questionnaire

Appendix 2 Diagnostic criteria for major depressive episode in DSM-IV TR

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.
(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
(4) insomnia or hypersomnia nearly every day
(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
(6) fatigue or loss of energy nearly every day
(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Appendix 3 Diagnostic criteria for generalised anxiety disorder in DSM-IV TR

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).

B. The person finds it difficult to control the worry.

C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months).
(1) restlessness or feeling keyed up or on edge
(2) being easily fatigued
(3) difficulty concentrating or mind going blank
(4) irritability
(5) muscle tension
(6) sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)

D. The focus of the anxiety and worry is not confined to features of an Axis I disorder, e.g., the anxiety or worry is not about having a Panic Attack (as in Panic Disorder), being embarrassed in public (as in Social Phobia), being contaminated (as in Obsessive-Compulsive Disorder), being away from home or close relatives (as in Separation Anxiety Disorder), gaining weight (as in Anorexia Nervosa), having multiple physical complaints (as in Somatization Disorder), or having a serious illness (as in Hypochondriasis), and the anxiety and worry do not occur exclusively during Posttraumatic Stress Disorder.

E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

F. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism) and does not occur exclusively during a Mood Disorder, a Psychotic Disorder, or a Pervasive Developmental Disorder.

Appendix 4 The Beck Anxiety Inventory

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

	Not At All	Mildly but it didn't bother me much.	Moderately - it wasn't pleasant at times	Severely – it bothered me a lot
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst happening	0	1	2	3
Dizzy or lightheaded	0	1	2	3
Heart pounding/racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky / unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint / lightheaded	0	1	2	3
Face flushed	0	1	2	3
Hot/cold sweats	0	1	2	3

Appendix 5 The Beck Depression Inventory

On this questionnaire are groups of statements. Please read each group of statements carefully, then pick out the one statement in each group which best describes the way you have been feeling in the past week including today.

1. 0 I do not feel sad.
   1 I feel sad
   2 I am sad all the time and I can't snap out of it.
   3 I am so sad and unhappy that I can't stand it.
2. 0 I am not particularly discouraged about the future.
   1 I feel discouraged about the future.
   2 I feel I have nothing to look forward to.
   3 I feel the future is hopeless and that things cannot improve.
3. 0 I do not feel like a failure.
   1 I feel I have failed more than the average person.
   2 As I look back on my life, all I can see is a lot of failures.
   3 I feel I am a complete failure as a person.
4. 0 I get as much satisfaction out of things as I used to.
   1 I don't enjoy things the way I used to.
   2 I don't get real satisfaction out of anything anymore.
   3 I am dissatisfied or bored with everything.
5. 0 I don't feel particularly guilty
   1 I feel guilty a good part of the time.
   2 I feel quite guilty most of the time.
   3 I feel guilty all of the time.
6. 0 I don't feel I am being punished.
   1 I feel I may be punished.
   2 I expect to be punished.
   3 I feel I am being punished.
7. 0 I don't feel disappointed in myself.
   1 I am disappointed in myself.
   2 I am disgusted with myself.
   3 I hate myself.

8.

0 I don't feel I am any worse than anybody else.

1 I am critical of myself for my weaknesses or mistakes.

2 I blame myself all the time for my faults.

3 I blame myself for everything bad that happens.

9.

0 I don't have any thoughts of killing myself.

1 I have thoughts of killing myself, but I would not carry them out.

2 I would like to kill myself.

3 I would kill myself if I had the chance.

10.

0 I don't cry any more than usual.

1 I cry more now than I used to.

2 I cry all the time now.

3 I used to be able to cry, but now I can't cry even though I want to.

11.

0 I am no more irritated by things than I ever was.

1 I am slightly more irritated now than usual.

2 I am quite annoyed or irritated a good deal of the time.

3 I feel irritated all the time.

12.

0 I have not lost interest in other people.

1 I am less interested in other people than I used to be.

2 I have lost most of my interest in other people.

3 I have lost all of my interest in other people.

13.

0 I make decisions about as well as I ever could.

1 I put off making decisions more than I used to.

2 I have greater difficulty in making decisions more than I used to.

3 I can't make decisions at all anymore.

14.

0 I don't feel that I look any worse than I used to.

1 I am worried that I am looking old or unattractive.

2 I feel that there are permanent changes in my appearance that make me look unattractive.

3 I believe that I look ugly.

15.

0 I can work about as well as before.

1 It takes an extra effort to get started at doing something.

2 I have to push myself very hard to do anything.

3 I can't do any work at all.

16.

0 I can sleep as well as usual.

1 I don't sleep as well as I used to.

2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.

3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.

0 I don't get more tired than usual.

1 I get tired more easily than I used to.

2 I get tired from doing almost anything.

3 I am too tired to do anything.

18.

0 My appetite is no worse than usual.

1 My appetite is not as good as it used to be.

2 My appetite is much worse now.

3 I have no appetite at all anymore.

19.

0 I haven't lost much weight, if any, lately.

1 I have lost more than five pounds.

2 I have lost more than ten pounds.

3 I have lost more than fifteen pounds.

20.

