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The mechanisms and loci of human vestibular perception

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Abstract

This thesis' primary aims were to characterise the *what*, *where* and *how* of vestibular cortical processing. A secondary aim was to assess the effects of early visual deprivation on vestibular perception, in particular the *what* and *where*.

The *What*: Using an angular vestibular navigation paradigm with physiological range stimuli, we quantitatively demonstrated that healthy subjects were able to actively reproduce spatial and kinetic parameters of a passively travelled trajectory (displacement, time, velocity and acceleration). Early blind subjects showed no deficit in the perception of raw vestibular signals but were relatively impaired in more complex spatial vestibular navigation tasks. Congenitally blind subjects did not show the normal prolongation of the vestibular signal coming from the labyrinth (i.e. velocity storage mechanism) at perceptual level and two blind subjects who had superior navigational ability also had ultra-short vestibular time constants. Based upon a questionnaire assessment of these subjects, we concluded that frequent exposure to specific activities (e.g. down-hill skiing for one subject!) may be protective in allowing a normal navigational capacity in these subjects. The mechanism for the ultra-short time constants and their role in superior navigational performance remains unclear.

The *Where*: Using repetitive transcranial stimulation (rTMS) to the right posterior parietal cortex we disrupted the perceptual encoding of vestibular signals during a passive yaw-plane rotation. We found no effect of rTMS on vestibular encoding with occipital cortical stimulation in sighted or blind subjects.

The *How:* We hypothesised that vestibular signals may be encoded via an internal model at perceptual level. Using a novel paradigm, we found that by perturbing the internal estimate of displacement of a previously travelled trajectory (yaw plane rotation), we could alter the perception of motion duration but not velocity, of the rotation, a finding consistent with our hypothesis.

The last experiment in this thesis was developed in an attempt to bridge the gap between brainstem and perceptual vestibular function. We quantitatively show that brainstem thresholds to angular acceleration are lower than for cortical (perceptual) thresholds. The hypothesis that we aim to test in the future is that patients who show a large dichotomy between brainstem and cortical thresholds to angular acceleration may be either objectively compromised by worse balance function or subjectively worse as defined by their symptoms of dizziness and disorientation.

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Lastly a huge thank you to my wife Maria whose support has allowed me to do all of this, and to my children, Lara and Luca who make me keep it all in perspective.

Contents

Figures

Tables

Abbreviations

Avor	Angular VOR
BA	Brodmann area
CTC	'Complete The Circle' (a path completion vestibular navigation task.)
DVN	Dorsal vestibular nucleus
ECS	Electrical cortical stimulation
EEG	Electroencephalograph
GBS	'Go Back to Start' (a path reversal vestibular navigation task.)
IPS	Intraparietal sulcus
MVN	Medial vestibular nucleus
OBE	Out-of-body experience
OKN	Optokinetic nystagmus
PET	Positron emission tomography
PIVC	Posterior insular vestibular cortex
PPC	Posterior parietal cortex
rTMS	Repetitive transcranial magnetic stimulation
SRT	Self-rotation test
TPJ	Temporo-parietal junction
VIM	Nucleus ventrointermedius
VIP	Ventral intraparietal area (in the parietal cortex)
VPLs	Nucleus ventroposterior lateralis pars superioris
VOR	Vestibular-ocular reflex
VPLo	Nucleus ventroposterior lateralis pars oralis

Chapter 1

INTRODUCTION

The Universe in which we live is bounded by the laws of physics and, as physical beings, we can sense some of its properties. Of the multiple dimensions that characterise the Universe, we can perceive three physical spatial dimensions and possess a sense of linear time. From the dimensions of space and time we can derive measures of velocity, acceleration and thus force. This thesis explores how the brain utilises vestibular stimuli in perceiving space, motion and time and where in the brain might such percepts be processed.

Perceiving motion and space

Vision and audition relay information about the environment to the brain whilst the vestibular system relays information about self-motion. Thus spatial dimensions of the environment can be constructed by the visual and auditory systems in a remote sense, i.e. the observer need not move through the environment to sense its structure. On the other hand, the vestibular system cannot participate in the 'remote' sensing of the environmental structure since it detects head accelerations. The inability of the vestibular

system to construct a 'remote' or environment-based percept of space is due to its independence of external cues unlike the visual and auditory systems.

In the pre-modern era, philosophers considered the act of perceiving a special sense to be an active process (Plato, 427 – 347 B.C.) culminating in the Kantian philosophy of an internal construction (not reconstruction) of external reality (Kant, 1781). With the introduction of the scientific method to biology, scientists described the 'passive' role of the special senses. Johannes Müller (1801 – 1858) showed that the act of seeing occurred only when the optic nerve was externally stimulated and was not due to the internal production of light. Von Helmholtz (1878) argued that perception was a combination of a passive process in line with the Müllerian Law of Specific Nerve energies (1826) but also of an internal active reconstruction by the brain. Current theories of perception would agree with Helmholtz's view. In any case, the early idea of a purely active sensorium is embedded in our language with verbs like to see or to hear. In contrast to the relationships between the traditional special sensory organs and their senses, the role of the vestibular organs in detecting head acceleration was never quite so obvious. As a result there are no verbs to describe what we do with our vestibular apparatus. Thus vertigo, predominantly a pathological sensation, has no equivalent verb. This is an important omission in our vocabulary since the vestibular apparatus is the only organ which can signal self-motion in absolute space. In contrast the visual and auditory systems signal self-movement with respect to an external reference frame.

When faced with a large moving visual scene we initially *see* object movement and if we choose to, we can visually track it using smooth pursuit, but then we may *vestibulate* (feel movement). This visually-induced vestibulation called vection, is mediated by the convergence of visual inputs onto vestibular neurons (Dichans & Brandt, 1972; Waespe & Henn, 1977) and is just one example of the symbiotic relationship between visual and vestibular cues in analysing dynamic motion signals. Thus whilst visual input can engender a sense of movement, it effects this action by utilising the mechanics of the vestibulatory machine.

Like dynamic motion signals, spatial dimensions can be accurately derived by visual or vestibular information. Whilst static spatial dimension may be obtained directly from visual input, spatial dimensions cannot be directly obtained from vestibular signals but must be derived. It is not known if the complementarity that exists between vision and vestibular signals in processing dynamic stimuli also pertains to the static spatial domain. Thus is the conversion from dynamic vestibular input to spatial dimension dependent upon visuospatial mechanisms? Part of the answer to this question may be found in this thesis. It may be that visuospatial mechanisms can be used but are not *sine qua non* in this regard since other sensory modalities may be utilised for calibrating space derived from vestibular input in absolute dimensions. In addition, the necessity for calibrating vestibular-derived space in absolute units is dependent upon the type of spatial dimension. Thus when vestibular signals are used for the simplest form of navigation such as a single segment homing, then the spatial dimension may be in abstract units. This means that in some situations, there need not be any cross-modal sensory interaction

between the vestibular system and other 'spatially sensitive' sensory systems, for successful spatial navigation. In more complicated forms of navigation, then appropriate cognitive strategies must be utilised when navigation using absolute spatial dimensions is required.

Vestibular signals at perceptual level

This thesis will demonstrate both qualitatively and quantitatively, that angular displacement, velocity, acceleration and motion duration are all encoded at perceptual level. Prior to this there was only quantitative evidence for angular displacement and only semi-quantitative for angular velocity and motion duration. It has not been previously demonstrated that angular acceleration reaches perceptual level. It is known that all of these signals are present at brainstem level (Hess, 2001). The question is whether all of these signals ascend to perceptual level veridically or might there be some further supra-brainstem processing? Current evidence indicates that the velocity storage mechanism is present at perceptual level and that there is a strong correlation between VOR slow phase velocity and perceptual time constants for the velocity storage mechanism (Okada et al., 1999). This strongly suggests that for the velocity storage mechanism at least, there is no further supra-brainstem processing.

What questions does this thesis strive to answer?

(1) What vestibular signals are processed at perceptual level?

Evidence will be presented to show that motion duration and head angular velocity, displacement and acceleration are all present at perceptual level.

(2) How is vestibular-derived space encoded at perceptual level?

Is there simply a veridical transmission of brainstem-derived position signals or is there some additional perceptual processing? Evidence is provided for the perceptual encoding of angular motion signals via an internal model. The concept of a supra-brainstem neural integration in deriving perceived displacement is discussed.

(3) Is there objective evidence for a dichotomous processing of vestibular signals between brainstem and perceptual systems?

We assessed this by simultaneously measuring perceptual and VOR (vestibulo-ocular reflex) thresholds to angular acceleration. As a separate but related question, we considered whether age-related changes in the dichotomy between vestibular-derived brainstem and perceptual signals could explain increased postural instability in some elderly patients.

(4) What is the role of the visual system in the perceptual processing of vestibular signals?

The perceptual processing of vestibular signals in congenitally blind subjects is compared to that in sighted subjects. This thesis will show that congenital blindness does not affect the perception of raw vestibular signals. True spatial navigation using only vestibular input is worse in some, but not all congenitally blind subjects. Early blind subjects who are exposed to physical exercises involving coordinated whole body motion from an early age and maintained throughout life, may develop the ability to utilise vestibular signals in accurate spatial navigation. Early blind subjects who showed superior vestibular navigation performance also demonstrated ultra-short vestibular time constants. It remains unclear if ultra-short vestibular time constants are causally or casually related to enhanced navigation performance.

(5) What areas of the brain may be involved in the encoding of position and kinetic signals derived from vestibular stimulation?

Repetitive transcranial magnetic stimulation (rTMS) was used to disrupt the encoding of vestibular signals during the passive phase of an angular navigation task in which only vestibular signals were available for assessing whole body displacement. It was found that the right posterior parietal cortex was involved in the perceptual processing of vestibular-derived displacement but not kinematic signals. This technique will afford further insight into the cortical processing of vestibular signals.

Chapter 2

PERIPHERAL & BRAINSTEM VESTIBULAR FUNCTION

The peripheral apparati.

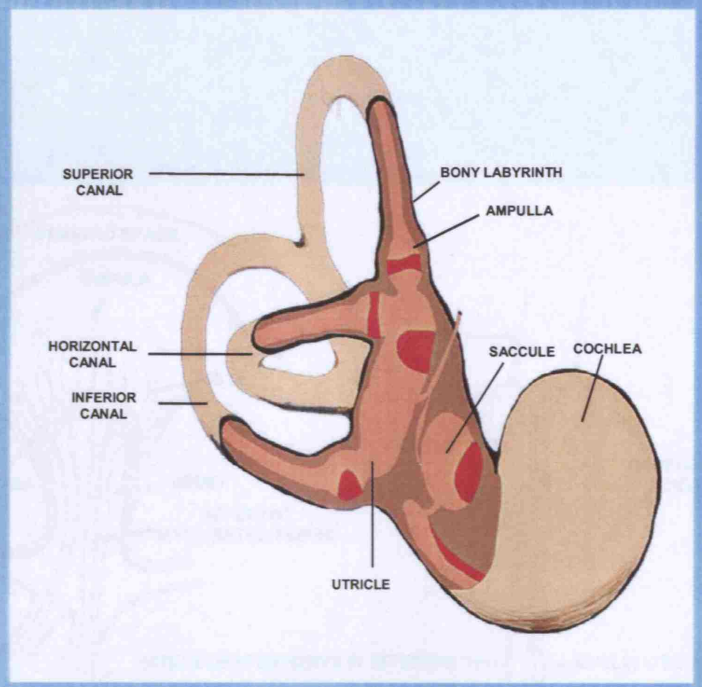
The vestibular system consists of the peripheral vestibular apparati, their immediate nervous connections with the vestibular nuclei in the brainstem and the secondary connections via the vestibular nuclei with other parts of the central nervous system. The peripheral vestibular apparati, the brainstem vestibular nuclei and their interconnections have been conserved to a remarkable degree during evolution so that the basic layout has not changed much for several hundred million years.

The human peripheral vestibular organ, of which there are two and whose conformation is mirror symmetric, is shown in figure 2.1. The bony labyrinth lies in the petrous temporal bone and encompasses the membranous labyrinth which actually floats within this bony space in a liquid called perilymph. The membranous labyrinth itself is also filled with a liquid called endolymph. The vestibular labyrinth consists of three paired semicircular canals and two otolithic receptors, the utricle and saccule. The semicircular canals, which are sensitive to angular acceleration, are named for their orientation in

space, thus there are two horizontal (or lateral), two anterior (or superior) and two posterior (or inferior) semicircular canals.

Figure 2.1

The peripheral vestibular apparatus



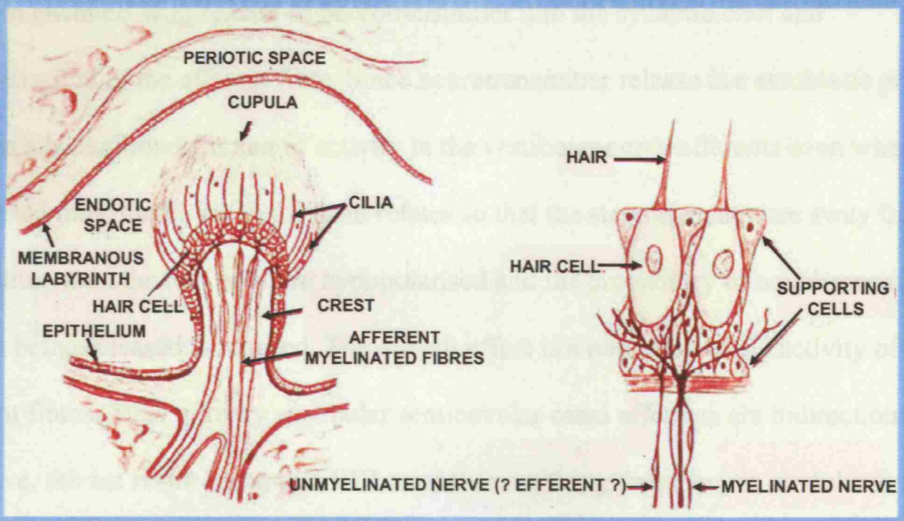
The sensory receptors that transduce angular acceleration are called the cristae (figure 2.2). The three canals on each side are orientated orthogonally to each other and thus can respond to head rotations in the 3 dimensions of physical space. The sensory organs of the utricle and saccule that transduce linear acceleration are called the maculae and are orientated approximately vertically and horizontally respectively.

In the semicircular canals, the sensory elements that transduce angular acceleration are concentrated in the sensory epithelium (i.e. the cristae) and are contained in the ampulla. The cristae consists of a sheet of supporting and hair cells. The apical surface of each hair cell faces the endolymph and is covered with cilia. In the semicircular canals the

gelatinous cupula is fixed to the top of the cilia and completely occludes the lumen of the ampulla. Due to the conformation of this structure there is a differential deformation of

Figure 2.2

Structure of cristae within semi-circular canals



the different cilia for a given acceleration i.e. there is a heterogeneous response across the population of hair cells. Thus for a given accelerating stimulus there is not only a differential output in terms of the activity of the vestibular nerve output as a whole, but also there will be differential activation of individual sensory afferent fibres within the nerve.

The hair cells in the cristae of the semicircular canals are morphologically polarised in terms of the cilial orientation. Intracellular recordings (Corey and Hudspeth, 1979) have shown that the output of the hair cell transduction machinery is correlated with the hair

bundle displacement and not the velocity of displacement. When the stereocilia are displaced (specifically, so that the stereocilia deviate towards the kinocilia), mechanically gated ion channels in the apical portion of the hair cell open and result in hair cell depolarisation due to an influx of potassium ions from the endolymph. This depolarisation then induces the efflux of calcium ions into the hair cells via voltage-gated calcium channels with release of neurotransmitter into the synaptic cleft and depolarisation of the afferent fibre. Since neurotransmitter release is a stochastic process there is a background amount of activity in the vestibular nerve afferents even when there is no head movement. When the head rotates so that the stereocilia deviate away from the kinocilium then the hair cells are hypopolarised and the probability of neurotransmitter quanta being released is reduced. The overall effect is a reduction in the activity of the afferent fibres. Thus primary vestibular semicircular canal afferents are bidirectionally sensitive, the net result being that VIII cranial nerve firing frequency is modulated about a spontaneous resting value in response to angular accelerations (Goldberg & Fernandez, 1971a). Analysis of the activity in such afferents indicates that they convey parameters encoding angular head velocity.

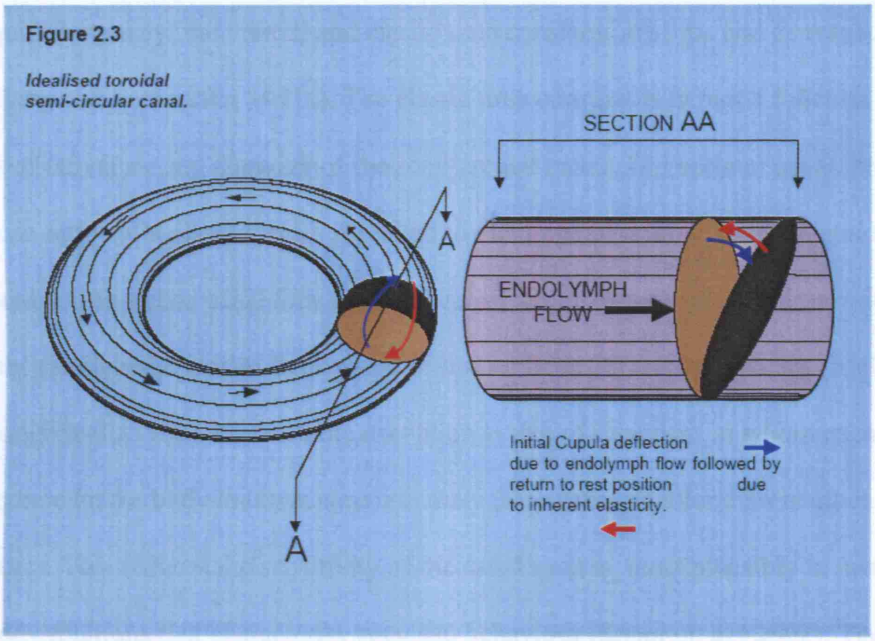
The understanding of the structure to function relationship in the semi-circular canal transduction process has been complicated by several findings. Firstly, electrophysiological (Fernandez & Goldberg, 1971;Goldberg & Fernandez, 1971a,b) and modelling data (Young & Oman, 1969) suggest there is some form of peripheral adaptation to angular acceleration, the functional relevance of which remains unclear. Secondly, anatomico-electrophysiological data suggests a heterogeneous population of

primary afferent-receptor units. Goldberg & Fernandez (1971a,b) found that two types of canal afferents, regular and irregular, in whom there appeared to be an anatomical compartmentalisation on the cristae as well as a differential response to rotations of differing kinetics. The so-called irregular afferents being better suited to encoding high acceleration rotations versus low frequency rotations for which the regular units appeared better suited for their transmission. The relevance of the heterogeneity of primary vestibular afferents has become even less clear unclear since it was found that the silencing of irregular units by anodal galvanic stimulation had no functional effect on the aVOR (Goldberg, 2000). In addition most secondary neurones have a mixed input in terms of primary afferent innervation and their discharge regularity or response dynamics need not resemble their primary afferent inputs (Goldberg, 2000).

Despite these complexities however, models that approximate crista function to a simple torsional pendulum (Steinhausen, 1933) can accurately predict the workings of the aVOR in response to angular head acceleration. This models assumes that an individual canal is a perfect torus (Fig. 2.3) containing an ideal fluid and the cupula to be perfectly elastic (and forms a perfect watertight seal) thus producing a restoring force proportional to its displacement from its rest position.

Figure 2.3

Idealised toroidal semi-circular canal.



The input to this system is the instantaneous angular head position θ_h, resolved to the plane of the canal (i.e. a movement in a plane at 90° to the canal plane is not transduced), resulting in a cupular displacement of θ_c. The transfer function defining the input-output (viz: θ_h - θ_c) transduction of this system is given by:

$$\frac{\theta_h}{\theta_c} = \frac{(rD + k)^{-1}}{(rD + k)^{-1} + (MD^2)^{-1}} = \frac{D^2}{D^2 + (r/M)\,D + k/M}$$

where r = viscous constants; k = elastic constants and M = inertial constants of the system. In reality the semicircular canals are highly damped and so behave like two first-order high-pass units in series:

$$\frac{\theta_h}{\theta_c} = \left(\frac{D}{\lambda + D}\right)\left(\frac{D}{\mu + D}\right)$$

where $\lambda.\mu = K / M$ and $\lambda + \mu = r / M$ $\therefore \lambda = (K / M)(M / r) = k / r.$

The inertial time constant is thus given by M / r and the elastic time constant by r / k. In the squirrel monkey, the inertial and elastic time constants are 3ms and 6s respectively (Goldberg and Fernandez, 1971a). The elastic time constant is in part a function of the radius of curvature and diameter of the semicircular canal. The optimal canal frequency response range of a given species is related to the range of normal head dynamics given the fact that the elastic canal time constant varies with the mass of the animal which itself roughly parallels the typical frequencies of head movement for that species (Melville Jones and Spell, 1963). One notable exception is that of cetaceans in whom canal arc size, corrected for body mass, is approximately three times smaller than in other mammals. This reduces the sensitivity of the canal system, most plausibly to match the fast body rotations that characterise cetacean behaviour (Spoor et. al., 2002). The resultant behaviour of the cupula is such that the temporo-kinetic profile of cupular deflection follows faithfully the time-course of head instantaneous velocity for the usual head movement dynamic range for a particular species.

The utricular and saccular macculae respond to linear acceleration including acceleration due to gravity ($\boldsymbol{g}$). These sensory apparati can thus detect tilt since the resultant acceleration $\boldsymbol{g'}$ (see Figure 2.4), as measured by a vertically aligned accelerometer when tilted $\theta°$ (see below) from the vertical is related to $\boldsymbol{g}$ by $\boldsymbol{g'} = \boldsymbol{g}.(\cos \theta°)^{-1}$. Einstein's equivalence principle implies that a linear accelerometer cannot distinguish acceleration due to gravity from any other linear acceleration. As a result an interesting conflict which must be resolved by the brain is to decide when there is tilt versus linear translation since

a linear acceleration ***a'*** may give an identical resultant acceleration vector ***g'*** as does a tilt of θ° and is related to ***g*** and θ° by ***a'*** = ***g***.(tan θ°).

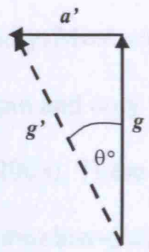
This conflict has attracted much experimental and theoretical effort but I shall not go further detail but direct the reader to a recent review on this topic (Angelaki et al., 2001). I will also not delve any deeper into otolith physiology since the work presented in this thesis is based upon rotational stimuli. Needless to say however, the principles are similar to that for the semicircular canal mechanisms apart from the sensitivity to linear acceleration and the fact that the otolith afferents encode linear head acceleration.

The brainstem machinery

The best known function of the vestibular system is the generation of the vestibulo-ocular

Figure 2.4

Resolving acceleration due to linear motion versus that due to gravity



a' = force due to linear acceleration
g = force due to acceleration due to gravity
g' = resultant force

reflex (VOR). The VOR is an open loop control system with a very short response latency of about 10ms, an order of magnitude faster than visually-mediated mechanisms. The VOR is primary in stabilising the image upon the fovea during head movements. Thus during a head rotation to the VOR generates an oculomotor signal that drives the eyes in the opposite direction to the head.

The brainstem machinery

The primary vestibular afferents are bipolar cells whose cell bodies lie in Scarpa's ganglion within the internal auditory meatus. Their distal axons synapse with the hair cells in the canal cristae. The central axons pass into the brainstem between the restiform body and the spinal tract of the trigeminal nucleus and then bifurcate into ascending and descending branches. The ascending branch synapses within the superior vestibular nucleus and cerebellum and the descending branch passes to the medial, lateral and descending vestibular nuclei. Although the primary vestibular afferents show some heterogeneity in their anatomical connections and signalling characteristics (as discussed above and see Fernandez & Goldberg, 1971; Goldberg & Fernandez, 1971a,b), the majority of secondary afferents are innervated by all types of primary afferents. In addition most excitatory secondary vestibular afferents are innervated by primary afferents monosynaptically. Most second-order vestibular neurones respond to both visual and vestibular input and only a minority respond to vestibular stimulation exclusively (Barmack, 2003). These second-order neurones innervate the appropriate motorneurones to generate slow-phase eye movements. The elicited eye-movements occur in the plane of the stimulated canal. Consider the case for the horizontal canal, conceptually the easiest to visualise. When the head is rotated to the left, the left horizontal canal is stimulated leading to activation of the motorneurones and interneurones in the right abducens nucleus. Right abducens motorneurone activation results in contraction of the right lateral rectus muscle. Activation of the interneurones within the right abducens nucleus then stimulates the left medial rectus motorneurones.

