Central Adaptation after Peripheral Vestibular Injury

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Statement of Originality

The research presented in this thesis is my work. Other work or contributions are referenced and assistance acknowledged. The vestibular neuritis longitudinal study described in chapter 3 was done in conjunction with imperial college research fellow and PhD candidate Miss Sian Cousins, also working in the Neuro-otology group. The content of this thesis reflects only that work for which I took a primary role. Points of note in this regard are:

- The longitudinal study continues subsequent to my departure from the Neuro-otology research group. The subjects presented here in chapter 3 are limited only to those I was personally involved in for both acute and follow-up study assessments (n=16). The results analysis presented in chapter 3 of this thesis is my work alone. Only the perceptual threshold paradigm rather than the supra-threshold velocity step paradigm is presented here to reflect relative involvement in analysis.
- I was the sole experimenter for both the galvanic (chapter 2) and functional MRI (chapter 4) experiments.

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Nicholas John Cutfield
Abstract

This thesis examines how the human brain adapts after peripheral vestibular injury.

Vestibular perceptual function is used as a probe of cortical vestibular function. A paradigm determining vestibular perceptual thresholds to yaw axis rotation by a method of limits is described. Asymmetry in the thresholds is induced in normal subjects with galvanic vestibular stimulation. In patients with acute vestibular neuritis, perceptual thresholds were bilaterally elevated, with less asymmetry when compared to the brainstem reflexive function.

Thresholds were measured in a prospective longitudinal study in vestibular neuritis patients, assessed acutely and at follow-up (n=16). Assessments comprised vestibular caloric testing, visual dependency measures, questionnaire measures of symptom load, anxiety, depression and fear of body sensations. Clinical recruitment found a low rate of correct diagnoses by referring clinicians. Symptomatic outcome at follow-up was associated with increased visual dependence, asymmetric caloric function, increased anxiety and depression. It was also associated with increased fear and anxiety of body sensations present acutely, suggesting this may be predisposing.

The anatomical substrate of central compensation was investigated in patients with bilateral vestibular failure (n=12) and normal controls (n=15) using functional MRI. A novel air turbine-powered vibrating device was developed to provide high and low levels of proprioceptive stimulus to neck rotator muscles. This was combined with a horizontal visual motion paradigm in a factorial design. A lateralised interaction was found in the lateral occipital visual processing areas in the avestibular patients. In addition to the known visual-vestibular interaction, this demonstrates a visuo-proprioceptive interaction, which may reflect compensation after vestibular injury.
Conclusions: Vestibular perceptual function can be measured in disease, and is elevated in patients with acute peripheral vestibulopathy. Specific psychological and physiological factors associated with clinical recovery after vestibular neuritis are proposed. Functional MRI shows that proprioceptive signals interact with visual motion signals in patients with vestibular failure.
Ethical Approval

In addition to ethical approval existing for research done by the Imperial College Neuro-otology group, for the research described in this thesis two additional ethical approval applications were drafted by myself and approved:


Related Publications

Journal Articles:


In Preparation:

Cutfield N, Sharp D, ... ... Bronstein, AM. Cortical plasticity after vestibular failure demonstrated by the interaction between proprioceptive input and visual processing in avestibular patients.

Book Chapter


Conference Proceedings


Cousins S; Cutfield N; Seemungal B; Gresty M; Bronstein A. Vestibular perception after acute vestibular neuritis. 13th Congress of the European-Federation-of-Neurological-Societies, Sep 2009, Journal of Neurology
Cutfield NJ; Cousins SE; Faldon ME; Gresty MA; Bronstein AM. Vestibular perceptual thresholds for acceleration are bilaterally increased in acute vestibular neuritis. 12th Congress of the European-Federation-of-Neurological-Societies. European Journal of Neurology 15:410-411. (Madrid, Aug 2008).

Additional Conference Oral Presentations


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Acknowledgments

Thank you to all members of the Imperial College Neuro-otology Group, with whom it was a privilege and pleasure to get to know, discuss and work with.

Professor Adolfo Bronstein, thank you for your supervision, and for provoking a change in thinking, perhaps subtle in my case, towards that more of a 'clinician scientist.’ Thank you also for mentoring another New Zealand trainee neurologist; neurological vestibular and ocular-motor expertise residing in New Zealand is due exclusively to your teaching. Special thanks in the Neuro-otology group goes to Dave Buckwell for his multiple skills, helping with software applications, writing code and fabricating the vibrotactile fMRI device.

Dr David Sharp, Imperial College London, thank you for your invaluable advice and assistance with the MRI study, and your friendship.

Thank you of course also to my wife, Miriam Sharpe, who graciously deferred her own projects to allow me to complete the work described here, and her continuing love and support.
And the most important part of experimentation is not doing the experiment but making notes, very accurate quantitative notes — in ink. I am told that a great many clever people feel they can keep notes in their heads. I have often observed with pleasure that such persons do not have heads in which to keep their notes. This is very good, because thus the world never sees their results and science is not encumbered with them.

Pickerbaugh apparently believed that this research would take six weeks; Martin had hoped to do it in two years; and with the present interruptions it would require two hundred.

Sinclair Lewis

Arrowsmith, 1925
Chapter One

Human Vestibular System

The vestibular system is the sense of self-orientation and motion of the head. When working normally, in a natural environment, the sensations are not usually consciously perceived. It operates continuously and, in natural circumstances, it cannot be turned off, or be directed to, or away from, any object in the environment. It does not convey information about objects in the environment, like all other senses of hearing, vision, touch or smell. Information regarding orientation and position are generally combined with other senses such as vision, hearing, touch. It projects information to the brainstem (eye muscle motor neurons and autonomic centres), spinal cord and cerebral cortex. The importance of a functioning vestibular system is most readily apparent in the case of dysfunction, or disease.

Anatomy

The human membranous labyrinth lies within the bony labyrinth in the petrous temporal bone. Three semicircular canals contain the cristae, which sense rotation. The otolith organs, the utricle and saccule, have the maculae which sense linear motion and static head tilt in relation to gravity. Hair cells in the cristae and maculae have stereocilia, which when deflected cause hyper or depolarization, depending on whether they are deflected to or away from the single kinocilium also projected from each hair cell. The stereocilia are oriented so they can respond to forces in a particular direction. The cilia of the cristae project into the gelatinous cupula. The cilia of the macula project into a membrane, which also has otoconia, calcium carbonate crystals.

The labyrinthine or internal auditory artery supplies the labyrinth, and usually is a branch of the anterior inferior cerebellar artery (AICA) or occasionally branches directly from the basilar artery.
Primary neurons from the cristae and maculae pass to the vestibular, or Scarpa's ganglion. The superior branch of the vestibular nerve innervates the utricle, and the superior and horizontal semicircular canals, and the inferior branch innervates the posterior canal and the saccule. Secondary neurons project from Scarpa's ganglion to the vestibular nuclei, located in the ponto-medullary brainstem. There are four major vestibular nuclei, which project to the spinal cord, cerebellum, autonomic centres, the oculomotor nuclei and the cerebral cortex via the thalamus (Leigh and Zee 2006). The thalamocortical projections are particularly relevant for the work described in this thesis.

Figure 1: 1934 drawing of the membranous right labyrinth, cochlea and nerves. Max Brödel Archives.

**Physiology**

The change in position of the cupula in the semicircular canals is roughly proportional to angular head velocity; hence the semicircular canals effectively mechanically integrate angular head acceleration, supported by recordings in vestibular nerve semicircular canal afferent fibres. The elastic cupula will return to its primary position with sustained head accelerations, with a time constant of about 6 seconds. The hair cells have a tonic resting output, so the firing rate is either increased or decreased. The canals operate in pairs, e.g. head rotation to the left will increase firing rate from the left horizontal canal and decrease in the
corresponding right canal. Eye movements are produced by each canal in the plane of the canal, Ewald’s first law.

The saccule macular is on the medial wall of the saccule, and this is orientated for detecting vertical forces. The utricle macular is on the floor of the utricle, and will therefore detect horizontal plane translations and tilts off this plane. The maculae may also detect rotation as they are offset from the centre of rotation in the yaw axis.

The otolith organs detect linear accelerations through inertia of the otoconia layer, and because of gravity also detect head tilts (torsional ocular counter-roll is a simple bedside clinical test of otolith function). It is more difficult to test the physical characteristics of the otolith organs, as the maculae are curved and respond to linear accelerations in multiple planes.

In addition to the semicircular canals acting as mechanical integrators, in that the cupula detects acceleration but the vestibular nerve conveys a velocity signal, there is also partial integration of this velocity signal occurring in the brainstem before transmission to oculomotor nerves. This was noted in animal studies with eye position and vestibular nerve recording. When a monkey is stopped suddenly from constant angular velocity, the vestibular nerve velocity signal decays with a time constant of 7-10s. However, the slow phase of the eye movements decay with a longer time constant, 15-20s. This temporal storage of the signal is known as ‘velocity storage’ and the responsible neural circuit ‘brainstem integrator’(Buttner and Waespe 1981).

The Vestibular-Ocular Reflex (VOR)

The prime role of the VOR is to stabilize gaze with head motion. Head motion occurs much of the time during ambulation or conversation, and the continuous stabilizing function of the VOR remains subconscious while it is working normally. Patients with acquired absence of vestibular function report oscillopsia with any head movement. The VOR generates compensatory eye
movements in the opposite direction of head motion, with the same velocity. If the head rotates more than e.g. 45 degrees then the anatomical constraints mean the position of the eye is ‘reset’ with a fast phase.

Figure 2: Vestibular Ocular Reflex, shown for horizontal yaw axis head rotation to the right which elicits a leftwards slow phase eye movement. Neurons with increased firing are shown in bold. Inter-neurons between the right and left vestibular nuclei, as well as spinal and thalamocortical projections are not shown.

The horizontal vestibulo-ocular reflex is assessed at the bedside by performing the Halmagyi 'Head Impulse' or 'Head Thrust' Test (Halmagyi and Curthoys 1988). Passive low amplitude unpredictable fast head rotations interrogate a higher frequency response of the VOR. Failure to retain fixation is revealed by a visible (to the examiner) 'catch-up' re-fixation saccade. This has been shown to be a reliable clinical sign for unilateral de-afferentation (Halmagyi, Curthoys et al. 1990) and when compared to quantitative assessment of the VOR gain by the gold standard of magnetic search coils (Jorns-Haderli, Straumann et al. 2007). A ‘Doll's manoeuvre’, with slower head movements, is a less sensitive test as one functioning VOR pathway and visual enhancement of the VOR may be adequate for a normal appearing response. The ability of the head impulse test to detect relative differences between left and right labyrinthine function relies on Ewald’s second law: The vestibular afferent signals of a given ear are greater when the head is rotated in the direction of that ear, rather than away from that ear (Ewald 1882).
Vestibular Projections

As well as projections from the vestibular nuclei to ocularmotor nuclei, there are also vestibulo-spinal and ascending projections to the ventral posteromedial thalamus. The exact nature of the direct and indirect thalamocortical projections in humans is subject to debate.

![Diagram of vestibular projections](image)

Figure 3: Direct vestibular nuclei projections: spinal, ocularmotor and thalamic. For detailed pathways arising from individual canal signals see Figure2-3 p33 Leigh & Zee.

Evolution

The vestibulo-ocular system shows a high degree of conservation between species, which reflects the fundamental role it plays in self-orientation. An orienting mechanosensory system is common to disparate species. Although some lay people are surprised to learn that the ear functions as more than a hearing organ, it is in fact the vestibular system that is fundamental with development of auditory function only occurring in a proportion of species: in some vertebrates and arthropods (Fritzsch, Beisel et al. 2007). Ear, jaw, brain and eye muscle development are intrinsically linked, but some clues as to the development of the vestibular system can be gained by comparing the vestibular structures across species.

Many marine non-vertebrates, such as bi-valves have a simple statocyst that can detect gravity. A statocyst is a sac containing a 'statolith', a mineralised mass connected to sensory hairs, which stimulate neurons that can then signal
movement to correctly reorient the species. This can occur with extremely simple nervous systems. Even in very ‘primitive’ species correct body orientation remains vital for survival, as keeping a soft underbelly on the ocean floor, and not exposed to predators, has obvious survival benefit. Several non-vertebrates, such as some crustaceans can also detect angular acceleration in addition to the linear acceleration of a gravity vector.

Lancelets are perhaps the simplest of craniates, boasting a 'brain-like blister'. They are chordates, in a sister phylum to vertebrates. They have no lateral eyes, no ears and therefore no VOR system. Moving into the vertebrates, hagfish are craniates, but have no jaws. Fossil evidence suggests little evolution of hagfish in 300 million years, hence hagfish are commonly used for studying conservation of functions in biology generally, for example (Cutfield, Cutfield et al. 1979). They are thought to be the oldest and one of the simplest vertebrates, although some recent molecular evidence has caused debate regarding exact phylogenetic status. Hagfish have eyes, but no eye muscles, and it is thought the eyes do not move. Hagfish have a single simple vertical semicircular canal, a ‘torus’.

Lampreys, are vertebrates with a jaw, and have six eye muscles per eye. The lamprey has two distinct vertical semicircular canals, but does not have a horizontal semicircular canal. They have oculomotor, trochlear and abducens nuclei, but the pattern of innervation from these nuclei to the eye muscles is distinct from that of bony fish, and from tetrapods such as mammals. Lampreys do not appear to have any internuclear neurons in their oculomotor system.

Presence of a horizontal semicircular canal is associated with more advanced jaw development, and is present in elasmobranchs such as rays, and bony fish and tetrapods, such as mammals. Bony fish and tetrapods share the same fundamental components of the vestibular organ, brainstem nuclei, innervation and eye muscles (Fritzsch 1998; Fritzsch, Beisel et al. 2002). A conserved set of genes regulating development of vestibular system are starting to be identified, but the control mechanisms are not yet understood (Fritzsch, Beisel et al. 2007). A simple schematic of the evolution is shown in the figure.
Clinical Vestibular Disorders

A brief clinical summary of clinical vestibular assessment, in particular vestibular neuritis, but also some other more common vestibular disorders, follows. These illustrate aspects of the physiology of the vestibular system; provide background for diagnostic issues for clinical recruitment of human
patients with vestibular neuritis, and the starting point for physiological compensation and clinical recovery after vestibular disease.

**Symptoms**

Vertigo is a disabling sensation of inappropriate motion. This may be of self-motion or of motion of the environment. Vertigo is most commonly used to describe a rotatory motion, or a spinning sensation, as is commonly perceived with peripheral vestibular disturbances. Other types of motion, such as ‘rocking’ can also be perceived in certain vestibular conditions.

Patients often use the words ‘dizziness’, ‘vertigo’, ‘off-balance’ and ‘light-headedness’ interchangeably. It is important to explore the sensation that is being experienced regardless of the particular term used, and determine the circumstances in which it appears. Provoking and positional circumstances are vital in determining the cause of vertigo, which may have a vestibular origin, or not (Bronstein and Lempert 2006).

**Clinical Examination in Vestibular Disorders**

Examination includes inspection for nystagmus, gaze limitations, the VOR, hearing, and additional cranial nerve signs. Nystagmus is defined in the direction of the fast phase, although in pathological nystagmus the primary disorder is the slow phase abnormality. Nystagmus due to both recent onset peripheral and central vestibular disorders is invariably associated with oscillopsia or vertigo. Nystagmus that is chronic may be asymptomatic. Nystagmus intensity can increase when gaze is in the direction of the fast-phase, and the converse. This can occur with central and peripheral disorders, when due to the latter it is referred to as Alexander’s Law (Jeffcoat, Shelukhin et al. 2008). Midline cerebellar disease can produce nystagmus in certain head postures, such as the head down.

Eye movements requiring intact cerebellar and other central pathways include VOR suppression, pursuit and saccadic eye movements. The Hallpike Manoeuvre (Cawthorne, Dix et al. 1956) checks for positioning nystagmus due to Benign Paroxysmal Positional Vertigo or cerebellar disease.
**Vestibular Neuritis**

The terms ‘Vestibular neuritis’ ‘labyrinthitis’ or ‘acute idiopathic unilateral peripheral vestibulopathy’ are used interchangeably. In routine practice it is difficult to be certain if the pathological inflammation is in the vestibular nerve or the labyrinth, but is thought to be the former in the majority of cases. The dominant symptom is an intense horizontal vertigo over minutes to several hours with spontaneous recovery over days to weeks. There is nearly always nausea and usually vomiting in the first one two days. An upper respiratory tract infection is identified on history in about 50 per cent of cases.

The incidence is cited as 3.5 per 100,000 of the general population per year (Sekitani, Imate et al. 1993), and is commonly seen in emergency departments and in general practice. There is relatively little epidemiology on acute vertigo, however some reports and anecdotal experience would suggest a greater prevalence (Neuhauser, von Brevern et al. 2005).

There should be no deafness or severe headache at onset (which suggests a possible haemorrhage), although headache may often develop after vomiting. Clinical examination shows a horizontal nystagmus, fast phase away from the affected ear. There may be a small torsional component to the nystagmus, fast phase at the top of the eye in the same direction as the horizontal component. The nystagmus increases with gaze directed towards the fast phase. Gait is unsteady and veers towards the affected ear, but there is no limb ataxia on heel-shin or finger-nose testing. The Head Impulse Test should be positive on head rotation towards the affected ear, but there should be no other neurological signs. Standard MRI or CT brain is normal, audiometry normal. Caloric testing or quantitative video head impulse testing can be used to confirm the asymmetric vestibulo-ocular reflex.
Figure 5: Nystagmus in left vestibular neuritis, there is a dominant right horizontal fast phase with a right torsional component. The nystagmus is spontaneous and increases in intensity when gaze is directed in the direction of the fast phase. The arrows indicate the directions of the fast phases or ‘beats’ of the nystagmus.

Vestibular neuritis usually affects mainly the superior division of the vestibular nerve (Fetter and Dichgans 1996). The standard tests of the bedside head-impulse test and caloric irrigations both test primarily horizontal semicircular canal function, i.e. superior canal function. Less commonly, the inferior division of the vestibular nerve is involved, innervating the posterior semicircular canal and the saccule. To test this, vestibular evoked myogenic potentials (VEMP) can be used, using 100dB clicks that produce an electromyographic response in neck rotator muscles, with a reduced response in inferior vestibular nerve dysfunction (Halmagyi, Aw et al. 2002; Jiang 2008).

Pathophysiology

Vestibular neuritis is of unknown aetiology, but is presumed to be viral (Bartual-Pastor 2005). This is based upon epidemiology that upper respiratory tract infections often precede vestibular neuritis and cases can occur in clusters suggestive of a mini-epidemic (Davis 1993).

Atrophy of the vestibular nerve and hair cells has been found on autopsy, in people thought to have had prior vestibular neuritis. Such atrophy has been identified in other known viral conditions (Schuknecht and Kitamura 1981). Degeneration of Scarpa’s ganglion has also been found with a normal vestibular end organ, and cellular infiltrates surrounding vestibular nerve fibres at the internal acoustic meatus (Bartual-Pastor 2005). Postmortem studies have detected HSV-1 DNA by polymerase chain reaction in vestibular ganglia in normal subjects (Arbusow, Strupp et al. 2000), suggesting a population
prevalence of latent HSV-1 infection. Inflammation associated with reactivation of latent HSV-1 infection is a current accepted hypothesis, but direct evidence for this is still lacking.

**Acute Treatment and Corticosteroids**

Acute phase treatment with nausea and vomiting consists of intra-venous hydration and anti-emetics, such as prochlorperazine. Head and eye movement exercises can be used to aid balance recovery.

Several studies have reported improved vestibular function with early use of oral corticosteroids e.g. (Kitahara, Kondoh et al. 2003; Strupp, Zingler et al. 2004). (Strupp, Zingler et al. 2004) performed a randomised trial in a factorial design with corticosteroids and valaciclovir. Improvement in vestibular function as measured by caloric testing was found in the groups exposed to the corticosteroid. This result appeared consistent with current knowledge of another inflammatory cranial neuropathy, Bell's palsy, where a post herpes viral inflammatory response is likely responsible for an acquired facial neuropathy. The treatment of acute phase Bell's palsy is corticosteroid alone, although previously an antiviral was also co-prescribed. As the (Strupp, Zingler et al. 2004) study supported an attractive hypothesis and was published in a high impact clinical journal it was adopted in clinical practice in many centres. Of note is that this study did not include any clinical outcome data. As discussed further in this thesis, there is much more to clinical recovery than the VOR or caloric test result alone.

(Shupak, Issa et al. 2008) included an established clinical outcome measure, the Dizziness Handicap Inventory (Jacobson and Newman 1990) and found no benefit with use of corticosteroids at 12 months in this behavioural outcome measure.

The design and dosage of the corticosteroid trials vary, but a meta-analysis (Goudakos, Markou et al. 2010) concluded a beneficial effect with regard to rates of complete caloric recovery at one year. (Fishman, Burgess et al.) counter that a
random-effects statistical model should have been used given the heterogeneity in the data, and that there is no true significant difference. Their own recent Cochrane review accepted 4 randomised control trials for inclusion. The review concluded that “...on the currently available data, there is insufficient evidence to support the use of corticosteroids in the management of patients with idiopathic acute vestibular dysfunction...”. As not infrequently stated by this authority, they continue “...Large-scale, adequately powered and well-designed randomized controlled trials are needed ...