0 I am no more worried about my health than usual.

1 I am worried about physical problems such as aches and pains, or upset stomach, or constipation.

2 I am very worried about physical problems and it's hard to think of much else.

3 I am so worried about my physical problems that I cannot think about anything else.

21.

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I have almost no interest in sex.

3 I have lost interest in sex completely.

Appendix 6 The Vertigo Symptom Scale

The following questions ask about the type of symptoms you experience and how many times you have experienced each of the symptoms listed below during the past 12 months (or since the vertigo started, if you have had vertigo for less than one year).

The meanings of the numbered responses are:

0	1	2	3	4
Never	A few times (1-3 times a year)	Several times (4-12 times a year)	Quite often (on average, more than once a month)	Very often (on average, more than once a week)

How often do you have the following symptoms:

1. A feeling that things are spinning or moving around, lasting:(please answer all the categories)
   a) Less than two minutes 0 1 2 3 4
   b) Up to 20 minutes 0 1 2 3 4
   c) 20 minutes to 1 hour 0 1 2 3 4
   d) Several hours 0 1 2 3 4
   e) More than 12 hours 0 1 2 3 4

2. Pains in the heart or chest region 0 1 2 3 4

3. Hot or cold spells 0 1 2 3 4

4. Unsteadiness so severe that you actually fall 0 1 2 3 4

5. Nausea (feeling sick), stomach churning 0 1 2 3 4

6. Tension/soreness in your muscles 0 1 2 3 4

7. A feeling of being light-headed, ”swimmy” or giddy, lasting :(please answer all the categories)
   a) Less than two minutes 0 1 2 3 4
   b) Up to 20 minutes 0 1 2 3 4
   c) 20 minutes to 1 hour 0 1 2 3 4

d) Several hours	0	1	2	3	4
e) More than 12 hours	0	1	2	3	4
8. Trembling, shivering	0	1	2	3	4
9. Feeling of pressure in the ear(s)	0	1	2	3	4
10. Heart pounding or fluttering	0	1	2	3	4
11. Vomiting	0	1	2	3	4
12. Heavy feeling in arms or legs	0	1	2	3	4
13. Visual disturbances (e.g. blurring spots before the eyes)	0	1	2	3	4
14. Headache or feeling of pressure in the head	0	1	2	3	4
15. Unable to walk or stand properly without support	0	1	2	3	4
16. Difficulty breathing, short of breath	0	1	2	3	4
17. Loss of concentration or memory	0	1	2	3	4
18. Feeling unsteady about to lose balance, lasting: (PLEASE ANSWER ALL THE CATEGORIES)					
a) Less than two minutes	0	1	2	3	4
b) Up to 20 minutes	0	1	2	3	4
c) 20 minutes to 1 hour	0	1	2	3	4
d) Several hours	0	1	2	3	4
e) More than 12 hours	0	1	2	3	4
19. Tingling, prickling or numbness in parts of the body	0	1	2	3	4
20. Pains in the lower part of your					

back	0	1	2	3	4
21. Excessive sweating	0	1	2	3	4
22. Feeling faint, about to black out	0	1	2	3	4

Thank you for filling in the questionnaire.

Abbreviations

5-HT	5 hydroxytryptamine
ABR	auditory brainstem reponse
BAI	Beck anxiety inventory
BDI	Beck depression inventory
BPPV	benign paroxysmal positional vertigo
CGRP	calcitonin gene related peptide
CSD	cortical spreading depression
EMG	eectromyography
ENG	electronystagmography
FHM	familial hemiplegic migraine
GABA	gamma amino butyric acid
GAD	generalised anxiety disorder
ICC	intraclass correlation coefficient
ICHD-II	International Classification of Headache Disorders
IHS	International Headache Society
LOC	lateral olivocochlear
MOC	medial olivocochlear
MRI	magnetic resonance imaging
NAR	normalized amplitude ratio
OAE(q/n)	otoacoustic emission (in quiet/noise)
SD	standard deviation
SL	sensation level
SPL	sound pressure level
TEOAE	transient evoked otoacoustic emission
Ts	total suppression
VEMP	vestibular evoked myogenic potential
VM/MV	vestibular migraine/migrainous vertigo
VSS-AA	vertigo symptom scale-autonomic anxiety
VSS-V	vertigo symptom scale-vertigo severity/frequency

List of international and national conference presentations and publications derived from this work

Psychopathology in vestibular migraine: what is the mechanism?
Poster presentation and Winner of Best Poster Presentation
International Headache Congress, Berlin, Germany, 2011

Audiovestibular sensory processing in migraine, Invited lecture, British Association of Audiological Physician, Hallpike symposium, London 2011

Sensory processing in vestibular migraine
Platform presentation and published abstract, Barany Society, Reykjavik, Iceland 2010 *J Vestib Res*. 2010;20(3-4):79-340

Vertigo as a migraine trigger
Poster highlighted for oral discussion and published abstract, European Federation of Neurological Societies, Florence, Italy 2009 *Eur J Neurol* 2009 Suppl. 3 **16** 77

Otoacoustic emissions in vestibular migraine
Platform presentation, British Society of Neuro-otology Meeting, Leicester, November 2009

Suppression of otoacoustic emissions in migraine
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The relationship between migraine and vertigo
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