The result is a conjugate movement of the eyes in a rightward direction as the head itself rotates to the left. The inhibitory secondary vestibular afferents are complementary to the excitatory secondary afferents although their influence is less profound. Their connections are correspondingly complementary so for example those afferents mediating horizontal canal effects connect with the ipsilateral (as opposed to contralateral) abducens nucleus.

Modelling brainstem vestibular function via the VOR

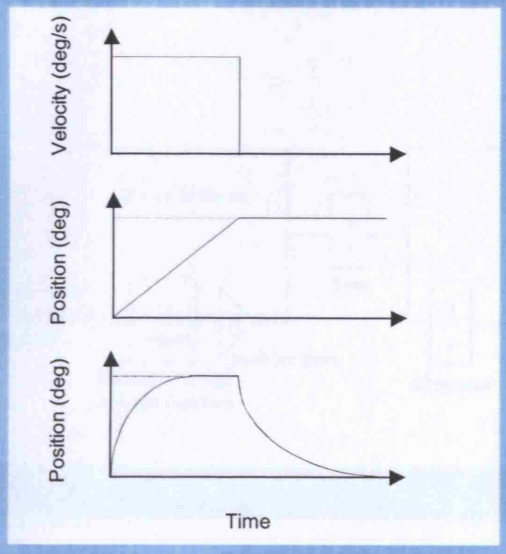
The vestibular signals in the primary vestibular afferents enter the CNS at brainstem level. An understanding of how the brainstem processes incoming semicircular canal signals is imperative to understanding the subject of this thesis, that is, the perceptual processing of vestibular signals. Fundamental to the understanding of models of the VOR is the neural integrator. Integration is a summing algorithm. Consider a body travelling at constant speed v over time t. The distance travelled is given by $v*t$ which is equal to the area under a curve for a velocity vs. time plot of the body's motion. What if the body's velocity changes in a non-linear way over time? If we break this velocity-time up into many small components each roughly rectangular in shape, then the distance travelled for each increment approximates to the instantaneous velocity multiplied by the time increment, i.e. the area of the rectangular segment. Thus the total distance travelled is the sum of all the individual areas. So a perfect integrator summates the incremental inputs and maintains the summed total.

Consider Figure 2.5 in which the input signal is eye velocity. The output of such a process is the distance travelled by the eye, i.e. eye position in degrees. In the top panel is a schematic eye velocity profile. At the end of such an eye movement, the eye will have deviated from the straight ahead position to a head eccentric position. The position of the eye can be derived by integrating the velocity signal. Now, when the eye is held in a head eccentric position it will naturally tend to return to the straight ahead due to elastic forces. Thus to maintain the eye eccentrically there must be a position signal to maintain the eyes at this position and this is done by the neural integrator, a distributed network of neurones in the brainstem and cerebellum. A perfect integrator as demonstrated in figure 2.5

Figure 2.5

Principle of neural integration.

The top panel shows a velocity command to the eye plant. The middle and bottom panels show the eye position responses for ideal and leaky integrators respectively.



(middle panel) maintains its output *ad infinitum*. Experiments have shown that the brainstem neural integrators are not perfect but are leaky (as in Figure 2.5 lower panel),

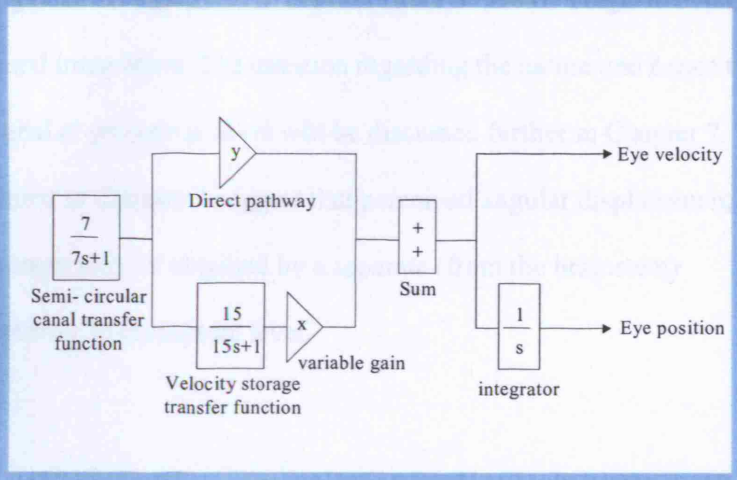
thus the summed result of an integration will tend to fall over time. This fall is exponential in nature and the rate of decline is defined by the exponential time constant. The longer the time constant the more 'perfect' the integrator, the shorter the time constant means a leakier integrator.

We can now turn to some accepted models of the brainstem elaboration of the VOR signal. Figure 2.6 shows a systems approach (Raphan and Cohen, 1996). Firstly there is an extra-brainstem integration that occurs in the semi-circular canals in which head

Figure 2.6

A systems approach to modelling the brainstem VOR.

The time constants for the semi-circular canal response and the brainstem neural integrator are 7 and 15 s respectively.



acceleration is integrated to velocity. The canal integrators have a time-constant of about 5 - 7s (Buttner & Waespe, 1981). The velocity signal from the canal drives the eyes by

both direct and indirect pathways. In the indirect pathway there is a prolongation of the head velocity signal by brainstem mechanisms and the time constant of this integrator is 15s. Lastly, in deriving eye position there is a further integration of the processed velocity signal to displacement. When this velocity to position integrator is deficient, then there is gaze evoked nystagmus. Here the integrator is excessively leaky and so there is centripetal drift of the eyes due to elastic forces. The retinal-slip mechanisms then prompt a saccade to maintain gaze fixation on the object of interest.

Whilst the occurrence of such velocity to position integration in the brainstem is beyond doubt, it is not clear if the vestibular-derived position signals at cortical and/or perceptual level represent ascending position signals from the brainstem or position signals obtained by a parallel cortical neural integration. The question regarding the nature and hence the origin of the position signal at perceptual level will be discussed further in Chapter 7. The experimental data presented in Chapter 7 suggest that perceived angular displacement derived from vestibular input may be obtained by a separate (from the brainstem) temporal integration occurring at perceptual level.

Chapter 3

HIGHER VESTIBULAR FUNCTION- WHAT IS KNOWN?

Asymmetrical activation of the vestibular organs result in activation of several neural systems including vestibulo-spinal pathways causing latero-torsion of the para-spinal muscles, the vestibulo-ocular reflex (VOR) causing nystagmus, the brainstem causing nausea via vestibulo-autonomic loops and also the sensation of vertigo due to ascending inputs to presumably vestibular cortical areas. As discussed in chapter 2, the vestibular control of eye movements involves velocity and position signals. It is thus not unreasonable to expect such signals to be present at perceptual level. What is the evidence?

Ernst Mach, the forefather of modern vestibular psychophysics (Mach, 1875), correctly deduced that there was a specialised sensory system sensitive to *head* acceleration and that the sensory organ responsible for transducing such stimuli was the vestibular apparatus. He described the perceptual consequences of vestibular stimulation including motion perception distinct from visual input and conversely, perception of self-motion generated from object motion (i.e. vection). Whilst Mach laid the fundamentals for vestibular research, his work was primarily qualitative.

Angular acceleration perceptual thresholds

The first semi-quantitative approach to vestibular perception was the investigation of the perception of angular acceleration. Dodge (1923) was the first to produce a figure for angular acceleration perceptual threshold of 1 – 2°/s^2. Groen and Jonkees (1948) were able to retrospectively calculate a value of 0.5°/s^2 from Mach's earlier data, a value that accords well with more recent research (Table 1) including our own (Chapter 10) in which we show that brainstem (VOR) thresholds are lower than perceptual thresholds.

Table 3.1: Angular acceleration perceptual thresholds (z-axis rotational axis)

Author(s)	Threshold (°/s^2)
Mach (1875) (retrospective calculation Groen and Jonkees)	0.5
Dodge (1923)	1 – 2
Graybiel (1948)	0.12
Groen and jonkees (1948)	0.18 – 2.0
Meiry (1965)	0.1 – 0.2
Seemungal et al. (2005) – see Chapter 9	1.18 – 1.39

Subjective angular velocity magnitude estimation

Whilst the work done from Mach onwards has established that humans feel a sense of motion from vestibular stimulation, it was well into the 20th century before researchers began to try to quantify this sensation, i.e. 'how fast are you spinning?' The various

methods used included (a) 'magnitude estimation' (b) direct reporting via hand-held devices or (c) indirect methods obtained by a calculation of velocity perception from subjects' serial reporting of subjective displacement.

Parsons (1970) was the first to use the then new method of 'magnitude estimation' in quantifying the perception of angular velocity from vestibular stimulation. 'Magnitude estimation' required subjects to compare sensations in terms of angular velocity ('turning speed') elicited during test rotations, relative to the sensation elicited by a standard rotation. Magnitude estimation was particularly useful in delineating the temporal change of velocity perception as in determining the vestibular velocity time constant. This early work showed that the temporal change of velocity perception roughly paralleled the slow-phase velocity of VOR nystagmus although more rigorous quantitative methods required the development of more recent 'direct methods' (Okada et al., 1999).

Direct methods involved the manipulation of hand-held devices, e.g. a dial which was adjusted to the instantaneous perception of angular velocity (Guedry & Ceran, 1958 – see Guedry 1974). More recent direct methods have been developed in our lab (Okada et al., 1999) using a hand held wheel that drives the central spindle of a tachometer which outputs an analogue voltage that indicated perceived angular velocity (as described in chapter 6). Here subjects again subjects rotate the tachometer wheel at a speed in a relative manner.

Displacement techniques (Von Békésy, 1955; Guedry & Lauver, 1961; Benson, 1968) consisted of subjects indicating where they perceived their position to be at specific time or signalling whenever they perceived that they had moved through a specific angle such as 90° or 180°. The subjective angular velocity was calculated from the latter technique by dividing the perceived angle moved by the time taken to move through this perceived angle.

Both 'magnitude estimation' and 'direct methods' suffer from being relative techniques in terms of angular velocity perception. Displacement estimation techniques are in some ways based upon absolute angular perception but the derivation of angular velocity is necessarily indirect since it must be calculated and also yields a poor temporal resolution of velocity perception. Of the techniques, the direct method developed by Okada et al. (1999) has the best temporal resolution of instantaneous subjective angular velocity. At present however, the ergonomics and signal-to-noise ratio characteristics of the current apparatus, obviate a direct equivalence in hand turning speed and subjective angular velocity for most subjects.

Subjective angular displacement estimation

Measurement of subjective angular displacement following passive rotations in the dark were measured by Guedry et al. (1971) by use of one of two devices. Firstly, following a dark rotation, subjects would rotate a light back to the origin of rotation. The angular deviation of the light was indicated via a potentiometer. The other device used a circular dial where subjects would indicate their perceived location with respect to the points of a

compass. More recent techniques have used electro-oculography to record the size (in degrees) of what is termed the 'remembered saccade' in which following a head-fixed, and eyes-straight ahead, dark rotation, subjects made a saccade to the remembered location of the start position (Bloomberg et al., 1988). These techniques all show that given optimal vestibular stimuli in terms of frequency range, humans can accurately locate their position in space using only vestibular signals.

Simultaneous vestibular perception of angular kinetics and displacement

The quantitative exploration of human vestibular perception was enabled by development of the self-rotation test (Metcalfe and Gresty, 1992). This test (and subsequent linear variants) employed the use of a motorised rotating chair to passively rotate a subject in the dark to a position or orientation in space. This phase is called the stimulus phase. In the response phase subjects use a hand held device to operate the chair to return the subject to their start position by rotating in a direction opposite to the stimulus. This test essentially isolates the vestibular signal in both stimulus and response phases. Whilst early tests assessed primarily displacement perception and showed that humans can accurately estimate their angular displacement, Berthoz et al. (1995), using a linear variant, gave qualitative evidence that memory of vestibular signals in the brain may involve the use of temporally encoded signals. In Chapter 5, using a modified self-rotation test and employing physiological range vestibular stimuli, I discuss the quantitative (and qualitative) encoding of vestibular signals in terms of velocity, acceleration, displacement and motion duration.

Modelling the relationship between velocity and time vs. space perception

Until now, researchers have modelled the interaction between visual and vestibular signals with respect to velocity signals i.e. vestibular head velocity and optic flow visual velocity signals. In Chapter 7 the use of a new visual-vestibular mismatch technique is discussed. This technique utilises a mismatch between visual and vestibular derived displacement estimates. This technique was developed in order to investigate the derivation and encoding of perceived angular displacement from its temporo-kinetic parameters.

Chapter 4

VESTIBULAR CORTEX

Introduction

Knowledge about the processing of vestibular signals at cortical level in vertebrates or in humans is scant. The first evidence for specialised vestibular cortical areas in humans came from case reports of patients with focal lesions and from intra-operative cortical electrical stimulation (ECS) studies of the cerebral cortex (Foerster, 1936; de Morsier, 1938; Penfield, 1957). More recently, neuro-imaging studies using vection-inducing (optic flow; Brandt et al., 1998; Kleinschmidt et al., 2002; Dieterich et al. 2003), vertigo-inducing stimuli (caloric stimulation: Bottini et al., 1994; Suzuki et al., 2001; Fasold et al., 2002; Emri et al., 2003; Naito et al., 2003; Dieterich et al., 2003) or galvanic vestibular stimulation (Vitte et al., 1996; Lobel et al., 1998; Bucher et al., 1998; Bense et al., 2001), and one using small head movements (Petit and Beauchamp, 2003) have isolated vestibular-associated cortical regions. Evoked potentials studies have also been performed (hood & Kayan, 1985; Probst & Wist, 1990; de Waele et al., 2001). There has been a recent appreciation that cortical strokes may present with rotatory vertigo (Brandt et al., 1995; Cereda et al., 2002; Boiten et al., 2003). In the last 5 years there has been a re-awakening in the use of direct electrical stimulation of the cortex which have

pinpointed several vestibular cortical regions (Blanke et al., 2000; 2002; 2004; Kahane et al., 2003).

Ascending pathways

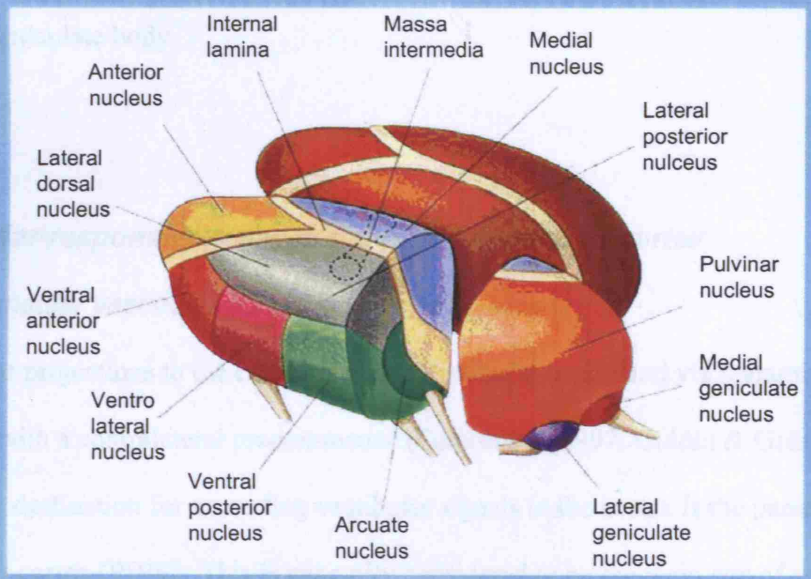
Brainstem-thalamo-cortical route

Several animal studies have demonstrated that neurones in the vestibular nuclei project to the thalamus (Sans et al., 1970; Frederickson et al., 1974; Odkvist et al., 1977; Lang et al., 1979;). Vestibulothalamic projections are mainly bilateral and involve several thalamic areas. In cats (Kotchabhakdi et al., 1980) there are three main vestibulothalamic projections; (a) caudal parts of the medial and descending vestibular nuclei project to posterior nucleus (including the magnocellular part of the medial geniculate body), the ventrobasal complex and the adjacent ventral lateral nucleus; (b) the superior nucleus projects primarily to the contra-lateral nucleus paracentralis and (c) inner part of the MVN and DVN project to the contra-lateral ventral nucleus of the lateral geniculate body. Magnin and Fuchs (1977) recorded neurons in primates in the oral part of the ventroposterior nucleus (or nucleus ventroposterior lateralis pars oralis, viz.VPLo) that discharged as a function of head velocity but not with saccades, smooth pursuit or fixation eye movements suggesting that VPLo acts as a vestibular relay nucleus and is not concerned with vestibular/visual or vestibular/oculomotor interactions.

Thalamocortical projections have been characterised in the squirrel monkey (Akbarian et al., 1992). In this species the oral and superior ventroposterior nucleus (VPLo and VPLs)

Figure 4.1

Thalamic Nuclei



project bilaterally to area 3a. The posterior insular vestibular cortex (PIVC) receives projections from the posterior part of the VPL nuclear complex. The parietotemporal association, area T3, mainly involved in visual-optokinetic signal processing, receives projections from the medial, lateral and inferior pulvinar.

In man intra-operative electrical stimulation during stereotactic surgery has suggested two discrete vestibulothalamic pathways mediating vestibular sensation in man (Hawrylyshyn et al., 1978): (a) an anterior relay situated ventral to the medial lemniscus, passing lateral to the red nucleus and dorsal to the subthalamic nucleus prior to

terminating in the nucleus ventrointermedius (VIM) (comparable to VPLo in primates); indeed in man VIM stimulation results in right vestibular cortex deactivation on PET (Ceballos-Baumann et al., 2001) and (b) a posterior relay associated with the auditory pathway (lateral lemniscus and brachium of the inferior colliculus) projected to the medial geniculate body.

Vestibular-responsive areas in the primate cerebral cortex

Parieto-insular vestibular cortex (PIVC)

Vestibular projections to the cortex from the vestibular nuclei and via thalamic relays are bilateral with a contralateral predominance (Fukushima, 1997; Guldin & Grüsser, 1998). The main destination for ascending vestibular signals to the cortex is the parieto-insular vestibular cortex (PIVC). This is generally considered to be the main site of vestibular cortical processing in the primate and is located in the posterior bank of the insular cortex which abuts the temporal cortex. Anterior to PIVC is the secondary somatosensory area of the parietal operculum and caudal to PIVC is the secondary auditory area. From PIVC, other cortical areas including 6, 3a, and 7a, receive vestibular signals. Using single unit recordings, Grüsser and co-workers demonstrated that more than fifty percent of cortical neurones found in PIVC were vestibular responsive (Grüsser et al., 1990,a,b). Two thirds of PIVC neurones responded to vestibular stimulation. Cells showing activation during contra-lateral rotation (type II) were more commonly found than those activated by ipsilateral rotation (type I). Given that type II cells were most common (circa 60%), then PIVC as a whole would tend to be activated by contralateral head rotation.

The proportions of type I and II responsive neurones in the brainstem and thalamus are similar to those recorded in the PIVC (Fuchs and Kim, 1979; Buettner et al., 1978; Buttner et al., 1977) suggesting no major additional cortical processing in terms of population coding for laterality in the yaw-plane. However, since neurones were screened for vestibular reactivity by yaw-rotation responses, it may be that some neurones with non-yaw sensitivity were missed. However, 18 neurones were tested in 3 planes of rotation; of these 12 showed a triaxial response, 4 biaxial and 2 uniaxial. Thus the majority of PIVC neurones responded to 3-dimensional head movement potentially encompassing a large repertoire of 3-D head movements, particularly when the responses of multiple neurones are combined. This is clearly different from brainstem neurones whose vestibular and optokinetic sensitivity is encoded in a semi-circular canal-based reference frame (Graf et al., 1988; Wylie and Frost, 1993). In terms of the signals carried at cortical level, most PIVC neurones encoded angular head velocity although Mergner found some cells in the PIVC that encoded head position (Mergner et al., 1985). Thus in PIVC, the kinematic representation is roughly similar to the brainstem.

Virtually all vestibular sensitive neurones in PIVC were also responsive to large field optokinetic (OKN) stimuli and somatosensory stimulation, including passive neck-on-body rotations. Indeed the most powerful stimulus was a head rotation (active or passive) in the light (viz. concurrent vestibular, OKN and somatosensory stimulation). Of 44 neurones which were active during horizontal OKN stimuli, 29 were activated by yaw vestibular rotation in a 'synergistic' direction (i.e. opposite direction to OKN since during rightward head rotation, observed optic flow is to the left); 13 out of 29 were activated

antagonistically and 2 were biphasic. The OKN response was not modulated by gravity since their activity was dependent upon a head-based reference frame. Optic flow visuo-vestibular interaction was assessed for 11 out of 29 synergistic neurones. Head rotation in the light (i.e. 'natural condition') showed no change in mean neuronal activity compared to rotation in the dark. Individual neurones however showed either no change, significant decrease or increase in activation in rotation in the light compared to dark conditions. For example, one 'synergistic' neurone was activated by rightward vestibular and leftward OKN stimulation respectively showed summative activity during rightward rotation in the light compared to the dark. During leftward *deceleration* in the dark, the neurone was activated by the apparent 'rightward' vestibular signal but in the light, activity was suppressed by the rightward visual signal. For antagonistic neurones, there was no significant modulation of the vestibular-induced activity with concurrent OKN stimulation. When comparing OKN visuo-vestibular interaction at PIVC level with vestibular nucleus and thalamus, one sees an increase in the number of antagonistic units; from 5% to 15% to 30% for brainstem, thalamus and cortex respectively. In terms of the origin of the visual signals to the PIVC, there are four possible pathways (Akbarian et al., 1988; Berthoz, 1996):

(a) Retina → Nuc. Optic Tract → Vestibular nuclei → Thalamus → PIVC

(b) Retina → Superior colliculi → Inferior Pulvinar → Sup. Pulvinar → PIVC

(c) Retina → Lat Gen Nuc. → Pulvinar → VPS/area T3 → PIVC

(d) Retina → Lat Gen Nuc. → Area 19 → VPS/area T3 → PIVC

Somewhat surprisingly, there are no direct projections to PIVC from visual cortical areas sensitive to large field stimuli such as MT or MST. However, area 6 is strongly connected to both PIVC and area T3 (termed area VPS - visual posterior sylvian) and may provide a route for cortical visual input. Area T3 (or VPS) was found to contain vestibular and OKN sensitive neurones but with a functional dominance of optic flow input (Guldin and Grusser, 1998). Interestingly tracer studies show area T3 to be not only strongly connected to area 6 but also the cingulate cortex (see below). Both cingulate cortex and area 6 are strongly connected to both PIVC and area 3a (a premotor area with vestibular sensitive neurones). Berthoz (1996) suggests the existence of a vestibular loop to PIVC through the connections of area 3a, T3 and cingulate cortex. The other main projection from PIVC is area 2v, the macaque homologue of human area 7a (see below).

Vestibular cortical areas in humans

Temporo-parietal cortex

Up until recently, interpretation of results in human vestibular cortical studies may have been biased into accepting a rigid homology between primate PIVC and the human locus. In fact electrical cortical stimulation (ECS) in mesial areas such as posterior insular, a locus of activation found in some human neuro-imaging studies (Bottini et al., 1994; Bucher et al., 1998; Brandt & Dieterich, 1999; Emri et al., 2003), was only rarely found to elicit vestibular responses in a recent large ECS study involving more than 200 patients and 10,000 ECS sites (Kahane et al., 2003: see Figure 4.2 and Table 4).

There have been three lesion studies reporting dizziness a result of cortical stroke. Cereda et al. (2002) identified 4 patients out of a database of 4,800 with stroke isolated to the insular, i.e., a rare occurrence. All 4 patients described initial dizziness but also symptoms compatible with more posterior insults (2 with dysphasia and 2 with sensory hemi-disturbance) suggesting transient ischaemia of temporo-parietal areas although 3 out of 4 patients had early diffusion weighted imaging (a very sensitive imaging modality for ischaemia) showing infarct localised to the posterior insular. It may well be that these 4 patients did have dizziness due to their posterior insular lesions but also had unusual symptoms for this location of stroke suggesting idiosyncratic cerebral representation in these patients. We do not have however, the important denominator in this study from the vestibular point of view, i.e., how many cortical strokes presented with dizziness overall out of 4,800 cases. Brandt et al. (1995) report another case of posterior insular stroke presenting with dizziness but the lesion clearly also involved the superior temporal gyrus, a locus found to elicit vestibular sensations with ECS (Kahane et al., 2003). Boiten et al. (2003) reported a single case presenting with dizziness due to a stroke in the left medial temporal gyrus, adjacent to the superior temporal sulcus and not involving the insular.