**Clinical Recovery after Vestibular Neuritis**

Most patients make an excellent recovery, and recurrence of the prolonged vertigo is extremely rare. Recovery usually occurs within several weeks in those that recover well. Imbalance is the initial main persisting symptom rather than vertigo for those who have persisting symptoms. Persisting symptoms can occur in up to 30-50%, and continue for more than ten years. In some 'chronic' patients, dysfunction has increased from that which occurred initially (Imate and Sekitani 1993). Recovery is thought to be due to combination of improvement in peripheral and central vestibular function. There is improvement in the peripheral function or the afferent vestibular signal. A proportion have a persisting ‘canal paresis’ yet still make a clinical recovery, presumably due to adaptation of the brain to the altered vestibular afferent signal. There is however a poor correlation between clinical recovery and VOR measurements (Bergenius and Perols 1999; Godemann, Siefert et al. 2005; Kammerlind, Ledin et al. 2005). Up to 20% of patients who have apparently fully recovered peripheral vestibular function after vestibular neuritis, as measured by caloric testing, still experience symptoms of postural imbalance and impaired vision with head movements (Bronstein and Lempert 2006), suggesting perturbed vestibular processing despite apparent reflex recovery.

Children likely have better outcome from vestibular neuritis compared to adults. As with adults, a preceding respiratory tract infection is found in about 50%, and
one study showed absence of significant long term symptoms in children, and a persisting canal paresis in just 14% (Tahara, Sekitani et al. 1993).

Many people recover and perform well. An anecdotal example on the highly functioning end of the spectrum is of a professional tennis player who took the remainder of a season off after vestibular neuritis, but subsequently retained the ability to play to a high level and regain temporarily a world ranking in the top 50 (Wikipedia 2012).

Given the striking divergence in clinical outcomes after the same condition, with the associated morbidity, societal and economic impacts, it is vital to understand the variance in clinical outcome.

The potential roles of perceptual function, visual dependency, psychological factors and functional brain changes in compensation after vestibular loss forms the theme of this thesis, and these factors are discussed in the following chapters.

**Differential Diagnosis of Vestibular Neuritis**

The clinically important differential of acute onset continuous vertigo is an acute cerebellar or brainstem lesion such as ischaemic stroke. Additional neurological signs may be present, including deafness, Horner’s Syndrome, facial paralysis or numbness, hemisensory disturbance, gait or limb ataxia. An isolated infarction of the labyrinthine artery causes acute vertigo and deafness without other signs. Spontaneous labyrinthine haemorrhage is a rare cause of sudden onset vertigo and deafness, and can be diagnosed by magnetic resonance imaging (Shinohara, Yamamoto et al. 2000). Inflammatory demyelination, either para-infectious or most commonly due to multiple sclerosis, can also present with a brainstem syndrome including vertigo and nystagmus. The first attack of migrainous vertigo or Meniere’s Disease can present with horizontal nystagmus and vertigo, although the vertigo and nystagmus may resolve more quickly. Alcohol toxicity can cause vertigo with spontaneous nystagmus (Fetter, Haslwanter et al. 1999),
but can usually be identified from other clues. Suppurative inner ear infection (bacterial labyrinthitis) can extend from the middle to the inner ear. Acoustic neuromas presenting with vertigo alone, without deafness, facial numbness or weakness, are rare.

**Table 1: Differential Diagnosis of Vestibular Neuritis**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vestibular Neuritis</td>
<td>Vertigo, nausea, imbalance, nystagmus fast phase away from affected ear, impaired VOR with head movement to the affected ear No deafness, tinnitus, other neurological signs</td>
</tr>
<tr>
<td>Brainstem / Cerebellar Stroke or Demyelination</td>
<td>Nystagmus central-type Cerebellar, brainstem, or other neurological signs</td>
</tr>
<tr>
<td>First attack migrainous vertigo*</td>
<td>Nystagmus usually central-type, photosensitivity and other migrainous features emerge</td>
</tr>
<tr>
<td>First attack Meniere's disease*</td>
<td>With recurrence will have deafness, tinnitus or aural fullness</td>
</tr>
<tr>
<td>Labyrinthine stroke</td>
<td>Acute deafness and vertigo</td>
</tr>
<tr>
<td>Bacterial labyrinthitis</td>
<td>Middle ear infection</td>
</tr>
<tr>
<td>Perilymph fistula</td>
<td>Precipitated by pressure or sound</td>
</tr>
<tr>
<td>Alcohol toxicity</td>
<td>Familiar presentation</td>
</tr>
<tr>
<td>Acoustic neuroma</td>
<td>Preceding progressive hearing loss</td>
</tr>
</tbody>
</table>

Migrainous vertigo has been reported in up to 23 per cent of ‘migraineurs’ (Vukovic, Plavec et al. 2007). The vertigo is of variable duration from ten minutes to several days, in some cases. A ‘rocking’ sensation is typical but the vertigo can be rotatory. Any nystagmus resolves completely after the attack. Other migrainous symptoms evolving during the attack are suggestive. Vertigo induced by caloric testing has precipitated full-blown migraine with accompanying vertigo (Seemungal, Rudge et al. 2006).

**Other Common Vestibular Disorders**

Benign paroxysmal positional vertigo (BPPV) is the commonest vestibular disorder (Brandt, Huppert et al. 2006). This usually involves the (anatomically lower) posterior semicircular canal. It is caused by 'canalo-lithiasis', dislodged otoconia from the utricle aggregating in the canal. Trauma, age and prior inner
ear disease are predisposing. The vertigo is usually less than 30 seconds; intense rotatory, but frequent attacks can result in reports of continuous imbalance. They occur in clusters with any number of episodes a day, for days to months. Rolling over in bed can provoke an attack, fully awakening the patient. The Hallpike manoeuvre is diagnostic, with torsional nystagmus in the direction of the affected ear (Cawthorne, Dix et al. 1956). Although the therapeutic manoeuvres can terminate bouts of attacks the condition tends to recur within a year in 40 per cent of cases, and in approximately 50 per cent of cases within 5 to 8 years (Hain, Helminski et al. 2000; Brandt, Huppert et al. 2006).

Figure 6: Nystagmus in right posterior (inferior) canal BPPV, there will be a dominant right torsional fast phase with an up-beating component. There should be latency and fatiguability.

Figure 7: Modified Hallpike for right posterior canal BPPV followed by a therapeutic Sermont manoeuvre (3), showing desired clearance of otoconia from the canal. Reproduced from (Cutfield 2011).
Positional downbeat, prolonged or non-fatiguing nystagmus can be a presenting feature of degenerative cerebellar disorders (Bertholon, Bronstein et al. 2002; Strupp, Zwergal et al. 2007).

Meniere’s Disease is characterized by recurrent vertigo associated with cochlear symptoms: a ‘roaring’ or ‘rushing’ tinnitus, a feeling of aural ‘pressure’ or ‘fullness’ and hearing loss, and usually presents between the ages of 30 and 50 years. Endolymphatic hydrops and expansion of the endolymphatic space within the labyrinth has been found, but the cause of this is usually not known. During attacks nystagmus may be present and can persist for several days: initially beating towards the affected ear in the ‘irritative phase’, and later beating away from the affected ear in the ‘paretic phase’. A second reversal in direction is sometimes seen hence the direction of the nystagmus does not discriminate the affected side. Eye movements are normal between attacks, and audiometry is required (American Academy of Otolaryngology, 1995). Treatment includes low salt diet, diuretics, betahistine, or in severe cases, middle ear injections of ototoxic gentamicin. Intra-tympanic corticosteroid injections are used and being trialed (personal communication K Agarwal, Neuro-otology Group, Imperial College, London).

The Tullio Phenomenon (Halmagyi, Curthoys et al. 2005; Kaski, Davies et al. 2012) is dysequilibrium or vertigo, oscillopsia and nystagmus provoked by loud sounds. Typical triggering sounds are those of an aircraft or motorcycle, but symptoms can also be provoked by the voice or playing a wind musical instrument. Dehiscence of the 1mm thick bone of the superior semicircular canal occurs in 0.7 per cent of unselected autopsy cases (Minor, Cremer et al. 2001), which allows sounds to be transmitted directly to the semicircular canal and can be seen on high resolution CT imaging. The symptoms of the Tullio Phenomenon can also occur with a perilymphatic fistula, an abnormal communication between the perilymphatic space and the middle ear due to defects in the round or oval windows, or in the bone surrounding the labyrinth. The condition may be congenital, but causes include barotrauma as from diving, surgery, erosive infection or tumour. Vestibular-evoked myogenic potentials are
easier to induce due to enhanced bone transmission (Colebatch, Day et al. 1998). Treatment includes bed rest and avoidance of physical effort that may give pressure surges. Surgical repair is possible depending on the anatomy.

Bilateral Vestibular Failure: The vestibular organ is more susceptible than the cochlea to ototoxicity from gentamicin (Seemungal and Bronstein 2007), and this is the most frequently identified cause. Autoimmune and inflammatory causes of vestibular loss usually involve one side first. Meniere’s Disease can progress to bilateral vestibular failure, but the diagnosis should be apparent from the tinnitus and deafness, usually over many years. Patients can present with imbalance or oscillopsia during head movement due to complete absence of the VOR. Examination shows bilateral impaired VOR and dynamic visual acuity. Treatment involves education, vestibular and physical rehabilitation with adaptation the presumed mechanism for improvement in function over several months.

Cerebellar disease, especially midline, can present with an ataxic, wide-based gait, without inco-ordination of the limbs on finger-nose or heel-shin testing. Eye movement examination can show overshoot or undershoot of saccades, impaired smooth pursuit and suppression of the vestibulo-ocular reflex. A syndrome of downbeat nystagmus (often with vertical oscillopsia) and moderate gait unsteadiness is relatively common in balance clinics. Genetic testing for the common spino-cerebellar ataxias and Episodic Ataxia Type 2 can be considered. Imbalance, only when walking, may suggest other neurological disorders such as peripheral neuropathy, Parkinsonism, cerebrovascular white matter disease or a cerebellar disorder.
Table 2: Clinical Assessments in Vestibular Disease

<table>
<thead>
<tr>
<th>Feature on history</th>
<th>Consider:</th>
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<tbody>
<tr>
<td>Vertigo rotational</td>
<td>Vestibular origin, peripheral or central</td>
</tr>
<tr>
<td>Vertigo positional</td>
<td>BPPV, migraine, or cerebellar</td>
</tr>
<tr>
<td>Gait imbalance</td>
<td>Bilateral loss of function, or neurological</td>
</tr>
<tr>
<td>Postural light-headedness</td>
<td>Exclude presyncopal postural hypotension</td>
</tr>
<tr>
<td>Auditory symptoms</td>
<td>Migraine’s</td>
</tr>
<tr>
<td>Headache or migrainous features</td>
<td>Migrainous vertigo</td>
</tr>
<tr>
<td>Pressure changes, coughing, sneezing</td>
<td>Perilymphatic fistula</td>
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Clinical Examination:

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<tr>
<th>Implication:</th>
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<tbody>
<tr>
<td>Eye movement examination</td>
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<tr>
<td>Head impulse test</td>
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<tr>
<td>Positional manoeuvres</td>
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<tr>
<td>Postural blood pressure</td>
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<tr>
<td>Gait and postural reflexes</td>
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<tr>
<td>Romberg test</td>
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<tr>
<td>Joint position and vibration perception in feet</td>
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<tr>
<td>Full neurological examination</td>
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Investigations:

<table>
<thead>
<tr>
<th>Indication:</th>
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</thead>
<tbody>
<tr>
<td>Pure-tone audiometry</td>
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<tr>
<td></td>
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<tr>
<td>Caloric testing</td>
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<td></td>
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<td></td>
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<tr>
<td>Rotational testing with eye movement</td>
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<tr>
<td>recording eg electro-oculography</td>
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<td></td>
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<tr>
<td>MRI brain, including cerebellum,</td>
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<tr>
<td>cerebello-pontine angles and</td>
</tr>
<tr>
<td>craniocervical junction</td>
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<td></td>
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<tr>
<td>MRI spine</td>
</tr>
<tr>
<td>Vestibular-evoked Myogenic Potential</td>
</tr>
<tr>
<td>Autoimmune blood tests</td>
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<tr>
<td></td>
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<tr>
<td>Cerebellar and peripheral neuropathy screening blood tests (listed in previous paragraph)</td>
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Non-vestibular Dizziness

Many causes of dizziness generally do not originate in the vestibular organ and nerve. For example, headache with vertigo may suggest vestibular migraine, but persisting vertigo, or vomiting, can induce a secondary headache. Severe sudden occipital headache preceding vertigo may indicate a haemorrhage in the posterior fossa. Light-headedness or pre-syncope is the commonest cause of non-specific ‘dizziness’. Some people experience a few seconds of ‘true’ rotatory vertigo during a syncopal event. Light-headed dizziness may accompany anaemia, and also hypoglycemia (Service 1995). Imbalance of gait is a feature of peripheral neuropathy, Parkinsonism, cerebral white matter and cerebellar disease. Orthostatic hypotension is common with increasing age and is exacerbated by some antihypertensive medications such as for hypertension. Checking postural blood pressure, lying and standing, must be routine. Cardiac investigations and referral may be required when there is the suspicion of an arrhythmia or an abnormal electrocardiogram. Anxiety and panic attacks are also a common cause of dizziness. Vestibular pathology causing chronic dizziness can provoke a high rate of secondary anxiety (Bronstein and Lempert 2006).
Chapter Two

Vestibular Perception

Introduction

Conscious awareness or attention to vestibular sensations does not seem to occur often in the normally functioning vestibular system, in normal environments. In contrast, very prominent vestibular sensation occurs with vestibular disease and with exposure to ‘abnormal’ accelerations, e.g. a roller coaster or other mechanised transport. Standard clinical vestibular tests only focuses on the brainstem mediated reflexes and do not assess perceptual or cerebral vestibular functions. Testing perceptual function might be desirable for several reasons: the standard VOR based reflexive tests do not test the whole ascending sensory pathway, and moreover, the standard tests do not correlate well with symptomatic outcome in clinical syndromes such as vestibular neuritis (Bergenius and Perols 1999; Palla and Straumann 2004; Kammerlind, Ledin et al. 2005).

Functional brain imaging also provides a window into cerebral cortical processes. It does not allow for natural stimulation of the peripheral vestibular system, with subjects’ heads unable to move while in the scanning environment. Brain imaging and the vestibular system is covered in Chapter 4.

Psychophysics: Perceptual Thresholds

Many standard clinical tests of sensory function in humans rely on sensory perceptual threshold measurement, e.g. a Snellen chart is the mainstay for assessing visual acuity and pure tone audiometry for hearing. These psychophysical sensory perception tests probe the entire pathway from the sensory organ to the cerebral cortex, rather than part of the pathway e.g. an electroretinogram or a brainstem auditory evoked potential. There is no current
clinical test of vestibular function that tests the entire sensory organ to cerebral cortical pathway.

‘Psychophysics’ is not a commonly used term, at least not among neurologists or other clinicians. In 1860 Gustav Fechner defined psychophysics as representing the connection between the physical world and conscious sensations. Fechner’s law proposes a linear increase in sensation magnitude is associated with a logarithmic increase in stimulus intensity. This was unchallenged until the 1950s when Stanley Stevens proposed ‘Stevens’ Power Law’, which has not, however, usurped Fechner’s law. Stevens’ data was thought to more directly measure absolute sensation magnitude, rather than discrimination ability between different magnitudes of sensations. However, sensation perception magnitude cannot currently be directly measured in humans: subjects have to perceive and cognitively process a signal before reporting perception or absence of the signal. Although promising functional brain imaging and EEG tests may be able to provide non-invasive probes of consciousness and awareness (Cruse, Chennu et al.; Cruse and Owen), such methods do not currently measure magnitude of sensory perceptions. Therefore all measures of sensory perception magnitude are currently indirect, and the concept of an ‘absolute’ sensory threshold in this respect is probably conceptually artificial (McKenna 1985; Gescheider 1988). The term ‘absolute’ is used here in keeping with conventional usage to distinguish between the different designs of the perceptual threshold paradigms.

Perceptual threshold measures can be ‘discriminatory’ or ‘absolute’. An example of determining a discriminatory threshold is the simultaneous application of two objects at varying distances apart e.g. ‘two point discrimination’ as can be done in a clinical neurological examination, or being able to detect a difference in volume of two sounds. ‘Absolute’ thresholds are determined by applying known stimulus intensities and the subjects reporting their perception of these when faced with a categorical choice e.g. indicating ‘yes’ to hearing the volume of a sound stimulus as done in pure tone audiometry.
Threshold determination is generally not straightforward, given subject responses are not 100% reliable for a given stimulus and the specific experimental setup affects the results. The proportion of correct responses can be plotted on the ‘y’ axis and the intensity of the physical stimulation on the ‘x’ axis e.g. increasing volume for hearing, or angular acceleration for the vestibular system. This gives a curve, which is an example of the sigmoid ‘psychometric function’ curve. The threshold can be defined as the point of inflexion on the curve, or at the stimulus intensity where a defined proportion of correct responses occur. 50% perceived correctly is the most common point, but the threshold may be set higher or lower depending on the circumstances. Various biases and errors can alter the curve, as well as the derived thresholds.

![Psychometric Function Curve](image)

**Figure 8: An example of the psychometric function curve with the threshold set at a 50% detection rate**

Important factors that can influence threshold reporting include time of exposure to the physical stimulus (see Mulder’s law below), as well as influences from habituation, expectation and fatigue.

Techniques for determining ‘absolute’ thresholds include:

1. Limits Method. A sub-threshold stimulus is applied and gradually increased until perceived (ascending limit), or alternatively a supra-threshold stimulus is applied and decreased until the subject reports they no longer perceive it (descending method of limits).
2. **Constant Stimuli Method.** Fixed stimuli intensities are presented in random order, which increases the number of trials, but reduces some forms of bias (e.g. habituation, where subjects expect to start to perceive a stimulus after a certain period into an ascending limits trial).

3. **Adaptive Staircase Methods.** These seek to make the limits methods more efficient in defining a threshold and the number of trials. These modify the stimulus intensity in a given trial dependent on the preceding response.

4. **Adjustment / Average Error.** The subject themselves adjusts the stimulus intensity until it is the same intensity as another stimulus or the background.

These methods can be combined in protocols aiming to optimise efficiency of trial number.

**Vestibular Perceptual Thresholds**

As vestibular signals are normally combined with other orienting sensory information such as vision, hearing and proprioception, any testing of vestibular sensations and perception requires removal of these other senses. This means vestibular perceptual testing has to be done in a dark room, without auditory clues, and therefore the testing environment, by definition, cannot be truly natural.

Vestibular psychophysics, and perhaps modern vestibular physiology as well, began with Ernst Mach. His 1875 book *Grundlinien der Lehre von den Bewegunsempfindungen*, translates as ‘Fundamentals of the Theory of Motion Perception’. This treatise encompassed several major advances in understanding, including proposing the labyrinth as the sensory organ, that the stimulus detected is acceleration, and that the stimulus is detected via a pressure difference across the cupula. Mach conducted psychophysical experiments on a rotating chair, measured thresholds and explored vestibular-visual interactions, discussed further here in chapters 3 and 4 (Henn 1984). Vestibular psychophysics continued to be investigated until the mid 20th century, but has
subsequently been relatively neglected as a field. This appears to have coincided with availability of techniques able to record eye position accurately causing an emphasis on measurement of the VOR. Consequently most of the vestibular perceptual or psychophysical literature is in the pre-Medline era, but a brief summary of some of this earlier 20th century work remains instructive. (Bekesy 1955) describes an important series of vestibular psychophysical experiments conducted on a rotating Barany chair applying sinusoidal motion in the yaw plane. Although there is little in the way of statistics presented, some important results included:

1. A subject rotated slowly (period 80s) in the yaw plane will perceive displacement in addition to rotation, or of swinging. This occurred even if the head was flexed forward 30 degrees to concentrate the stimulus on the horizontal canals. Subjects indicated their position in the dark by pointing their finger. Asymmetry in the sensation of displacement was found despite symmetric sinusoidal chair rotation, perhaps related to a degree of inherent asymmetry in normal subjects.

2. Separate sensations of displacement and rotation adapt independently, and the thresholds for these sensations were different, supporting distinct sensory perceptual signals from canals and otolith organs.

3. When recording vestibular perceptual thresholds using continuous near threshold sinusoidal rotations it was noted that perception of rotation also occurs in subjects seated in a stationary chair in darkness with no physical stimulus (as is now known so does a low amplitude spontaneous nystagmus in many).

4. Perception of sinusoidal yaw axis rotation has a lesser degree of perceived magnitude (indicated by compensatory finger pointing) than the actual magnitude of the rotation.

5. When the amplitude of the sinusoidal oscillations was near threshold for perception, the sensed oscillations did not always remain symmetrical, with asymmetry lasting 1-2 minutes before sensations became symmetric again. This was interpreted as being due to a degree of asymmetry in the perceptual thresholds.
6. After continuous slow sinusoidal rotations for 15 minutes are stopped, the sensation may take a cycle, more than one minute, to completely disappear.

7. Bekesy effectively used an 'adjustment method' of thresholds, with the subject tuning the amplitude of the sinusoidal rotation above and below their perceptual threshold. Using this method, he found most subjects did not have a constant threshold measure. The threshold amplitude increased over time. He found that the control tests of sitting still for 20 minutes did not result in increasing perceptual thresholds, and that it was application of the stimulus motion that resulted in the threshold being increased.

Much of the early to mid 20th century work is summarised by (Guedry 1974). Part II 'Subjective Reactions to Semicircular Canal Stimulation by Simple Angular Acceleration' is of particular relevance. The “sensation cupulogram”, plots of apparent cupula displacement against acceleration or velocity stimuli were used to infer thresholds and dynamics of the perceptual system.

Four stimuli profiles of yaw-axis rotation were used in these early experiments:

1. A velocity step with a sudden acceleration to a constant angular velocity
2. Velocity ramps have a constant acceleration with a linear increase in velocity up to a target angular velocity
3. Velocity triangles recede in profile with equal magnitude deceleration
4. Sinusoidal stimuli
Figure 9: Yaw axis rotation stimulation profiles for vestibular threshold studies. Curves are shown for angular acceleration (a), velocity (v) and horizontal canal cupula displacement (d) against time on the x axis. Adapted from Guedry (1974).

When using the impulse and ramp stimuli, the perceptual response appears to be elicited by the angular acceleration, as the perception decays during periods of constant velocity. In the case of sinusoidal stimulation, the stimulus frequency affects the properties of the cupula afferent signal. Higher frequencies, approximating natural head movement, tend to produce a velocity signal, but at very low frequencies, the cupula output is closer to the angular acceleration, i.e. at low frequencies the cupula is no longer mechanically integrating to give a velocity output signal.

A light target fixed in front of subjects modulates the perception of rotations, termed the ‘oculogyral effect.’ In darkness the purely vestibular perception of rotation is known as ‘somatogyral.’ (Guedry 1974) tabulates 20 estimates of vestibular perceptual thresholds to yaw axis angular acceleration in the dark in human subjects from Mach in 1875 to 1965. These were mostly somatogyral experiments. The values of mean threshold to perception of constant angular acceleration vary considerably between 0.035deg/s² and 4.0 deg/s². The differences are attributed to “individual differences among subjects, variations in psychological procedures, and differences in equipment used for producing and measuring the stimuli.” The duration of the stimulus in the various experiments is not summarised, and this is clearly important. Mulder in 1908 proposed the
law that the product of the threshold for angular acceleration and time of the stimulus is constant. Subsequent reports have investigated varying stimulus magnitude or duration and have broadly conformed to Mulder’s law, e.g. (Clark and Stewart 1968).

The key points evident from the ‘early’ vestibular psychophysics to consider when contemplating vestibular threshold paradigms include:

1. The theoretical contention that there may not be an “absolute sensory perceptual threshold”; perceptual thresholds are all measured indirectly.
2. That the “normal” threshold is particular to an individual experimental paradigm.
3. Vestibular perceptual thresholds can increase between trials during a testing session in normal subjects
4. Mulder’s law, i.e. the product of stimulus time and the time exposed to the stimulus form a constant.

(Rodenburg, Stassen et al. 1981) revisited Mulder’s law and measured thresholds to fixed angular accelerations for somatogyral around the yaw axis as a function of duration. (Rodenburg, Maas et al. 1981) also plotted and compared the psychometric curves for vestibular and auditory function. The standard ‘S’ shape is produced when stimulus intensity is plotted on a log10 scale. The curve can be described by a Gaussian distribution function with a median (50% threshold point) and standard deviation. This standard deviation reflects inter-individual variability, which was 5.5dB, similar to the inter-individual variability of 5.7dB.

More recently there has been a resurgence of interest in vestibular perception e.g. (Gianna et al. 1995, Gianna et al. 1996, Seemungal, Gunaratne et al. 2004; Grabherr, Nicoucar et al. 2008; Merfeld 2011). Inter-subject variability and likely contributions of somatosensory cues to motion perception were noted in the earlier of these more recent studies. In addition to perceptual thresholds of motion detection, the relative magnitude of perception can be estimated with a ‘velocity step’. Sudden acceleration to a constant angular velocity produces an
initial high perception of rotation, which then decays. Okada et al. described a new method for quantifying vestibular perception (Okada, Grunfeld et al. 1999). A tachometer (or wheel) is turned by subjects at a rate indicating the magnitude of their perception of their rotation, in response to step velocities. This allowed the perceptual vestibular response to be recorded simultaneously with a brainstem measure of vestibular function by horizontal eye movement recording in human subjects. This was applied in normal subjects, and in those with congenital nystagmus. An important result was the time constant of decay of velocity perception was similar to the time constant of decay of the slow phase of nystagmus, suggesting velocity storage also applied to the ascending cortical signal. Additionally, patients with congenital nystagmus had shorter time constants, perhaps as a by-product of suppressing another head position perceptual signal, visual motion.

Patients with acquired ophthalmoplegia cannot produce a normal vestibulo-ocular reflex, and might be expected to have oscillopsia, or visual image slip on the retina with head movements. Four subjects also had shortened time constants of vestibular perception in the same paradigm (Grunfeld, Shallo-Hoffmann et al. 2003). This may also be an adaptive or compensatory mechanism to limit potential oscillopsia. These perceptual time constants were found to be shortened by exposure to preceding rotational and optokinetic stimulation (Grunfeld, Okada et al. 2000). This modulation of the central processing of vestibular inputs supports the use of optokinetic stimuli in some patients with vestibular disorders e.g. with “visual dependence” as discussed in the following chapter.

Additional to these studies utilising perception of rotation with velocity steps, vestibular perceptual thresholds have also been revisited. (Seemungal, Gunaratne et al. 2004) describe a paradigm recording perceptual thresholds combined with eye movement recording, allowing the VOR and perceptual threshold to be simultaneously recorded. Velocity ramps of fixed duration, 5s acceleration and 5s deceleration were applied. Within each trial the angular acceleration was constant, but was varied according to an automated binary
search algorithm, designed to ‘home in’ on the threshold with an efficient use of trials. A categorical ‘left’ or ‘right’ perception of motion was applied, in part to mitigate any expectation bias resulting from a subtle vibration present in the chair motor with initiation of rotation. This paradigm gave perceptual thresholds in normal subjects of about 0.5deg/s² in young and 1 deg/s² in older subjects. The perceptual thresholds are in the range of the results in the earlier 20th century literature.

(Grabherr, Nicoucar et al. 2008) also investigated vestibular perceptual thresholds to yaw axis rotation. This study used sinusoidal rotation and plotted the thresholds against different frequencies of rotation (0.5 – 5Hz). An adaptive staircase method of threshold determination was used. They found increasing velocity thresholds at lower frequencies of stimulation, below 0.2Hz. They interpret this effect as being consistent with a mechanical high-pass property of the semicircular canal, rather than due to e.g. velocity storage.

There are not easily locatable previous studies on the effects of peripheral vestibular lesions on vestibular perceptual thresholds. How unilateral loss of function in vestibular neuritis would impact upon thresholds is not therefore known. It is possible that the continuous functional directional coupling between canal pairs means they are in effect a functional unit at the perceptual level. It is not possible to volitionally suppress one dysfunctional vestibular organ, in contrast to e.g. temporarily patching a deviated or blurry eye.

In summary, current standard clinical tests such as the horizontal head impulse test, caloric irrigation and Barany chair electro-oculography are all assessing the horizontal VOR. In other sensory systems, clinical testing involves a perceptual component, which tests the entire sensory organ to cerebral cortex pathway e.g. a Snellen chart for visual acuity, and pure tone audiometry for hearing. To more fully test the vestibular system, incorporation of a perceptual test might provide more information. To test this however does require exclusion of sensory information from other senses, which may be potentially challenging in clinical situations.
This chapter describes validation of a new vestibular perceptual paradigm for testing in human patients, including the perturbing of the perceptual thresholds with galvanic vestibular stimulation.

**Galvanic Vestibular Stimulation (GVS)**

Luigi Galvani developed the eponymous zinc-copper cell and applied it to nerves in frogs' legs in 1780. Applying electrical current from a galvanic cell to the human head has been practiced since the early 19th century yet despite continuing attempts over 200 years, applying current to the head is not yet established as being of therapeutic benefit (with the notable exception of firmly established electroconvulsive therapy for refractory depression). Johann Purkyné reported inducing imbalance when applying current to the head in 1820, and this is likely to be the first definitely described galvanic vestibular stimulation (GVS). Eduard Hitzig noted nystagmus induced by GVS in 1874 in both humans and dogs (Bos, Jongkees et al. 1968; Fitzpatrick and Day 2004).

An advantage of GVS is the potential to more selectively experimentally perturb the peripheral vestibular system. Other vestibular stimuli such as whole body rotations may stimulate proprioceptive and mechanoreceptors, with visual and auditory clues. Caloric irrigation is the other more commonly used method. GVS has also been applied to patients with peripheral vestibular lesions (Bos, Jongkees et al. 1968) and with posterior fossa abnormalities (Pfaltz and Koike 1968). As with the study of vestibular perception GVS has been relatively neglected with a recent resurgence in interest (Day 1999).

To induce vestibular effects in humans, typically 0.5 to 1mA current is required for DC stimulation. Other waveforms e.g. sinusoidal, can be applied. A variable resistor is incorporated to regulate the desired current, with 6-9V required. GVS is usually applied in a 'binaural' fashion, applying an anodal electrode to the mastoid process of one ear and cathodal electrode to the other, although it is possible to apply both anode and cathode to selectively perturb a single vestibular nerve.
A detailed review of the physiology of GVS is included in (Fitzpatrick and Day 2004). GVS is likely to predominantly act on the primary vestibular afferent nerves. This is because the effects can be recorded in Scarpa’s ganglion, that GVS effects can still be produced after labyrinthectomy, but cannot be induced when the eighth nerves are excised. Overall GVS does not produce a constant response with a constant DC current applied. Some studies have shown adaptation of individual nerve firing rates after a step change in current. Short duration responses to GVS show increasing eye movement response to increasing current in a linear relationship (MacDougall, Brizuela et al. 2003). GVS may preferentially stimulate irregular firing vestibular afferents, which project more to the spinal cord than to oculomotor nuclei.

GVS does not have an equivalent motion vector of stimulation, as it affects most if not all the vestibular afferents. However the overall CNS motion signal of GVS is of rotation due to modulation of semicircular canal signals. The effects of GVS on the pitch plane seem to mostly cancel out, and the overall vector of equivalent motion is rotation mainly in the roll plane, with a yaw axis component. This is assessed by psychophysical experiments of whole body rotation (Fitzpatrick, Marsden et al. 2002).

The 3D eye movement response to 0.5mA constant current GVS has been measured in normal subjects using the gold standard of magnetic search coils. A dominant torsional vector is found in both the onset and offset of DC GVS, with a nystagmus magnitude in the order of 0.5°. A lesser magnitude horizontal component is present, with little vertical eye movement induced (Severac Cauquil, Faldon et al. 2003). This is consistent with psychophysical experiments of whole body rotation (Fitzpatrick, Marsden et al. 2002) and modeling on the canal effects of GVS (Fitzpatrick and Day 2004).

With binaural GVS, anodal current reduces ipsilateral firing rates. In the case of the yaw axis rotation vector determined by the horizontal semicircular canals, anodal current in the left ear will reduce afferent firing rate, simulating rotation to the side of the cathode.
Blindfolding a walking subject and administering GVS causes subjects to reliably deviate towards the side of the anode. By then applying GVS to blindfolded subjects taken on a route in a wheelchair, subject estimation of start position showed an error in the opposite direction. The authors suggest the deviation of the path is due to alteration of perception of the path taken (Fitzpatrick and Day 2004). Additionally, the direction of induced sway by GVS can be affected by the head posture in relation to the body.

GVS also induces a vestibulo-colic EMG response in humans, distinct from vestibular-induced leg EMG signals (Watson and Colebatch 1998; Watson and Colebatch 1998; Watson, Fagan et al. 1998). This may explain the variation in GVS sway with head position, and reflect the role of vestibular projections in both head and whole body postural control.

Responses to continuous DC GVS decay, and oculomotor and perceptual responses are most consistent in the first few seconds. To provide longer lasting GVS effects, a pseudorandom signal by summing sine waves can be generated, administering very brief but relatively high peak currents of up to 5mA. The induced postural instability on posturography was thought to be similar to that of astronauts on returning to earth, and less severe, but similar to, subjects with bilateral vestibular failure (MacDougall, Moore et al. 2006).

The visual-vestibular interaction (see chapter 4) effects on postural control have been investigated with GVS. Increasing visual information, both before and after GVS, modulated the GVS-induced postural response (Day and Guerraz 2007) supporting central processing of GVS signals in the case of postural control. Finally, GVS has also been used in relation to the postulated association between vestibular and memory function. Recent reports of sub-threshold GVS modulating memory function in humans and animals is reviewed in (Smith, Geddes et al. 2010).
In summary, GVS is a relatively technically straightforward stimulus to apply to the primary vestibular nerves, but the physiological effects are more complex. In the last 12 years the oculomotor and perceptual effects of GVS are being better elucidated. GVS may yet play a role in routine clinical diagnostics, but at the least, is a valid tool to perturb vestibular signals in humans.

Methods

Perceptual Threshold Paradigm

(Seemungal, Gunaratne et al. 2004) described a method for determining perceptual thresholds in normal younger and older subjects. This method made it possible to determine a perceptual threshold, while simultaneously recording eye movement position with infrared oculography. This protocol was piloted in three vertiginous individuals within 48 hours of onset of acute vestibular neuritis. A large number of individual trials (16 to more than 30) were required to produce a threshold, and the large number of trials was not tolerated well. In one of these patients the staircase search algorithm would ‘tune in’ to the presumed perceptual threshold before these thresholds were no longer detected, and the algorithm would reset to trying to define a threshold in a higher range, suggesting subject fatigue was shifting the psychometric threshold detection curve. This was analogous to intra-session increasing thresholds in normal subjects (Bekesy 1955). The inter-session reliability of this method in two normal subjects showed considerable variation, with a 2-fold variation in thresholds. Within-subject reliability on repeated sessions was not further investigated here once it became clear this method was not appropriate for testing patients with acute vertigo. It may be that the sensory deprivation (dark, sound masked room) inherent in vestibular perceptual testing produces greater fatigue effects or other modulators of attention.

In this thesis a new technique of determining the angular threshold was developed. An alternative to a staircase algorithm, which was at least tolerated by healthy subjects, is a traditional ascending method of limits approach. This
allows a much shorter number of trials to be applied, with increasing stimulus intensity applied within each trial. Because tolerability to testing was vital (anticipating using this as part of multiple tests in vertiginous patients with acute VN) a fixed number of trials was performed, set at n=6. This allowed an estimate of the vestibular perceptual threshold to angular acceleration.

Increasing angular acceleration was adopted, rather than a velocity step with constant angular acceleration. This avoided accumulating too fast an angular velocity before reaching the perceptual threshold, as would be possible with a low constant angular acceleration.

A single trial consisted of applying progressively increasing acceleration in the yaw plane, increasing by 0.5\,deg/s^2 every 3 seconds to either the left or the right. Subjects sat on a Contravez Inc. Barany chair with the head fixed by resting on a chin bar, in complete darkness. Subjects were asked to check for any visible light before testing. They were instructed to keep their eyes open and looking ahead during trials, but to blink and relax during the 1-minute pauses between trials. White noise was amplified through headphones to mask any extraneous noise. The Barany chair had a DC motor with no perceptible vibrations produced even at low velocities. A controller is held in the hands with two buttons, one to indicate perception of left direction and one for the right (Figure 10). Identical instructions were given to all subjects to push the button “as soon as you know you are moving in that direction.” Six rotations were applied; directions were randomized by Latin square. A pause of 1 minute was given between rotations. Simultaneous horizontal eye position recording was done to generate a relative threshold for the horizontal vestibular ocular reflex, the ‘nystagmus threshold’.

After initiation of rotation and the VOR, a blink often occurred with the first nystagmus fast phase. The larger relative amplitude of the blink artifact was greater with infrared video system compared to electronystagmography (ENG). Both could be sampled with an analogue system, therefore ENG recording (two binaural and a central earth skin electrode) was used.
Figure 10: The subject is seated in a Barany chair with a chin bar fixing the head position. ENG electrodes record horizontal eye position and hand-held buttons indicate perception of left or right rotation. Trials were done in complete darkness so the optokinetic curtain shown is not relevant. The speakers provide sound-masking with white noise.

Signals were recorded and processed using in-house ‘Analysis’ software\(^1\). The thresholds are recorded in time, for which there is a corresponding angular velocity, frequency and acceleration. Statistical analyses were done with the raw data in units of time to avoid potential distortions from e.g. non-linear transformations to acceleration. The threshold values in time can then be variably transformed to other units, depending on the context or reflecting convention in the vestibular literature.

Asymmetry is determined by the Jongkee’s formula throughout this thesis:

\[
\text{Asymmetry} = \frac{\text{Abs} (L-R)}{(L+R)}
\]

which yields a positive ratio between 0 and 1. Depending on the situation, Left and Right sides may be substituted by: Ipsilesional and Contralesional sides, or Anodal and Cathodal sides.

Perceptual thresholds: The off-line analysis of the nystagmic thresholds required signal processing due to the presence of spontaneous nystagmus in subjects with acute vestibular neuritis. Combining the assessment of changes in the slope of the slow phase of the nystagmus with changes in the differentiated

\(^1\) Analysis software was written and supported by Mr David Buckwell, Neuro-otology, Imperial College.
eye position recording reflecting eye velocity, a threshold for the modulation of the nystagmus by VOR could be produced, even in the presence of spontaneous resting nystagmus, as shown in figure 11.

Figure 11: Nystagmic and Perceptual Threshold determination in a subject with spontaneous right-beating nystagmus due to acute left vestibular neuritis. Button pushes indicate the perceptual thresholds in response to chair rotation. The nystagmus threshold can be determined by the slow phase eye velocity, produced by differentiating and desaccading the eye position signal.

Galvanic Stimulation

Galvanic vestibular stimulation (GVS) was applied in a ‘binaural’ fashion. The mastoid processes were cleaned with a skin wipe, with care taken not to use abrasive gels used for skin surface recording electrodes, such as for EEG or ENG, as these may produce ‘microcuts’ that can channel electrical current and induce discomfort. Conducting electrode gel was applied under 10cm² flexible carbon electrodes², with the edges fixed to the skin with occlusive skin tape (3M) and containing the gel to the area under the electrode. A constant current DC 1mA

² Kindly supplied by Professor Brian Day, University College London.
binaural current was administered, with anodal and cathodal electrodes each applied to the left and right ears. The galvanic cell was fixed to the Barany chair and controlled via the chair channels.

The Galvanic current was applied in a pseudorandom fashion 0-3 seconds prior to initial (sub-threshold) Barany chair rotation, and stopped after the perceptual threshold was reached, indicated with a button push. In the normal subjects, this occurred within a maximum of 15s. Discomfort did not occur at durations of under 15s GVS. Trials were done with the anode on each of the right and left mastoid processes for each subject. Experiments were performed initially with the head in the neutral position and with the head flexed forward 60 degrees, mostly testing the vertical canals. The head position was fixed using a chin bar and forehead rest respectively.

**Subjects**

Perceptual and nystagmus thresholds were initially measured in twelve healthy normal subjects 8 female, mean age 46 years (22-72), as a control group to 16 patients with acute vestibular neuritis. Vestibular neuritis patients all had positive head impulse tests, canal paresis on caloric testing, and the other clinical criteria described in chapter 1. They were tested within 72 hours of onset. Seven were female, mean age 50 years (22-69). Seven had received prochlorperazine in the Emergency department within 24 hours, two within 6 hours. No patients had received corticosteroids in keeping with local practice and supported by the subsequent Cochrane review (Fishman, Burgess et al. 2011).

Three subjects with absent vestibular function were also tested (mean age 57, two with gentamicin exposure and one with idiopathic vestibular failure). They had absent clinical head impulse tests, ocular counter-roll to head tilt, and a maximum slow phase velocity of 6°/s on bithermal caloric testing at 30 and 44°C (approximately 10% of the normal response).
For the Galvanic stimulation normal subjects were assessed in the head neutral (upright, n=5) and head roll position (see diagram to the right of Fig 7; n=8, 6 female, mean age 30 years).

Results

Normal Subjects

The novel paradigm using a ‘limit finding’ approach for vestibular perceptual threshold determination was viable for both normal subjects and for testing patients with acute vestibular neuritis. The testing was well tolerated, and the time required was usually within 10 minutes. The mean time to perceptual threshold for normal subjects was 9.6s (s.e 0.82s), which is at an angular velocity of 9°/s, and angular acceleration having just increased to 2°/s². Although threshold paradigms are not directly comparable, this is consistent with the thresholds tabulated in (Guedry 1974). The mean nystagmus threshold was 6.0s (s.e. 0.6s), equivalent to 4.5°/s and 1°/s². Raw units of time are kept rather than converting to angular velocity or acceleration to avoid non-linear effects on statistical analyses.

Bilateral Vestibular Failure

Testing of three patients with acquired chronic bilateral vestibular loss showed that they did not detect the angular rotation within 33s, by which time the chair was rotating at 99°/s² and those trials were stopped to avoid achieving higher angular velocities. Vestibular nystagmus was not induced in the patients with bilateral failure, confirming absent function of their horizontal VOR. This validates the protocol as providing a purely vestibular stimulus as non-vestibular inputs did not provide a sensation of motion in these patients, e.g. incompletely masked auditory clues, or relative air pressure on uncovered skin surfaces.