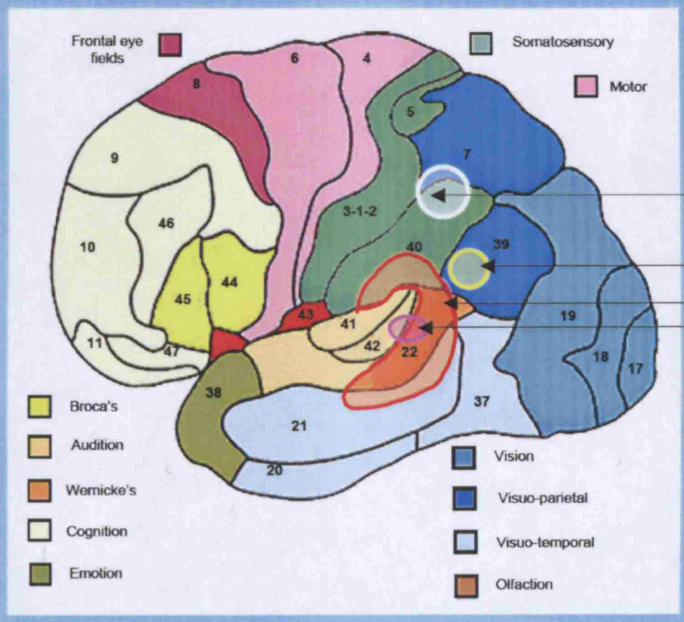
Despite the recent consensus that humans possessed a PIVC analogue, not all neuro-imaging studies found a significant vestibular-mediated insular activation (Lobel et al.,1998; Bense et al., 2000; Fasold et al., 2002) even if some authors (Bense et al., 2000; Fasold et al., 2002) gave elaborate explanations for the lack of finding posterior insular activation based upon inter-individual variation in this region. Many of these studies however, did show TPJ and/or superior temporal gyrus activation consistent with ECS

studies (Friberg et al., 1985; Bottini et al., 1994; Lobel et al., 1998; Suzuki et al., 2001; Fasold et al. 2002). This attempt to explain the 'missing' insular activation may have stemmed from the expectation to find activation in this locus given previous animal data (Guldin & Grusser, 1998). Petit and Beauchamp (2003) also report PIVC activation in an fMRI study in which head movements were compared to eye movements. The most significant area of activation in this study was actually the supramarginal gyrus, followed by cuneus and then a perisylvian region including PIVC but also extending up to the temporoparietal junction (TPJ) at the level of the parietal operculum.

Figure 4.2

Human vestibular cortical areas

Vestibular loci as assesed by response to electrical stimulation. Numbers refer to Brodmann areas.



This study, although ground breaking (since it assessed the neural correlates of natural vestibular stimuli i.e. head motion), was difficult to control for somatosensory stimulation associated with head movement in addition to the difficulties in maintaining accurate co-registration of fMRI signals.

In contrast, the current burden of evidence, from older and more recent ECS studies as well as neuro-imaging and lesion studies support the location of the main vestibular cortex in the temporo-parietal cortex, specifically at the TPJ and adjacent superior and middle (mid to posterior aspect) temporal gyrus (BA 21, 22, 39, 40) in addition to the parietal operculum at the upper bank of the sylvian fissure (BA 40, 43) (Penfield (1957; Israel et al., 1995; Friberg et al., 1995; Lobel et al., 1998; Suzuki et al., 2001; Blanke et al., 2002; Boiten et al. 2003; Kahane et al., 2003; Blanke et al., 2004). There is also psychophysical evidence in lesion patients who had a common lesion intersection overlying the superior temporal gyrus (adjacent to the TPJ) in whom performance was impaired in a spatial updating saccadic task requiring vestibular input (Israel et al., 1995).

The extensive study by Kahane et al. (2003) provides the most compelling evidence for a difference between monkey and human vestibular cortical representations. They found TPJ loci in 24 of 41 cortical sites that elicited vestibular symptoms (Figure 4 and Table 4). TPJ electrical stimulation tended to elicit yaw-plane rotatory sensations. This area extended above and below the Sylvian fissure, mainly inside Brodmann areas 40, 21, and 22. This vestibular sensitive site also included two other areas (a) the parietal operculum in 9 of 24 temporoparietal sites, stimulation of which elicited pitch plane illusions and (b)

the mid and posterior part of the first and second temporal gyri in 15 of 24

Table 4: Electrical cortical stimulation loci producing vestibular symptoms
(Kahane et al., 2003. n=44, 28 patients)

Patient No.	Hz	ESmA	Anatomical Structure	BA	Code	Clinical Responses Vestibular Illusions	Symptoms
Temporal lobe							
9111a	1	3	R amygdala	—	I	Head spinning	—
9712a	1	3	R amygdala	—	T	Levitation, lightness	—
9409a	50	3	R hippocampus	—	Y	Rotatory (head), horizontal, clockwise	L visual hallucinations
9431a	1	3	R inf longit fasciculus	—	Y	Rotatory (head), horizontal, counterclockwise	—
9431b	1	3	R inf longit fasciculus	—	Y	"a circle which turns in the head," counterclockwise	—
9817	50	1	L 2d T gyrus (polarpart)	21	I	Swaying motion (head)	—
9712b	1	3	R 2d T gyrus, midpart	21	T	Levitation, lightness	—
9431c	1	3	R 2d T gyrus, midpart	21	Y	Rotatory (head), horizontal, counterclockwise	Feeling of eye jerking
9111b	1	3	R 2d T gyrus, midpart	21	Y	Rotatory (head), horizontal, unknown direction	L auditory hallucinations
9712c	1	3	R 2d T gyrus, midpart	21	P	Rolling forwards (**whole body + environment**)	—
9111c	1	3	R 2d T gyrus, midpart	21	Y	Rotatory (head), horizontal, counterclockwise	L auditory hal lucinations
9612	1	3	R 2d T gyrus, postpart	21/39	Y	Rotatory (head + **environment**), horizontal clockwise	Nausea, diplopia
9701	1	3	R 1st T gyrus, midpart	22	I	Head spinning, dizziness	—
9023	1	2	R 1st T gyrus, midpart	22	Y	Rotatory (head), horizontal, unknown di- rection	Auditory illu- sions
9911a	50	3	R 1st T gyrus, midpart	22	R	Disequilibrium toward the right	L auditory illusions
9434a	50	3	R 1st T gyrus, midpart	22	Y	Rotatory (head), horizontal, unknown direction	Auditory illusions
9431d	1	3	R 1st T gyrus, midpart	22/42	Y	Rotatory (head), horizontal, counterclockwise	Auditory illusions
9028	50	2	R 1st T gyrus, midpart	22/42	R	Sensation to be pushed (head) toward the left	Shiver
9605	50	3	R 1st T gyrus, postpart	22	Y	Rotatory (head + **environment**), horizontal, counterclockwise	Visual illusions
9820a	50	2	R 1st T gyrus, postpart	22	Y	Rotatory (**whole body**), horizontal, counterclockwise	Anxiety
9433	50	3	L 1st T gyrus, postpart	22/40	Y	Rotatory (**environment**), horizontal, clockwise	—

Vestibular symptoms are classified as yaw plane illusions (Y), pitch plane illusions (P), roll plane illusions (R), translations (T), and indefinable sensations of body motion (I). ES = electrical stimulation frequency (Hz) and intensity (mA); *x, y, z* = millimetric stereotactic coordinates in the proportional atlas of Talairach and Tournoux; BA = Brodmann area; R = right; L = left.

temporoparietal sites which preferentially caused yaw plane illusions.

Table 4: continued

Patient No.	Hz	ES mA	Anatomical Structure	BA	Code	Clinical Responses Vestibular Illusions	Symptoms
Frontal lobe							
9911b	50	1	R 3rd frontal gyrus	45	R	Body oscillations toward the right and left	—
9820b	1	3	R frontal operculum	44	I	Desequilibrium, drunken sensation (thorax)	—
9911c	50	1	L ant cingulate gyrus	32	I	Swaying motion (whole body)	Nausea
9625b	50	1.2	R ant cingulate gyrus	24	P	Sensation of rocking motion (head&trunk), backward	Anxiety, thoracic feeling
9920	50	0.4	L suppl motor area	6	I	Desequilibrium, unsteadiness	—
Occipital lobe							
9719	1	3	L cuneus	18	T	Sensation of sinking into the bed, of being heavier	Feeling sleepy
9434c	1	3	R lingual gyrus	18	Y	Rotatory (environment), horizontal, coun-terclockwise	
Insula							—
9917	1	3	R insula, parietal part	—	Y	Rotatory (head), horizontal, counterclock-wise, +/- falling flat	—
Parietal lobe							
9015	50	1	R parietal operculum	43	R	Sensation to be tilted toward the right	—
9440	1	3	R parietal operculum	40	P	Sensation of body oscillations, forward+ backward	—
0023	50	1	R parietal operculum	40	P	Sensation to be thrusted forward	—
9409b	50	3	L parietal operculum	40	Y	Rotatory (head), horizontal, counterclock- wise	R arm heaviness
9228a	1	3	R parietal operculum	40	I	Head spinning, dizziness	—
9228b	50	1.5	R parietal operculum	40	R	Sensation to be attracted (head 3 body) toward the right	—
9516	50	3	R parietal operculum	40	P	Falling backward	L arm heaviness
9328	50	3	R parietal operculum	40	I	Head spinning	—
9502	50	3	R parietal operculum	40	P	Falling backward (head + trunk)	—
9706	50	1	L sup longit fasciculus	—	T	Sensation of flying	—
9901	50	3	L precuneus	7	Y	Rotatory (head), horizontal, counterclockwise	—
9434b	50	3	R precuneus	7	Y	Rotatory (**environment**), horizontal, counterclockwise	L dysesthesia (trunk + leg)
9625a	50	1.6	R precuneus	7	R	Sensation to be pushed (head) from the left toward the right	—
9228c	50	2	R precuneus	7	T	Sensation of falling flat	Oscillopsia
9017	50	3	R deepness of cing sulcus	7/5	T	Sensation of falling flat	Diffuse tingling

Although many studies have shown a contralateral encoding of vestibular signals with a right hemisphere dominance (Bense et al., 2000), Dietrich et al. (2003) have shown that this hemispheric dominance varies with handedness. Indeed evidence from the ECS studies (Blanke et al., 2000; Kahane et al., 2003) show that the direction of felt rotation (head or whole body) is contralaterally encoded, i.e. a perception of leftward rotation is processed by the right hemisphere.

Posterior Parietal cortex

The posterior parietal cortex (PPC) is an important cortical processing site for spatial perception and coordinating spatial information necessary for spatially directed motor action (for review see Mesulam 1998; Colby and Goldberg 1999). Neurones encoding vestibular-derived position have been found in monkey area 7a (Brotchie et al., 1995; Snyder et al., 1998) and neurones encoding spatio-kinetic vestibular signals have been found in the intraparietal sulcus in the anterior, ventral and medial intraparietal (VIP & MIP) areas (Gulin & Grusser, 1998; Bremmer et al., 2002b; Klam and Graf, 2003). Area VIP neurones are also sensitive to large field optokinetic stimuli (Bremmer et al., 2002a) as well as tactile input (Duhamel et al., 1998). Neuroanatomical evidence confirms multi-modal sensory input to area VIP (Lewis and Van Essen 2000a). Both VIP and MIP vestibular neurones may show different activation patterns during active versus passive vestibular stimulation, in particular over a third of neurones may change directional sensitivity (i.e. activation with ipsi versus contralateral head rotation and vice versa; Klam and Graf, 2003).

Snyder et al. (1998) demonstrated that half of all area 7a and LIP (lateral IP) neurones that had eye gain fields (i.e. neurones sensitive to *eye-gaze* direction) also had head gain fields during active gaze shifts. The head gain fields were still present when the monkey's whole body was then rotated in the dark demonstrating that these area 7a neurones had vestibular input. In particular this input was a *position* signal which updated the spatial coding of these neurones with respect to a world-centric (allocentric) frame of reference.

Two human ECS studies have demonstrated vestibular responses with stimulation at the anterior intraparietal sulcus (IPS) (Foerster, 1936; Blanke et al., 2000). Blanke et al. (2000) recorded a contralateral rotational sensation with left anterior IPS stimulation. This location may correspond to area 2v, considered one of main vestibular cortical loci in primates (Guldin & Grusser, 1998). More posterior loci including angular gyrus in the parietal lobe (BA 39) and an area connecting it to posterior areas of the superior temporal lobe, may be associated with vestibular sensations but also with 'out-of-body' sensations (Blanke et al., 2002; 2004).

Medial Superior Temporal Cortex (MST)

Medial and Dorsal MST (MSTm & MSTd respectively) neurones are responsive to optic flow input and appear to encode heading direction from optic flow cues. MSTd (but not MSTm) neurones also appear to be sensitive to vestibular input (Page and Duffy, 1994).

Neuronal recordings show that some MSTd neurones show a temporal integration of incoming vestibular signals (for linear motion) suggestive of a cortical vestibular integration. MSTd neurones' responses to motion in the dark are facilitated during motion in the light suggesting that neurones here combine head velocity information from both vestibular and visual inputs. Such neuronal activation would make area MSTd ideally placed to participate in the perception of self-motion.

Hippocampus

Hippocampal spatial cell function is influenced by vestibular input (Taube, 1998). In particular, head direction cells in rats (Taube, 1998) and primates (O'Mara et al., 1994) are updated by inertial input. Head direction cells firing rate increases when the animals head orientation assumes a specific direction. This orientation-specific activation can be altered by (undetected) erroneous visual input suggesting a visual dominance in this system. Recent studies have challenged this view however since place and head direction cells function is permanently disrupted after vestibular ablation (Russell et al., 2003; Stackman et al., 2002). Recent studies suggest that a similar hippocampal navigational mechanisms are present in humans (Ekstrom et al., 2003).

There is at present no evidence for direct connections between brainstem vestibular nuclear complex and the hippocampus. Vestibular input to the hippocampus, mainly via the parahippocapus, may arrive from other cortical areas with vestibular input, mainly the posterior parietal cortex (Cavada & Goldman-Rakic, 1989; Rockland & Van Hoesen, 1999). In particular, area 7a has strong bi-directional connections with area CA1 (either

direct or indirect via hippocampal area TF). Both area 7a and CA1 possess neurones whose activity is modulated by vestibular signals during angular orientation (O'Mara et al., 1994; Snyder et al., 1998). That both of these areas are connected suggests that they may be involved in a network involved in spatial navigation although further study is required to elucidate this idea.

Other cortical sites

Grusser and co-workers have shown vestibular projections and vestibular driven single-unit activity in motor cortex primarily area 3a (Guldin & Grusser, 1998). Area 3a is important in motor control of the neck muscles, a logical finding given the functional symbiosis between neck movements and vestibular signals. There is little data on vestibular projections and interaction to primary visual cortex. Tomko et al. (1981) however, showed that static head tilt altered the receptive field orientation of 27% of visual cortical neurones. However Brandt et al. (1998), using functional neuro-imaging, have shown that there is a reciprocal inhibition between parieto-temporal areas and primary visual cortex with activation of the former and de-activation of the latter with vestibular stimulation. The converse occurs during optokinetic stimulation. Ecologically this is advantageous since perception of self-motion can be generated from visual or vestibular input.

Conclusions

The data on loci of ascending vestibular signals in man is sparse however human Vim nucleus in the thalamus may play a major role in relaying such signals to cortical level.

Perception of vestibular-derived kinetic parameters may be mediated by temporoparietal cortex, mainly at the TPJ and superior (mid to posterior) temporal gyrus. Interestingly, the majority of sensations elicited at this site tended to be head yaw-axis (not body) rotations. Vestibular sensitive PPC neurones may also play an important role in the perception of self-motion but possibly more so for perception of position in space derived from multi-modal input including visual and vestibular input. The strong reciprocal connections between the PPC and the hippocampal formation would support this notion (Cavada & Goldman-Rakic, 1989; Rockland & Van Hoesen, 1999). The lack of major navigational deficits in humans with hippocampal lesions suggests that in humans, the neuronal machinery required for spatial navigation is distributed. Lastly, the recent publications regarding 'out-of-body' experiences in ECS to a region incorporating angular gyrus and posterior parts of the superior temporal lobe (Blanke et al., 2002; 2004), has opened up a new area of investigation in the link between vestibular perception and representation of body motion. There may well be a somatotopic representation of body part and whole-body motion as demonstrated by the differential sensations elicited by ECS at TPJ (head rotation), IPS (whole body rotation) and angular gyrus loci (complex whole body motion such as flying).

Chapter 5

VESTIBULAR NAVIGATION IN SIGHTED SUBJECTS

Introduction

Humans are able to navigate in the dark using only haptic and inertial (vestibular) cues of self-motion, a process termed path integration (PI) (Mitttelstaedt & Mitttelstaedt, 1980). Early experiments in dark navigation were unable to fully disentangle the relative contributions from vestibular and haptic information during active locomotion (Loomis et al., 1999). The use of avestibular patients in dark navigation experiments has alluded to the pivotal role of the vestibular system during locomotor navigation in the absence of visual landmarks primarily for turning but less so for linear motion (Glasauer, 2002). However it was only with the development of the SRT or self-rotation test (Metcalfe and Gresty, 1992) that investigation of vestibular navigation without contamination from other sensory cues could be undertaken. A modified SRT was developed to explore two related but distinct areas of vestibular navigation: (a) to investigate the encoding of vestibular kinematics including velocity, acceleration and motion duration (b) to assess true spatial vestibular navigation. In addition, we developed the modified SRT to assess these aspects of vestibular navigation in patient groups, e.g. in congenitally blind subjects as discussed in Chapter 6.

Overview of the self-rotation test and linear equivalents

The self-rotation test described in this Chapter was based upon the paradigm originally described by Metcalfe and Gresty (1992) as shown in Figure 5.1. In the original test, subjects were rotated in the dark on a Barany chair with raised cosine velocity waveforms at 30°/s peak velocity over 2s (amplitude 30°) and 60°/s peak velocity over 2, 3, 4, 5 and 6s, yielding amplitudes of 60°, 90°, 120°, 150° and 180° respectively. Subjects had to rotate themselves back to the start by means of a chair-mounted joystick. The joystick could control chair velocity (left or right) by sending a voltage to the chair servo mechanism so that a constant displacement of the joystick gave a constant chair angular velocity up to a maximum of 60°/s.

Figure 5.1

Self-rotation test apparatus.

Subjects sat on a motorised Barany chair with white noise sound masking delivered by headphones. The chair mounted joystick controlled chair velocity.

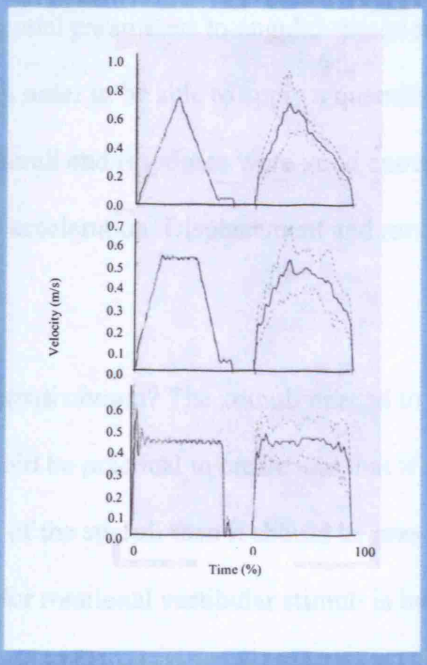
Initial results from self rotation experiments (and linear analogues) confirmed that humans were able to accurately navigate in space during path reproduction tasks using

only vestibular cues (Metcalfe and Gresty, 1992; Berthoz, 1995). Metcalfe and Gresty (1992) found that the strategy used by subjects was a purely spatial one, i.e. they did not reproduce the waveform of the stimulus velocity profile but used rhomboid type velocity responses. This suggested that vestibular navigation used only the position signal and the velocity profile was not available for accurate spatial navigation. The major shortcoming of the experimental paradigm was that subjects could use temporal cues in spatial navigation since all of the stimuli except for one, had the same peak velocity. In addition, the peak velocity of the stimuli and response was only 60°/s. This left a large dynamic range unexplored. For example, during a normal head movement, the peak angular velocity may lie between 100°/s – 200°/s.

Figure 5.2

Linear vestibular navigation.

Linear velocity traces from a linear path reproduction task (from Berthoz et al., 1995). The paired traces represent stimulus on the left and averaged responses on the right.



Berthoz et al. (1995) showed qualitatively that humans were able to store the spatiotemporal profile of whole-body translation (Figure 5.2). Quantitative analysis however, was limited by the poor dynamic properties of the apparatus, including a 250msdelay between subject response and response of the apparatus. In addition the stimulus kinetics were not within the optimal range for vestibular stimulation.

METHODS

Development of the modified self-rotation test

The modified SRT experiment was designed with a capability sufficient to examine the contributions of kinetic and spatial parameters to angular spatial navigation using physiological range stimuli. In order to be able to apply a quantitative approach it was essential that the quality of stimuli and responses were good enough to allow accurate readings of peak velocity and acceleration. Displacement and motion duration readings posed little technical problem.

So how were the rotational stimuli chosen? The stimuli needed to be within the optimal vestibular range; that they would be practical to create and that if subjects wanted to reproduce the velocity profile of the stimuli then it should be reasonably easy to do so. The optimal frequency range for rotational vestibular stimuli is between 0.1 and 1 Hz (Mayne, 1974). Thus stimuli stimulus periods of 1s (1 Hz) to 6s (0.167 Hz) were chosen. The next question was the shape of the velocity stimulus. Since the semi-circular canals are sensitive to angular acceleration, a stimulus which has a continuously changing

velocity is an optimal stimulus. A raised cosine velocity stimulus was thus chosen. The next question was what peak velocities to use. This was determined by the fact that the largest required displacement stimulus was 360° (for reasons to be explained later). Thus subjects would be rotated over 360° within 6s which means using a peak velocity of 120°. The lowest peak velocity was determined by a requirement to maintain subjects above angular acceleration threshold. Thus 30° peak velocity stimulus over 6s gave a peak angular velocity of $16°/s^2$ well above previous estimates of angular acceleration perceptual thresholds (see Chapter 3, Table 1). Stimuli of peak velocities 60°/s and 90°/s were chosen for the middle range. Ultimately there were 24 different velocity waveforms (Table 5.1) left and right giving a total of 48 stimuli. Thus subjects were unable to use counting strategies to facilitate their angular orientation.

Table 5.1: Stimulus parameters used in vestibular navigation tasks (GBS and CTC)

	Peak Velocity	30°/s	60°/s	90°/s	120°/s
Period					
1s		15°	30°	45°	60°
2s		30°	60°	90°	120°
3s		45°	90°	135°	180°
4s		60°	120°	180°	240°
5s		75°	150°	225°	300°
6s		90°	180°	270°	360°
		Displacement			

The next issue was optimising subject response. Now, theoretically subjects could use one of two strategies; (1) they could convert the kinetic stimulus parameters to displacement and then recover their estimate of angular displacement or (2) they could reproduce the kinetics of movement. To enable subjects to consider using the second strategy it was necessary to make the maximum attainable velocity and acceleration from the joystick greater than that of the maximal stimulus values. Considering that the highest stimulus acceleration was 377°/s^2, this was not necessarily easy for subjects to do. To overcome this all subjects were allowed a minimum period of practice of 20 minutes (or longer depending on dexterity) in which the initial gain of the joystick output was reduced to 0.1 of the level used in the experiment. As subjects improved in dexterity, the joystick gain was incrementally increased until the maximal attainable angular velocity from the joystick was 140°/s. The maximal attainable acceleration was dependent upon the temporal profile of joystick manipulation but in practice was around 600°/s^2. Subjects were given free practice in the dark and with sound masking and so never had any visual feedback during the practice session. The rationale for this was to avoid subjects learning a hand-based mapping of optic flow head velocity. It was presumed that subjects possessed a pre-calibrated vestibular signal derived from their daily activities right up until they entered the laboratory and during periods in which the lights were switched on. In the latter case any head movement in the light is an opportunity to calibrate the vestibular system from concurrent optic flow. Indeed the use of calibrating stimuli in previous vestibular navigation experiments may engender non-vestibular navigation since there is the real possibility of subjects not calibrating the vestibular signal but calibrating the joystick device to visually observed motion.