Acute Unilateral Vestibular Paresis due to Vestibular Neuritis

Perceptual and nystagmus thresholds were elevated in 16 patients with acute vestibular neuritis, in both the ipsilesional and contralesional rotations.
Nystagmus thresholds could not be reliably calculated for 3 of 16 of the acute VN subjects due to increased noise in the signal in the presence of vigorous spontaneous nystagmus. Independent samples t-tests showed a significant elevation of the mean thresholds for the acute VN subjects compared to the normal control group for perception (p<0.001) and nystagmus (p = 0.007, 2 tailed, equal variances not assumed).

![Figure 12: Thresholds in sixteen subjects with vestibular neuritis and normal controls. Results are average of left and right rotations, and raw units of time are shown. Medians, quartiles and ranges are shown. The perceptual thresholds are higher than the reflex VOR nystagmus thresholds. The thresholds are elevated in acute VN subjects.](image)

The degree of asymmetry of perceptual and nystagmus thresholds in patients with acute VN was 0.20 and 0.22, which is much less than the expected asymmetry in the VOR function by caloric testing in the VN patients; the percentage asymmetry of the peak slow phase nystagmus velocity by Jongkee’s formula of 0.52, shown in figure 13. The difference between the caloric asymmetry using general linear model repeated measures analysis is <0.001.

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When binaural DC GVS was applied to normal subjects, a similar degree of asymmetry in the perceptual threshold could be experimentally induced. The perceptual thresholds were relatively greater for chair rotations in the direction of the anode, as shown in the figure. This only occurred when the head was flexed forward in the roll plane (t=3.4, Sig =0.08). Ocular thresholds were not obtained in the roll plane as torsional eye recordings in this position could not be obtained.
Figure 14: Perceptual thresholds with GVS in normal subjects in the head up neutral and head down roll plane postures. Perceptual thresholds were increased for chair rotations in the direction of the anode, only when the head was flexed forward into the roll plane. Bars are mean thresholds with standard errors. * t=3.4, Sig 0.08.

Discussion

This is a novel paradigm for determining vestibular perceptual and nystagmus thresholds simultaneously by applying increasing angular accelerations in a limit finding threshold approach. The vestibular perceptual threshold results in the normal subjects are consistent with those reported in the older vestibular psychophysics studies. It is worth remembering that perceptual thresholds are affected by multiple factors, including the experimental set up, instructions to subjects, and the duration of stimulus (Guedry 1974; Rodenburg, Stassen et al. 1981). Vestibular perceptual threshold norms are therefore likely to be accurate only for the specific paradigm they are recorded in.

The inherent coupling of vestibular threshold stimuli (e.g. left versus rightward rotation) gives rise to unique properties for vestibular thresholds compared to many thresholds tested in other sensory systems. This has prompted a recent
reappraisal of signal detection theory (mathematical principles of signal
detection over baseline noise) for the vestibular system, with suggestion of a
specific ‘vestibular bias’ (Merfeld 2011). Currently, application of this theory to
perceptual threshold paradigm design is not straightforward, but this approach
is a current area of interest (MacNeilage, Banks et al. 2010; Mallery, Olomu et al.
2010).

**Perceptual Thresholds in Acute Unilateral Vestibular Dysfunction**

No previous studies have examined vestibular perceptual thresholds in acute
peripheral vestibular lesions. Perceptual thresholds were bilaterally elevated in
the patients with acute unilateral peripheral vestibular impairment, with
relatively little asymmetry.

This is in contrast to the visual system, where loss of one eye produces only
subtle visual deficits rather than a major loss in binocular visual acuity (Steeves,
Gonzalez et al. 2008). The difference is likely to be related to the functional
directional coupling between canal pairs, which make them a *de facto* single
functional unit. Unlike vision or hearing one cannot ‘at will’ suppress the
function of one labyrinth (as in closing one eye). Acute VN produces intense
vertigo, which might interfere with attention to the perceptual threshold task.

Possible contributing explanations for the bilaterally induced perceptual
thresholds include:

1. Increased noise in the cortical signal, due to the acute vertigo, resulting in a
reduced direction-noise signal ration and impaired direction-specific perception.
However this would not account for the reduced asymmetry in the nystagmus
thresholds, compared to the caloric asymmetry.

2. This paradigm applies a low, but increasing, acceleration stimulus. Symmetry
is mostly maintained because this low-frequency stimulus is within the dynamic
range of the ‘off direction’ of the cupula in the intact contralateral side.

3. Reduced attention and concentration in ability to perform the task in the
presence of a distressing acute illness. Additionally, cognitive dysfunction is
thought to be associated with vestibular disease (Smith, Geddes et al. 2010), and
could contribute to the perceptual threshold being raised above that of the elevated VOR thresholds, but again does not explain the reduced asymmetry of the nystagmus thresholds.

4. ‘Perceptual shut-down’ reflecting suppression of vestibular cortical signaling in the context of acute imbalance in the ascending signal. This may be a ‘cortical’ version of the central suppression of brainstem vestibular function observed in early phases of vestibular compensation following a unilateral lesion; reviewed in (Halmagyi, Weber et al. 2010).

It would seem that the finding of a relatively small asymmetry mostly reflects the preserved ability of the contralateral horizontal semicircular canal to detect accelerations both in the ‘on’ and ‘off’ directions. The overall threshold increase may reflect a central suppression of vestibular inputs as a ‘protective’ or ‘compensatory’ mechanism to the disorienting asymmetric perceptual signal perceived as vertigo.

Effects of prochlorperazine cannot be completely excluded, as some of subjects had received this within the previous 24 hours, but only two patients had received medication within six hours to testing. Subjects were tested as soon as they were well enough to tolerate the procedure. It is not possible to depart from routine clinical care, so some antiemetic exposure in human studies is currently unavoidable.

To further explore potential effects of the acute illness itself (here VN) on attention and performance in the perceptual threshold paradigm, testing another clinical group with a non-vestibular acute illness might provide further data on the importance of a specifically vestibular clinical syndrome on perceptual threshold testing compared to other acute clinical conditions. There are pros and cons from studying both neurological and non-neurological disorders. It may be that associations between spatial orientation and attention could be difficult to untangle in this paradigm alone.
The relative lack of perceptual asymmetry has also been found with a high frequency stimulus perceptual paradigm of velocity perception to step rotation (Seemungal, Cousins et al. 2010). The sensitivity of the contralateral healthy canal in the ‘OFF’ direction will be lower at high frequencies, so this result also supports central ‘shut down’ as the mechanism.

**Galvanic Vestibular Stimulation in Normal Subjects**

DC binaural GVS was able to experimentally induce asymmetry in the perceptual thresholds in normal subjects. This argues against an intrinsic property of this threshold paradigm not giving asymmetric results. This induced asymmetry only occurred with the head flexed forward into the roll plane. This is consistent with the dominant vector of DC GVS being torsional (Severac Cauquil, Faldon et al. 2003; Fitzpatrick and Day 2004). By flexing the head forward in the roll plane, the dominant vector of the Galvanic stimulation on the vestibular system is more closely aligned with the axis of rotation for this experiment i.e. roll. As the DC GVS alters the resting discharge rate in the vestibular nerve (Goldberg 2000), the likely mechanism is that the DC GVS-induced change in firing rate combines with the change in the vestibular nerve firing due to the rotational stimulus, to make a vestibular threshold easier or harder to attain. Theoretically this might be possible with the head in the neutral posture, but here modulation of the thresholds was only achieved with the head in the roll plane, optimising alignment of the axes of the rotational and electrical stimuli.

The effects of GVS on eye movements and perception typically decay within 10s. Despite this, the GVS was able to perturb the perceptual threshold in this paradigm. Other forms of Galvanic stimuli have been developed to reduce the decay of GVS effects (MacDougall, Moore et al. 2006). It is not known whether more sophisticated stimuli using varying current would also induce an asymmetry such as is present here.

**Summary**

The novel paradigm developed allows the first recording of vestibular perceptual and nystagmic thresholds to angular acceleration in human subjects with acute
unilateral loss of peripheral vestibular function, acute VN. Subjects with bilateral vestibular failure did not perceive the motion at all; therefore the paradigm assesses only the vestibular system. In subjects with acute VN, the perceptual thresholds are elevated in both ipsilesional and contralesional directions of motion, with less asymmetry than might be expected with severe unilateral loss of peripheral vestibular function. The relative lack of asymmetry in the thresholds could be due to preserved ability of the healthy labyrinth to sense rotation in the on and off canal directions. The bilateral increase in nystagmic and perceptual thresholds is likely to represent an early defense system effectively ‘shutting down’ vestibular input into the CNS in the presence of an acute lesion. This paradigm provides an additional tool to assess the human vestibular system, specifically the perceptual (cortical) system, which may be required to further understand the problem of clinical recovery in vestibular disease. Application to this task is presented in the next chapter.
Chapter Three

Recovery after Vestibular Neuritis

Introduction

This chapter assesses factors that may determine clinical recovery and outcome after vestibular neuritis (VN). An introduction to VN is provided in chapter 1. Brain imaging findings relating to adaptation and central compensation after vestibular dysfunction follows in chapter 4.

Reflex function recovery after Vestibular Neuritis

It is thought that both recovery of peripheral VOR function and ‘central’ brainstem compensatory processes play a role in the improvement in initial acute asymmetry of afferent vestibular signals after VN (Allum and Ledin 1999). Animal vestibular nuclear recordings show evidence of ‘central compensation’ after loss of peripheral vestibular function (Smith and Curthoys 1988; Smith and Curthoys 1988). This compensates for the large initial asymmetry in vestibular afferent signals, and is reflected behaviourally by improvement in both nystagmus and acute imbalance (Halmagyi, Weber et al. 2010), while postural control was shown to improve early in guinea pigs (Curthoys, Smith et al. 1988). The changes in nystagmus early after deafferentation show that ‘central compensation’ occurs in the brainstem, but these animal studies do not give information about central compensation in other locations such as the cerebral cortex.

Caloric testing has been the mainstay of clinical vestibular function testing. Failure of caloric testing to recover to normal after VN has been noted. Perhaps because this occurs in some patients with a poor clinical recovery there has been a pervading assumption that reflex recovery measured by caloric tests was the important measure determining clinical recovery. In relatively recent studies, symptomatic outcome measures have not been included e.g. (Strupp, Zingler et al. 2004).
Most importantly, long-term follow-up studies do not show a good correlation between symptomatic outcome and caloric results (Okinaka, Sekitani et al. 1993; Bergenius and Perols 1999; Kammerlind, Ledin et al. 2005). Therefore, although there are brainstem compensatory processes that reduce afferent signal asymmetry in vestibular afferent activity in the acute phase of VN, reflex measures of the VOR do not correlate with longer-term outcome.

Caloric testing only tests a low frequency component of the VOR, and a high frequency quantitative head impulse test is a complementary higher frequency VOR measure (Perez and Rama-Lopez 2003; Palla, Straumann et al. 2008). The high frequency head impulse test improves with time after VN (Palla and Straumann 2004). (Schmid-Priscoveanu, Bohmer et al. 2001) found abnormalities in the (high frequency) head impulse test in all patients when only 64% had abnormal caloric testing. However a recent study of 47 patients with VN found that like caloric testing, the high frequency VOR does not correlate with clinical outcome (Palla, Straumann et al. 2008). Other abnormalities of reflex vestibular function have been shown to persist, but at lesser rates than for caloric paresis, e.g. vibration-induced nystagmus, head shaking nystagmus and a positive head impulse test persisted (Choi, Oh et al. 2007).

VN predominantly affects the superior division of the vestibular nerve, but can involve the inferior division as well (Aw, Fetter et al. 2001). Otolith function has been investigated as a candidate factor determining clinical recovery. (Tian, Ishiyama et al. 2007) used eccentric yaw rotations after unilateral vestibular deafferentation to surgery and showed a persisting reduction in the contralateral otolith gain to 0.3. By contrast, in 51 subjects with VN, otolith dysfunction improved rapidly and was not found to be predictive of clinical outcome (Kim, Hong et al. 2008). Therefore, although inferior vestibular nerve involvement might produce a more complete initial impairment involving all three semicircular canals and otolith function, the available evidence does not support this as being deterministic in clinical outcome.
Visual Dependency and Visual Verticality

The concept of ‘visual dependence’ is of a variation in sensory ‘style’ with increased reliance on visual clues for spatial orientation, to the point that prominent visual flow can disturb balance. This can be pathological and is associated with vestibular disease. It is presumed that the central compensatory process associated with peripheral vestibular impairment can in some individuals increase susceptibility to certain visual scenes or visual motion. This idea arose from patients with vestibular diseases reporting ‘visual vertigo’: increased symptoms of imbalance and vertigo with moving visual scenes. Examples in every day life include the visual flow of people passing in a shopping street, traffic or trains moving past, or brightly lit supermarket aisles. Acute anxiety or panic attacks do need to be considered as an alternative differential diagnosis in some, as the situations may be provocative for agoraphobia and co-existing anxiety is common. Experimental evidence robustly supports the concept of visual dependency.

(Dichgans, Held et al. 1972) made the seminal report that a moving visual field rotating around the axis of a subject’s line of sight altered the perception of verticality. A target disc tending 32° of visual field was rotated at angular velocities up to 130 deg/s, and the subjects set a target edge to vertical. The magnitude of the effect on perception of verticality, now known as the ‘Subjective Visual Vertical’ (SVV) was in the order of 15°, with one subject reported as having a 40° alteration. Vestibular detection of gravity is usually thought to be related to otolith function, however alterations in SVV can be produced from semicircular canal stimulation (Pavlou, Wijnberg et al. 2003).

(Guerraz, Yardley et al. 2001) showed an increase in SVV in patients reporting ‘visual vertigo’ using a static measure of visual dependence on perception of verticality (Rod and Frame test) and the dynamic ‘Rod and Disc’ measure. The effect sizes were even greater in subjects with bilateral vestibular failure (BVF). As well as assessing verticality, this also induced changes in posturography, again increased in patients with visual vertigo, with a greater effect in subjects with BVF. An earlier study (Bisdorff, Wolsley et al. 1996) tested subjective
postural verticality with subjects in a motorized gimbal, allowing inclusion of vestibular, proprioceptive and postural information as well as vision contributing to assessment of verticality. Patients with unilateral vestibular lesions who had an abnormal SVV did not necessarily have abnormalities of subjective postural verticality. In contrast to subjects with visual vertigo following VN, alterations in SVV with unilateral vestibular loss due to Meniere’s disease were not found (Lopez, Lacour et al. 2006).

As ‘visual vertigo’ is a distressing symptom, it is clearly relevant to symptomatic recovery. Visual vertigo is associated with alterations in the SVV, and visual dependence remains a plausible candidate for reflecting central compensatory processes (for example upregulation of visual signals for spatial orientation), and contributing to clinical outcome.

**Psychological Factors in Clinical Recovery**

The interplay of psychological factors in chronic disease generally, and neurological disease is well established. For example 47% of 300 new patient referrals to neurology clinics met DSM IV criteria for anxiety or depression diagnoses (Carson, Ringbauer et al. 2000). Teasing out cause and effect of these associations from an underlying neurological disorder can be more difficult. Psychogenic dizziness accounted for 9% of patients attending a balance clinic in one report (Ardic and Atesci 2006), yet 45% of all the patients attending this clinic had abnormal psychological scales. This is a very similar proportion to the general neurology clinic and emphasizes that the presence of e.g. anxiety in a patient, does not in itself guide the diagnosis as one of a peripheral vestibular disorder, anxiety-related dizziness or other. There is an emerging literature exploring psychological factors in the specific case of acute vestibular neuritis, mainly from a single group of investigators.

Noting that acute vertigo can trigger acute anxiety, (Godemann, Linden et al. 2004) recorded anxiety levels by the SSTAI (Spielberger State Trait Anxiety Inventory), within two days of onset of VN and again at six weeks. They also
used questionnaires to assess disease coping and personality tools such as the agoraphobic cognitions questionnaire, body sensation questionnaire, and personality disorder and type inventory. Elevated anxiety scores acutely occurred in two thirds of patients with acute vestibular neuritis. The anxiety scores were abnormal, but improved at six weeks, and correlated with apprehension and the fear of physical symptoms. There was no relationship found with VOR function measured by caloric testing.

A longer follow-up period study examined patients at one year, with 29% reporting persisting vertigo (Godemann, Siefert et al. 2005). Dynamic posturography showed abnormalities in only two of 75 patients. Psychological factors were measured with questionnaires including the STAI, agoraphobic cognitions questionnaire, and the body sensations questionnaire (BSQ). Persisting symptoms of vertigo best correlated with body-related anxiety. This suggests that anxiety regarding somatic symptoms contributes to the persisting symptoms of vertigo.

Acute onset vertigo is commonly a traumatic experience with accompanying panic not uncommon, often associated with the assumption of a serious CNS event. One conclusion postulated from this work was that catastrophic thoughts in the early phase predicted outcome (Godemann, Koffroth et al. 2004), but a later report concluded that it is not fear occurring on the first day of vestibular neuritis that is predictive of ongoing problems (Godemann, Schabowska et al. 2006). They suggest that at 1 week, 6 weeks and 6 months after VN, presence of fear regarding vertigo does increasingly predict risk of a longer-term panic or somatoform disorder.

These studies do suggest an important role of anxiety and phobic cognitions in the longer-term outcome after VN. However, as for visual dependence, the relative importance compared to other measures cannot be assessed on the current data.
Summary

After VN, clinical outcome varies. This is independent of reflex vestibular function when measuring vestibular function solely by caloric testing, head impulse testing posturography or VEMPs. The mechanisms of the central compensatory processes (brainstem and possibly cerebral) are not well understood. Psychological factors such as anxiety are prevalent after VN but causality has not been proven for this association. Increased visual dependence may play a role in symptomatic recovery in at least a proportion of patients. Vestibular perceptual function has not been previously assessed after vestibular neuritis.

Reflex vestibular function, vestibular perceptual tests, visual dependency and psychological scores have not previously been combined in a longitudinal study of VN. This chapter describes the first attempt at combining all of these measures in a prospective observational clinical study.

Methods

Recruitment of subjects with acute vestibular neuritis

Approval to recruit patients with acute vestibular neuritis was granted from Charing Cross Hospital A&E department and the Hammersmith Hospitals NHS ethics committee, as well as from Hammersmith Hospital and St Mary’s Hospital, which during this study were merged into the Imperial College NHS Trust. There is no emergency department at Hammersmith Hospital although there is an acute internal medicine service assessing acute community referrals. Given the proximity-related ability to attend rapidly, recruitment efforts focused on the Charing Cross Hospital Emergency Department. This has an approximate catchment of 300 000 people, although other clinical services serve as referral centres for much larger populations covering West London.

Teaching sessions were given to A&E medical staff at 12 weekly intervals, and were timed to coincide with new intakes of junior doctors rotating onto the
service. The teaching included diagnosis of vestibular neuritis, videos of the nystagmus and hands-on demonstrations of head impulse and Hallpike tests. Advertising posters specified simple points on how to diagnose vestibular neuritis, including exclusion if there was any change in hearing or additional neurological signs.

Patients were assessed in the A&E within 2 hours of referral. In the case of a typical history but minimal or no clinical signs, caloric testing was done to determine if a canal paresis was evident. Consent was obtained and the study assessments were scheduled as soon as the patients were well enough to tolerate this. In practice this was when subjects no longer required intra-venous hydration and parenteral anti-emics. As these factors are also favorable for timing of discharge from hospital, testing in the acute phase was usually done en route to discharge from hospital, in the presence of persisting nystagmus, vertigo and imbalance.

Although dynamic posturogaphy is incorporated in some vestibular clinical studies, it was not included in this study given the need to cap the number of assessments for patients suffering from vertigo, and that it is an indirect measure of vestibular function also relying on function of other systems.

**Vestibular Neuritis Subject Assessments**

At acute and follow-up assessments, subjects underwent a battery of tests. These comprised:

1. Clinical vestibular examination
2. Vestibular Perceptual testing
3. Visual Dependency Rod-Disc test
4. Symptomatic Questionnaire Scores
5. Psychological Questionnaire Scores
6. Bithermal Caloric testing
Test times varied and breaks between assessments were given. Including breaks, total assessment time was 90-120 minutes. Follow-up (3 month) assessments were also done.

**Reflex function**

All acute VN subjects required a positive clinical head impulse test for diagnosis and inclusion. Routine caloric testing was done on all subjects, according to standard clinical assessment. This comprised bithermal (30° and 44°) irrigations to both ears. Eye movements were recorded in complete darkness with infra-red oculography. The peak slow phase velocity of the induced nystagmus was recorded. Results for left and right are converted to ipsilesional and contralesional, and are means of the two thermal irrigations to each ear. Asymmetry is produced by Jongkee's formula. Caloric testing was conducted last in each testing session as it required little active cooperation from subjects apart from keeping their eyes open when recording. VEMPs were not locally established at the commencement of this project, but may still have been omitted due to the need to limit total assessment time for acutely vertiginous patients.

**Perceptual function**

The simultaneous perceptual and nystagmus limits threshold paradigm described fully in chapter 2 was done at acute and follow-up assessments. This test was always done first for the patients, to minimize effect of fatigue from undergoing assessment and knowledge that this would modulate the threshold results.

**Visual Dependency**

The Rod and Disc Test (Dichgans, Held et al. 1972) was used to measure visual dependency. This was done using a 16 inch diameter laptop display to allow semi-automated data acquisitions and a degree of portability. Subjects sat in darkness using a chin rest and used a computer mouse wheel to adjust a displayed rod on a dark screen background to perceived vertical. The rod was tilted on an angle of +/- 40°. A disc of luminous dots was either static, or rotated
at 30°/s clockwise or anticlockwise around the rod. To avoid possible clues of verticality from the screen luminosity lighting the laptop case or keyboard, subjects viewed the screen through a cone of diameter 25cm at the head end. A ‘rod and frame’ test as a measure of ‘static’ visual dependency was not utilized as piloting this on the laptop in 12 normal subjects gave only a mean of 0.3° deviations. The laptop rod-disc paradigm was validated in 16 normal and three subjects with bilaterally absent vestibular function. The rod-disc paradigm was effective at inducing altered perception of verticality with a mean deviation of 6.9° in the normal subjects. This was a robust response but less in magnitude than the 9.8° reported in normal subjects using conventional apparatus in (Guerraz, Yardley et al. 2001).

The rod and disc test in the VN subjects was done with four trials in each of three conditions, background dots static, clockwise and anticlockwise rotation. The ‘true visual vertical’ is defined as the mean deviation of the rod with the background static. The ‘dynamic visual vertical’ is the mean deviation induced by the rotating background dots, averaged for the clockwise and anticlockwise rotations.

**Questionnaire Measures**

The Dizziness Handicap Inventory (Jacobson and Newman 1990) is a pragmatic scale assessing perception of handicap with real-world examples. A normalised score 0-4 was used as an overall measure of recovery, with 0-1.3 representing mild handicap, 1.4-2.6 moderate handicap and 2.7-4 severe handicap. However this was developed for and used in the clinical scenario of chronic dizziness. Similarly the Vertigo Symptom Scale (Yardley, Masson et al. 1992) scores frequency of symptoms over specified time intervals, and in this respect it is not designed for, or suitable for the acute scenario. A symptom severity tool for intensity of acute vertigo was not available, therefore, a simple 10 point visual analogue scale was also presented for subjects to grade their subjective perception of their dizziness severity.
The Hospital Anxiety and Depression scale (Zigmond and Snaith 1983) was used as a quick established measure. Scores range from 0 (no anxiety) to 21 (high level of anxiety), with a depression score also from 0-21. The Body Sensations Questionnaire (Chambless, Caputo et al. 1984) measures intensity of fear from body sensations on 17 items, scoring from 17-85. The questionnaire forms are contained in the Appendix.

Results

Clinical Recruitment

Over the first one year of recruitment only 16% of 90 consecutive referrals from the Charing Cross Emergency Department were found to represent definite vestibular neuritis. This figure is not the epidemiology of acute vertigo presentations, but reflects presentations of acute vertigo thought to probably be vestibular neuritis. This does also not reflect the emergency department staff seeking a specialist neurology or neuro-otology opinion for a suspected alternative cause of the vertigo, as this issue was always clearly delineated with the referring doctors. Non-study-recruitment referrals made to the author described as “probably not” vestibular neuritis are excluded.

Table 3 Neuro-otological Diagnosis in Emergency Department Vestibular Neuritis

<table>
<thead>
<tr>
<th>Neuro-otology Diagnosis</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vestibular Neuritis</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>BPPV – ‘posterior canal’</td>
<td>29</td>
<td>32</td>
</tr>
<tr>
<td>BPPV – ‘horizontal canal’</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>History of acute vestibulopathy but normal assessment</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Vestibular Migraine</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Stroke or Vascular Brainstem events</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Meniere’s disease</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Presyncopal dizziness</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Anxiety</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>TOTAL</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

Results in this chapter are presented for the first 16 patients with acute vestibular neuritis at the acute phase and at follow-up. With two patients
excluded it took 17 months and considerable unscheduled clinical assessments to recruit this number. This was likely partly due to an acute neuro-otological clinical service not having existed prior to commencement of this study, and secondly, the rate of accurate referring diagnoses was lower than expected.

Table 3 shows the clinical characteristics of the first 16 subjects with acute vestibular neuritis who attended follow-up. None of the subjects had a history of prior vertigo or CNS disease. Mean age was 49 years (22-69), 8 female. All had a positive head impulse test and the clinical diagnostic criteria described in Chapter 1, including subacute vertigo, nausea and absence of other central signs. None of the patients received corticosteroids for acute VN. Two had pre-existing mood disorders, one currently treated with Risperidone. Eight had received anti-emetics since onset of VN, but none had received this within six hours of testing. Follow-up assessments for this group were done at a mean 73 (range 44-104) days after onset.

Two subjects included no longer had spontaneous nystagmus by the time of first assessment, but had a persisting positive head impulse test and caloric paresis. For the two subjects excluded due to complete lack of follow-up data, telephone contact at 4 months suggests a reasonable clinical recovery with a return to rowing and playing tennis respectively, but quantitative data could not be obtained.
Table 4: Clinical Characteristics of Acute Vestibular Neuritis Subjects. Nystagmus degrees 1st: spontaneous nystagmus with gaze in direction of fast phase, 2nd with gaze neutral as well, 3rd present in all horizontal gaze directions. Medication shows timing in days (d) when received.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>VN side</th>
<th>Nystagmus Degree</th>
<th>PMHx</th>
<th>Medical Treatment Prior to Initial Assessment</th>
<th>Days after VN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>M</td>
<td>L</td>
<td>0</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>M</td>
<td>L</td>
<td>2</td>
<td></td>
<td>Cyclizine 50mg - 3d</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>M</td>
<td>L</td>
<td>1</td>
<td></td>
<td>Cyclizine 10mg - 3d</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>F</td>
<td>R</td>
<td>2</td>
<td></td>
<td>Prochlorperazine -2d</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>M</td>
<td>L</td>
<td>3</td>
<td></td>
<td>Occupation-induced tinnitus</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>F</td>
<td>L</td>
<td>2</td>
<td></td>
<td>Prior Depression</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>56</td>
<td>F</td>
<td>R</td>
<td>2</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>M</td>
<td>R</td>
<td>3</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>27</td>
<td>F</td>
<td>R</td>
<td>2</td>
<td></td>
<td>Prochlorperazine -2d</td>
<td>3</td>
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<tr>
<td>10</td>
<td>66</td>
<td>F</td>
<td>R</td>
<td>1</td>
<td></td>
<td>Cyclizine 50mg, Prochlorperazine 25mg -1d</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>52</td>
<td>M</td>
<td>L</td>
<td>2</td>
<td></td>
<td>Prochlorperazine -1d</td>
<td>1</td>
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<tr>
<td>12</td>
<td>58</td>
<td>F</td>
<td>R</td>
<td>0</td>
<td></td>
<td>Cyclizine &gt;2d</td>
<td>3</td>
</tr>
<tr>
<td>13</td>
<td>61</td>
<td>F</td>
<td>R</td>
<td>1</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>64</td>
<td>M</td>
<td>R</td>
<td>2</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>60</td>
<td>M</td>
<td>R</td>
<td>2</td>
<td></td>
<td>Bipolar Affective Disorder Rx: risperidone</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>31</td>
<td>F</td>
<td>L</td>
<td>2</td>
<td></td>
<td>Prochlorperazine -1d</td>
<td>4</td>
</tr>
</tbody>
</table>

VN Subjects Group Results

Results are described in the text for each measure at acute and follow-up stages using General Linear Model (GLM) repeated measures within-subject analysis, SPSS 19.0, unless otherwise specified. The figures graphically display the complete dataset using boxplots indicating median, quartiles, range +/- outliers.

VOR reflex function

Subjectively, caloric testing was well tolerated by the acutely VN subjects as the vestibular stimulation was not worse than they had recently experienced due to VN. Boxplot of the caloric data shows an expected increase in both the ipsilesional and contralesional responses at follow-up. One subject declined caloric testing at follow-up. Overall mean caloric slow phase velocity acutely is
13.9°/s, SE 1.84°/s) and at follow-up 24.5°/s SE 3.6°/s. There is an expected highly significant improvement in this and in the asymmetry (GLM repeated measures p<0.001 and p=0.009 respectively). Three subjects had a positive head impulse test at follow-up.

Figure 15: Box-plot of mean Peak Slow Phase Velocity of Bithermal (30° and 44°) Caloric Irrigations in acute (n=16) and follow-up (n=15). Median, quartiles and ranges are shown for the boxplots in the following figures.

Vestibular Thresholds: Perception and Nystagmus

As shown earlier in chapter 2, perceptual thresholds were elevated acutely in the VN subjects compared to normals. These elevated thresholds persisted in the VN patients at follow-up. There was no significant improvement in the elevated perceptual thresholds at follow-up (acute versus follow-up ipsilesional perceptual thresholds p=0.110, contralesional perceptual thresholds p=0.946). Ipsilesional nystagmus thresholds were also not significantly changed at follow-up (ipsilesional p=0.046, contralesional p=0.110). The boxplot figures display the overall combined ipsilesional and contralesional magnitude of the perceptual and nystagmus thresholds, and the relative lack of asymmetry in both of these acutely and at follow-up.
Visual Dependency

Acute there was a mean abnormal true visual vertical (static background) of 5.8° (s.e. 1.5°) in the VN subjects. This is consistent with an acute ocular torsion response in VN and improved to 1.2 (s.e. 2.1°) at follow-up (p=0.054). Overall
the acute VN dynamic visual vertical (rotating background measuring visual
dependence) was 7.6 (s.e. 1.7°) acutely and 5.8° (s.e. 1.4°) at follow-up.

Figure 18: Boxplot of Visual Vertical, dynamic and true, in VN subjects, displaying
medians, quartiles and ranges. Normal dynamic Visual Vertical with this laptop display
technique is 2 deg (s.e. 0.34 deg).

Questionnaire Scores

For the VN subjects as a group, all measurements improved at follow-up. Acute
and follow-up mean scores respectively are: Visual analogue score (VAS) 8.7,
1.2, 1.0; Dizziness handicap inventory (DHI) 2.3, 0.61, 0.27; Anxiety component
of the Hospital and Depression Score (HADS) 5.38, 3.25, 1.60; and Body
Sensations Questionnaire (BSQ) 2.7, 2.5, 2.1. The boxplot shows these scores
after all being adjusted to 10 point scale. Of note, the simple VAS shows a
greater relative dynamic change from acute to follow-up than the DHI,
suggesting that the VAS is a good measure of acute symptomatic dizziness.
Figure 19: Boxplot of scores adjusted to a common 10 point scale for both acute and follow-up assessments. Shown are the Dizziness Handicap Inventory (DHI), Visual Analogue Score (VAS), Anxiety component of the Hospital and Depression Scale, HADS, and the Body Sensations Questionnaire (BSQ).

When considering individual outcomes, a plot of individual VN subjects’ DHI and VAS scores shows the VAS is more consistently elevated acutely than the DHI acutely, suggesting it may be a better measure of acute dizziness. At follow-up (green circles) two subjects (6 and 7) had a poorer symptomatic outcome with both raised DHI and VAS scores. However, any degree of disability (DHI greater than zero) may reflect suboptimal recovery.
Figure 20: Scatter plot of individual VN subjects visual analogue score (VAS, x-axis) and the dizziness handicap inventory (DHI, y-axis) normalized to a 4 point scale. The green circles, follow-up, for subjects 6 and 7 had high DHI and VAS scores. The VAS is more consistently high than DHI acutely.

Correlational Analyses of Measures with Symptomatic Outcome

The simple visual analogue score was found to be a simple practical measure that could be used in the acute setting and improved with follow-up, but it is speculative if this is valid as a symptomatic outcome measure. The DHI is an established performance-based questionnaire reflecting clinical recovery, the multiple items give relative robustness, and use of this allows comparison to other studies. As contemporaneous physiological and perceptual measures are available at the follow-up assessment the follow-up DHI is selected as the best symptomatic outcome measure.

There are a very large number of potential comparisons that could be made with the multiple measures in this study, all with some a priori justification. If this were done in an unselected manner, revision of thresholds for statistical significance would be required, such as a Bonferonni correction. Therefore a factor analysis was first done on the entire data set initially to probe correlations in an unbiased fashion (SPSS 19, Data reduction, Factor Analysis using Principal Component Analysis). Two factors were extracted, accounting for 61% and 39%
of the variance respectively. There are highly loaded factors in follow-up for multiple questionnaires, physiological measures, visual dependence, but less heavily loaded factors for the perceptual and nystagmus threshold paradigm.

Table 5: Principal Component Analysis (SPSS 19) Extracted Factors 1 (61% of total variance) and Factor 2 (39% of total variance). Results are means, unless specified as ipsilesional, contralesional or a Jongkee's measure of asymmetry. ‘DHI’ dizziness handicap inventory, 'VAS visual analogue score,'HADs’ Hospital Anxiety and Depression Score, ‘VV’ visual vertical, ‘Cal’ Caloric, ‘ipsi’ ipsilesional, ‘contra’ contralesional, ‘Perceptual’ and ‘Nystagmus’ refer to thresholds.

<table>
<thead>
<tr>
<th>Component Matrixa</th>
<th>Component 1</th>
<th>Component 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Acute DHI</td>
<td>-.220</td>
<td>.975</td>
</tr>
<tr>
<td>Acute VAS</td>
<td>-.984</td>
<td>.176</td>
</tr>
<tr>
<td>Acute HADs</td>
<td>-.133</td>
<td>.991</td>
</tr>
<tr>
<td>Acute HADs (anxiety)</td>
<td>.645</td>
<td>.764</td>
</tr>
<tr>
<td>Follow-up DHI</td>
<td>1.000</td>
<td>.024</td>
</tr>
<tr>
<td>Follow-up VAS</td>
<td>.941</td>
<td>.339</td>
</tr>
<tr>
<td>Acute Caloric</td>
<td>-.906</td>
<td>.424</td>
</tr>
<tr>
<td>Acute Cal Asymmetry</td>
<td>.910</td>
<td>.414</td>
</tr>
<tr>
<td>Acute VV Dynamic</td>
<td>.942</td>
<td>.335</td>
</tr>
<tr>
<td>Follow-up VV Dynamic</td>
<td>.876</td>
<td>-.483</td>
</tr>
<tr>
<td>Acute Perceptual Ipsi</td>
<td>.361</td>
<td>-.933</td>
</tr>
<tr>
<td>Acute Perceptual Contra</td>
<td>-.989</td>
<td>.145</td>
</tr>
<tr>
<td>Follow-up Perceptual Ipsi</td>
<td>-.398</td>
<td>-.917</td>
</tr>
<tr>
<td>Follow-up Perceptual Contra</td>
<td>-.748</td>
<td>.664</td>
</tr>
<tr>
<td>Acute Nystagmus Ipsi</td>
<td>.904</td>
<td>.427</td>
</tr>
<tr>
<td>Acute Nystagmus Ipsi Threshold</td>
<td>.975</td>
<td>.222</td>
</tr>
<tr>
<td>Acute Hads Depression</td>
<td>-.339</td>
<td>.941</td>
</tr>
<tr>
<td>Acute BSQ</td>
<td>.756</td>
<td>.655</td>
</tr>
<tr>
<td>Follow-up HADs</td>
<td>.815</td>
<td>-.580</td>
</tr>
<tr>
<td>Follow-up HADsanxiety</td>
<td>.013</td>
<td>-1.000</td>
</tr>
<tr>
<td>Follow-up Hads Depression</td>
<td>.984</td>
<td>-.176</td>
</tr>
<tr>
<td>Follow-up BSQ</td>
<td>.928</td>
<td>-.373</td>
</tr>
<tr>
<td>Acute Cal ipsi</td>
<td>-.973</td>
<td>-.229</td>
</tr>
<tr>
<td>Acute Cal contra</td>
<td>-.629</td>
<td>.778</td>
</tr>
<tr>
<td>Follow-up Caloric</td>
<td>.050</td>
<td>-.999</td>
</tr>
<tr>
<td>Follow-up Cal Asymmetry</td>
<td>.997</td>
<td>.081</td>
</tr>
<tr>
<td>Follow-up Cal ipsi</td>
<td>-.733</td>
<td>-.681</td>
</tr>
<tr>
<td>Follow-up Cal contra</td>
<td>.537</td>
<td>-.843</td>
</tr>
</tbody>
</table>
Extraction Method: Principal Component Analysis.
2 components extracted.

The correlation matrix for the selected outcome measure of follow-up DHI and candidate alternate outcome measure VAS is shown below. There are high correlations between the DHI and the VAS, along with correlations with the dynamic visual vertical, caloric asymmetry acutely and at follow-up, the BSQ, and follow-up HADS. Perceptual measures were not strongly correlated with follow-up DHI and VAS.

Table 6: Principal Component Analysis Correlation Matrix for Follow-up DHI and VAS.

<table>
<thead>
<tr>
<th>Correlation</th>
<th>Follow-up DHI</th>
<th>Follow-up VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute DHI</td>
<td>-0.197</td>
<td>0.124</td>
</tr>
<tr>
<td>Acute VAS</td>
<td>-0.98</td>
<td>-0.866</td>
</tr>
<tr>
<td>Acute HADS</td>
<td>-0.109</td>
<td>0.212</td>
</tr>
<tr>
<td>Acute HADSanxiety</td>
<td>0.663</td>
<td>0.866</td>
</tr>
<tr>
<td>Acute Hads Depression</td>
<td>-0.317</td>
<td>0</td>
</tr>
<tr>
<td>Acute BSQ</td>
<td>0.771</td>
<td>0.933</td>
</tr>
<tr>
<td>Follow-up DHI</td>
<td>1</td>
<td>0.948</td>
</tr>
<tr>
<td>Follow-up VAS</td>
<td>0.948</td>
<td>1</td>
</tr>
<tr>
<td>Follow-up HADS</td>
<td>0.801</td>
<td>0.569</td>
</tr>
<tr>
<td>Follow-up HADSanxiety</td>
<td>-0.011</td>
<td>-0.327</td>
</tr>
<tr>
<td>Follow-up Hads Depression</td>
<td>0.98</td>
<td>0.866</td>
</tr>
<tr>
<td>Follow-up BSQ</td>
<td>0.919</td>
<td>0.746</td>
</tr>
<tr>
<td>Acute Caloric</td>
<td>-0.895</td>
<td>-0.708</td>
</tr>
<tr>
<td>Acute Cal Asymmetry</td>
<td>0.92</td>
<td>0.997</td>
</tr>
</tbody>
</table>
Acute Cal ipsi -0.979 -0.993  
Acute Cal contra -0.61 -0.327  
Follow-up Caloric 0.026 -0.292  
Follow-up Cal Asymmetry 0.998 0.965  
Follow-up Cal ipsi -0.749 -0.92  
Follow-up Cal contra 0.517 0.219  
Acute VV Dynamic 0.95 1  
Follow-up VV Dynamic 0.864 0.66  
Acute Perceptual Ipsip 0.338 0.023  
Acute Perceptual Contra -0.986 -0.881  
Acute Perceptual Threshold -0.685 -0.881  
Acute Perceptual Asymmetry 0.626 0.841  
Follow-up Perceptual Ipsip -0.42 -0.686  
Follow-up Perceptual Contra -0.732 -0.478  
Follow-up Perceptual Threshold -0.772 -0.934  
Follow-up Perceptual Asymmetry -0.186 0.135  
Acute Nystagmus Ipsip 0.914 0.996  
Acute Nystagmus Threshold 0.98 0.992  
Acute Nystagmus Contra 0.954 1  
Acute Nystagmus Threshold -1 -0.947  
Follow-up Nystagmus Ipsip 0.989 0.892  
Follow-up Nystagmus Contra 0.685 0.418  
Follow-up Nystagmus 0.879 0.682  
Follow-up Nystagmus Asymmetry -0.693 -0.886

Relationships derived from the principal component analysis relating to the clinical outcome measure ‘follow-up DHI’ were then confirmed with bivariate Pearson two-tailed correlation analyses.

Table 7: Correlations with Follow-up DHI. Two-tailed significance levels Pearson correlations, SPSS 19.0.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Acute</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Visual Dependence (dynamic visual vertical)</td>
<td>&lt;0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>Caloric Testing</td>
<td>-</td>
<td>Asymmetry &lt;0.001</td>
</tr>
<tr>
<td>HADS</td>
<td>-</td>
<td>&lt;0.001, anxiety 0.002, depression &lt;0.001</td>
</tr>
<tr>
<td>BSQ</td>
<td>0.046</td>
<td>0.002</td>
</tr>
</tbody>
</table>

As indicated by the principal component analysis correlation matrix, there were not significant correlations between the threshold paradigm perceptual measures and the follow-up DHI in this group.
Discussion

Diagnostic Accuracy of VN and Clinical Recruitment

The low accuracy for diagnosis of vestibular neuritis occurred despite regular teaching on diagnosing acute vestibular conditions, and enthusiasm from the emergency service for the study. Although “Probable Vestibular Neuritis” was sought to gain a sensitive inclusive strategy to recruitment, the relatively low diagnostic accuracy may represent the difficulty for some doctors to rapidly gain the ability to recognise nystagmus characteristics, and the inadequacy of the teaching sessions as a prime strategy. There may be an induced diagnostic bias from the presence of study recruitment posters prompting consideration of vestibular neuritis more often than otherwise would have occurred. Lack of nystagmus recognition by doctors without an interest in eye movements or vestibular function is probably common. In UK hospitals clinical services involved in assessing vertigo comprise emergency medicine, acute medicine, ENT, neurology, audio-vestibular medicine and neuro-otology, dependent largely on local expertise. An anecdote is illustrative on this point: a highly regarded senior consultant neurologist on informal discussion on vestibular clinical examination confesses that although they always performed a Hallpike manoeuvre for their dizzy patients, they did not attempt to identify or define any nystagmus, and would treat for BPPV empirically upon symptoms.