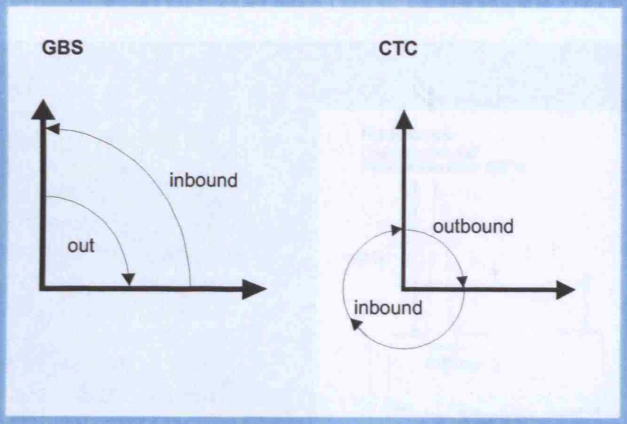
Distinction between path reproduction and completion

Previous studies of inertially-guided navigation in humans (*sine* efferent and proprioceptive information), including the self-rotation test as described above, have usually assessed performance without explicitly assessing strategy and those addressing strategy deployed paradigms in which the navigation task was limited to a 'mirror' reproduction of imposed movement (Metcalfe and Gresty, 1992; Israel et al, 1995; Israel et al., 1996; Israel et al., 1997). Thus so far, there has been a limited investigation of true spatial navigation using only vestibular cues. This is because, taking the self-rotation test as an example, whatever strategy subjects used, be it reproducing the kinetics or displacement of the stimuli, subjects need not calibrate the stimulus, a simple matching of the to and fro' vectors of whatever dimension, would be adequate to complete the self-rotation task however erroneous the internal percept of the reproduced parameter(s). Such navigation has been termed 'Vector Navigation' by animal experimentalists for obvious reasons (Etienne et al., 1998).

A new task called Complete The Circle (CTC; Figure 5.3) was devised. In CTC, following an outbound stimulus, subjects would be required to continue in the same direction and in so doing return to the origin. The original self-rotation test, essentially a path reversal task, was re-named Go Back to Start (GBS; Figure 5.3). The ability to perform CTC requires converting the stimulus dynamics into position and then navigating to the start using only a position strategy.

Figure 5.3

Schematic plan of GBS and CTC tasks.



We formally assessed vestibular navigation in 12 healthy individuals (mean age 30 years, standard deviation 10 years) during GBS and CTC. Apart from free practice as discussed above, subjects were given practice experiments for both GBS and CTC again without any visual or auditory feedback. During the practice experiment subjects were encouraged to try various strategies but by the end of the practice session they should have decided upon respective strategies for CTC and GBS with which they should stick to during the experimental sessions. There were 4 experimental blocks, 2 GBS and 2 CTC in alternating fashion. The presentation of stimuli in each of the 4 blocks was randomised but the stimuli within a pair of GBS or CTC blocks was fixed. Thus at the end of the experiment, all subjects received the same set of stimuli albeit in different order. In addition the same set of stimuli were used for GBS and CTC.

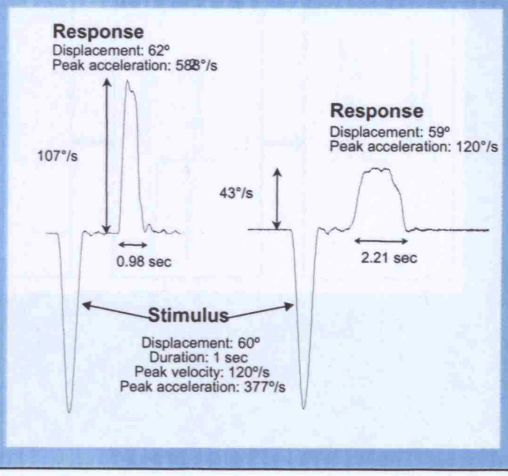
Data recording and processing

The chair tachometer output was recorded at 250Hz and analysed off-line. Figure 5.4 show representative chair velocity traces obtained during pilot studies.

Figure 5.4

Chair velocity recordings from GBS condition.
The left panel shows an individual trace (i.e. not averaged) from a subject attempting to match stimulus kinetics, whilst the right panel shows a trace from another subject attempting to match the stimulus displacement only.

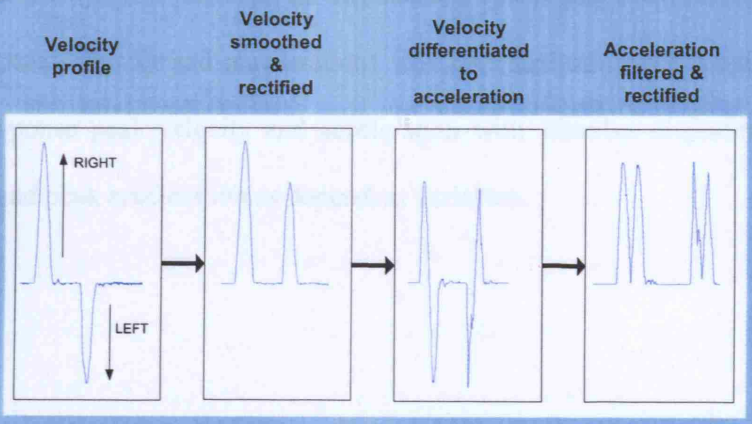
Up is rightward rotation.



Angular displacement was obtained by integrating the velocity trace, peak angular acceleration by taking the maximum value of the differentiated velocity trace, and duration of movement was measured directly from the record. The velocity waveforms were smoothed prior to differentiation (to acceleration) using a using a 5 point moving average smoother. After differentiation, the waveform was filtered using a Predictive Finite Impulse Response Median Hybrid filter (PFMH) (Heinoven & Neuvo, 1988). Figure 5.5 demonstrates the sequence of processing in measuring the peak acceleration.

Figure 5.5

Transformation of velocity trace to acceleration.



Data analysis

Displacement performance:

Quantitative analysis of displacement performance was obtained by linear regression between stimulus and response displacements.

Navigational strategy:

Strategy was also qualitatively assessed by observation of the chair angular velocity records. Figure 5.4 demonstrates how an observation of responses in the GBS task could allude to strategy. Essentially subjects could match the dynamics of the stimulus by reproducing the shape of the stimulus or they could reproduce the displacement; in the latter case the morphology of the response velocity waveform would not match that of the

stimulus. Quantitative analysis of the strategy used in reproducing the stimulus displacement was obtained by multi-regression analysis to identify the stimulus parameters that most predict the response displacement. Encoding of stimulus kinetics by subjects (i.e. peak velocity and acceleration) was also analysed by a multi-regression analysis of response peak velocity and acceleration with stimulus displacement, time, peak velocity and peak acceleration as dependent variables.

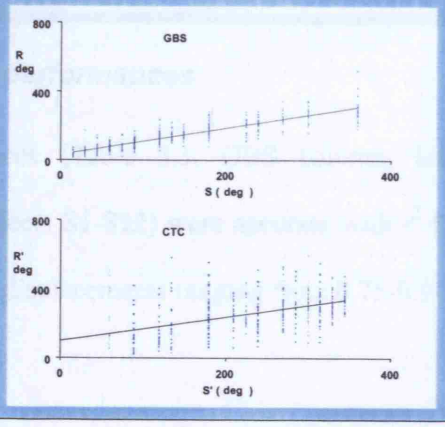
RESULTS

GBS (Path reproduction): Group performance

Sighted subjects were highly accurate in reproducing the angular displacement with a cumulative regression analysis between stimulus (S) and response (R) displacements (Figure 5.6) of $R = 0.76\ S + 31°$ and a square of the correlation coefficient (r^2) of 0.80 ($P < 0.0001$; i.e. r value = 0.89).

Figure 5.6

Group performance. *Stimulus displacement, S vs. response displacement R & R' respectively for GBS (path reproduction) and CTC (path completion) tasks.*



GBS: Group strategy

Inspection of the response velocity traces suggested two broad types of strategy; (1) a velocity profile matching strategy or (2) a displacement matching strategy (Figure 5.4). The overall group strategy was quantified by a multiple regression analysis (n = 561) of the combined responses (Table 5.2) with response angle being the dependent variable and stimulus displacement, peak velocity, duration and peak acceleration as predictors. This showed that whilst stimulus angle was the most important predictor (based upon β values in Table 5.2) of response angle, stimulus peak velocity and peak acceleration but not stimulus duration, were also significant contributors ($P < 0.0001$). Overall, the group reproduced a stimulus displacement by matching both its static (displacement) and dynamic (velocity and acceleration) components.

Table 5.2: Multiple regression- Predictors of response angle

Stimulus angle, velocity, duration, acceleration vs response angle

Model		Angle	Velocity	Duration	Accel.
n	**r^2**	**β**	**β**	**β**	**β**
561	0.84	0.75	0.20	-	- 0.14

GBS: Individuals' performances

Individual performances (Table 5.3, GBS column, left-hand side- *'Displacement performance'*; for subjects S1-S12) were accurate with r^2 for linear regressions between stimulus and response displacements ranging from 0.75-0.94 ($P < 0.0001$ for all).

Table 5.3: Individual performance and strategy

Subject no., sex and age	Displacement performance Linear regression- Stimulus vs response angle				Predictors of response angle Multiple regression for GBS- Stimulus angle, velocity, time, acceleration vs response angle					
	GBS- Angle		CTC- Angle		Model		Angle	Velocity	Time	Accel
	r^2	B	r^2	β	n	β	β	β	β	β
S1 (F – 26)	0.90	1.0	0.18^{Ψ}	0.45^{Ψ}	48	0.81	0.57^{Ψ}		0.34^{Ψ}	
S2 (M – 24)	0.84	0.76	0.79	0.84	48	0.88		0.72	0.38^{τ}	-0.39^{τ}
S3 (F – 26)	0.92	0.83	0.74	0.68	48	0.93	0.68	$.29^{\Psi}$		
S4 (M – 55)	0.82	0.61	0.55	0.81	48	0.83	0.49^{Ψ}	$.40^{\Psi}$		
S5 (M – 39)	0.80	0.63	0.69	0.72	47	0.82	0.70^{τ}			
S6 (F – 24)	0.94	1.0	0.73	0.90	43	0.94	1.00			
S7 (M – 23)	0.89	0.83	0.72	0.84	48	0.90	0.69			-0.23^{Ψ}
S8 (M – 22)	0.74	0.78	0.15	0.38	48	0.78	0.60^{Ψ}			-0.36^{τ}
S9 (M – 22)	0.90	0.74	0.67	0.97	47	0.90	0.78			
S10 (M – 35)	0.76	0.56	0.02	0.11	48	0.81		0.48^{Ψ}		
S11 (M - 34)	0.75	0.58	0.55	0.54	48	0.84		0.71^{τ}		-0.32^{Ψ}
S12 (M - 25)	0.90	0.74	0.69	0.74	48	0.90	0.86			

This shows the correlation coefficients (r^2), the standardised and un-standardised slopes (β and B respectively) and the number of data points per analysis (n) for linear and multiple regressions for individual data. Note that the multiple regression anaylses for subjects B3 and B5 showed that none of the individual independent variables had β values which were significantly different from zero although for both subjects the β-values for 'angle' were only just non-significant. All r^2 and β values have a P value <0.0001 unless otherwise stated (Ψ = P <0.05, τ = P <0.01). Non-significant r^2, B and β values are omitted.

GBS: ***Individuals' strategy***

Subjects' strategy could be obtained by two methods:

(1) Qualitative method: that of inspecting the raw records. Subjects who used a dynamic matching strategy would reproduce the shape of the stimulus velocity profile whilst those matching displacement would produce a step-like response (Figures 5.4 & 5.7).

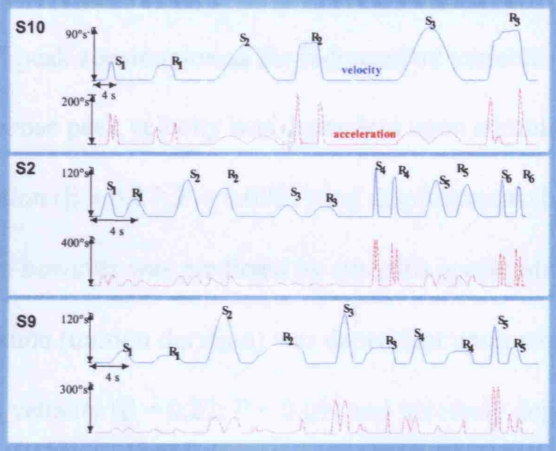
(2) Quantitative method: For each response, angular displacement, peak angular velocity and acceleration and motion duration was obtained. A multiple regression of this data enabled a quantitative assessment of the predictors of response displacement as defined by the standardised slope (β) of the regression with respect to its significance (i.e. $P < 0.05$ that $\beta = 0$) and magnitude (Table 5.3, *'Predictors of response angle'*).

A comparison between the raw traces and the results of the multiple regression analysis showed a good agreement between the two methods in deriving the strategy used by subjects. Compare the data in Table 5.3 and the recorded angular velocity and acceleration traces as shown in Figure 5.7. Thus in figure 5.7 the traces suggest that subject S10 matched the peak velocity but not the peak acceleration of the stimuli; multi-regression analysis for this subject (Table 5.3, right-hand side) confirms the empirical impression. Similarly, S2 in Figure 5.7 is trying to replicate the shape of the velocity profile, implying a matching of stimulus dynamics; this impression is confirmed quantitatively (Table 5.3, right-hand side), in that response displacement is significantly predicted by stimulus dynamics but not displacement.

Figure 5.7

Qualitative strategy in GBS for 3 subjects.

In each panel, the upper and lower traces show the rectified velocity and corresponding acceleration profiles respectively for stimulus (S) and response (R) during the GBS task. The upper panel shows S10's strategy which involved matching the peak velocity but not the peak acceleration. The middle panel shows responses from S2 where there is matching of velocity and acceleration. The lowermost panel shows the response strategy of S9 who ignored stimulus dynamics and recovers the response displacement only.



Indeed S2 reported that he tried to reproduce the 'feel' of the movement and did not try to 'visualise' his position. Figure 5.7 ('S9', bottom) shows the typical responses of subject S9 who matched only stimulus displacement and not dynamics. Overall there were four subjects who uniquely (S5, S6, S9 and S12) used stimulus displacement in deriving response displacement (Table 5.3, right-hand side). Three subjects (S2, S10 and S11) adopted a motion-dynamic matching strategy, with significant contributions to response angle from stimulus velocity, acceleration and/or duration but none from stimulus angle (Table 5.3, right-hand side). five subjects (S1, S3, S4, S7 and S8) showed a mixed strategy utilising both displacement and dynamic data in completing the GBS task (Table 5.3, right-hand side). In summary, subjects demonstrated a variety of strategies with similar accuracy in performing the task.

Encoding of velocity, time and acceleration

Group analysis- A multiple regression analysis (with stimulus displacement, peak velocity, duration and peak acceleration as the independent variables) for sighted group data showed that response peak velocity was dependent upon stimulus velocity ($\beta = 0.42$; $P < 0.0001$), acceleration ($\beta = 0.27$; $P < 0.0001$) and displacement ($\beta = 0.24$; $P < 0.05$). Response acceleration however was predicted by stimulus acceleration only ($\beta = 0.84$; $P < 0.0001$). Response time (motion duration) was dependent upon stimulus time ($\beta = 0.58$; $P < 0.0001$), stimulus velocity ($\beta = 0.22$; $P < 0.01$) and inversely dependent upon stimulus acceleration ($\beta = -0.27$; $P < 0.0001$) but not stimulus displacement ($P = 0.6$).

Individual analysis - Using the same analysis for individual data (Table 5.4) showed that in all but 3 subjects' (S3, S5 & S10), response acceleration was predicted solely by stimulus peak acceleration. Five subjects' (S4, S6, S8, S10 & S11) peak velocity response was uniquely predicted by stimulus velocity. Four subjects' (S2, S7, S9 & S12) response peak velocity was predicted by stimulus peak acceleration and another stimulus parameter. Two subjects (S1 & S3) showed no significant predictors to response peak velocity. Eleven out of 12 subjects' response time was significantly predicted by stimulus time. Of these 11 subjects, 3 had stimulus time as the only predictor of response time (S3, S6, S10). Four subjects (S1, S2, S5, S7) had stimulus angle as a predictor of response time (2 of these were inversely predictive), and 3 of these subjects used a step-response velocity profile (e.g. S9 in Figure 5.7) of relatively uniform peak velocity ('displacement-matching strategy') which explains the correlation between stimulus angle and response time. Five subjects had stimulus velocity as a significant predictor of response time.

Seven subjects' response time was inversely predicted by stimulus acceleration. Overall these results confirm that humans can accurately reproduce stimulus kinetics during vestibular navigation (Table 5.4). In addition, the perceptual representation of head angular velocity appears to be distinct from that of head angular acceleration.

Table 5.4: Individual temporokinetic-matching during GBS.

Subject	**Multiple regression analysis.** **For deriving predictors of response temporokinetic parameters from stimulus angle (θ), velocity (v), acceleration (a) and time (t).**														
	Response peak velocity Versus Stimulus θ, v, t, a					Response peak acceleration Versus Stimulus θ, v, t, a					Response motion duration Versus Stimulus θ, v, t, a				
	Model	θ	v	t	a	Model	θ	v	t	a	Model	θ	v	T	a
	r^2	β	β	β	β	r2	β	β	β	β	r^2	β	β	B	β
S1						0.72				0.85	0.80	0.57		0.34	
S2	0.88		0.80		0.26	0.87				1.23	0.92	-0.69	0.87	0.94	-0.64
S3											0.64			0.60	
S4	0.43		0.74			0.61				0.97	0.81		0.42	0.40	-0.35
S5	0.62			-0.59							0.83	-0.63	0.5	1.20	
S6	0.83		0.76			0.76				1.12	0.72			0.88	
S7	0.85		0.45		0.39	0.91				1.1	0.83	0.50		0.65	-0.33
S8	0.69		0.75			0.68				0.69	0.85				-0.35
S9	0.81	0.61			0.35	0.76				0.74	0.86			0.77	-0.28
S10	0.61		0.99								0.67			0.42	
S11	0.81		0.78			0.82				1.27	0.88			0.82	-0.33
S12	0.71	0.88			0.53	0.59				0.80	0.86		0.56	0.73	-0.41

CTC (Path completion): Group performance

Group displacement performance

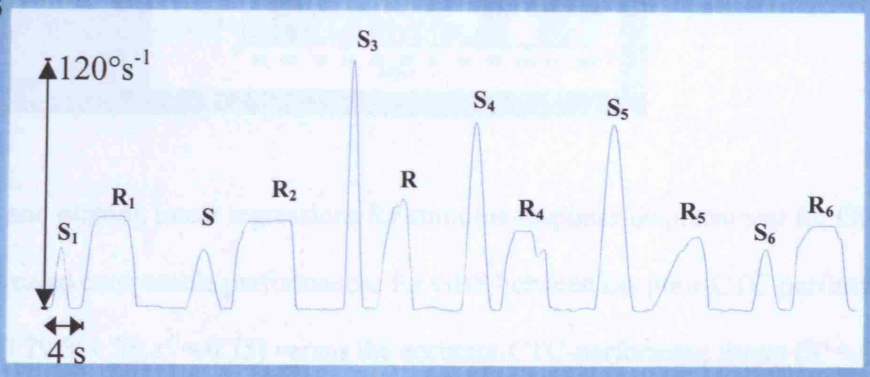
The performance in this task was assessed by comparing the angle required to complete the circle (S′) and the response angle (R′) and was described by $R' = 0.72\ S' + 88°$ and $r^2 = 0.35$ (Fig 5.6). As a group, the subjects showed more variability in the CTC (r^2 significantly different; $P < 0.05$, Fisher's r' transformation) as compared to the GBS task although the slopes of the respective regressions were not significantly different ($P > 0.05$, Students two-tailed t-test).

CTC: Group and individual strategy

Strategy was uniform across subjects in that there was no correlation between stimulus peak velocity vs. response peak velocity; stimulus peak acceleration vs. response peak acceleration and stimulus duration vs. response duration. All subjects employed a strategy of producing a stepwise velocity response (Fig. 5.8).

Figure 5.8

Qualitative strategy.in CTC for S1.



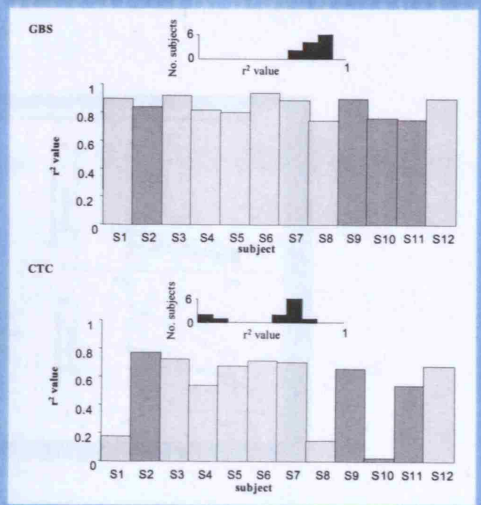
CTC: Individuals' Performance

CTC performance was not normally distributed. There were two clusters (bimodal) at opposite ends of the performance scale as seen in Fig. 5.9. This suggests that the ability to perform this task was an 'all or none' phenomenon as opposed to GBS where performance was normally distributed with a single cluster as seen in Fig. 5.9. Three subjects' CTC performances with low r^2 values (S1, S8 & S10) were responsible for this bimodality (Table 5.7). Separating the data according to CTC performance into two groups (i.e. S1, S8, S10- poor CTC performers versus the other 9 subjects- accurate CTC

Figure 5.9

Distribution of r^2 values obtained for displacement responses in GBS and CTC.

This shows a single cluster of r^2 values for GBS but a bi-modal pattern for CTC.



performers) and plotting linear regressions for stimulus-response displacement for GBS and CTC revealed comparable performances for GBS between the poor-CTC-performing group ($R' = 0.79\ S' + 33$, $r^2 = 0.75$) versus the accurate-CTC-performing group ($R' = 0.75\ S' + 30$, $r^2 = 0.82$). Additionally, the accurate-CTC-performing group showed similar CTC performance ($R' = 0.79\ S' + 54$, $r^2 = 0.55$) to its GBS performance as opposed to the poor-CTC-performing group whose CTC regression yielded $R' = 0.36\ S' + 237$, $r^2 = 0.06$.

This suggests that GBS performance (and strategy; see Table 3) did not predict CTC performance.

Analysis of response displacement performance to 180 degree stimuli

One argument for a difference between GBS and CTC could be that the stimulus-response combinations are different. Thus a 15° stimulus requires a 15° response during GBS but a 345° response in CTC. Uniquely however, a 180° stimulus requires a 180° response for both CTC and GBS. A sub-analysis of the 180° stimulus-response for grouped data showed a significantly lower % error rate for GBS versus CTC (Fig. 5.10).

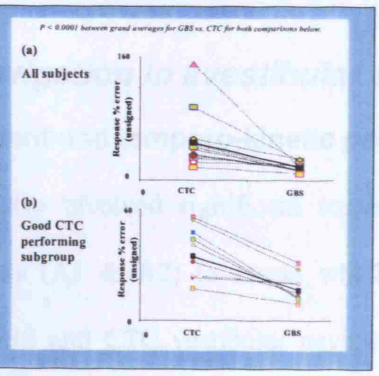
Figure 5.10

Performance for 180 degree stimulus for GBS and CTC.

Percentage error of response displacement compared to stimulus displacement of 180° for GBS and CTC. The graphs show individual and grand average (black squares) responses for:

(a) all 12 subjects

(b) all subjects less the 3 poor CTC performers (i.e. 9 subjects)



Indeed all individuals showed the same bias in more accurate 180° responses during GBS (Fig. 5.10). This confirms the impression that GBS and CTC tasks are performed using different navigatory modes.

Correlating GBS and CTC performances

Simple correlation analysis was used to compare GBS and CTC performance for the 12 subjects by correlating r^2 and slopes for GBS and CTC-derived response-stimulus

displacement regressions. This gave squared correlation coefficients of 0.14 and 0.03 for r^2 and slopes respectively thus confirming that there was no link between GBS and CTC performance. Inspection of Table 5.3 also suggested that there was no link between GBS strategy and performance for either GBS or CTC. Since subjects matching kinetics in GBS would clearly be using a different strategy from that in CTC (a pure spatial task), it may be more appropriate to compare GBS and CTC performances only for those 4 subjects using a spatial GBS strategy. In this case there were again no significant correlations between GBS ad CTC performances as assessed by the response-stimulus displacement regression r squares or slopes ($P>0.05$ for both and $r^2 = 0.21$ and 0.37 respectively).