An important finding was the high rate of BPPV that was misidentified as vestibular neuritis, at a rate twice that of correct identification of vestibular neuritis. BPPV is a distressing condition, and often disabling until the bout terminates. As there are quick simple effective treatments available, it is clearly desirable to attempt treatment with a Sermont or Epley manoeuvre in the emergency setting. This avoids individual patient morbidity, as well as social and economic costs awaiting an outpatient clinic or spontaneous resolution of a bout of BPPV. Increased education of emergency and other primary care doctors would seem desirable, given the prevalence of BPPV and dizziness as a presenting symptom (Brandt, Huppert et al. 2006).
An unexpected finding was the 16% of patients who had a typical history for an acute peripheral vestibulopathy, i.e. subacute onset of rotatory vertigo and oscillopsia with nausea +/- vomiting, with no provoking cause, persisting for several hours to a day, which then had improved symptomatically by the time of assessment in the emergency department. They had a normal vestibular clinical examination, and no evidence of a canal paresis on bithermal caloric irrigation. It is not clear what the appropriate diagnosis for this group of patients is. As standard caloric testing only assesses the superior vestibular nerve pathway, and that VEMPs were not done, it is possible that some of this group may have had the less common ‘inferior’ vestibular neuritis. Most vestibular expertise in the UK has clinical contact in the outpatient setting and would not encounter relatively unselected patients in the A&E. It is also possible these patients did have a short lived mild peripheral vestibulopathy, e.g. mild vestibular neuritis, or an early presentation of Meniere’s without auditory features, but this remains speculative unless these patients re-present. It does seem plausible however that on any future retrospective history in an outpatient setting, these patients could be misdiagnosed as having had vestibular neuritis with canal recovery. This is important for any research on vestibular disease, in that clearly it should not rely on classification based on retrospective diagnoses of clinicians, even with vestibular expertise, and that clinical assessment at the time of the acute syndrome might be necessary for accurate diagnoses.

The presence of four patients with ischaemic events in this sample may be potentially concerning. However this is usually the important differential diagnosis to make, and it is impossible to avoid the fact that referring doctors were aware they were receiving a neurological opinion and assistance in requesting urgent MRI scanning, if indicated. Prior to commencing this study, the local neurology service did not frequently attend the emergency department, as generally the acute medicine service would be first involved.

It is possible this did result in less rigorous exclusion of ischaemia prior to referral. This factor does not alone account for the high rates of BPPV that were
not diagnosed prior to referral; as discussed, that is a condition that can, and it is easily argued should, be treated by acute services.

Early in the course of Meniere’s an attack may mimic an acute peripheral vestibulopathy due to vestibular neuritis, but Meniere’s disease was not misidentified as vestibular neuritis in this sample, despite the fact that acute Meniere’s presentations did occur during this recruitment period. This is likely to be related to ready identification of the associated auditory features of tinnitus and/or deafness with Meniere’s attacks. Vestibular migraine, not yet accepted as a distinct entity by the International Headache Society, and all focal neurological symptoms due to migraine, should in practice be a diagnosis of exclusion. The patients classified here all had additional features of migraine, a unilateral retro-orbital throbbing headache, sensory hypersensitivity such as photophobia, or history of recurrent similar episodes. Two of these patients had a horizontal nystagmus lasting 30-60 minutes during the attack.

**VOR Function**

A statistically significant association was found for caloric asymmetry at follow-up in relation to the follow-up DHI. This is surprising, as discussed earlier, other studies with larger numbers have not shown this to be a reliable determinant of clinical outcome. It is still possible that a degree of a caloric paresis is a pre-requisite for some patients to have a poorly compensated suboptimal symptomatic outcome, yet for others with poorer outcome, failure of full peripheral recovery is not reflected in caloric testing alone. It is difficult to make a firm conclusion from this sample size, but it does support continuing to include the clinically standard caloric testing in long-term assessments of these patients to understand the associations further.

**Perceptual function**

The perceptual thresholds improve at follow-up assessment, but are still elevated compared to the normal control group (chapter 2). The persisting increased thresholds after VN might raise the possibility of a persistent change in
cerebral cortical processing of vestibular inputs. Alternatively this may reflect ongoing peripheral dysfunction. It is not clear how much of the brainstem ‘central compensation’ the cortical signal is subject to. It is possible that it bypasses some or all of this, and reflects a more basic measure of vestibular function.

Alteration in perceptual thresholds has not been investigated previously for a ‘natural’ direct vestibular stimulus, i.e. angular acceleration. How these change over the much longer term will be interesting to study, and also in association with other vestibular diseases, e.g. with a fluctuating vestibular deficit. The perceptual threshold measures did not correlate with the selected symptomatic outcome measure. Given this, it is unlikely that this measure will be predictive of outcome in individual VN patients. This does not mean it does not reflect the physiology, as it is possible the vestibular perceptual measure does reflect a part of a central adaptation or compensation after VN, but not a part that is strongly associated with symptomatic outcome; i.e. after VN cortical recovery or adaptation post VN may affect perceptual thresholds, but not be associated with a symptomatically successful, or otherwise, process.

Visual Dependency

There is increased visual dependency acutely which improves, but not to normal, at follow-up. Furthermore, this is significantly associated with symptomatic outcome. There are several possible explanations for this association. For example, in the absence of ‘sensible’ afferent vestibular signals in the acute phase of VN, an acute shift to increased visual dependence for spatial orientation may be an appropriate compensatory strategy. The persistence of this shift in ‘sensory style’ may be an undesirable byproduct of an ‘acute’ response, or alternatively it may reflect an ongoing response to altered vestibular cortical signal processing. The acute visual dependency measure does not necessarily reflect a predisposing tendency to using visual information, such as a ‘sensory style’. The lack of a significant association between the DHI and the perceptual measures does not allow further elaboration on this here.
Psychological Factors

Symptomatic outcome of follow-up DHI was significantly associated with follow-up scores on the BSQ, and both anxiety and depression components of the HADS. The association of anxiety and vestibular dysfunction is well established, and in the specific case of VN. However, as with other measures, determining whether an association is from cause or effect has been difficult to prove.

Most interestingly here, the BSQ *acutely* was significantly associated with the follow-up DHI. The BSQ measures fear and anxiety related to body sensations. It may be that those with a pre-existing tendency to anxiety from bodily symptoms are particularly prone to the trauma of intense acute vertigo. In fact, others have regarded acute vertigo as a trauma capable of producing a post-traumatic stress disorder.

In contrast, the HAD was elevated acutely but not strongly associated with symptomatic outcome. This likely reflects the acute anxiety induced in the acute state. Depression does not have an as strongly established association with vestibular dysfunction, as does anxiety. The presence of two of sixteen patients who had pre-existing mood disorders may have biased the follow-up DHI association result.

Summary

Combining these measures in a single study allows for the first time direct comparison of multiple domains of assessment. The results here suggest an interplay of vestibular dysfunction, visual dependency, anxiety, fear of body sensations associated all being associated with a poorer clinical outcome after VN. The association of raised BSQ and visual dependence might suggest that a predisposing psychological profile, or a tendency to exaggerated visual
dependence may be predictive of symptomatic outcome. This is the first study of a vestibular perceptual threshold after VN, and although it was not found to be significantly correlated with symptomatic outcome in this small cohort, it will be interesting to follow the raised perceptual thresholds over the longer term and with a greater number of subjects.

It must be conceded that the described cohort here is small in number in relation to the number of measures, and to validate models that might accurately describe and be predictive of clinical outcome will require a considerably larger cohort. Fortunately this may be possible, as this longitudinal study continues to accrue subjects.

So far, the brain has been treated somewhat as a ‘black box’. An almost facile statement is that the interactions between psychological factors, visual dependence and symptom reporting will involve cerebral cortical circuits. Exploring the anatomical substrates of the interactions of vestibular, visual and another spatial orienting signal is the subject of the next chapter.
Chapter Four

Multisensory Interactions: Functional MRI of Proprioceptive and Visual Stimuli in Patients with Bilateral Vestibular Failure and Normal Controls

Functional MRI

In the late 20th century functional neuro-imaging has revolutionised neuroscience by providing a non-invasive probe of brain function. The imaging provides a 4-dimensional temporal and spatial map of neuronal activity, by direct or indirect measures. Positron emission tomography (PET) was the initial dominant technique, but along with single-photon emission tomography (SPECT), it has largely been replaced by functional magnetic resonance imaging (fMRI). This is due to the availability of MRI facilities, which are in routine clinical use in the developed world, along with not requiring ionising radiation exposure and better, imaging resolution. The operating energy requirements of MRI are mainly to cool the large electromagnet with liquid helium (Weishaupt, Köchli et al. 2006).

Very briefly, MRI ‘works’ by aligning the axis of proton spins in a resonant state by applying a magnetic field, currently the usual magnitude is 1.5-3 Tesla. A radio-frequency pulse perturbs the ‘spin axis’ of all the protons. Depending on the local molecular environment, the protons will realign their axes of spinning back to that of the applied magnetic field with a variable time course, emitting a weak radio-frequency signal as they lose energy in the process. The 3D location of the emitted weak radiofrequency signal is determined by processing data from the MRI detector. Different imaging sequences are gained by examining
time constants and phase characteristics during a return to an equilibrium state. Broadly, these characteristics also determine the tissue-specific signals within a given sequence. Echo planar imaging (EPI) sequences, commonly used in fMRI, are fast to obtain, which is desirable for gaining temporal data in fMRI. The trade off is a reduced spatial resolution compared to other sequences (Weishaupt, Köchli et al. 2006).

**The Blood Oxygen Level Dependent (BOLD) Signal**

Neuronal activity is measured indirectly with fMRI. This is achieved by detecting an increase in the local blood flow, but perfusion itself is not directly measured. Increasing synaptic activity increases metabolic demand with more oxygenated blood arriving reducing local deoxyhaemoglobin, the latter being paramagnetic and decreasing the local MR signal. The Blood Oxygen Level Dependent (BOLD) signal is overall determined by several factors related to increased local neuronal activity: increased cerebral blood flow, blood volume and a ‘local field inhomogeneity’ induced by deoxyhaemoglobin (Logothetis, Pauls et al. 2001; Logothetis and Wandell 2004). There is typically a 3-4s delay after a stimulus before the BOLD response, in contrast to single neuronal unit potentials which respond much more rapidly (Kim, Ronen et al. 2004). It is thought the production of the BOLD effect is primarily due to neuronal inputs, and processing of these, rather than neuronal output. Supporting the concept that the metabolic demands of processing input potentials drive the BOLD response, it has been found that local cerebral vasculature density correlates with both the number of synapses instead of the number of neurons (Logothetis and Wandell 2004), and also the magnitude of the fMRI signal (Harrison, Harel, Panesar 2002).

The haemodynamic response function (HRF) describes the time course of the BOLD signal after a stimulus. The magnitude of the change is only 5% in the motor cortex compared to the background signal. There is an initial reduction correlating with consumption of oxygen, followed by a large compensatory increase in local cerebral blood flow. The shape of the HRF curve may vary
between subjects, and may be modelled in different ways (Huettel, Song et al. 2004). The signal is averaged over multiple 'runs' of fMRI data acquisition to detect the BOLD signal over the background noise.

Functional MRI Experimental Design

FMRI experiments can be designed in block or event related designs. Blocked designs compare an experimental condition to a control condition. The blocks have fixed duration of a stimulus, and the HRF generally does not return to baseline during the stimulus. This design gives greater power in detecting differences in a given brain voxel in 3D space. The disadvantage is that blocked designs do not well describe the temporal change in activity. Event related designs can do this and estimate the shape of the HRF. For a short (<2s) stimulus, an inter-stimulus interval is typically 12-14s to allow the HRF to return to baseline. The timing of activity in different brain regions may also be inferred, but event related designs have a relatively reduced detection power compared to block designs (Huettel, Song et al. 2004).

fMRI Signal Pre-processing

Data requires processing before statistical analysis to remove artefacts and minimise noise. Artefacts and noise can be generated due to movement from head motion, blood flow, or breathing. There can also be within-subject variability due to fatigue. Pre-processing prepares the fMRI data for statistical comparisons in relation to the stimuli or ‘contrasts’, and involves three main processes:

1. Realignment: All images are realigned to a reference slice, using six parameters of rotation and translation. This ideally corrects for changes in head position, but not changes in head shape (Lazar 2008).

2. Normalisation: So that the functional data can be mapped to the structural images, the images are aligned by a rigid body transformation. Because of inter-subject variability in brain shape, the images are scaled to a standard stereotaxic
brain space. Standard brain templates are available for this, such as the widely used Montreal Neurological Institute templates.

3. Smoothing: To improve signal to noise ratio the difference in MR signal is smoothed between adjacent voxels.

**Statistical Analysis:** General Linear Model (GLM)

fMRI analysis involves a linear regression to be performed at every single voxel, the GLM involves modelling the BOLD signal time course at every voxel to the expected time course from a given stimulus or confound. A weighting parameter is calculated for each voxel at each time point to minimise a sum of squares difference between the modelled and measured signal (analogous to standard linear regression). The GLM is most elegantly expressed as a vector equation

\[ Y = X\beta + \varepsilon \]

with 'N' time points and 'p' regressors. X is an 'N x p' matrix, 'Y' and 'ε' being column vectors of height N, and 'β' a column vector of height p. X is the design matrix, where each column represents a stimulus in the experiment, which can be a stimulus condition or confounder. When \( \beta N \) is significantly greater than zero, then that voxel has a significant activation from a stimulus. The design matrix can be set up to compare differences between two signals, and can be visualised graphically by displaying the numerical values in a grey scale image.
Figure 21: Design matrix for modeling two stimuli in the columns to the general linear model. Time progresses downwards vertically. The position of the red line corresponds to the colour intensity, modelling the predicted signal value.

www.fmrib.ox.ac.uk/fsl/feat5/glm.html

‘Contrasts’ of interest are specified (e.g. presence of a given stimulus in relation to a control stimulus), and a statistical parametric map is generated. This is a graphical representation of the statistical analysis performed at each value, shown as a t or F-statistic. Local peaks of activation are defined by the highest statistical value and number of voxels within a region. A ‘first level’ analysis is performed for each subject, and a second level analysis allows between-group analyses (Lazar 2008). An issue of controversy in fMRI over recent years is what the appropriate level of statistical significance should be. A single fMRI experiment may easily make more than 100 000 comparisons, producing potential false positives. A more stringent threshold of significance e.g. 0.01 instead of 0.05 carries the risk of not revealing true effects, but will have less false positives. Several approaches are proposed to limit false positives. These include avoiding uncorrected thresholds, using a ‘false discovery rate’ as an alternative to Gaussian statistics, and combining an intensity threshold with a spatial threshold, i.e. the number of neighbouring voxels at a given level of significance (Bennett, Wolford et al. 2009; Lieberman and Cunningham 2009).
Vestibular fMRI

Vestibular cerebral cortical projections

Relatively little is known about vestibular cortical areas compared to the processing of other sensory symptoms, such as vision. The parieto-insular vestibular cortex (PIVC) is thought to be the main vestibular region in non-human primates, but multiple areas are activated from thalamocortical vestibular afferents and indirect projections. Along with the PIVC, areas activated directly or indirectly include the ventral intraparietal area (VIP), somatosensory cortex (area 2v, 3av), intraparietal sulcus, caudal inferior parietal lobe (area 7), area MST, motor cortex (area 4), cingulum and hippocampus.

In humans an exclusive primary vestibular cortical region has not yet been identified. This raises the possibility that human vestibular cortical areas all may be multimodal or ‘polysensory’. Human cortical areas have been identified by functional imaging utilizing galvanic e.g. (Lobel, Kleine et al. 1998) or caloric stimulation, or with acute imbalance in ascending vestibular signals after peripheral or brainstem vestibular injury. Vestibular cortical areas identified include the posterior insula and tempo-parietal junction (analogous to the PIVC), the posterior parietal cortex, somatosensory cortex and premotor cortex including the frontal eye fields. A recent review summarizes all of the current human and non human studies in detail (Lopez and Blanke).

Structural grey matter changes measured by Voxel-based morphometry have also been found in subjects with vestibular disease. In patients with bilateral vestibular failure there was hippocampal atrophy (Brandt, Schautzer et al. 2005) and increases in the primary somatosensory cortex and in the medial temporal gyrus (Helmchen, Klinkenstein et al.). The hippocampal atrophy in humans was associated with impaired spatial memory performance, which has been experimentally found in rats with bilateral vestibular nerve sections, as well (Baek, Zheng et al.). This opens questions on the wider cognitive implications of vestibular injury, which may also be relevant to variable clinical recovery in humans. The grey matter increases found by (Helmchen, Klinkenstein et al.)
2011) are suggested to directly reflect ‘multisensory compensation’ for the vestibular injury. After vestibular neuritis, a unilateral peripheral vestibulopathy, an increase in the gray matter of the medial vestibular nucleus was found along with relative atrophy of the left hippocampus. With residual unilateral vestibular dysfunction, there was an increase in the visual motion area V5 / MT (zu Eulenburg, Stoeter et al.), supporting an increased dependence on visual motion processing. This may be an anatomical correlate of visual dependency, as discussed in the previous chapter.

**Visual-Vestibular Interactions demonstrated with fMRI**

FMRI studies have shown a ‘reciprocal inhibition’ of visual and vestibular systems (Brandt, Bartenstein et al. 1998; Dieterich, Bense et al. 2003; Dieterich, Bauermann et al. 2007). Visual stimulation gave bilateral activations of a visual network with bilateral deactivations of cortical areas representing vestibular network. The visual motion activations were increased in avestibular, compared to healthy subjects (Dieterich, Bauermann et al. 2007). Conversely vestibular stimulation deactivated visual cortical areas(Bense, Stephan et al. 2001; Dieterich, Bense et al. 2003). Subjects with unilateral vestibular failure also had lesser activation from visual motion optokinetic stimulation using fMRI (Deutschlander, Hufner et al. 2008).

This ‘reciprocal inhibition’ may allow resolution of apparently contradictory sensory inputs, and also may be central to the compensation process after loss of sensory inputs contributing to balance, spatial orientation and gaze stability.

One study distinguishing perception of self motion additional from visual motion stimuli during fMRI gave expected activations in visual motion cortical areas, but with the addition of the cerebellar nodulus (Kleinschmidt, Thilo et al. 2002). The roles of the cerebellum in resolving interacting vestibular, visual motion and other sensory signals of head position, such as proprioception, is also not yet clear. A more recent study using vestibular galvanic stimulation activated human motion sensitive visual cortex MST (but not the adjacent MT) in darkness. MST may be more associated with optic flow, perception of self motion (Smith,
Wall et al.). Therefore vestibular stimulation may not consistently deactivate visual motion cortical areas, but at least interacts with these visual processing areas.

**Neck Proprioceptive Cerebral Cortical Projections**

In non-human primates neck muscle proprioceptive afferents have been shown to modulate activity in Parieto-Vestibular Insular Cortex (PIVC), 3a, and the Lateral Intraparietal Cortex. Tracer injection studies have shown further projections to areas separately shown as having ‘polysensory’ inputs, including the ventral intraparietal area (VIP), Frontal Eye Field (FEF) and somatosensory S2 (Akbarian, Grusser et al. 1992; Guldin, Akbarian et al. 1992)

In humans two functional brain imaging studies have been done with vibratory stimulation of muscle spindle afferents. A PET study showed increased blood flow in somatosensory S2 and the medial insula(Bottini, Karnath et al. 2001), and an fMRI study showed similar activations along with a networks involving the intraparietal sulcus, motor, premotor and frontal eye fields (Fasold, Heinau et al. 2008). These coincide with areas found to be part of the vestibular networks in both humans and other primates.

**Cervical-Ocular Reflex**

In addition to the well known vestibular-ocular reflex there is a lesser known cervico-ocular ‘neck-eye’ reflex, which can be induced by head movement, or by vibrating neck muscles, e.g. rotators such as sternomastoid, splenius capitus and some trapezius fibres. Generally, vibrotactile stimulation of tendons or muscles can induce ‘kinesthetic’ illusions(Goodwin, McCloskey et al. 1972). Neck muscle stimulation in particular gives a proprioceptive signal of relative head to trunk body position, and can induce illusions of body tilt, body rotation, or visual motion and impaired pointing to visual targets (Biguer, Donaldson et al. 1988). These illusions are more prominent in darkness in the absence of stabilizing visual input.
Nystagmus is also induced with neck vibration, with torsional, horizontal and vertical components. The vector of the nystagmus varies when vestibular function is absent. The vibratory stimulus is not inadvertently stimulating the vestibular organs, as these effects are not only present but up-regulated when vestibular function is reduced (Bronstein and Hood 1986; Bronstein, Mossman et al. 1991; Karlberg, Aw et al. 2003). The associated illusion of altered orientation in space is proposed to be likely due to a central modification of spatial orientation rather than brainstem mechanisms, as the amplitude of the induced nystagmus is 1°, but the illusory displacement of the ‘subjective straight ahead’ is 6° (Popov, Lekhel et al. 1999).

**Multisensory compensation**

Spatial orientation, balance and gaze stabilization involve processing of signals from multiple sensory systems including vestibular, visual and proprioceptive signals. How and where these complementary sensory signals are integrated and processed in the human brain has not been fully elucidated. Multisensory compensation is thought to occur after altered afferent inputs, and is likely to play a role in clinical recovery after injury to a sensory system. Understanding these processes may help explain why clinical recovery can be variable after injury to a sensory system, e.g. after unilateral peripheral vestibular loss, as detailed for vestibular neuritis in chapter 1.

In summary there is a convergence of vestibular and proprioceptive human in cerebral cortical areas. These areas are modulated by visual motion stimuli, with a visuo-vestibular reciprocal inhibition established. How the proprioceptive head position signal interacts with the other systems is not known. Unraveling the roles of these sensory systems, all contributing to balance, gaze and spatial awareness, in ‘multi-sensory’ central compensation has theoretical and practical implications for understanding clinical recovery following vestibular lesions.
Rationale of fMRI Experiment

Based upon:

1. There is an established visual-vestibular ‘reciprocal inhibition’.
2. Cortical neck proprioceptive signals are also likely to interact with visual motion and vestibular signals due to overlapping cortical projections of neck proprioceptive and vestibular signals, and also simply as a virtue of being another sensory system contributing to balance and self-orientation.
3. Proprioceptive head positional signals (both brainstem reflexive and perceptual) are upregulated in patients with vestibular loss.

It therefore follows that alterations in processing of proprioceptive signals may not just be an independent adaptive response to vestibular loss, but that proprioceptive signals might also interact with visual motion processing, in visual motion cortical areas. This would effectively be an extension to the known vestibular-visual interactions.

The specific hypothesis to be tested in the fMRI experiment that follows is that patients with stable end organ bilateral vestibular failure will have an altered interaction between proprioceptive head position and visual motion cortical signals.

Methods

Subjects

12 subjects with absent vestibular function were recruited from neuro-otology clinics with a mean age of 51 (range 29-67) years, 6 female. Absent vestibular function was established for more than 9 months in all cases, and determined by absent clinical vestibular reflexes (head impulse test, ocular counter-roll) and by less than 5°/s peak slow phase nystagmus velocity on bithermal (30°C and 44°C) caloric irrigation, corresponding to approximately 10% of the normal response. The cause of bilateral vestibular failure was aminoglycoside exposure (6) and idiopathic (6), (Rinne, Bronstein et al. 1995). Fifteen control subjects with no
vestibular or neurological deficits had a mean age of 46 (range 25-72) years, 3 female). One control subject was excluded after an incidental posterior fossa arachnoid cyst was found on structural MRI. All subjects, vestibular and normal controls, were fully right handed, as determined by the Edinburgh Handedness Inventory. The Hammersmith Hospitals NHS Trust Ethics Committee approved this study.

**Data acquisition for fMRI**

MRI was done using a Siemens 3 Tesla scanner with a 32-channel head coil. T1 Magnetization Prepared RApid Gradient Echo (MPRAGE) structural images were acquired for each subject, voxel size 1 x 1 x 1mm. For the functional study EPI scans of the whole brain were done (TR=2s, slice thickness 5mm). A functional run consisted of 10 volumes for each of four conditions, with four runs completed (160 volumes in total). Baseline EPI were acquired with fixation on a simple centred light visual dot target on a dark background before the first, and after the final and fourth runs, as an additional control.

**Visual Motion and Neck Proprioceptive fMRI Stimuli**

An angled mirror on the MRI head coil directed view to a 42-inch LCD monitor mounted 2.5m behind the subjects’ heads in the scanner, giving a horizontal field of view of 21°. Vertical black and white stripes (7 black, 7 white, each subtending 0.67°) were displayed in conditions static (S), and motion (M), tracking horizontally at 6°/s in the M condition. The direction of motion was left to right on the LCD screen, but subjects viewed this motion via the head coil mounted mirror as right to left.

To apply a neck muscle proprioceptive stimulus in the MRI environment a custom Dacron and Nylon vibrotactile stimulator was developed to avoid use of any metal or otherwise electromagnetic components. This utilized the air input, air turbine rotor and air output from a recently developed MRI limb positioning device (Elhawary, Zivanovic et al. 2008). The turbine rotor was connected
directly to an axle attached with an eccentric Dacron ‘weight’, housed in a 26mm diameter 52mm long cylinder (Figure 22). The eccentric fixation of the Dacron ‘weight’ causes the device to vibrate at a frequency dependent on the airflow and pressure. The device was powered by the high-pressure medical air supply, which was directed via the MRI control room to allow adjustments to the required airflow.

The device was optimized by applying it over the right splenius captius of seated normal subjects in a dark room, looking at a red point light source. Development of the device included adjusting the shape and length of the axle and distal end to allow this to be applied to the left splenius capitus and trapezius muscles in subjects with a head coil applied. The eccentric weight (Dacron) in particular required fine-tuning in positioning and size to generate appropriate frequencies and amplitude of vibration. Physiological responses were found in normal subjects seated in a dark room with deviation of perception of light position and ‘subjective straight ahead’ occurred at 100Hz, not at 30Hz, as well as perturbation of self-orientation. It was not technically possible in the MRI environment to record neck vibration-induced nystagmus with available equipment. When applied to subjects the vibrotactile device displacement produced was 0.4mm for both the high H and low L frequency conditions, and the frequency and amplitude of the vibration produced was checked offline with an analogue accelerometer before and after subjects. A second back-up device was made to insure against mechanical failure, but was not required.

Prior to MRI scanning, the vibrotactile device was applied to subjects prior to acquisition to gain familiarity with the device and the stimulus. The vibrating end of the device was taped over left splenius capitus and then vacuum pads secured it into place inside the head coil. Additional vacuum-moulded pads were used to securely immobilize the head to prevent additional vibration-induced head movement. An increased volume of noise produced by the air turbine in the H compared to the L condition was mitigated by the background noise of the fMRI scanner during acquisition, but could not be completely controlled for due to bone conduction of sound.
The same frequency stimulus was applied to all subjects and subjects were not screened for magnitude of subjective responses; noting subjective perceptions induced by the vibrotactile stimulus were expected to be less during this experiment than in other reports done in darkness e.g. (Fasold, Heinau et al. 2008) due to light being required for the simultaneously applied visual motion paradigm.

Figure 22: Schematic cutaway of dacron and nylon constructed air turbine driven device to provide a vibrotactile stimulus in the MRI environment.

The proprioceptive stimulus was applied to the right neck to align the anticipated horizontal component of slow phase eye movement with the visual stimulus motion. The visual motion paradigm was written in C/C++ and presented to the LCD monitor via a laptop visual display output. Airflow regulation was adjusted manually with timing signals from the laptop.
fMRI Experimental Design

The visual stimuli M and S were applied in a factorial design with the H and L vibrotactile stimuli to give four conditions: MH, SH, ML, SL representing visual motion 100Hz vibration, visual static 100Hz vibration, visual motion 30Hz vibration, visual static 30Hz vibration respectively. These are shown in the figure below. A block design was used, with blocks of length 20 seconds for each condition. One run consisted of a single block of each of the four conditions presented in a pseudorandomised order, i.e. four blocks in total. The total experiment consisted of four runs, resulting in a total of four blocks of each condition presented.
**Optokinetic stimulus**

<table>
<thead>
<tr>
<th>Proprinoceptive Stimulus</th>
<th>Motion (M)</th>
<th>Static (S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100Hz (H)</td>
<td>MH</td>
<td>SH</td>
</tr>
<tr>
<td>30Hz (L)</td>
<td>ML</td>
<td>SL</td>
</tr>
</tbody>
</table>

Figure 24: Factorial Design of Proprioceptive and Visual Motion Stimuli

**Functional MRI Analysis**

fMRI data were analyzed using the FSL software package, specifically the random effects general linear model tools, FEAT version 5.98 (Smith, Jenkinson et al. 2004). Standard image pre-processing was done (realignment, normalization and spatial smoothing to 6mm). Temporal high-pass filtering was done at 0.02 Hz to correct for baseline drift in the signal. FMRIB’s Linear Image Registration Tool was used to register EPI functional datasets into standard MNI space using the participant’s own T1 1mm structural images. FMRI data were analysed using voxel-wise time series analysis within the General Linear Model (GLM). The design matrix used a standard hemodynamic response function for modeling. Blocks from the four conditions (MH, SH, ML, SL) were modeled in the design matrix for each run. A factorial analysis of variance (ANOVA) investigated effects of visual motion, proprioceptive input and group effects using FMRIB’s Local Analysis of Mixed Effects (Beckmann, Jenkinson et al. 2003). Analysis was first done for a 2x2 factorial analysis for each of the two subject groups (patients and normals), before doing between-group comparisons. Final statistical images were thresholded using Gaussian Random Field based cluster inference with a threshold of Z>2.3 and a cluster significance threshold of p<0.05.

**Voxel-based morphometry analysis**

Voxel-based morphometry analysis was done on the structural images using FSL-VBM (Ashburner and Friston 2000; Good, Johnsrude et al. 2001; Smith, 2004).
Jenkinson et al. 2004). T1 structural images were brain-extracted using BET (Smith 2002), tissue-type segmentation was carried out using FAST4 (Zhang, Brady et al. 2001). The resulting grey-matter partial volume images were then aligned to MNI152 standard space using the FSL registration tool FLIRT (Jenkinson and Smith 2001). Images were averaged to create a study-specific template, to which the individual grey matter images were then re-registered. The segmented images were smoothed at 3 mm and thresholded at t of 2.3. A voxel-wise GLM was applied using permutation-based non-parametric testing, correcting for multiple comparisons across space.

Results

Effect of Visual Motion

Main Effect: The main effect of visual motion ((MH + ML) > (SH + SL)) gave a similar pattern of activation in the vestibular patients and controls, see figure 24. Activation was observed in the occipital lobe, with peaks in the lingual gyrus, occipital pole bilaterally, intracalcarine cortex and the inferior part of the lateral occipital cortex bilaterally. Bilateral activation was present in motion-sensitive visual cortex V5/MT, as expected (Malikovic, Amunts et al. 2007). Direct whole brain comparison of the two groups showed no statistically significant differential activation.

The reverse effect of visual motion ((SH + SL) > (MH + ML)) shows regions where activation was greater when the static visual stimulus was presented. Overall there were again no significant between-group differences on direct comparison. In the vestibular patients, activation was greater in the superior temporal gyri bilaterally, as well as in the left parietal operculum. In the normal controls, similar activations were seen in the parietal and temporal lobes, with peaks in the right planum temporale and parietal operculum, as well as the left supramarginal gyrus. In addition, a significant activation was present in the midline and left cerebellum VI in the controls.
**Figure 25: Main Effect of Visual Motion:** Activation in the figure is shown for visual motion versus static \((\text{MH} + \text{ML}) > (\text{SH} + \text{SL})\) in controls (A) and patients (B). Bars on the right represent parameter estimates for the four conditions: MH, ML, SH, SL. These are measured in a 10mm diameter sphere centred at the peak voxel of the contrast for patients (MNI coordinates -18, -90, 12) and controls (-6, -92, -2). The results are superimposed on the MNI 152 T1 2mm brain template. Left (L). The colour bars show the Z scores represented on the activation maps with a significance threshold of Z=2.3 and a cluster threshold of \(P<0.05^3\).

**Table 8: Activation Cluster Local Maxima : Main Effect of Visual Motion.** Z statistic is followed by MNI coordinates of the maxima.

<table>
<thead>
<tr>
<th>Local Cluster Maxima</th>
<th>Z</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Occipital Fusiform</td>
<td>5.3</td>
<td>-16</td>
<td>-78</td>
<td>-10</td>
</tr>
<tr>
<td>Right Lateral Occipital</td>
<td>4.61</td>
<td>46</td>
<td>-70</td>
<td>-2</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Lateral Occipital</td>
<td>5.41</td>
<td>46</td>
<td>-76</td>
<td>4</td>
</tr>
</tbody>
</table>

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3 Thanks to Dr David Sharp and Dr Greg Scott, Imperial College London, for assistance with fMRI results figure production.
Table 9: Activation Cluster Local Maxima: Reverse Effect of Visual Motion. Z statistic is followed by MNI coordinates of the maxima.

<table>
<thead>
<tr>
<th>Local Cluster Maxima</th>
<th>Z</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right planum temporale</td>
<td>4.05</td>
<td>60</td>
<td>-16</td>
<td>8</td>
</tr>
<tr>
<td>Cerebellum, Left VI</td>
<td>3.49</td>
<td>-26</td>
<td>-58</td>
<td>-26</td>
</tr>
<tr>
<td>Left opercular</td>
<td>3.42</td>
<td>-54</td>
<td>-16</td>
<td>10</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left superior temporal</td>
<td>3.94</td>
<td>-56</td>
<td>-10</td>
<td>0</td>
</tr>
<tr>
<td>Right superior temporal</td>
<td>3.89</td>
<td>62</td>
<td>-22</td>
<td>12</td>
</tr>
</tbody>
</table>

Avestibular patients show a reduced response to visual motion during high proprioceptive input.

There was a significant group difference when the effect of different levels of proprioceptive input on visual responses was examined. For the main effect of proprioception ((MH + SH) > (ML + SL)), a high level of proprioceptive input was associated with less activation of visual cortical regions in the patients with vestibular loss. This suggests an inhibitory interaction between the two modalities. Less visual activation during the high proprioceptive stimulus was observed in parts of the medial occipital lobe, with peaks of deactivation within the intracalcarine cortex and occipital pole. No modulation of lateral visual areas, including V5/MT, was observed for the overall effect of proprioception. Reduced visual activation was also observed when proprioceptive input was high in the right ventromedial prefrontal cortex and midline cerebellar regions. The reverse contrast ((ML + SL) > (MH + SH)) demonstrated that high levels of proprioceptive input were associated with increased activation within the temporal poles and orbitofrontal cortex bilaterally in the patient group.

In the control group, changing proprioceptive input did not affect visual responses. The direct contrast between patients and controls for the contrast ((MH + SH) > (ML + SL)) confirmed that the effect of high-levels of proprioceptive input on visual cortical responses was significantly greater in the
patients than controls. A greater reduction of visual response was seen in midline occipital regions, including the intracalcarine cortex and occipital pole. In patients, midline and left lateralized cerebellar responses were also reduced by high proprioceptive input.

In controls, high proprioceptive input was associated with right lateralized reductions of activation in the post-central gyrus, the paracingulate gyrus and the superior temporal sulcus. Increased activation for this contrast was observed within the left inferior temporal region.

Figure 26: Reduced visual response in the context of high levels of proprioceptive input in avestibular patients. Brain regions shown where activation is significantly less in the patients compared to controls for the main effect of high versus low proprioceptive input ((MH + SH) > (ML + SL)).

<table>
<thead>
<tr>
<th>Cluster Local Maxima</th>
<th>Z</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right occipital pole</td>
<td>3.32</td>
<td>22</td>
<td>-100</td>
<td>8</td>
</tr>
<tr>
<td>Cerebellar vermis</td>
<td>3.28</td>
<td>0</td>
<td>-52</td>
<td>-36</td>
</tr>
</tbody>
</table>

Table 10: Local Maxima for activations in avestibular patients with high versus low proprioceptive input.

Visual Motion area V5/MT responses to moving stimuli are influenced by proprioceptive input in avestibular patients
In lateral occipital regions including visual motion sensitive cortex V5/MT the effect of high levels of proprioceptive input was only observed in patients in the context of visual motion. This was demonstrated by the interaction between visual motion and proprioception ((ML+SH) > (MH+SL)), which showed an asymmetric pattern of activation in lateral parts of the left occipital pole and the inferior part of the lateral occipital cortex, with differential activation specifically seen within V5/MT. In addition, activation for this interaction was observed in the cerebellar vermis and left cerebellar hemisphere, particular in left VI (Fig. 26 and Table 12). This interaction effect was the result of significantly less visual cortical activation associated with visual motion when proprioceptive input was high, demonstrated by the contrast ML > MH. For this contrast, extensive activation was observed in the left lateral occipital cortex including V5/MT, closely overlapping with the interaction effect. Additional differences in activation were also observed within the intracalcarine cortex bilaterally and the occipital pole on the right, in keeping with the main effect of proprioception described above. Differences in cerebellar activation similar to the interaction effect were also observed in this contrast.

In the patient group, the effect of proprioceptive input on visual responses to static stimuli was confined to medial occipital regions. The contrast of high and low proprioceptive input in the context of static visual input (SL > SH) was associated with activation in the intracalcarine cortex and medial occipital pole, in keeping with the main effect of proprioceptive input. The reverse contrast (SH > SL) showed no significant activation within visual regions.

In contrast to the patients, controls showed no significant interaction between motion and proprioceptive input within occipital regions, suggesting a heightened responsiveness to proprioceptive input in the vestibular patients. Although the direct group contrast for the interaction ((ML+SH) > (MH+SL)) showed no significant differences using a stringent whole brain correction, a more lenient uncorrected threshold of $P<0.001$ did show left lateralized group differences in activation within the lateral occipital pole, the inferior part of the lateral occipital cortex and the inferior temporal gyrus. In addition, when the
varying levels of proprioceptive input in the context of visual motion were compared across the groups, activation differences were present using standard whole brain correction. The contrast of ML > MH showed a greater reduction in cortical response to visual motion in the patient than control groups, a result which overlapped closely with the interaction difference between the groups. Peaks of differential activation were seen around the intracalcarine cortex, the inferior temporal gyrus and the lateral occipital cortex.

Figure 27: Interaction between visual motion and proprioceptive input in vestibular patients. Plots of the parameter estimates for the four conditions in patients and, for the purpose of illustration, in controls using a 10mm diameter sphere centred at the peak voxel of the interaction in patients (MNI coordinates -22,-92,10). Radiological convention for left and right is used, i.e. left brain appears on the right side of the displayed axial image.
Table 11: Activation Cluster Local Maxima for Interaction of ML + SH > MH + SL

<table>
<thead>
<tr>
<th>Cluster Local Maxima</th>
<th>Z</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left lateral occipital cortex</td>
<td>3.81</td>
<td>-36</td>
<td>-76</td>
<td>8</td>
</tr>
<tr>
<td>Cerebellar vermis</td>
<td>3.68</td>
<td>4</td>
<td>-50</td>
<td>-32</td>
</tr>
<tr>
<td>Cerebellum, left VI</td>
<td>3.67</td>
<td>-10</td>
<td>-72</td>
<td>-24</td>
</tr>
</tbody>
</table>

Figure 28: Reduced visual response to visual motion stimulus in avestibular patients. Brain regions showing less activation in patients than controls for the contrast of high versus low proprioceptive input in the context of visual motion simulation (MH > ML).

Table 12: Activation Cluster Local Maxima for MH > ML in avestibular patients.

<table>
<thead>
<tr>
<th>Cluster Local Maxima</th>
<th>Z</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left lateral occipital cortex</td>
<td>3.41</td>
<td>-18</td>
<td>-84</td>
<td>20</td>
</tr>
</tbody>
</table>

Voxel based morphometry results

Voxel based morphometry analysis of cortical structure showed no significant differences between the patient group with bilateral vestibular loss (n=12) and the normal control (n=15) group.
Discussion

The key findings are:

1. Similar activations present for the main effect of visual motion in both avestibular patients and controls, i.e. a visual-vestibular interaction was not directly observed during this experiment.

2. A high level of proprioceptive input was associated with less activation of visual motion-induced cortical activation in the avestibular patients, suggesting an inhibitory interaction between visual motion and proprioception.

3. Differential activation due to visual motion in the presence of a high proprioceptive stimulus in the avestibular patients was lateralized, in the left lateral visual processing areas encompassing V5/MT, left cerebellum VI and present in the cerebellar vermis.

4. Normal controls did not show a significant interaction between visual motion and proprioceptive input in occipital cortex, suggesting an increased response to proprioceptive stimuli in the avestibular group.

5. No significant structural differences were seen between the groups using voxel-based morphometry.

Proprioceptive and Visual Motion Stimuli Interact

A new interaction between proprioceptive and visual motion stimuli using fMRI is demonstrated here combining both stimuli in a factorial experimental design. The presence of this interaction between visual motion and high neck proprioception in the avestibular patients shows that the effect of high levels of proprioceptive input on visual cortical responses is dependent on the type of visual processing occurring. The interaction identified is in the dorsal visual stream, and is lateralized. The area encompasses motion sensitive visual cortex areas MT and MST. Involvement of visual processing areas is consistent with activations and deactivations using vestibular stimuli in previous studies (Dieterich and Brandt 2008). Upregulation of a proprioceptive signal in avestibular patients is consistent with earlier physiological studies (Bronstein...
and Hood 1986), suggesting the cervico-ocular reflex may at least partially take on the role of the VOR in vestibular failure, as a compensatory mechanism. What has not been shown before is the demonstration of an interaction of a cervical proprioceptive and visual motion signal in avestibular patients.

The interaction also confirms that the effect of increased proprioceptive input is not an artifact of physical movement generated by the stimulator, as its effect on V5/MT and other lateral occipital regions was dependent on the presence of visual motion.