Vestibular navigation in avestibular subjects

GBS Displacement and temporo-kinetic performance

Since our tasks also involved significant somatosensory stimulation, we tested two avestibular subjects (A1 & A2) to assess whether such stimuli could be utilized in performing the GBS and CTC vestibular navigation tasks. Regressions for their GBS displacement performance gave r^2 values of 0.19 and 0.16 ($R = 0.01\ S + 6°$ and $R = 0.53\ S + 92°$) for A1 and A2 respectively. At lower peak accelerations these subjects did not have any perception of rotation at all and thus did not respond. At higher acceleration rotations, these 2 subjects could perceive somatosensory pressure against the chair. For example for A1, the probabilities of responding following 15.7, 31.4 or 62.8 $°/s^2$ peak acceleration stimuli was 0, 0.5 and 0.75 respectively. We analysed A1's performance following exclusion of stimuli with peak acceleration less than $62.8°/s^2$. Despite this,

displacement performance as defined by stimulus-response regressions gave $r^2 = 0.34$; R = 0.11 S + 11.5°. Kinetic stimulus matching obtained by stimulus-response regressions gave the following results respectively: Velocity: $r^2 = 0.16$, R = 0.23 S + 12.5°/s; Acceleration: $r^2 = 0.08$, R = 0.18 S + 75.2°/s^2; Time: $r^2 = 0.13$, R = 0.19 S + 0.68s. Using a similar analysis, we analysed performance for A2 by removing stimuli whose peak acceleration was less than 47.1°/s^2. For A2, we obtained stimulus-response regressions as follows- Displacement: $r^2 = 0.13$, R = 0.42 + 126.8°; Velocity: $r^2 = 0.14$, R = 0.42 S + 36.7, Acceleration: $r^2 = 0.32$, R = 1.13 S + 127.5; Time: $r^2 = 0.06$, R = 0.14 S + 2s. Thus whilst avestibular subjects could perceive tactile stimuli at higher accelerations, they were unable to utilise this to perform accurate navigation.

CTC displacement performance

Displacement performances as defined by the regressions between angle required and angle made to complete the circle, gave r^2 values for both of 0.05 ($P > 0.05$), i.e. avestibular subjects showed a complete inability to perform this task.

Discussion

Our findings indicate that path reproduction tasks can be successfully performed via multifarious strategies including the use of displacement or motion-dynamic parameters independent of actual displacement. This exclusive use of motion dynamics is exemplified by subjects S2, S10 and S11 who made no use of rotational displacement in GBS, and simply matched kinetics. We suggest that these subjects may also employ vector addition in terms of velocity, time and acceleration; a type of 'navigation' based on 'hodokinetics' since the dynamics of movement are utilised to recover a path. Our results suggest that humans encode a representation of whole-body acceleration distinct from velocity. Animal data suggests that vestibular signals can be encoded in terms of acceleration in the cortex (Grusser et. al., 1990a; Grusser et. al., 1990b; Klam & Graf, 2003) and in head direction cells in the thalamus (Bassett & Taube 2001). In addition almost all vestibular sensitive neurones in the putative monkey vestibular cortex also respond vigorously to somatosensory input such as pressure to the back or neck (Grusser et. al., 1990a; Grusser et. al., 1990b). The results in the two avestibular patients, however, preclude any significant use of somatosensory input in either the reproduction of kinetics or of derived displacement in our vestibular navigation tasks. Thus the encoding of acceleration observed in humans is probably derived by a neuronal computation equivalent to a mathematical differentiation of the vestibular signal.

Inspection of Table 5.3 also shows that humans are able to combine dynamic and static measures of whole-body displacement in reproducing a whole-body displacement. That humans are able to do this suggests that angular displacement, velocity, acceleration and time may be stored in the form of an internal model which relates these individual

parameters of motion and displacement to each other. The form in which inertial head signals are perceptually encoded will be explored further in Chapter 7.

The vestibular navigation task, CTC, compelled subjects to use pure spatial strategies. CTC cannot be done by matching of stimulus vector magnitudes so good performance on GBS does not guarantee competence at CTC. Comparison of individuals' GBS and CTC performances (Table 5.3) shows a striking disparity in performance for some subjects in the GBS versus CTC conditions suggesting that these tasks involve different navigation modes. The use of different navigatory modes is confirmed by the sub-analysis of subjects' 180° responses for GBS and CTC (Fig. 5.10). Clearly, accurate performance on GBS as discussed above, could involve vector subtraction of angular displacement and/or inertial measures without the need for an accurate internal calibration of traveled angular displacement. A GBS performance with low variability (r^2) indicates that the subject's velocity signal, or integral thereof, is stable, but not necessarily calibrated since the ability to match to' and fro' vectors, even if uncalibrated, would alone ensure accuracy. CTC cannot be done by matching of vector magnitudes so good performance on GBS does not guarantee competence at CTC. Intuitively, CTC would require both vector algebra of displacement vectors and an internal representation of a 360° rotation. For example, a hypothetical subject performing CTC with intact vector algebra who incorrectly perceives a stimulus 360° rotation as 270°, would respond with a perceived angle of 90°, i.e. a real response of 120°. A plot of R' versus S' for this subjects would have an intercept of 120° but an r^2 of unity. Thus the r^2 of the CTC performance reflects the ability of a subject to recognise discrete angles as multiples of one another within the spatial setting of a circle. Subjects S1, S8 and S10 show high variability in performing CTC. Their performance in GBS (in particular that of S1 who adopted a predominantly

displacement matching strategy) suggests that their failure in CTC could not be due to an inability to perform vectorial navigation.

One spatial path integration mechanism that could be used for both GBS and CTC, that of a continuously updated heading (analogous to the head direction cell system observed in animals; for review see Taube, 1998), is supported by Ivanenko et al. (1997) in a passive navigation task and by Amorim et al. (1997) in an active locomotor task in the dark. In our experiment, four subjects (S5, S6, S9, S2) showed a pure displacement-matching strategy in GBS. Combining their responses to 180° stimuli for GBS (n = 18 pairs; mean response 162°; s.d. 25°) and CTC (n = 18; mean response 211°; s.d. 57°) showed that GBS and CTC responses were significantly different ($P < 0.01$; Student's t-test). Thus, the data suggests a difference in spatial processing between GBS and CTC in these subjects. Interestingly Amorim et al. (1997) described two different modes of spatial navigation in which subjects oriented themselves towards an external object either via a continuous updating during their locomotion or by an 'effortful' reconstruction, i.e. a spatial inferential process, at the terminus of their locomotor trajectory. Whilst continuous dynamic heading updating is a predominantly automatic process (Ivanenko et al., 1997), particularly compared to the more cognition-requiring spatial inferential mode, automatic updating itself is enhanced by cognitive input (Amorim et al., 1997; Farrell & Thomson, 1998; Yardley et al., 1999). Whilst it is likely that both automatic and cognitive navigational mechanisms are utilized to a greater or lesser extent during the tasks employed here, the main difference between GBS and CTC is that the latter requires an accurate perceptual spatial calibration whereas the former does not.

An 'all-or-none' navigational performance, as observed for CTC, has also been reported in a 3-D vestibular navigation task in humans (Glasauer et al., 1996) suggesting that such bi-modal performance may be a feature of human path integration when an accurate calibration of vestibular-derived space must be employed. Why might this be? It may be that during CTC, some subjects utilize spatial inferential processes which may require increased reliance upon cognitive navigational mechanisms (Amorim et al., 1997; Ivanenko et al., 1997; Farrell & Thomson, 1998). In mathematics, both spatial and numerical strategies can be used to solve spatial problems (Lord & Clausen-May, 2003). It is conceivable that cognitive strategies used in spatial navigation may similarly use either a numerical or spatial representation of angular displacement, in which displacement vector magnitudes are plotted or stored in a format which allows comparison between stimulus angle and an internal representation of a 360° which in turn is used to compute the required angle. Subjects who can do this may or may not be accurate, depending upon the accuracy of calibration of the velocity signal, but their variability is low (viz. high r^2 values for stimulus-response CTC displacement regressions). High variability in CTC implies that a subject is poor at computing the required angle. The mechanisms that might mediate such differences are unclear. Recent animal studies show that there is a tuning of hippocampal cells to environmental geometry as would occur in an Euclidean representation of space, and that this tuning may be experience related (O'Keefe & Burgess, 1996; Lever et al., 2002). That visual processes may also be involved in cognitive mapping but not for vector algebra, is suggested by a group of 6 congenitally blind subjects in whom the GBS-CTC performance differential is even more marked (cumulative r^2 for GBS and CTC were 0.73

and 0.14 respectively). This will be discussed in Chapter 6. The other cognitive mechanism whose failure could explain the 'all-or-nothing' CTC performance would be of working memory. The potential working memory burden for CTC is higher than GBS given the requirement for CTC performance involving manipulating stimulus and response angles from an internal representation of 360° versus maintenance of stimulus angle in GBS. Working memory task performances in general e.g., digit span, usually decline in a step-like fashion when the threshold of working memory capacity is breached.

Alternatively a non-linear process specific to CNS systems specialized for navigation could explain the bimodal CTC performance distribution although the evidence comes mainly from animal studies and its relevance to human navigation remains unclear. Such bimodality has been observed in rats' spatial performance and correlations between ensemble 'place cell' activity in the hippocampus and encoded location in repeated entries into a given environment (Barnes et al., 1997). For a given environmental exposure, the place cells were stable and correlations between repeated exposure epochs were high. In our study, CTC and GBS were performed in a single session in 2 alternating blocks each. In all cases the performances we observed (whether accurate or not) were consistent between the two blocks. Some authors (Redish & Touretzky, 1999) have suggested that the observed bimodal navigation performance in rats is due to the selection of the wrong reference frame and that pre-existing place cell maps for a novel environment do not exist. Other authors (McNaughton et al., 1996; Barnes et al., 1997)

contend that there are pre-existing spatial place cell maps and that the bimodal 'all-or-nothing' performances and ensemble place cell correlations described above were due to incorrect map selection. The human psychophysical analogue of these theories may be wrong selection or lack of availability of the appropriate navigational strategy given that humans use different modes of navigation when locomoting in the dark (Amorim et al., 1997).

Conclusion

Humans perceptually encode inertial signals of whole-body movement in working memory from vestibular input in terms of displacement, velocity, time and acceleration. The ability to 'home' in the dark using only vestibular input over a previously traveled path, i.e. path reproduction (viz. GBS), is common to all individuals. The ability to perform path completion tasks is not universal. Path completion tasks may require the selection of the correct cognitive strategy. Whether this cognitive strategy takes the form of a spatial map or numerical calculation is unclear. What is indeed clear is that the CTC task is not automatic but may require top-down cognitive intervention for its accurate performance. In the next chapter we will investigate how loss of vision at an early age may affect vestibular navigation in an effort to assess the contribution of vision to the development of a vestibular perception.

Chapter 6

VESTIBULAR PERCEPTION IN THE CONGENITALLY BLIND

Introduction

In Chapter 5 we have seen how normally subjects navigate in the dark using only vestibular input. In the light humans' ability to navigate is dominated by vision. Even in the dark, despite proprioceptive and vestibular input, a mental image of our location with respect to a remembered goal may guide our navigatory behaviour. Such visual mechanisms are not available to congenitally blind subjects thus the performance of blind subjects in vestibular navigation and perceptual tasks may allude to the role of vision in the development of vestibular perception in general.

During navigation in the dark, head-in-space displacement can be derived purely from the vestibular signal (Chapter 5, this thesis; Metcalfe and Gresty, 1992; Israel et al., 1995; Berthoz et al., 1995; Israel et al., 1996; Israel et. al., 1997). Angular displacement perception may be obtained from the time integral of the head velocity signal via a process recently called 'Path Integration' (or 'dead reckoning') (Mitttelstaedt M.L. & Mitttelstaedt H, 1980; Etienne et al. 1996; Mittelstaedt H., 2000) requiring a computation of position and trajectory from relative signals of self motion. Sighted navigation utilises visual landmarks and is termed 'Landmark Navigation' (Etienne et. al., 1996), or

'navigation by pilotage', in which positional information can be observed directly. Landmark navigation and dead reckoning are complementary; the former is highly accurate but depends upon environmental cues, whilst the latter, although purely egocentric, requires periodic landmark calibration. Landmark navigation may involve the acquisition of a mental representation of the spatial relationships between landmarks within the environment which some consider to be indicative of a cognitive map (Gallistel & Cramer, 1996; McNaughton et. al., 1996; Etienne et. al., 1996). Whilst the ability to mentally visualise such maps may be the preserve of the sighted, it remains unknown how congenital blindness affects the ability to utilise vestibular signals in either mode of navigation. Previous studies in the blind did not isolate the use of vestibular signals as opposed to proprioceptive (and other) inputs (Loomis et al., 2001; Thinus-Blanc & Gaunet, 1997).

The influence of congenital blindness on vestibular navigation is unknown but is an important consideration given that neuronal systems involved in vestibular-dependent spatial orientation such as head direction (HD) cells in animals, appear to be dominated by visual input (Taube, 1998). For example, a HD cells' firing rate is maximal when the animal's head assumes a specific angular orientation relative to a particular visual landmark. If the animal is rotated in the dark then vestibular input updates the HD cell orientation. If however, the visual landmark is secretly moved, so that when the light is turned on there is a mismatch between the vestibularly updated HD cell's orientational firing and its previous orientation relative to the visual landmark, then the HD cell's orientation is rotated towards the visual landmark (Knierim et al., 1998). Despite this observation, vestibular but not visual ablation, resulted in the permanent disruption of HD

cell function (Stackman & Taube, 1997; Save et al., 1998; Stackman et al. 2002). Thus, when both vision and vestibular input is available, HD cell activity is dominated by vision, yet in the absence of an intact vestibular system, the HD cell system is non-functional. Whilst this conundrum has yet to be satisfactorily explained, it does suggest the pivotal role of the vestibular system in spatial navigation and particularly its key interaction with the visual system in this.

Navigational performance in the congenitally blind during locomotor tasks, for which there is abundant data (Loomis et al., 1999; Gaunet and Thinus-Blanc, 1997), may indirectly reflect vestibular function in this group. During *Route navigation* tasks i.e., walking tasks between locations previously directly linked by locomotor activity, congenitally blind and sighted subjects display equivalent performance (Rieser et al., 1986; Loomis et al., 1999; Gaunet and Thinus-Blanc, 1997). Route navigation mechanisms rely upon a representation of the "path structure" (e.g. 2 steps ahead, 90° right turn etc.) without reference to external landmarks (Lederman et al. 1985; Bigelow, 1991; Foulke, 1982). During *Inferential tasks,* i.e., tasks requiring the derivation of novel spatial relationships from previously experienced spatial measures, congenitally blind subjects show a decrement in performance compared to sighted subjects in most, but not all, studies (Rieser et al., 1986; Loomis et al., 1999; Gaunet & Thinus-Blanc, 1997). If these findings reflect vestibular function in the congenitally blind then they suggest that perception of vestibular signals is intact in this group although the relative failure in 'inferential' navigational tasks may imply a deficit in the utilization of this information during navigation.

Walking tasks, however, tell us little about the vestibular contribution since vestibular and haptic signals cannot be isolated during locomotion. Navigation tasks which isolate vestibular input have demonstrated that humans can orient with only vestibular signals of angular velocity (Chapter 5; Metcalfe & Gresty, 1992; Israel et al.,1995; Israel et al.,1996; von Brevern et al., 1997;Siegler et al., 2000). We thus tested 'homing' ability during angular vestibular navigation for path reversal (*route navigation* – GBS task; see Chapter 5) and path completion (*inferential navigation* – CTC task) tasks in congenitally blind subjects using the same methodology used in Chapter 5.

Path reversal tasks can assess basic vestibular function since this task is impaired in avestibular subjects (Brookes et al., 1993). In addition, the reproduction of vestibular-derived motion-dynamic signals, as occurs in sighted subjects, may inform regarding the perceptual encoding of such signals in the congenital blind. Angular path completion tasks may assess calibrated spatial mechanisms as discussed in Chapter 5.

Congenitally blind subjects may have an impairment in some cognitive aspects of spatial processing (Cornoldi et. al., 1991) rather than differences in the vestibular sensorial transduction process (including the velocity storage mechanism, discussed below). To disentangle the contribution of sensory transduction versus cognitive processes during vestibular navigation in congenitally blind subjects, we assessed their vestibular navigatory capacity during simple path reproduction and path completion tasks. Whilst the path reproduction vestibular navigation task tested the basic fidelity of the vestibulo-spatial transduction process, the path completion task required a greater amount of cognitive processing e.g., adequate capacity of spatial working memory of the type

necessary for manipulation of spatial representations. Given the stability of animal neuronal systems involved in spatial navigation in the face of early or late blindness (Stackman & Taube, 1997; Kneirim et al., 1998; Save et al., 1998; Stackman et al., 2002), and the ability of congenitally blind humans to calibrate egocentric space (Lessard et al., 1998), we hypothesised that angular path reproduction tasks would be little affected by congenital blindness. This would also imply that the perception of the raw vestibular signal (head velocity) and its derived measures (head displacement and acceleration), are not visually dependent. Conversely, human data suggests a relative impairment in specific cognitive aspects of spatial processing in the congenitally blind (Cornoldi et. al., 1991; Thinus-Blanc & Gaunet, 1997). We thus hypothesised that the congenitally blind would show a relative impairment in path completion tasks.

The inconsistency in the literature regarding blind versus sighted subjects' navigational capacity may be related to individual subject differences (Thinus-Blanc & Gaunet, 1997; Loomis et al., 2001). We assessed two factors (a) the vestibular time constant obtained via a perceptual method and (b) the innate skill and lifetime spatial experience of the blind volunteers. The velocity storage mechanism improves the low frequency response of the vestibular input signal (Solomon and Cohen, 1992a,b). Its existence is demonstrated by stepwise rotation of the head to a constant velocity. Following the step, elastic forces exponentially restore the cupula to its resting position with a **time constant** (**tc**) of 7s (Buttner & Waespe, 1981). However, the recorded vestibular slow phase component of the evoked nystagmus decline with a tc of 15s. Thus, the vestibulo-ocular response is prolonged by a 'velocity store' mechanism, effected by brainstem circuits

(Buettner et. al., 1978; Blair & Gavin, 1981; Cannon & Robinson, 1985;). Since congenitally blind subjects have no coordinated eye movement (Kompf & Piper, 1987), we used a perceptual method to obtain the perceptual vestibular tc. Previous studies have shown the perceptual method to correlate highly with brainstem measures of the tc (Okada et al., 1999). Abnormalities in vestibular tc could potentially be inimical for accurate vestibular navigation.

Abnormalities of vestibular tc in congenitally blind subjects could thus allude to a related question: is the emergence and maturation of the velocity store mechanism visually dependent? The velocity store mechanism undergoes visually-mediated post-developmental plasticity as demonstrated in patients with excessive retinal slip who show attenuated time constants (Okada et al., 1999; Grunfeld et al., 2003;). Human neonates' velocity storage mechanism develops only after two months suggesting its visually-dependent maturation (Weissman, et al., 1989; Ornitz et al., 1985), a conclusion supported by animal visual-deprivation studies (Tusa et al., 2001; Harris & Cynader, 1981). There is however no quantitative data regarding vestibular reactions in congenitally blind patients. We tested the hypothesis that the human vestibular storage mechanism is visually dependent with a technique (Okada et al., 1999) previously used to show that the brainstem velocity storage mechanism is accurately reflected at perceptual level. The method permits vestibular time constants to be estimated in patient groups in whom there is no co-ordinated eye movement, e.g. the

Lastly, some authors have argued that reports showing differences between congenitally blind and sighted subjects as being due to inter-individual differences and not to do with early blindness *per se* (Thinus-Blanc & Gaunet, 1997; Loomis et al., 2001). Therefore, we addressed the issue of lifetime physical activity as a possible contributor to vestibular perception at both sensory processing (velocity storage mechanism, see below) and cognitive levels of spatial navigation by use of a questionnaire.

In summary, the hypotheses to be tested are: (1) the development and maintenance of the velocity storage mechanism is visually dependent; (2) perception of vestibular signals, both raw (head velocity) and processed (displacement and acceleration) is not visually dependent (3) navigation tasks which require minimal cognitive input (e.g. path reproduction) are not visually dependent (4) navigation tasks which require cognitive input (e.g. path completion) are impaired in the cognitively blind (4) lifetime exposure to physical activity may affect vestibular perceptual function.

Methods

Subjects

We tested 6 congenitally blind (mean age 38 years, standard deviation 8 years). Blind subjects' characteristics are shown below in Table 6.1. Blind subjects were questioned with respect to lifetime physical activity, particularly those activities requiring use of vestibulo-spatial processing (Table 6.1, bottom). Duration of physical activity was divided into three epochs; 10 years of age or less, 11 to 18 years and after 18 years. One

point was given for reported physical activity in each epoch. Subjects were asked to rate themselves in terms of sporting ability with respect to their blind peers in one of the following categories; poor (0 points), medium (1 point), good (2 points) and exceptional (3 points). Lastly, subjects were ascribed scores for the type of activities in which they participated. More points were awarded for those activities requiring both spatial orientation and vestibular stimulation. Subject B6 scored 3 out of 3 in this category for skiing. In contrast blind cricket involves only minimal vestibular orientational skill since this sport requires primarily co-ordination between hand and auditory cues and the target (a sound-emitting ball) always comes from the same spatial location.

Table 6.1: Subjects' characteristics and life-time activity scores

Subject	Age (yrs)	Sex	*Age and cause of blindness*	Employment	Physical activity (age when started-yrs)	Activity score
B1	50	F	Birth, retrolental fibroplasia	Telephonist	Physical education (<10-16)	1
B2	42	M	Birth, micro-ophthalmia	Telephonist	Blind cricket (11-16)	3
B3	39	F	<10 months, retinoblastoma	Welfare rights worker	Water skiing, dancing (34-present)	3
B4	35	M	<10 months, retinoblastoma	Musician (drummer)	Blind cricket, football (<10-16), music (11-present)	8
B5	26	M	Birth, glaucoma	Sales manager	Blind cricket, bowling (25- present)	2
B6	39	F	<10 months, retinoblastoma	Physiotherapist	Judo, goalball (<10-19), skiing (17-19; 29-present)	9

Activity scoring schema

Duration of activity (0 – 3; 1 point per epoch)		**Subjective report of sporting ability** (0 – 3)		**Degree of Vestibulo-spatial activity** (0 – 3)	
<10	1	Poor	0	Very little or None	0
11-18	1	Average	1	Some	1
>18	1	Above average	2	Medium	2
		Very good	3	Great deal	3

All subjects had orientation and mobility training at 10 - 11 years of age.

Perceptual vestibular time constant- Experimental protocol

Subjects indicated their perceived instantaneous angular velocity of whole-body rotation using the apparatus Figure 6.1 and is based upon the apparatus devised by Okada et al., 1999. It consisted of a motorised rotating chair in which subjects were rotated at a constant velocity of 90°/s for 1 minute and then brought to a sudden stop. In subjects with an intact vestibular system, this deceleration resulted in a sensation of rotation which is in a direction opposite to that of initial chair rotation. Subjects were instructed to rotate a chair-mounted hand-wheel at an angular velocity proportional to their perceived self-rotation. The wheel's central spindle drove an on-axis tachometer (British Encoder Products, UK) whose voltage output was proportional to the angular velocity with which it was turned (see Fig. 6.2, *Results* section). Four stopping responses were obtained for each subject. Auditory cues were removed by the use of white noise masking delivered by headphones.

Figure 6.1

Apparatus for obtaining the perceptual vestibular time constant.

Subjects rotated a chair-mounted wheel at a rate proportional to their perceived angular velocity. The wheel drove a concentrically mounted tachometer whose d.c. voltage output was proportional to the angular velocity of the wheel.

Perceptual vestibular time constant- data analysis

The hand-wheel tachometer output and chair velocity signals were digitised at 250Hz and recorded onto a computer hard disk. An exponential curve was fit (least mean squares method) to the tachometer responses (see Fig. 6.2, *Results* section). The goodness of fit was assessed by the r^2 value.

Vestibular navigation tasks.

We assessed vestibular navigatory capacity using the modified self-rotation test using the protocols described in Chapter 5 i.e. GBS (path reproduction) and CTC (path completion).

Results

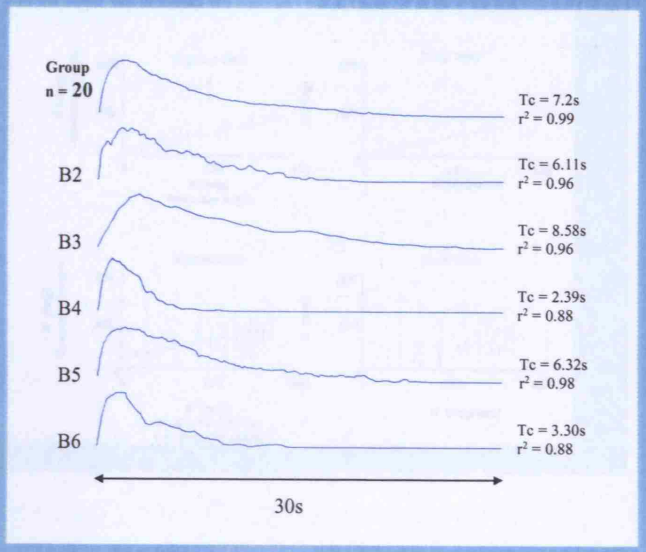
Velocity storage time constant

The blind subjects had a mean time constant measured by exponential fit of the grand average of 7.23s (Figure 6.2). The r^2 of the exponential fit was 0.99. Individual time

Figure 6.2

Averaged tachometer responses used in obtaining the perceptual vestibular time constant.

traces for individual and grouped responses obtained from subjects rotating the chair-mounted wheel as in Figure 6.1.



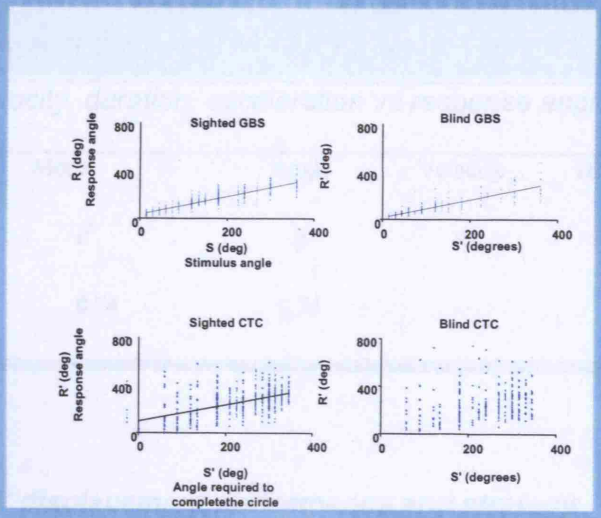
constants ranged from 2.39 to 8.58s (Figure 6.2) and gave a mean time constant of 5.34s (S.D. 2.50). Normative data for sighted subjects has been previously obtained in our laboratory (Okada et. al., 1999) with a mean time constant of 15.8s (S.D. 7.7). The mean time constants between the congenitally blind and sighted groups was significantly different ($P < 0.001$; independent t-test).

GBS (Path reversal task): Group performance

Blind subjects' group GBS performance ($R = 0.74\ S + 17$; $r^2 = 0.77$) was the same as the sighted subjects with no difference ($P > 0.05$) in the B (Students two-tailed t-test) and r^2 values (Fishers r' transformation) between their respective regressions (Fig 6.3).

Figure 6.3

Comparative GBS and CTC performances for sighted and blind subjects



GBS: Group strategy

The overall strategy differed as defined by a multi-regression analysis of the combined responses for the blind group showed that only stimulus angle was a significant predictor of response angle (Table 6.2). This compares with the group strategy by sighted subjects (Chapter 5, Table 5.2, page 60) in whom a greater amount of kinetic-matching strategy was observed.

Table 6.2: Multiple regression- Predictors of response angle

Stimulus angle, velocity, duration, acceleration vs response angle

	Model	Angle	Velocity	Duration	Accel.
n	r^2	β	β	β	β
287	0.74	0.76	-	-	-

GBS: Individuals' displacement performance and strategy

Individual blind subjects' strategies were assessed in the same way as for the sighted group and the same correspondence between qualitative and quantitative methods of analysis was observed. Individual multiple regression analyses (Table 6.3, right-hand side) showed that stimulus angle was the only major contributor to response angle for B1, B3, B4, B5 and B6 (although just non-significant for B3 and B5). B2 showed significant contributions to response angle from stimulus velocity and acceleration. Thus, the blind group overall matched stimulus displacement in the GBS task.

Table 6.3: Individual performance and strategy

Subject no., sex and age	Displacement performance Linear regression- Stimulus vs response angle				Predictors of response angle Multiple regression for GBS- Stimulus angle, velocity, time, acceleration vs response angle					
	GBS- Angle		CTC- Angle		Model		Angle	Velocity	Time	Accel
	r^2	B	n	r^2	β	β	β	β	β	β
B1 (F – 50)	0.73	0.90	0.27	0.82	48	0.74	1.2			
B2 (M- 42)	0.74	0.63	0.22$^{\tau}$	0.49$^{\tau}$	48	0.79		.73$^{\tau}$		- 0.44$^{\Psi}$
B3 (F – 39)	0.71	0.47	0.0	0.0	47	0.73	footnote			
B4 (M – 35)	0.88	0.81	0.77	0.60	48	0.90	.68$^{\tau}$	0.39$^{\Psi}$		- 0.30$^{\Psi}$
B5 (M – 26)	0.61	0.71	0.27	0.46	48	0.63	footnote			
B6 (F - 39)	0.93	1.0	0.90	0.98	48	0.95	1.2		- 0.26	

This shows the correlation coefficients (r^2), the standardised and un-standardised slopes (β and B respectively) and the number of data points per analysis (n) for linear and multiple regressions for individual data. Note that the multiple regression anaylses for subjects B3 and B5 showed that none of the individual independent variables had β values which were significantly different from zero although for both subjects the β-values for 'angle' were only just non-significant. All r^2 and β values have a P value <0.0001 unless otherwise stated (Ψ = P <0.05, τ = P <0.01). Non-significant r^2, B and β values are omitted.

GBS Encoding of velocity, acceleration and motion duration

Group- Response velocity was dependent upon stimulus velocity ($\beta = 0.50$; $P<0.01$) and acceleration ($\beta = 0.18$; $P < 0.05$). Response acceleration, as for the sighted group, was predicted by stimulus acceleration only ($\beta = 0.48$; $P < 0.0001$).

Individuals- (Table 6.4) Three blind subjects' (B1, B4 & B5) response peak accelerations were predicted solely by stimulus peak acceleration. One blind subject's response

acceleration was predicted by stimulus acceleration and duration (B3). The other 2 blind subjects had no significant predictors of response peak acceleration (B2 & B6). Peak velocity response was uniquely predicted by stimulus velocity in only 1 blind subject (B4). One blind subject (B3) had stimulus acceleration as the only predictor of response peak velocity. Two blind subjects (B1 & B5) showed no significant predictors to response peak velocity.

Table 6.4: Individual temporokinetic-matching during GBS.

Subject	Multiple regression analysis. For deriving predictors of response temporokinetic parameters from stimulus angle (*θ*), velocity (*v*), acceleration (*a*) and time (*t*).													
	Response peak velocity Versus Stimulus ***θ***, ***v***, ***t***, ***a***					Response peak acceleration Versus Stimulus ***θ***, ***v***, ***t***, ***a***					Response motion duration Versus Stimulus ***θ***, ***v***, ***t***, ***a***				
	Model	*θ* β	v β	*t* β	*a* β	Model	*θ* β	v β	*t* β	*a* β	Model	*θ* β	v β	*t* B	*a* β
	r^2					r^2					r^2				
B1						0.49				0.84	0.68				
B2	0.63		1.1								0.54			0.71	
B3	0.60				0.80	0.80			0.47	1.42	0.63		0.69		0.75
B4	0.72		0.96			0.78				0.97	0.72			0.71	
B5						0.59				0.44	0.67			0.95	
B6	0.56		0.94			0.59				0.44	0.69	1.07			

These results show that congenitally blind humans can also encode head angular velocity and acceleration at perceptual level; i.e. perception of measured and derived vestibular signals is not affected by congenital blindness.

CTC: Performance.

Blind subjects' group CTC performance was significantly worse than the sighted group with the regression between angle required (S') and response angle (R') being described by $R' = 0.58\ S' + 112°$ and $r^2 = 0.14$ (See Figure 6.3 for graphical comparison; $P < 0.05$ for slopes and B and r^2 values using Students t-test and Fisher's r' transformation respectively). Like the sighted group, there was a bi-modal performance distribution amongst the blind group although in this case a minority of blind subjects (2 out of 6) were accurate in CTC (Table 6.3).

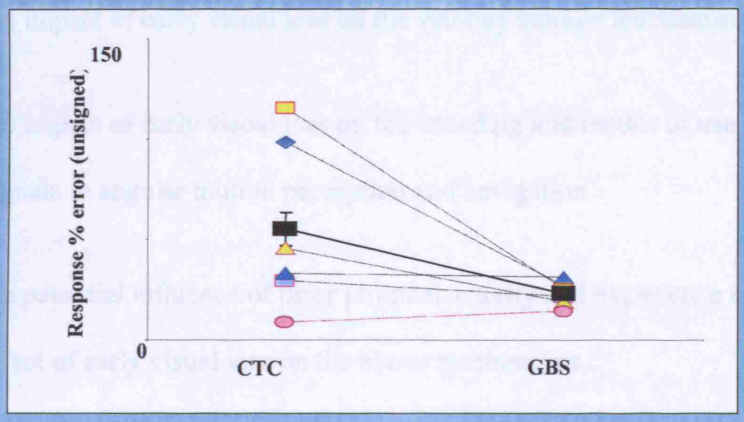
The two subjects with the best CTC performance (B4 and B6, Table 6.3) also had ultra-short vestibular time constants (Figure 6.2). On initial inspection this seems counterintuitive since predominantly large angle and thus potentially low frequency responses, are made in CTC as compared to GBS. However, subjects' responses (including the 2 subjects with ultra-low time constants) in CTC were rarely longer than 6 seconds thus relegating the velocity storage to secondary importance in this task.

Analysis to response displacement performance to 180 degree stimuli

A comparison between CTC and GBS responses to 180° stimuli (Figure 6.4) showed significantly worse CTC performance ($P < 0.001$; paired two-tailed t-test).

Figure 6.4

Performances for 180 deg stimulus for GBS and CTC.



CTC Strategy

As in the sighted group (Chapter 5), all blind subjects' responses showed a step-like 'displacement' strategy and with no significant correlation ($P > 0.05$) between stimulus and response kinetics.

Discussion

The aims of this study were to investigate:

(1) the impact of early visual loss on the velocity storage mechanism

(2) the impact of early visual loss on the encoding and modes of use of vestibular signals in angular motion perception and navigation

(3) the potential influence of prior physical activity and experience in modulating the effect of early visual loss on the above mechanisms.

Perceptual vestibular time constant

We found that vestibular time constants, as measured by perception of instantaneous angular velocity (Okada et al., 1999), are shortened by 50% in the congenitally blind. Thus the velocity storage mechanism is deficient, or absent, in congenitally blind subjects. It has been proposed that shortened time constants in some patient groups is an adaptive response to spatial disorientation and motion sickness (Grunfeld et al., 2003). Indeed, vestibular habituation results in a parallel reduction in motion sickness and the velocity time constant (Dai et al., 2003; Grunfeld et al. 2000). Congenitally blind patients however, do not have increased motion sickness susceptibility (Graybiel, 1970). The other possibility would be an attenuation of peripheral vestibular function in blind

patients but the results of the self-rotation test (GBS task) shown in this paper, and a previous report (Forssman, 1964), discount this. A lack of alternative sensory input with the potential to calibrate the vestibular velocity signal at low frequencies cannot explain the short time constant in the congenitally blind. Recent studies show that auditory spatial localisation can be accurately calibrated via non-visual modalities in the congenitally blind suggesting that a similar calibration may occur with vestibular signals (Lessard et al., 1998; Simon et al., 2002). Whilst we cannot exclude the possibility that the deficient velocity storage mechanism in congenitally blind subjects could be an adaptive phenomenon, the animal data (Tusa et al., 2001; Harris & Cynader, 1981) supports the more likely scenario that the velocity storage mechanism never develops in these subjects. We therefore suggest that the development of the velocity storage mechanism is critically dependent upon early vision although its subsequent plasticity may be driven by vestibular and/or visual mechanisms (Baloh, 1982; Grunfeld et al., 2000).

We observed in two blind patients (B4 and B6) an ultra-short time constant, i.e. a velocity discharging mechanism, implying an active neural suppression (high pass filter) of the semi-circular canal velocity output. This suggests that these subjects would be relatively insensitive to low frequency rotations. Ecologically, congenitally blind subjects would not need a prolonged vestibular time constant since they do not need a VOR and, additionally, prolonged post-rotatory sensations incumbent with longer time constants, would tend to induce disorientation. Thus these two subjects would be particularly sensitive to acceleration transients (or jerk), presumably helping with rapid postural

adjustments and thus stability. Since humans tend to turn their bodies with high frequency rotations, ultra-short time constants are unlikely to disadvantage these subjects. Ultra-short vestibular time constants (1 - 2s) have been reported (Demer and Zee, 1984) in albino subjects with congenital nystagmus, but these were measured with eye movement techniques. A larger study in congenital nystagmus patients, but using a perceptual method, found a time constant of 7s (Okada et al., 1999). The discrepancy between these two studies appears to be due to differences in the methodologies used, since defective ocular-motor (as opposed to vestibular) integrators are likely to be responsible for the ultra-short ocular-motor time constants.

Ultra-short time constants may reflect an extreme form of time constant adaptation but it is not clear how this could arise. It would be possible that a lack of cross-modal (visuo-vestibular) corroboration in congenital blindness may result in a further shortening of the already 'non-prolonged' time constant. In addition, recent studies in congenitally blind humans show that the concentrations of some neurotransmitter receptor subtypes in the cerebellum, but not cerebral hemispheres, differ from sighted subjects (Sanabria et al., 2001; Mishina et al., 2003). It is also known that cholinergic activation in the cerebellum (Tan et al., 1993) can result in a shortening of the velocity storage mechanism. Thus, a combination of disruption of the visual-vestibular synergy during rotation, with the possible correlate of abnormal neurotransmitter receptor concentrations in brainstem structures, may result in ultra-short time constants. On the basis that the ultra-short time constants were observed in the blind subjects with greater lifetime physical activity scores (Table 6.1), it is tempting to speculate that the cerebellum, with its prominent role

in both motor control and neural plasticity (Ungerleider et al., 2002), was involved prominently in these two cases.

Vestibular navigation- path reproduction

The question of spatial perception in the congenitally blind has been an area of much study and debate. Despite the crucial role of the vestibular signals in spatial navigation, the sole use of such signals during navigation by the congenitally blind has not been previously investigated. Until now, it was not even known if the integrity of perceived vestibular signals such as velocity and displacement, were equivalent to that in sighted subjects. A comparison between the results in Chapters 5 and 6 shows that this is indeed the case i.e., the perceptual processing of vestibular signals of angular displacement, velocity, acceleration and motion duration are equivalent between normally sighted and congenitally blind patients. Previous reports in the literature on spatial processing in the congenitally blind have been conflicting, with some reporting an impairment in spatial perception (Thinus-Blanc & Gaunet; 1997) and others a superior ability e.g. in localising sound (Lessard et al., 1998). Some studies report no impairment in navigatory capacity during active locomotion (Loomis et al., 2001). None of these reports however, have assessed congenitally blind subjects' ability to re-orient themselves using only vestibular signals. In those studies finding deficits in spatial orientation in the early blind, an inappropriate cognitive strategy was observed during their performance of the task (Thinus-Blanc & Gaunet, 1997). Incidentally, our findings show that the vestibular

signal required for many of these various spatial tasks, is inherently stable and appears to need no cross-calibration with concurrent dynamic or static visual signals.

Vestibular navigation- path completion

Blind subjects, as we saw for sighted subjects in Chapter 5, subjects showed an 'all or nothing' navigatory performance in CTC although a higher proportion (4 out of 6) of blind subjects were unable to perform CTC as compared to sighted subjects. The influence of geometric cues on allocentric spatial orientation in human infants (Hermer & Spelke, 1994; Gallistel & Cramer, 1996;) rats (Cheng, 1986) and on rat hippocampal cell recordings (O'Keefe & Burgess, 1996; Lever et al., 2002) is strongly modulated by vision. Thus it might be surprising that 2 blind subjects were at all able to perform CTC. The mental representation of environmental geometry used by sighted subjects to perform CTC may be described as visuo-spatial but it is clear that vision does not have a hegemony in all things spatial, particularly over the vestibular system with respect to the head direction cell system (Stackman et al., 2002). Thus a non-visual geometrical representation may be utilised by the two blind subjects who were proficient in CTC. However, the blind subjects were less proficient at CTC as a group. It may be that vision is a more efficient modality for developing a spatial sense but is not an absolute prerequisite.

Saturation of spatial working memory capacity may also explain the 'all or nothing' CTC performance. Cornoldi et al. (1991) found an impairment of spatial working memory capacity of congenitally blind subjects in a primarily haptic task. The CTC task may involve the maintenance and manipulation of encoded and memorised angles, e.g., the stimulus angle (S'), an internal representation of 360° and the target angle (R') to complete the circle (i.e. R' = 360° - S'). Recent functional neuro-imaging studies suggest that the neural correlates of spatial working memory involved in the organisation and execution of a sequence of spatial moves are different from that required for tasks involving active monitoring and manipulation of spatial memory (Owen et al., 1996). It is the latter type of spatial working memory that may be required for CTC and saturation of this form of spatial working memory may result in poor CTC performance. Inter-individual variation in spatial-working capacity may also explain the bi-modal 'all-or-nothing' CTC performance distribution in sighted subjects since when the working memory capacity is exceeded then one would expect a complete breakdown of perceived orientation.

How might we explain the individual deficits in CTC? With respect to the blind group, individual analysis of performance showed that 2 out of 6 blind subjects (B4 and B6), were able to accurately perform CTC. The only difference between these subjects compared to the other blind subjects was the fact that they had increased lifetime levels of physical activity involving vestibulo-spatial tasks as shown by the derived physical activity scores for these subjects in Table 6.1. Indeed Such activities could potentially help to calibrate a sense of space or indeed improve their spatial working capacity for

Euclidean manipulation. The other subjects were either involved in such activities for relatively short periods of time during their lifetime or not at all. It thus appears that activities involving co-ordinated whole-body movements, particularly with multi-modal spatial feedback (e.g. drum playing) may help early blind patients to develop an ability to manipulate space for the successful execution of more complex spatial tasks.

The evidence from animal studies is supportive regarding the maintenance of basic navigational systems in congenital blindness since congenitally blind rats possess normal hippocampal place cell function (Save et al., 1998). Interestingly congenitally blind rats' place cell firing was only co-ordinated following tactile exploration of the environment and concomitant with this was an increased exploratory behaviour in congenitally blind rats (Save et al., 1998). This supports our suggestion that co-ordinated motor activity is required to calibrate vestibular mechanisms in congenitally blind humans.

Thus whilst our data indicate that vision is important for the development of an ability to perform vestibular path completion navigation tasks, it is not absolutely essential. Additionally, vision is not required for the development of a raw vestibular perception. Visual loss may disadvantage individuals with respect to the repertoire and life-time load of spatial activities experienced which in turn may result in specific deficits in manipulating Euclidean space. One explanation could be limitations on specific types of spatial working memory. Conversely the importance of the vestibular system in spatial navigation is demonstrated by the navigational deficits in vestibular patients (von Brevern et al., 1997) and from animal studies in which vestibular ablation but not

blindness, results in a profound and persisting disruption of the head direction cell system (Hill & Best, 1981; Stackman & Taube, 1997; Save et al., 2001; Stackman et al., 2002).

Conclusion

In conclusion, early visual loss results in an absence of the vestibular velocity storage mechanism. This suggests that vision is *sine qua non* for its development. Congenitally blind subjects who are repetitively exposed to vestibulo-spatial stimuli may develop ultra-short vestibular time constants. This may reflect an active neural suppression of the low frequency, potentially disorienting components, of semicircular canal velocity output. Visual mechanisms are not required for the perception of vestibular signals but visual experience may facilitate the ability to manipulate vestibularly-derived angular space during angular path completion tasks. Congenitally blind subjects who are repetitively exposed to vestibulo-spatial tasks may overcome these relative impairments via the development of appropriate cognitive strategies required for the manipulation of Euclidean space. Thus the participation in activities affording spatial calibration of the vestibular signal, if taken up relatively early and continued throughout life, may lead to a normal ability in utilising vestibular signals during spatial navigation. In addition, repetitive spatially-directed motor activity in congenitally blind subjects, may maintain cognitive systems that are required during inferential spatial navigation.

Chapter 7

PERCEPTUAL ENCODING OF VESTIBULAR SIGNALS

Use of the Visual–Vestibular Displacement (VVD) mismatch paradigm.

Introduction

In Chapters 5 and 6 we saw how humans are able to navigate in the dark using only vestibular signals of head velocity by reproducing either the kinetics or displacement of perceived whole-body rotations. The ability to accurately perceive angular displacement using only vestibular input implies that the brain carries out a computation analogous to a temporal integration of the head velocity signal which the vestibular nerve conveys to the brain. The derivation of traveled distance (and orientation) from vestibular (and other sensory) input and its use in spatial navigation, is often called path integration (Mitttelstaedt & Mitttelstaedt, 1980).

It is known that humans can store kinetic parameters of head movement in working memory (Chapter 5; Seemungal et al., 2002; Berthoz et al. 1995, Israel et. al., 1996). Figure 7.1(a) shows how a typical angular head velocity profile angular may be temporally encoded at perceptual level. Current evidence suggests that perceived instantaneous angular head velocity directly reflects the brain-stem VOR signal (see

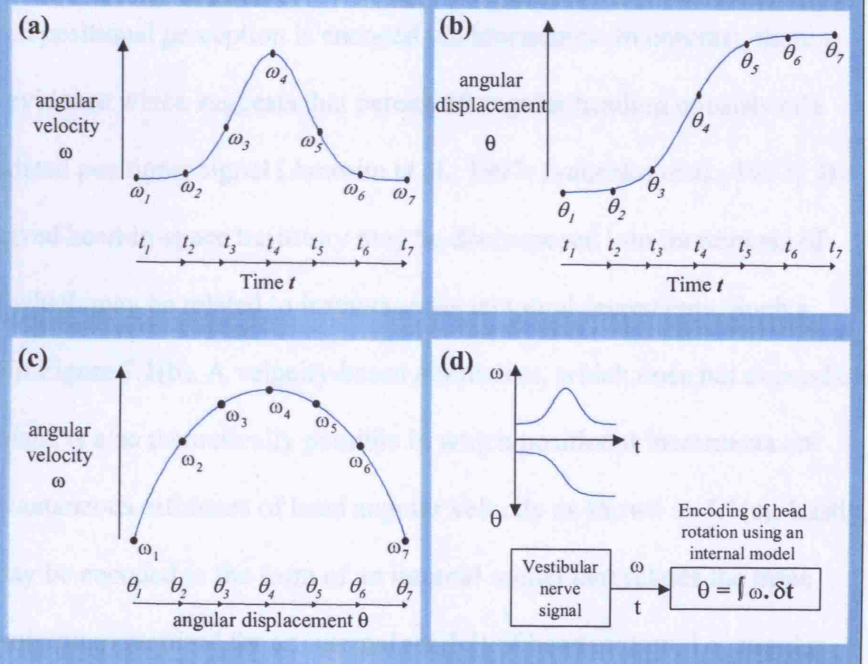
Okada et al., 1999 and Chapter 6 regarding perceptual vestibular time constant) but it is unknown if perceived angular displacement similarly directly reflects the brainstem neural integrator position signal output. Thus it is possible that all the parameters that define a head movement at perceptual level (positional and kinematic) could be processed at brainstem level with perceived vestibular-derived position (like velocity) merely reflecting ascending bottom-up signals. Against this proposition is that all ascending pathways so far identified that convey vestibular information to the cortex transmit head velocity information (Magnin and Fuchs, 1977 and Chapter 4), suggesting that positional information at cortical level, may arise from a separate, supra-brainstem temporal integration of head velocity signals.

Figure 7.1

Perceptual encoding of angular trajectories.