Animal data lend some support to the anatomical location of such interactions occurring in visual processing areas rather than in primarily vestibular or proprioceptive areas (as noted earlier, vestibular and neck proprioceptive stimuli activate shared areas). Earlier neuronal recording studies in monkeys had shown neurons around the lateral sulcus, encompassing the Parieto-insular vestibular cortex (PIVC) responded to vestibular stimulation (Grusser, Pause et al. 1990; Grusser, Pause et al. 1990.) Some of those cells were reported to show convergent somatosensory and visual motion inputs. However, more recent neuronal recording in Macaque monkeys shows again responses in PIVC neurons to vestibular stimulation, but in contrast did not find evidence of visual – vestibular integration occurring in the PIVC (Chen, DeAngelis et al. 2010). The same group has however identified vestibular-visual interactions in several visual processing areas examined (Chen, DeAngelis et al. 2010; Chen, DeAngelis et al. 2011b; Chen, Gu et al. 2008).

The laterality of the interaction in the visual processing areas shown here could conceivably be related to the specific vectors of the visual motion stimulus (right to left) and the proprioceptive stimulus, which was designed so that the horizontal component of slow phase eye movement would be congruent with the slow phase eye horizontal movement of the visual stimulus. However the dominant eye movement from a neck proprioceptive stimulus is torsional, which is difficult to combine with a simple visual motion paradigm. Alternatively,
there may be functional specialization of the left and right dorsal visual
processing streams for resolving these two sensory systems. This is in keeping
with vestibular networks also showing lateralization to the right side, in right
handed individuals (Dieterich and Brandt 2008).

The interaction in the cerebellar vermis is intriguing, as the vermis is integral to
vestibular processing and perception of self motion (Bronstein, Grunfeld et al.
2008). An interaction involving proprioceptive stimuli here is supportive of a
role for the cerebellum as an anatomical locus for converging sensory inputs and
perhaps as a relay station for perceptual inputs onwards to the cortex.

There have been only two earlier functional studies, one with fMRI, assessing the
effects of neck vibration with brain fMRI (Fasold, Heinau et al. 2008). Important
to the design of this paradigm is that low frequency vibration (~30Hz) induces
little or no movement illusion in the subjects whereas higher frequency vibration
(100-140Hz) more consistently does so. This was used here in the factorial
design as the low frequency vibration provides a superficial tactile control
stimulus with much less proprioceptive activation. In the (Fasold, Heinau et al.
2008) study the authors preselected the stimulus response by tuning the
stimulus frequency in order to maximize the effects of neck vibration and
therefore the fMRI findings. Differences in subject and frequency selection may
partly explain differences in observed activations. This fMRI study was also
done in darkness and it is possible that there were some fMRI signal effects
observed related to the vibration-induced nystagmus, which are larger in the
absence of visual fixation (Popov, Lekhel et al. 1996).

The MH>ML contrast (figure 28) signal includes some white matter. This may
represent an artefact of motion realignment or spatial normalization during EPI
image pre-processing.

The four runs took 12 minutes 40 seconds; the optimal number of runs and
duration of this paradigm is not known. Habituation effects can not be excluded
in this experiment. Any such effects however will not account for the key
interaction result given the factorial design and pseudorandomisation of the conditions across the runs.

**Structural Grey Matter Analysis with Voxel Based Morphometry**

In contrast to previous studies voxel based morphometry did not show a group difference in cortical anatomy between patients with vestibular loss and normal controls (Brandt, Schautzer et al. 2005). Two studies have shown cortical changes after unilateral vestibular loss, i.e. presence of asymmetric vestibular signals (zu Eulenburg, Stoeter et al. 2010; Helmchen, Klinkenstein et al. 2011). Both the patient group studied in this chapter and the one earlier study of subjects with bilateral vestibular loss (Brandt, Schautzer et al. 2005), had stable vestibular loss meeting accepted physiological criteria. However, the 10 subjects in (Brandt, Schautzer et al. 2005) are described as having acquired bilateral vestibular loss due to shwannoma surgery, and presumably many of the subjects in that study, if not all, will have had Neurofibromatosis type 2. One subject is reported as having complete bilateral deafness, but all subjects may have had some associated, often significant, hearing loss. None of the avestibular subjects in this study had prior neurosurgery, having acquired vestibular loss due to gentamicin toxicity or the syndrome of idiopathic vestibular failure. Regardless of whether differences in patient characteristics between the studies explains the differing result, at least in this experiment the absence of major differences in cortical anatomy suggests that the group differences in fMRI activations are not attributable primarily to altered cortical anatomy.

**Cerebral Adaptation and Compensation**

Balance, eye movements and spatial orientation are controlled by multiple input sources, including visual, proprioceptive and vestibular. A degree of overlap between these inputs allows the central process of compensation to develop. When one of the sensory channels is damaged by disease the remaining inputs can be re-weighted and able to take over some of the functions lost. An example
is the increase in the potency of the cervico-ocular reflex (or neck-eye reflex) following bilateral damage to the vestibule-ocular reflex (Bronstein 1986) which allows for some degree of gaze stability during head movements. Similarly, the influence of vision on postural control (Guerraz and Day 2005) and spatial orientation (Bisdorff, Wolsley et al. 1996) increases markedly after bilateral vestibular loss. Evidence indicates that the cerebellum plays a role in mediating the cervical input reweighting (Bronstein, Mossman et al. 1991) and, in agreement, only the avestibular patients showed a significant fMRI interaction between visual motion and neck vibration proprioceptive signals.

**Conclusions**

Proprioception also interacts with visual motion signals, with differential effects in normal subjects and patients with acquired bilateral vestibular loss. The overlap of visual motion, proprioceptive and vestibular cortical areas identified in humans and other primates is consistent with the concept of ‘polysensory’ cortical networks responsible for spatial orientation, balance, self-motion perception where these signals are interacting. The novel fMRI interaction demonstrated here in only the avestibular subjects represents an aspect of adaptation or compensation. Localizing a fMRI interaction involving a proprioceptive stimulus to a lateral visual processing area represents an interesting new advance in understanding adaptation after loss of vestibular function.
Chapter Five
Concluding Remarks

Aspects of central adaptation after peripheral vestibular injury are investigated in this thesis. Understanding these processes better may help determine variable clinical outcome, and to develop more effective treatments and rehabilitation strategies. The research presented makes the following advances:

1. Validation of a novel vestibular perceptual threshold paradigm is in patient groups, and by perturbation with GVS in normal subjects, which can be used in subjects with acute vertigo.
2. Determining vestibular perceptual thresholds in acute vestibular neuritis patients, which are bilaterally elevated with less asymmetry than is present with reflexive brainstem measure.
3. Combining the above measure of vestibular perceptual function with those of visual dependence, brainstem reflex function and psychological features in a longitudinal study, to delineate the role of these candidate factors determining clinical outcome after vestibular neuritis. The results suggest high levels of fear and anxiety regarding body sensations present acutely may be predictive of poorer outcome, and other factors develop in association with poorer recovery.
4. Defining a new anatomical correlate of adaptation after peripheral vestibular loss, by demonstrating a fMRI interaction of proprioception and visual motion, which in lateral visual processing cortex occurs in vestibular patients and not healthy controls.

Vestibular Perception

The elevated perceptual thresholds in patients after vestibular neuritis, suggests these are a valid measure of cortical vestibular processing but were not found to be predictive of clinical outcome vestibular neuritis patients at follow-up. Despite this, they likely reflect alterations in cortical vestibular processing.
rather than merely attention effects. It is not possible on the current data to support a specific relationship between vestibular perceptual function as presented in the threshold paradigm here, and overall clinical function and balance.

As vestibular inputs are normally perceived with complementary information from other sensory systems, and are not usually consciously perceived in the absence of disease, it may be that there is value in testing multiple sense function simultaneously. Conventional vestibular psychophysics occurs in experimental conditions of relative ‘sensory deprivation’, i.e. in darkness and with sound masking, to allow exclusive measurements of vestibular function. It might be possible to measure perception of self-orientation, such as thresholds to angular position, in the presence of proprioceptive, visual and vestibular signals, which could be selectively perturbed in factorial designs by tools employed here e.g. vibration to proprioceptive signals, GVS to vestibular inputs and virtual reality goggles to vision.

**Recovery after Vestibular Neuritis**

As there is not certainty yet on which factors determine outcome after peripheral vestibular injury such as vestibular neuritis, the approach presented here of combining the symptomatic, physiological, visual dependency and psychological factors in a prospective longitudinal study is required.

The association at follow-up of clinical outcome with caloric asymmetry is not surprising, although it is clear from multiple earlier studies cited that this is not a good correlate. The finding here could be due to it being contributory in a proportion of patients who both have a residual canal paresis, and compensate poorly.

The association of clinical recovery with visual dependence is consistent with the concept of ‘visual vertigo’, increased reliance on visual cues for spatial orientation in some poorly recovered patients. The association of outcome
correlating with high visual dependence present acutely is less clear, and a predisposing tendency to increased reliance on visual information for orientation is also possible.

Anxiety and depression are common in neurological, chronic, and vestibular disease, and the emergence of this at follow-up is not surprising. Acute phase anxiety or mood scoring did not predict outcome at follow-up.

Interestingly, the Body Sensations Questionnaire acutely was associated with clinical outcome at follow-up. In the context of a first episode of acute vertigo, anxiety regarding this seems a reasonable and rational response. However, the BSQ is measuring the propensity to anxiety and fear from a range of body sensations, many of which are likely to represent benign phenomena. Therefore, it is possible this association represents a predisposing propensity to be alarmed by ongoing abnormal vestibular sensations during the process of recovery. It is possible this induces a behavioral response that interferes with an optimal recovery, such as minimizing exposure to head motion.

Experienced vestibular specialists may already intuitively recognize this and may actually reflect this in their current clinical practice, e.g. taking special care to provide very strong reassurance to particular patients recovering from acute vertigo due to vestibular neuritis.

Conclusions regarding causation of clinical outcome after VN should be interpreted with a degree of caution given the sample size n=16. The associations reported here should be revised or refined with a future larger cohort.

**Structural and functional MRI changes after vestibular loss**

Although the negative voxel based morphometry result here does not agree with the single study showing differences between avestibular patients and normal controls, (Brandt, Schautzer et al. 2005), this earlier study used subjects after resection of bilateral vestibular shwannomas, so subjects will also have involved
auditory loss. This limits interpretation of their findings regarding vestibular loss. The lack of grey matter changes in the study presented here suggests the functional changes evident between the avestibular patients and normal controls in the fMRI are not primarily due to structural modification, specifically the proprioceptive signals interacting in lateral visual cortex.

Numerous further fMRI experiments utilizing factorial designs can be envisaged to further probe the interactions between the sensory systems contributing to balance and orientation. Varying the vectors of apparent motion of the stimuli are natural next steps. The lateral occipital visual processing areas, as well as other visual processing areas are now strong candidates for loci of integration of polysensory inputs relating to balance and self-orientation. These can be examined further, and event-related fMRI experiments may allow identification of hierarchical activation of networks. Longitudinal fMRI studies after loss of vestibular function could also show the time course of such adaptive changes reflecting compensation.

**Conclusion**

Human balance and spatial orientation rely on multiple senses. This thesis demonstrates that to better understand the adaptive processes after injury to peripheral vestibular function, it is necessary to acknowledge interactions that include not only visual motion signals, but also proprioceptive function. Such central adaptive processes are likely to reflect clinical recovery, but a causative role is yet to be demonstrated. Future experiments are suggested by the results presented here, specifically to further explore multisensory interactions and relationships to clinical recovery, which are outlined in the final chapter.
Chapter Six

Further Directions

Several new areas of research are suggested by the work in this thesis. These are listed below, grouped by the topics described in the thesis.

Perceptual Thresholds

The dynamic changes in vestibular perceptual thresholds after vestibular neuritis warrant further study and will be examined further in a larger cohort with continuing recruitment in the longitudinal vestibular neuritis study. Although not correlating with clinical outcome in the work presented here, they remain a candidate for a contribution to outcome, perhaps in certain subsets of patients, for example those with and without preserved brainstem reflex function. This should be examined when the cohort is numerically larger.

Galvanic Vestibular Stimulation was a useful tool to experimentally induce asymmetry in the vestibular perceptual thresholds in healthy subjects. However, there are several characteristics that mean this is not easy to employ in a routine clinical setting. The complex physiological effects on spatial orientation and ocular-motor control make simple interpretations of effects difficult and care must be taken administering electrical current.

Vestibular perceptual thresholds are by necessity determined with masking of other sensory information (they are performed in darkness with sound masking and physical barriers to minimize somatosensory cues). Trying to assess the vestibular cortical signal (and the integration of this with other sensory signals) in a ‘natural’ situation in humans is challenging. Given the inherent characteristics of most vestibular psychophysics (done in an artificial sensory-deprived testing environment), it may be that a combination of animal studies and further human fMRI studies are now the strongest candidates to advance the vestibular cortical signals, especially with respect to integration of multiple sensory signals.
Prospective Longitudinal Study in Vestibular Neuritis

Longitudinal Prospective studies are usually necessary to best determine clinical outcome. They can be resource intensive, requiring significant time in recruitment and assessment. The number of measures used needs to include all those that may contribute to outcome, but is practically limited by what is reasonable for unwell patients to undergo, and the statistical problems of using a large number of measures.

A standard approach in this situation is that associations from an initial study will need to be confirmed in a second independent cohort or study, employing only the relevant measures for the validating study. This will take several years more, but is a robust method to avoid false-positive findings.

Epidemiology of Acute Vertigo

In retrospect, given the time spent in the emergency department in assessing potential subjects, it is apparent that it would be highly feasible to conduct a more formal survey of acute vertigo presenting to the emergency room. This would be of value as there is a surprising paucity of epidemiological studies in common vestibular disorders.

It would also be most interesting (after ethical approval) to ascertain the clinical course of the patients with acute vertigo who were not diagnosed with acute vestibular neuritis and for whom no clear diagnosis was established.

Functional MRI

Further similar factorial fMRI designs may be able to tease out the characteristics of the interaction found here, with stimuli representing different effective vectors of motion.
The factorial design employed here is very useful for examining interactions between sensory systems. There are numerous further studies that could be conducted to investigate the nature of these interactions. Many experiments could be done in normal subjects, and then specific interactions examined in certain clinical populations, such as poorly recovered vestibular neuritis.

In this study, the vector of the slow phase eye movement induced by the proprioceptive stimulus in normal subjects was designed to be congruent with the eye movement induced by the visual motion stimulus. Further experiments with factorial designs should be done to explore the relationship between laterality of the visual and proprioceptive stimuli. This is of particular interest because of the laterality of the interaction identified in this thesis.

Combining proprioceptive (to left and right splenius capitis, high and low) stimuli with visual motion (left, right and static) in a factorial design would yield 4x3 = 12 conditions. This would need to be split into separate experiments to acquire adequate volumes of each condition.

Additionally, vestibular stimulation could also be combined with these stimuli as well. Caloric may be most suitable for normal subjects, rather than those with reduced vestibular function, where the vestibular cortical signal would be affected by the lack of normal vestibular function. Caloric irrigation into both left and right ears, with control irrigations of 37 degrees, increases the number of conditions by a factor of 4.

Auditory spatial orientation has not been considered in this thesis, but this may also interact with the other spatial senses. Collaborating with scientists established in this field may be required to develop physiologically realistic auditory stimuli that are suitable for the noisy MRI environment.

After determining fMRI characteristics of identified interactions, their presence, modulation and relevance to human disease should be explored. A priority would be to look at clinical scenarios in which outcome is variable and unpredictable, such as in vestibular neuritis.
Several additions would strengthen future similar fMRI experiments to confirm that the physiological effects of the stimuli are present during the acquisition. Eye recording ‘on-line’ with MRI compatible eye-tracking goggles would confirm expected nystagmus (optokinetic, vibration-induced or caloric vestibular).

**Clinical Relevance**

To know if a given fMRI result, such as the interaction shown in Chapter 4, might reflect a good, bad or neutral adaptive response after injury or disease, prospective fMRI studies could be done. For example, after loss of vestibular function due to Gentamicin, the time course and evolution of the interaction found here in Chapter 4 here could be correlated with the clinical status, to determine if the fMRI interaction is required for good clinical compensation, or is simply a ‘bystander’. Knowing this may also open up novel rehabilitative strategies: if an interaction between neck proprioception and visual motion is required for healthy adaptation, then it can be hypothesized there may be a role for stimulation of neck muscle proprioceptive afferents with mechanical vibration as part of a treatment strategy.

Envisaged experiments following on from this work could comprise a significant program of research over many years.
References


Appendix

Questionnaire Measures of Symptoms and Psychological Factors

Vertigo Visual Analogue Scale (VAS)

Please mark the severity of your vertigo on the line below. ‘10’ is the worst you can imagine, ‘1’ is if you can only just notice it.
Dizziness Handicap Inventory, DHI (Jacobson and Newman 1990)
The purpose of this scale is to identify difficulties that you may be experiencing as a result of your dizziness. Please answer Yes, No or Sometimes. Answer each question as it pertains to your dizziness only.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>Sometimes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does looking up increase your problem?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Because of your problem, do you feel frustrated?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Because of your problem, do you restrict your travel for business or recreation?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Does walking down the aisle of a supermarket increase your problem?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>5. Because of your problem, do you have difficulty getting into or out of bed?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>6. Does your problem significantly restrict your participation in social activities such as going out to dinner, going to movies, dancing, or to parties?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>7. Because of your problem, do you have difficulty reading?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>8. Does performing more ambitious activities like sports, dancing, household chores such as sweeping or putting dishes away increase your problem?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>9. Because of your problem, are you afraid to leave home without having someone with you?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>10. Because of your problem, have you been embarrassed in front of others?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>11. Do quick movements of your head increase your problem?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>12. Because of your problem, do you avoid heights?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>13. Does turning over in bed increase your problem?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>14. Because of your problem, is it difficult for you to do strenuous housework or yard work?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>15. Because of your problem, are you afraid people may think you are intoxicated?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>16. Because of your problem, is it difficult for you to go for a walk by yourself?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>17. Does walking down a sidewalk increase your problem?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>18. Because of your problem, is it difficult for you to concentrate?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>19. Because of your problem, is it difficult for you to go for a walk around your house in the dark?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>20. Because of your problem, are you afraid to stay home alone?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>21. Because of your problem, do you feel handicapped?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>22. Has your problem placed stress on your relationship with members of your family or friends?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>23. Because of your problem, are you depressed?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
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<td>24. Does your problem interfere with your job or household responsibilities?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
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<td>25. Does bending over increase your problem?</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
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Body Sensations Questionnaire, BSQ (Chambless, Caputo et al. 1984)

Below is a list of specific body sensations that may occur when you are nervous or in a fearer situation. Please mark down how afraid you are of these feelings. Use the following five point scale:

1. not at all  2. somewhat  3. moderately  4. very  5. extremely

......frightened by this sensation.

Please rate all items.

<table>
<thead>
<tr>
<th>Item</th>
<th>1</th>
<th>2</th>
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<th>4</th>
<th>5</th>
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</thead>
<tbody>
<tr>
<td>1. heart palpitations</td>
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<td>2. pressure or a heavy feeling in chest</td>
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<td>3. numbness in arms or legs</td>
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<td>4. tingling in the fingertips</td>
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<td>5. numbness in another part of your body</td>
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<td>6. feeling short of breath</td>
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<td>7. dizziness</td>
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<td>8. blurred or distorted vision</td>
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<td>9. nausea</td>
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<td>10. having &quot;butterflies&quot; in your stomach</td>
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<td>11. feeling a knot in your stomach</td>
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<td>12. having a lump in your throat</td>
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<td>13. wobbly or rubber legs</td>
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<td>14. sweating</td>
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<td>15. a dry throat</td>
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<td>16. feeling disoriented and confused</td>
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<td>17. feeling disconnected from your body: only partly present</td>
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<td>18. other (please describe)...............................................</td>
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Hospital Anxiety and Depression Score (Zigmond and Snaith 1983)

Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week (or since your illness started if less than a week). Don’t take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

Please tick appropriate statement in response to the following questions –

1. I feel tense or 'wound up':
   - Most of the time
   - A lot of the time
   - Time to time, occasionally
   - Not at all

2. I feel as if I am slowed down:
   - Nearly all of the time
   - Very often
   - Sometimes
   - Not at all

3. I still enjoy the things I used to enjoy:
   - Definitely as much
   - Not quite so much
   - Only a little
   - Not at all

4. I get a sort of frightened feeling like 'butterflies in the stomach':
   - Not at all
   - Occasionally
   - Quite often
   - Very often

5. I get a sort of frightened feeling like something awful is about to happen:
   - Very definitely and quite badly
   - Yes, but not too badly
   - A little, but it doesn't worry me
   - Not at all

6. I have lost interest in my appearance:
   - Definitely
   - I don't take as much care as I should
   - I may not take quite as much care
   - I take just as much care as ever

7. I can laugh and see the funny side of things:
   - As much as I always could
   - Not quite so much now
   - Definitely not so much now
   - Not at all

8. I feel restless as if I have to be on the move:
   - Very much indeed
   - Quite a lot
   - Not very much
   - Not at all
9. Worrying thoughts go through my mind:
   A great deal of the time
   A lot of the time
   From time to time but not too often
   Only occasionally

10. I look forward with enjoyment to things:
    A much as I ever did
    Rather less than I used to
    Definitely less than I used to
    Hardly at all

11. I feel cheerful:
    Not at all
    Not often
    Sometimes
    Most of the time

12. I get sudden feelings of panic:
    Very often indeed
    Quite often
    Not very often
    Not at all

13. I can sit at ease and feel relaxed:
    Definitely
    Usually
    Not often
    Not at all

14. I can enjoy a good book or radio or TV programme:
    Often
    Sometimes
    Not often
    Very seldom