Four different forms of encoding for a raised cosine angular velocity head rotation:

- *Temporal encoding of velocity (ω)*
- *Temporal encoding of angle (θ)*
- *Velocity encoding of angle*
- *Encoding via an internal model relating time, velocity and displacement*



Some authors have suggested that perceived head-in-space trajectories are encoded via a velocity profile (as shown in 7.1(a)) so that it is not displacement which is stored but movement kinematics (Berthoz et al., 1995), with positional information being recovered from kinematics as required. The inference regarding a velocity-based vestibular perceptual system is supported by the observation that the time-course of the exponential fall-off in the magnitude of the VOR following constant angular rotation of the head is also mirrored at perceptual level (Okada et al., 1999).

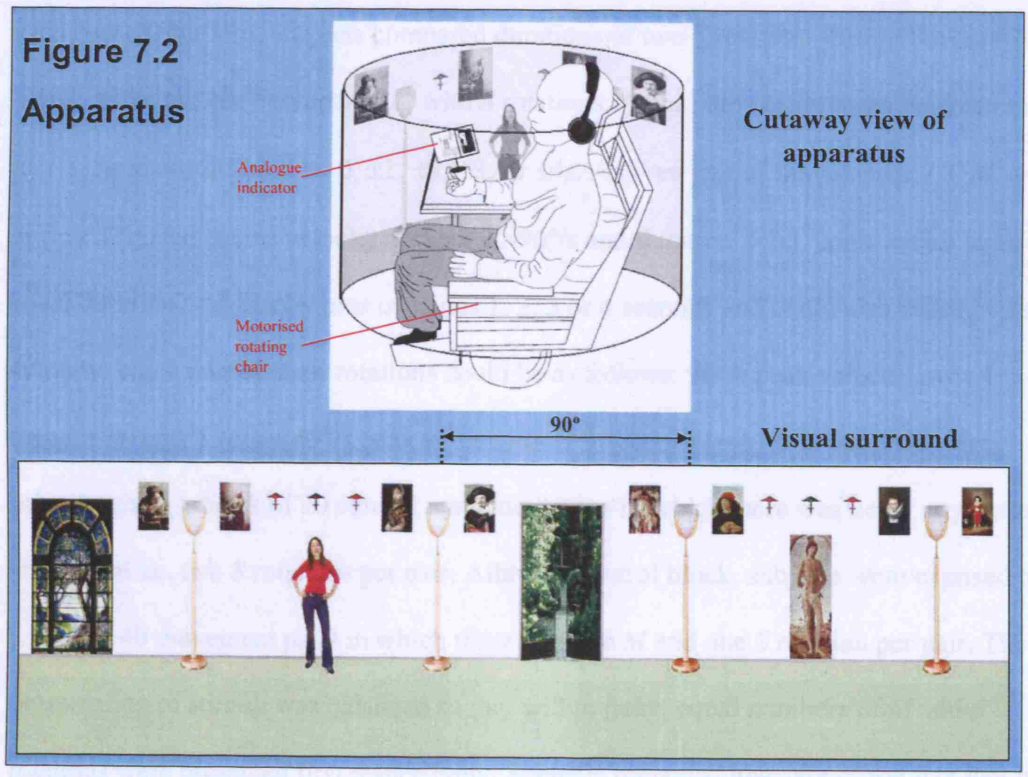
The data regarding a kinematic-based vestibular perception may however not relate directly to displacement perception. Thus, whilst the active reproduction of a passive kinematic profile confirms the existence of such signals at perceptual level, a concomitant accurate displacement performance does not necessarily mean that vestibular-derived positional perception is encoded via kinematics. In contrast, there is psychophysical evidence which suggests that perceived angular heading consists of a continuously updated positional signal (Amorim et al., 1997; Ivanenko et al., 1997). By analogy, a perceived head-in-space trajectory may be decomposed into increments of position each of which may be related to instantaneous temporal increments. Such a model is shown in Figure 7.1(b). A velocity-based alternative, which does not depend on a timing mechanism, is also theoretically possible in which positional increments are mapped onto instantaneous estimates of head angular velocity as shown in 7.1(c). Lastly, head rotations may be encoded in the form of an internal model that relates the three parameters (the minimum required for an internal model) of head motion, i.e. angular velocity, motion duration and angular displacement (Figure 7.1d).

Recent findings have suggested that humans and animals share common neuronal navigational systems (Burgess & O'Keefe, 2003; Ekstrom et al., 2003). Both humans and primates possess spatial view cells within the hippocampus which may indicate visually-derived angular heading (Ekstrom et al., 2003; Roll, 1999). Studies of rat head-direction (HD) cells show that the neural representation of angular orientation is dependent upon both idiothetic (e.g. vestibular) as well as landmark (visual) information (Taube, 1998; Brown et al., 2002). Although hippocampal spatial representations are updated by vestibular input, visual landmark information dominates when visual and vestibular-derived position is mismatched (Goodridge & Taube, 1995; Taube & Burton, 1995; Knierim et al., 1998). Interestingly however, there is a complete and permanent loss of function in neuronal navigational systems such as HD cell and place cells (PC) following vestibular ablation (Stackman & Taube, 1997; Stackman et al., 2002; Russell et al., 2003) suggesting the utilisation of some form of vestibular-based spatial encoding such as a velocity or temporally-based spatial encoding as outlined in Figure 7.1(a-d). Indeed hippocampal neurones may signal not only spatial attributes but also the kinematic parameters by which the animal moves through its environment (McNaughton et al., 1983; Huxter et al., 2003). We set out to assess what form of perceptual vestibular-derived encoding might be utilised at this path integration-landmark navigation interface in human subjects.

Methods

We devised an experiment using a visual-vestibular displacement (VVD) conflict in which there was a mismatch between idiothetic and visual landmark information. Note that this was not the traditional form of visual-vestibular conflict in which there is incongruence between self-motion and optic flow signals. Subjects were rotated in darkness (Figure 7.2 – apparatus) through discrete angles on a motorised rotating chair in the dark, but were allowed vision of the surrounding environment (a large semi-rigid curtain 5 ft in diameter, with images at 15° intervals) at the beginning and end of each rotation when the light was switched on, i.e. only static views of the environment were available. Subjects were naïve to the fact that during some chair rotations the curtain was rotated (called *M* or *Mismatch* rotations) whilst during others it remained stationary (called *S* or *Standard* rotations). After each *M* or *S* rotation, and whilst still in the dark, subjects indicated their perceived position using an analogue indicator with a miniature, to-scale version of the curtain and illuminated by a low intensity LED. The indicator device allowed visualisation of the miniature image in the dark. The sequence was as follows: (i) Lights on- subjects visualize current position relative to the curtain. (ii) Lights off- subjects rotated right or left. (iii) Subjects indicate perceived position. (iv) Lights on- subjects visualize position. (v) Lights off- subjects rotated in the opposite direction. (vi) Subjects indicated perceived position. (vii) Lights on- Subjects indicate if first or second movement was of longer duration. Chair and drum rotations were effected via position-control feedback using a custom-made digital controller in which the dynamic parameters in the feedback control loop could be adjusted.

During the experiments, all subjects were naïve to the fact that on some occasions visual and vestibular displacement was mismatched. Post-experiment interrogation revealed that none became aware of the mismatch during the experiment. To maintain naïvety, subjects participated in only one of the two experiments described below.



Time experiment

In the 'Time' experiment, 16 subjects (8 male, age range 21 – 47 years) were required to perform two tasks: (i) after every rotation and whilst still in the dark, they had to indicate their perceived position using a visual analogue indicator; (ii) after every pair of rotations, they were required to say which of the two rotations was longer in duration. For each pair of rotations, subjects compared durations of two *S* rotations during the control block; in the test they compared *M* with *S* rotations. Actual time differences between a pair of rotations differed by 0, ±1, ±2, ±3, or ±4s. A given pair of movements, i.e. *M* vs *S* or *S* vs *S* (raised cosine velocity of peak 20-90°/s and duration 2-7s), could either be of equal duration or differ by plus or minus 1, 2, 3 or 4 seconds and could also differ in peak velocity; e.g. a pair of chair rotations could be as follows: 90°/s peak velocity over 4 seconds (= 180°) versus 45°/s peak velocity over 3 seconds (= 67.5°). Subjects were initially given a block of 20 control movement pairs in which there was never any curtain movement i.e. two *S* rotations per pair. After the control block, subjects were exposed to a total of 40 movement pairs in which there was one *M* and one *S* rotation per pair. The presentation of stimuli was balanced so that within pairs, equal numbers of *M* and *S* rotations were presented first respectively. Subjects remained unaware of the fact that the curtain could or did indeed rotate. Two features of the experimental protocol ensured that subjects did not simply ignore the experimental paradigm and paid attention only to the motion duration: (i) the requirement to indicate perceived displacement after every rotation, and (ii) since the velocity profiles of a pair of comparison rotations were always

different, then both time and velocity information were required for an accurate estimation of perceived displacement.

Table 7.2: Stimulus pairs used in time VVD experiment

	R_x			R_y			
Rotation pair	T_x (s)	ω_x (°/s)	θ_x (°)	T_y (s)	ω_y (°/s)	θ_y (°)	$T_x - T_y$ (s)
1	3	60	90	3	90	45	0
2	4	45	90	4	90	180	0
3	3	45	67.5	3	45	67.5	0
4	5	20	50	5	30	75	0
5	3	20	30	2	30	30	1
6	4	90	180	3	45	67.5	1
7	4	60	120	5	60	150	-1
8	3	60	90	4	30	60	-1
9	5	45	112.5	3	45	67.5	2
10	5	60	150	3	30	45	2
11	4	30	60	6	20	60	-2
12	3	45	67.5	5	90	225	-2
13	6	45	135	3	45	67.5	3
14	6	30	90	3	60	90	3
15	2	30	30	5	20	50	-3
16	4	90	180	7	45	157.5	-3
17	7	30	105	3	60	90	4
18	7	45	157.5	3	90	135	4
19	2	30	30	6	20	60	-4
20	2	30	30	6	30	90	-4

Velocity experiment

The design of the 'Velocity' experiment was as for the 'Time' experiment but here the variable that was compared was peak angular velocity. All rotations were of constant acceleration (126°/s^2) but peak velocities differed by 0°/s, ± 20°/s, ± 40°/s or ± 60°/s between *M* vs *S* (test) or *S* vs *S* (control) rotation pairs with the actual peak velocities used being 20, 40, 60, 80, 100 and 120°/s. In the 'Velocity experiment' the number of test and control blocks was as for the 'Time experiment'. Only 6 subjects (age range 22 – 49) were tested since there was no effect at all of VVD mismatch on velocity perception, in

particular, during the zero velocity difference situation. In contrast, in the *'Time experiment'*, all subjects showed an effect on time perception which was most obvious when there was no time difference between paired rotations.

Data analysis: For each time difference (see figure 2; $T_x - T_y = 0, \pm1, \pm2, \pm3, \pm4$ sec) between stimulus pairings for *M* vs *S* (test) and *S* vs *S* (control) rotations, there were 32 data points. The McNemar test was used to test the difference between the paired proportions of subjects' responses for the control and test conditions. A probability < 0.05 was considered to be significant. Sigmaplot was used to obtain the least mean

Table 7.2: Stimulus pairs used in velocity VVD experiment

	R_x			R_y			
Rotation pair	V_x (°/s)	t_x (s)	θ_x (°)	V_y (°/s)	t_y (s)	θ_y (°)	$V_x - V_y$ (°/s)
1	40	1	20	40	1	20	0
2	40	1	20	40	1	20	0
3	60	1.5	45	60	1.5	45	0
4	60	1.5	45	60	1.5	45	0
5	80	2	80	80	2	80	0
6	80	2	80	80	2	80	0
7	120	3	180	120	3	180	0
8	120	3	180	120	3	180	0
9	60	1.5	45	40	1	20	20
10	80	2	80	60	1.5	45	20
11	100	2.5	125	80	2	80	20
12	120	3	180	100	2.5	125	20
13	40	1	20	60	1.5	45	-20
14	60	1.5	45	80	2	80	-20
15	80	2	80	100	2.5	125	-20
16	100	2.5	125	120	3	180	-20
17	80	2	80	40	1	20	40
18	100	2.5	125	60	1.5	45	40
19	100	2.5	125	60	1.5	45	40
20	120	3	180	80	2	80	40
21	40	1	20	80	2	80	-40
22	60	1.5	45	100	2.5	125	-40
23	60	1.5	45	100	2.5	125	-40
24	80	2	80	120	3	0	-40
25	100	2.5	125	40	1	20	60
26	100	2.5	125	40	1	20	60
27	120	3	180	60	1.5	45	60
28	120	3	180	60	1.5	45	60
29	40	1	20	100	2.5	125	-60
30	40	1	20	100	2.5	125	-60
31	60	1.5	45	120	3	180	-60
32	60	1.5	45	120	3	180	-60

squares fit a sigmoid function to both sets of test data in estimating the value of $T_x - T_y$ when the probability of subjects saying $T_x > T_y$ is 0.5.

Results

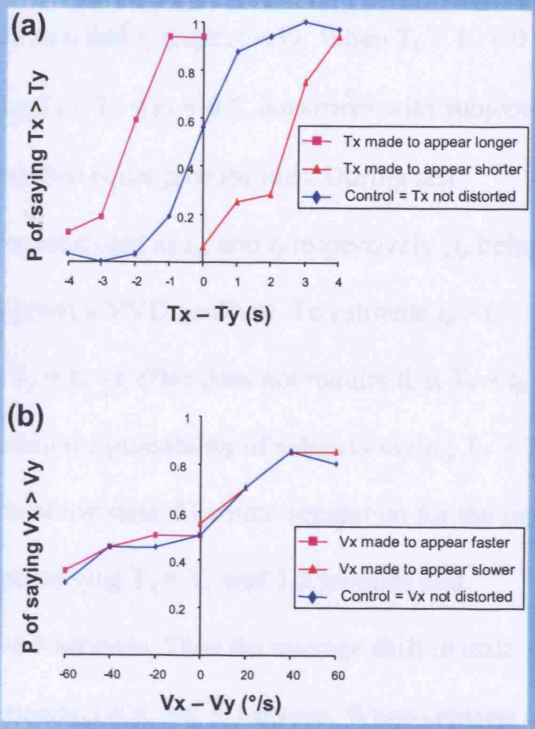
Subjects accurately indicated their displacement. For the 'Time' experiment, linear regressions for grouped subject data for control and test gave $I = 0.96R + 3.9°$ ($r^2 = 0.98$), and $I = 0.97R + 3.0°$ ($r^2 = 0.96$) respectively (where I = indicated displacement and R = real displacement). Regressions for the 'Velocity' experiment yielded $I = 0.95R + 8.0°$ (r2 =) $I = 0.90R + 9.0°$ (r^2 =) for control and 'test' respectively.

Figure 7.3 shows the results of subjects' forced-choice comparisons for the 'Time' (a) and (b) 'Velocity' experiments. By manipulating the perceived displacement we found a significant effect ($p < 0.05$) compared to control, on time comparisons between S and M rotations whose real duration differed by up to 3 seconds. Thus, for a given pair of rotations, if the curtain was manipulated so that the M rotation was made to appear smaller than its real magnitude, then subjects were likely to say that the M rotation was of shorter duration than the S even if the former were up to 3 seconds longer in duration. The effect did not hold for 4 seconds.

Figure 7.3

The effect of a visual-vestibular displacement (VVD) mismatch on perceived angular motion duration and velocity.

(a) The effect of a visual-vestibular displacement (VVD) mismatch on the estimation of perceived angular motion duration: this is expressed as the probability of subjects perceiving T_x, the duration of a rotation R_x, as greater than T_y, the duration of a rotation R_y, for $T_x - T_y$ from -4s to +4s. In control conditions, there is no distortion of visual displacement feedback. During test conditions the visual displacement feedback is distorted on Rx rotations but never on Ry rotations. The probability of perceiving $T_x > T_y$ for test conditions was significantly different ($P < 0.05$) from control for $T_x - T_y = 0, \pm1, \pm2$ and ±3 but not ±4 seconds. **(b)** The effect of a VVD mismatch on the estimation of perceived angular velocity: this is expressed as the probability of subjects perceiving V_x, the peak angular velocity of a rotation R_x, as greater than V_y, the peak angular velocity of a rotation R_y, for $V_x - V_y$ from -60°/s to +60°/s. During controls there is no displacement feedback distortion. During test conditions there is distorted displacement feedback on R_x but not R_y rotations. The probability of perceiving $V_x > V_y$ for test conditions was not significantly different ($P > 0.05$) from control for all values of $V_x - V_y$.



Conversely, if the *M* rotation was made to appear larger, then subjects perceived the *M* rotation to be of longer duration than the *S* rotation if the former were up to 3 seconds shorter duration then the latter. Thus given the appropriate visual displacement feedback, subjects could perceive e.g. a 3s *S* rotation of peak velocity 20°/s, and displacement 30° as of longer duration then a 6s *M* rotation of peak velocity 45°/s, and real displacement of 135° but apparent displacement of 67.5°. VVD mismatch had no effect on velocity comparisons (Figure 7.3b).

Regarding Figure 7.3a, during the control condition, T_x and T_y, the real durations of rotations R_x and R_y, are internally estimated as t_x and t_y respectively. When $T_x - T_y = 0$ sec, for the control, the probability of saying $T_x > T_y$ was ≈ 0.5, consistent with subjects making a forced-choice comparison between two equal probabilities. During test conditions, motion durations T_x and T_y were estimated as t_p, and t_y respectively (t_p being the internal estimate of motion duration T_x given a VVD conflict). To estimate $t_p - t_y$ from the test results, we assumed that $T_x - T_y = t_p - t_y$ (this does not require that $T_x = t_p$ or $T_y = t_y$) and obtained the value of $T_x - T_y$ when the probability of subjects saying $T_x > T_y = 0.5$, by fitting a sigmoid curve to both sets of test data. The time separation for the right hand curve at 50% probability of subjects perceiving $T_x > T_y$ was 1.5 seconds and similarly that for the left-hand curve was -1.8 seconds. Thus the average shift in time induced by the VVD mismatch was 1.65 seconds, i.e. $t_p = t_y \pm 1.65$ sec. When subjects compared t_y and t_p, if $t_p - t_y$ was sufficiently large (e.g. 4 seconds) then the probability of subjects getting the comparison between T_x and T_y wrong, approached zero.

Discussion

We found that visual landmark information updates the perception of inertially-derived angular displacement perception and that this spatial updating also updates the internal estimate of motion duration. This suggests that vestibularly-derived angular displacements are stored in working memory via an internal model (Figure 7.1(d)). This is because an encoding based upon only two parameters (Figure 7.1(a-c)) will not be able

to update the second parameter if the other is changed. Interestingly, the VVD mismatch had no effect upon velocity perception.

The hypothesis that perceived distance is the temporal integral of the vestibular signal has been explicitly tested once previously (Mergner et al., 1996). Similar to our experimental design, Mergner et al. (1996) had two groups performing magnitude estimation procedures following whole body rotations in the dark. The first group assessed perceived total angular displacement, and the second, perceived peak angular velocity. Their experimentally obtained velocity estimates accurately predicted perceived displacements when a simple neural integrator model, assuming an exponential decay (following acceleration transients) in perceived angular velocity of 20s, was employed. This experiment thus showed that perceived angular displacement was directly obtained from perceived angular velocity. The question regarding how these perceived space and motion parameters were stored in memory, i.e., in separate perceptual channels or via an internal model, was not explored. In addition, the issue of perceived time of motion travel was not addressed.

Figure 7.4 shows the possible consequences of a VVD mismatch on the perceptual temporal encoding of angular displacement and velocity (Figure 7.4a & b respectively).

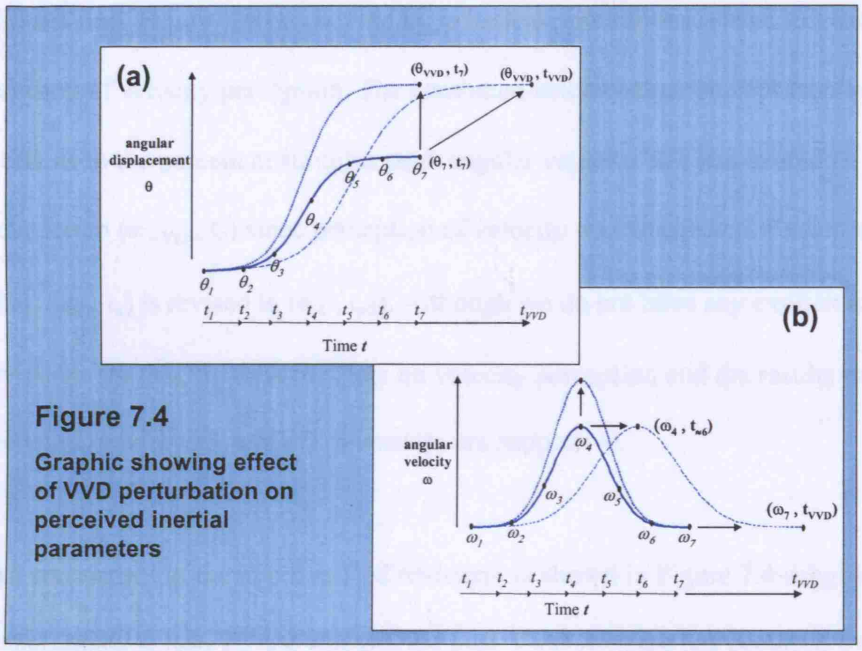


Figure 7.4

Graphic showing effect of VVD perturbation on perceived inertial parameters

In Figure 7.4a there are three possibilities following a VVD mismatch regarding the revision of the internal estimates of motion parameters: **(1)** A cognitively-based 'common sense'decision by the subject to say that the motion duration of the rotation in which there was a VVD mismatch that, for example, expanded the real displacement, was longer since past experience tells us that if we travel for a longer duration we tend to go further. If such a 'common sense' approach was used by subjects then we would have expected to have seen a similar effect on velocity estimations which is not what we found. It follows that there are two other possibilities as shown in Figure 7.4a, i.e. the combined displacement-time percept, labelled (θ_7 , t_7), in general, may be updated to either **(2)** (θ_{VVD} , t_7) or **(3)** (θ_{VVD} , t_{VVD}), where the subscript VVD pertains to the updated percept following a VVD mismatch. Our results support the latter form of updating since the former would not be associated with any motion duration revision post-VVD mismatch but rather would be associated with a revision of velocity percept, which we

did not find. Figure 7.4b shows the hypothetical possibilities related to post-VVD revision of velocity perception. The combined velocity-time percept labelled (ω_4 , t4), pertains to the percept at stimulus peak angular velocity. We can exclude a post-VVD revision to (ω_{VVD} , t_4) since perception of velocity was unaffected. Rather we hypothesise that (ω_4 , t_4) is revised to (ω_4 , $t_{\approx 6}$). Although we do not have any explicit experimental evidence for this, the lack of effect on velocity perception and the results on time perception following a VVD mismatch, are supportive.

An assessment of the hypothesised revisions as shown in Figure 7.4 suggests further experiments to test. To test whether the post-VVD revision has occurred over the entire representation of the time-displacement percept (Figure 7.4a) one could assess the updating of a flashed LED during the subject's rotation in the dark, for example at position θ_4 and compare this to a rotation when there is no VVD mismatch. The subject would simply indicate using the analogue indicator (Figure 7.1) at what position the LED came on. One could similarly test the displacement revision at other positions. Similarly, one could compare the velocity percepts between two rotations at a point in each rotation indicated by an LED flash. One could, for example, compare identical velocity profile rotations, with and without a VVD mismatch, at identical points in the rotation. Thus, considering Figure 7.4b, if the LED was flashed at t_4, the velocity percept in a VVD mismatch producing an expanded percept of motion duration, should result in a perceived angular velocity that was smaller than a non-VVD rotation.

Our finding of the stability of angular velocity perception in the face of a VVD mismatch was unexpected. This may be because the visual signals involved were static, landmark signals, as opposed to velocity-based optic flow visual signals which readily update and hence calibrate, vestibular signals of head velocity. The inability of non-velocity visual signals to update velocity vestibular signals is congruent with current theories (and engineering practice) of sensor fusion in which only signals of the same dimensions (or reference frame) can be combined (Loebis et al., 2002). On the other hand, the failure of velocity perception to change with updating of the position signal suggests that in the context of the internal model, vestibular signals of head velocity are more reliable than the time percept of motion duration. This suggests that angular velocity perception may be more robust than displacement perception to disruptors of cognitive function. This could be easily tested by assessing the relative degradation of velocity versus position perception in the face of increasing cognitive load.

Figure 7.5 demonstrates how the brain may model angular displacements for *M* and *S* rotations respectively based upon a vestibulo-spatial reference frame. For a rotation of real duration *T*, the internal estimates of the angular velocity ω and motion duration t_{vest}, are related to θ_{vest}, the internal estimate of the angular displacement derived from vestibular stimulation, by $\theta_{vest} = \int_0^{t_{vest}} \omega . \delta t$

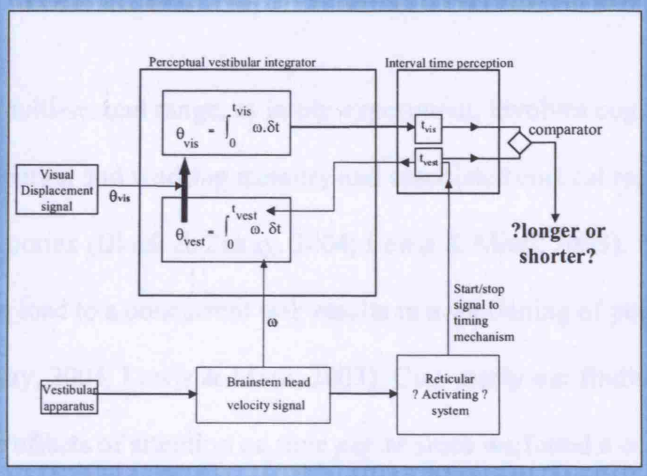
where t_{vest} and *0* are the limits of perceived motion duration in seconds. Consider a VVD mismatch in which the visually perceived angular displacement is θ_{vis}. For a 50% VVD mismatch, the vestibular estimate of displacement (θ_{vest}) is revised to a value that

approximates to the visually derived value (θ_{vis}). To maintain the internal consistency of the model, either ω and/or t must be revised. Our findings suggest that for a VVD mismatch it is the latter and not the former which is revised.

Figure 7.5

Schema of internal model of inertial and temporal estimates of head motion.

For a rotation of real duration *T*, the internal estimates of the angular velocity, motion duration and displacement are ω, t_{vest} and θ_{vest}, respectively.



Vestibular input is *the* crucial sense when vertebrates navigate. Vestibular ablation leads to a profound and permanent disruption of hippocampal place and head direction cell systems (Stackman & Taube, 2002; Russell et al., 2003). In contrast, despite the apparent dominance of the visual system in spatial navigation, congenital blindness has little effect on hippocampal place cell function (Save et al., 1998). Indeed why vestibular ablation and not visual loss, should so profoundly affect neuronal navigation systems continues to puzzle. Our finding that a travelled angle is perceptually encoded via an internal model makes sense if space is encoded in a vestibular-based format. That a static visual (landmark) input can update vestibular-derived space *and* the temporal qualities attached

to that space suggest that visual landmark input may indeed be encoded in a vestibular-based format during spatial navigation. Could this be the explanation for the profound disruption of hippocampal navigational systems with vestibular ablation? If so animal experimentalists should look for evidence of such internal models in the encoding of space within these systems.

Interval timing in the multi-second range, as in our experiment, involves cognitive mechanism such as attention and working memory and associated cortical regions such as prefrontal and parietal cortex (Block & Zakay, 2004; Lewis & Miall, 2003). It is known that increased attention load to a concurrent task results in a shortening of perceived duration (Block & Zakay, 2004; Lewis & Miall, 2003). Conversely our findings are not due to the non-specific effects of attention on time *per se* since we found a congruent and bi-directional effect of expanding or contracting perceived duration dependent upon perceived displacement.

The cortical loci underlying our proposed model in figure 7.4 are unclear. Interval time mechanisms, which are involved in our model, are dependent upon cognitive mechanisms. One locus for interval timing is the prefrontal cortex (Lewis & Miall, 2003), lesions of which interestingly, are associated with deficits in vestibular navigation (Berthoz, 1999). Although vestibular navigation deficits have not been reported with lesions affecting the posterior parietal cortex (PPC) (Berthoz, 1999), PPC neurones encode not only vestibular derived position signals (Snyder et al., 1998) but also encode

temporal intervals of visual stimuli (Leon & Shadlen, 2003). Whether PPC may be involved in the temporal integration of vestibular head velocity signals requires further investigation. Despite extensive demonstration of navigational systems in the hippocampus, lesions here do not result in severe deficits in spatial navigation (Holscher, 2003). This may be because hippocampal navigational systems function in concert with other areas and/or systems (Burgess et al., 2002). The PPC, with which there are strong reciprocal connections, could be one area that may work in concert with hippocampal and parahippocampal areas during spatial navigation (Burgess et al., 2002). Indeed, the rarity of topographical disorientation may reflect the requirement for multiple cortical areas to be lesioned. Luzzi et al. (2000) report a patient who developed topographical disorientation after a right parahippocampal stroke. Like this patient, recent evidence suggests that there is a right-sided dominance of medial temporal lobe involvement in spatial navigation and orientation. Crucially however, the patient reported by Luzzi et al. (2000) had suffered a right parietal stroke previously and one wonders whether it was the combination of lesions which lead to the observed spatial deficit. Prefrontal cortex may also work in concert with parietal and medial temporal lobe areas in the elaboration of the model illustrated in Figure 7.5. In addition to its participation in interval timing, prefrontal cortex is important in the maintenance and manipulation of multiple 'objects' held in working memory (Fletcher & Henson, 2001) as might be required in our VVD task in which parameters such as displacement, time and velocity must be held in memory and manipulated as required.

Conclusion

In conclusion, we have found evidence for the use of an internal model to encode inertially-perceived angular head rotations in humans. Theoretically, the fusion of visual landmark and inertial information during spatial navigation requires the use of a common reference frame. We suggest that this reference frame is vestibulo-spatial and hence may explain the profound effect of vestibular ablation on neuronal spatial systems despite adequate visual function.

Chapter 8

ENCODING OF VESTIBULAR SIGNALS IN HUMAN CEREBRAL CORTEX: an rTMS study

Introduction

The natural stimulus for the semi-circular canals is head angular acceleration. Whilst recent developments in neuro-imaging have allowed neuroscientists to explore neural function in humans, a major limitation of these studies for vestibular research is that head movement is usually minimised (see Chapter 4). Thus vestibular stimulation is obtained by caloric irrigation or galvanic stimulation. Whilst such studies result in the neuro-anatomical mapping of cortical areas related to vestibular processing, they are less able to inform us as to what types of signals with respect to head-in-space motion, are processed at which loci.

We developed a new paradigm using transcranial magnetic stimulation (TMS) to explore what areas of human cortex may be used in encoding of the vestibular signals for use in angular spatial navigation. TMS is based upon the principles of electromagnetic induction, i.e. an electric current generates a magnetic field and conversely an electrical current will be induced in a conductor exposed to a varying magnetic field. The size of the electrical current depends upon the rate of change of the magnetic field. In TMS studies, a transient current is passed through a coil which is applied to the skull. This

brief but rapidly rising and falling current generates a brief but powerful magnetic field which induces a current in the underlying neural tissue and results in a the stimulation of neurones. In many studies single pulses of TMS, each of about 100μs in duration, are used. Following such a TMS pulse, there will be a brief period of a few milliseconds in which stimulated neurones discharge followed by a longer period of suppressed activity. Depending on the strength of the TMS pulse, the resultant neuronal activation-inhibition response may last between 20 – 200ms.

A different approach is to disrupt neuronal function using the 'virtual brain lesion' technique (Pacual-Leone et al., 1999; Walsh & Rushworth, 1999). Single or repetitive (rTMS) pulses of TMS can transiently disrupt the function of an area of cerebral cortex underlying the TMS coil. Using this technique one can probe the function of cortical areas both in both space and time.

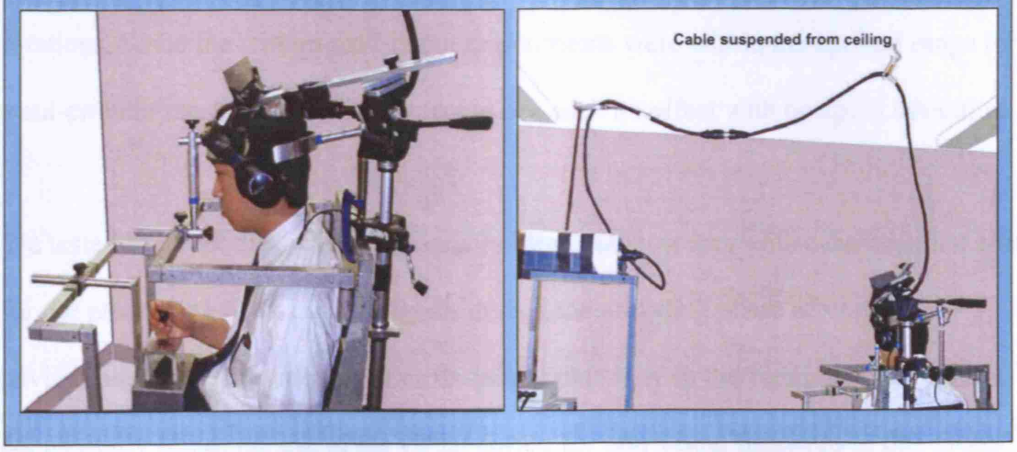
STUDY 1 –Vestibular signal encoding in occipital cortex in sighted and congenitally blind subjects.

We used a modified version of the self-rotation/path reproduction test labelled GBS in Chapter 5, where it is described in detail. The apparatus with the mounted TMS coil is shown in figure 8.1. There were several technical difficulties that we envisaged given that TMS on a rotating chair has not been performed previously. The initial obstacle was how to safely mount a TMS coil on a subject's head whilst rotating the chair. This was overcome firstly by suspending the coil cable above the chair at the centre of the rotational axis. The coil was then held firmly in space and fixed to the chair, above the

subject's head, but not fixed to the head. The subject's head was held firmly in place relative to the chair by anterior and posterior head rests. Thus the coil-fixed-to-chair/head-fixed-to-chair arrangement maintained both safety and good positioning of the coil over the head. In the event that the chair rotated out of control, the coil's vertical, on-axis mode of suspension, removed the possibility of the cable wrapping around the subject. There were no problems with excessive coiling of the cable since the 5m length of cable used allowed greater than 10 revolutions without obvious 'coiling' and our paradigm did not involve rotations greater than 180°. Also since rotations were left-right balanced, there was no net cable twist and never more than 360° twist distributed over 5m. Ultimately many of the envisaged problems did not materialise, and the apparatus was both easy to set up and safe to use.

Figure 8.1

Apparatus



In the first experiment we tried to disrupt encoding of vestibular signals in the occipital cortex using the dominant motor cortex as a control location. We designed an experiment to look at the effect of transiently disrupting occipital cortical function as compared to motor cortex on vestibular navigation. We hypothesised that there would be no difference in navigatory performance between the two conditions i.e. TMS_{motor} vs. TMS_{occ}. Whilst visual imagery is thought to play a role in some forms of vestibular navigation (Rieser & Frymire, 1995), there is no evidence that the occipital cortex plays a role in such imagery. Recent neuro-imaging studies have shown a reciprocal inhibition between patieto-insular vestibular cortex (PIVC) and occipital cortex (Brandt et al., 1998). Such a system could help to disambiguate self-motion perception when confronted with large moving visual scenes which could represent either true self-motion (vestibular input to self-motion) or object motion (visual input to self-motion i.e., vection). Conversely, inhibition of occipital cortex could enhance the processing of vestibular signals in the PIVC. Such enhanced processing could take the form of improved detection of vestibular signals at near threshold values and thus could improve vestibular navigation for low acceleration rotations. Since the stimuli used in our experiments were within the optimal range for the semi-circular canals, we did not expect to see such an effect with occipital inhibition.

We tested the hypothesis that congenitally blind subjects may utilise the occipital cortex for the processing of vestibular signals during the encoding phase of vestibular navigation. There is evidence for cross-modal plasticity in the cerebral cortex of the congenitally blind, i.e. use of the visual cortex for non-visual functions in this group. For example, Kujala et al. (2000) found activation of the occipital cortex during an auditory

task. Sadato et al. (1996) showed activation of visual cortical areas during Braille reading, whereas sighted subjects' visual cortex was deactivated. We hypothesised that congenitally blind subjects may utilise their occipital lobe during the encoding phase of angular vestibular navigation.

Methods

We applied rTMS during the encoding phase of the GBS paradigm. We modified the chair rotational stimuli as used in Chapter 5. Instead of stimuli of duration 1-6s we used 1–3s. Peak angular velocities were 30°/s, 60°/s, 90°/s and 120°/s. 6 right-handed sighted subjects (average age 34 yrs, range 25 – 50 yrs; 5 male) and 6 right-handed congenitally blind subjects (average age 42 yrs, range 28 – 58 yrs; 5 male) were allowed a free choice of strategy i.e. they could use kinetic or displacement matching strategies (see Chapter 5 for details about different strategies). To allow this, the peak angular velocity obtainable by the joystick was 140°/s. As previous (Chapter 5), subjects were allowed practice with the joystick in the dark and a practice experiment without TMS.

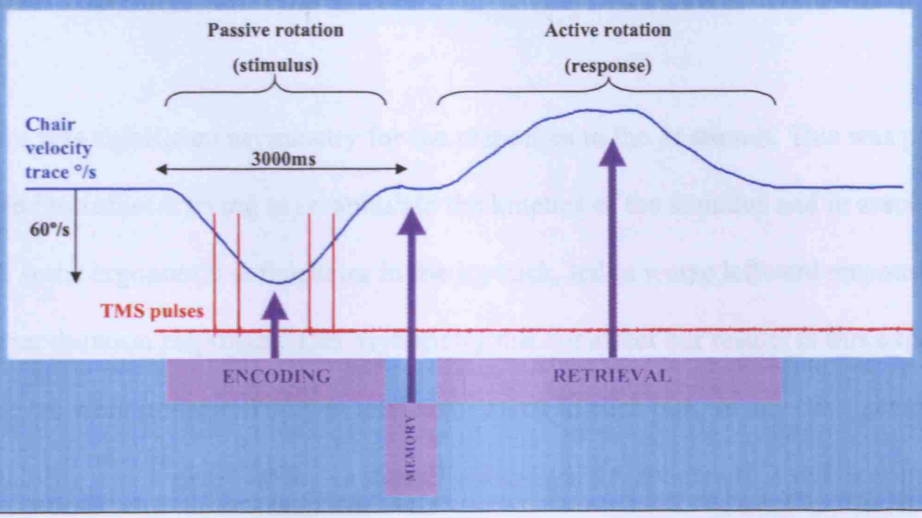
The TMS settings

We first located the motor representation of the 1st dorsal interroseous in the left motor cortex (all right handers) by observing a TMS induced muscle contraction. The motor threshold (MT) intensity to obtain this contraction was noted. We stimulated both motor cortex and occipital cortex at 10% below MT. Figure 8.2 shows the timing of TMS in relation to the chair rotation during the modified GBS task. During 2s and 3s rotations, four TMS pulses (at 400, 600, 1400 and 1600ms from start and 600, 900, 2100 & 2400ms

from start respectively) were applied as in Figure 8.2. Two TMS pulse were applied during 1s rotations (at 300 and 600ms). Also shown on Figure 8.2 are the three cognitive phases that can be assessed using this setup.

Figure 8.2

Timing of TMS stimuli with chair rotation.
Chair velocity trace (blue trace) showing stimulus and response and simultaneous TMS pulses during passive rotation phases.



The *encoding* phase pertains to transformation of the perceived inertial stimulus into the appropriate reference frame and its the laying down in memory; the *memory* phase pertains to that phase during which the encoded stimulus is maintained in working memory; finally during the *retrieval* phase the encoded inertial stimulus is accessed for transformation into appropriate internal estimates (e.g. perceived angle or kinematics of rotation) which can be compared to incoming sensory signals detected during the active reproduction phase.

Results: *Sighted subjects*

The main outcome assessed was percentage error of displacement of the response angle compared to the stimulus for both left and rightward responses. There was no difference between performance for the task during occipital (24.65 %) vs. left motor cortex (24.63 %) stimulation (paired t-test; P = 0.9, n = 144; Figure 8.3a, left-hand side). We then assessed the responses for each stimulus time (1, 2 and 3s) as shown in Figure 8.3b below.

There was significant asymmetry for the responses to the 1s stimuli. This was probably related to subjects trying to recapitulate the kinetics of the stimulus and in association with some ergonomic deficiencies in the joystick, led to worse leftward responses for shorter duration responses. This asymmetry did not affect our results in this experiment since we were interested only in total error made in each task. In any case, since response variability was highest for the 1s stimuli we analysed responses to 2 and 3s stimuli only as shown in Figure 8.3b, right-hand side. Again no significant difference was seen between displacement performance during occipital (17.12 %) vs. motor cortex (18.55 %;) stimulation when responses to 2 and 3sec stimuli were combined (P > 0.05, paired t-test; n = 96 per condition).

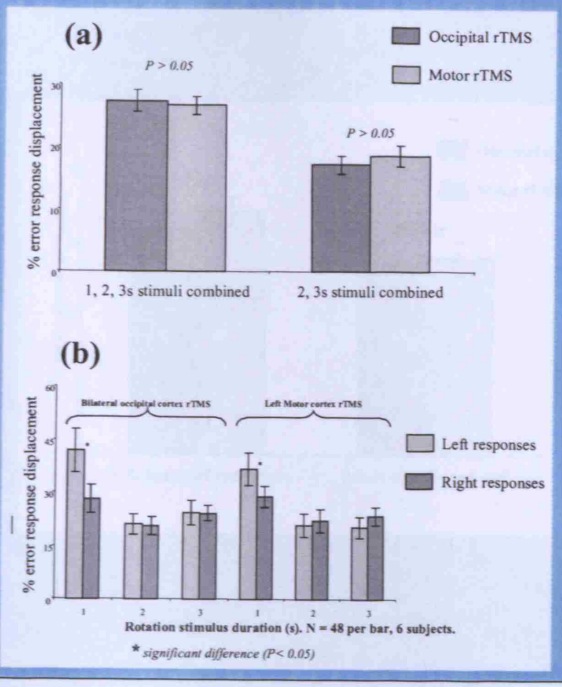
Figure 8.3

Sighted subjects

% error displacement performance for Occipital vs. Motor cortex rTMS stimulation

(a) Performance for combined responses to (left) 1,2 & 3s stimuli and (right) 2 & 3s stimuli.

(b) Performance for responses to 1,2 & 3s stimuli for occipital rTMS (left) and Motor rTMS (right).



Results: Blind subjects

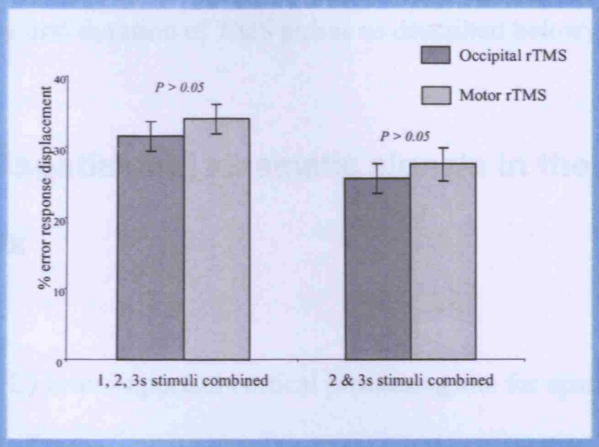
We did not find any significant differences in displacement performance when occipital TMS was compared to left motor cortex TMS either for all responses combined to 1,2 and 3 stimuli (31.5% vs 34.0% respectively ; $P > 0.05$; Figure 8.4, left-hand side) or for combined responses to 2 and 3s stimuli (Figure 8.4, right-hand side).

Figure 8.4

Blind subjects:

% error displacement performance for Occipital vs. Motor cortex rTMS stimulation

Performance for combined responses to (left) 1,2 & 3s stimuli and (right) 2 & 3s stimuli.



Conclusions

Our results did not support the use of occipital cortex in the perceptual processing of vestibular signals in either congenitally blind or sighted subjects. Technical reasons for our negative finding could involve insufficient stimulus either in duration, frequency or intensity at the occipital cortex. Another possibility is that since we allowed subjects a free strategy, i.e. spatial or kinetic matching, then if occipital cortex was indeed being used for a specific function during vestibular navigation, e.g. processing of displacement but not kinetic signals, then the use of a free strategy would dilute any possible observations. We decided to impose a homogenous strategy upon subjects per experiment in the next series of experiments i.e., either displacement or kinetics matching. In

addition, the asymmetrical responses noted for 1s stimuli meant that responses to 1s stimuli should be analysed with this bias in mind. For the second set of experiments we decided to increase the frequency and duration of TMS pulses as described below.

STUDY 2 – Encoding of spatial and kinematic signals in the posterior parietal cortex

The posterior parietal cortex (PPC) is an important cortical processing site for spatial perception and coordinating spatial information necessary for spatially directed motor action (for review see Mesulam 1998; Colby and Goldberg 1999). Vestibular sensitive neurones have been found in area 7a and in the intraparietal sulcus in the ventral and medial intraparietal (VIP & MIP) areas (Brotchie et al., 1995; Klam and Graf, 2003). Brotchie et al., (Brotchie et al.,1995) demonstrated that area 7a neurones had vestibular input. In particular this input was a *position* signal which updated the spatial coding of these neurones with respect to a world-centric (allocentric) frame of reference. They did not explicitly test whether these neurones encoded movement kinetics. Despite this, Israel et al. did not find a deficit in a spatial saccadic task requiring vestibular input for its successful performance (Israel et al., 1995a). Farrell and Robertson (2000) however, found impaired spatial updating in patients with right posterior cortical lesions during passive rotations whilst blindfolded, i.e. a task requiring similar sensory updating as that in the GBS task in Chapter 5. Philbeck et al. (2001) assessed vestibular navigation performance in 6 spatial neglect patients with parietal lesions (5 right parietal). They found that vestibular navigatory capacity was impaired (underestimation of displacement)

when patients underwent contralesional (typically leftward) whole-body rotations as compared to healthy controls and other brain-injured patients. Individual results were not displayed presumably because the study was only powered for group analysis, thus this data relates to right parietal function. Thus, unlike right parietal cortex, no deficits have been reported for left cortical lesion patients in vestibular navigation. One potential reason for the different reported results may be due to the use of different strategies during vestibular navigation. As discussed in Chapter 5, there are multiple strategies available for vestibular navigation including calibrated and uncalibrated spatial strategies as well kinematic strategies. The use of such strategies may not only be idiosyncratic but also dependent upon instruction by the investigator and experimental setting amongst others.

General methods

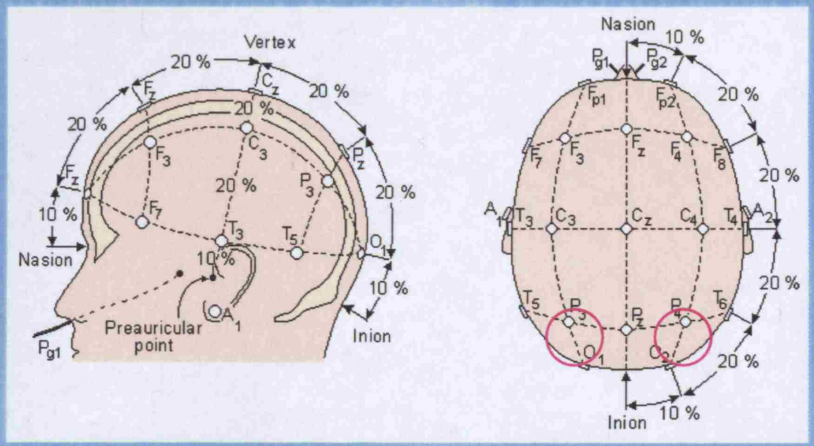
The experimental paradigm was as for the occipital TMS experiments including the use of the left motor cortex as a control site (motor representation of the 1st dorsal interroseous) but with the active site being the right posterior parietal cortex (PPC) and the use of a higher rTMS intensity and frequency viz., 10Hz at 10% above MT applied mid-rotation with the number of stimuli per rotation as follows: 1s rotation - 4 TMS pulses; 2s rotation – 8 TMS pulses; 3s rotation – 12 TMS pulses (i.e. rTMS train durations of 0.3s, 0.7s and 1.1s respectively). We localised the left and right PPC respectively using the 10-20 EEG P3 and P4 electrode placement locations as defined the International Federation in Electroencephalography and Clinical Neurophysiology system of EEG electrode placement (see Figure 8.5; Jasper, 1958). The 10-20 system has been

shown to locate P3 and P4 over right and left overlying Brodmann areas (BA) 7/40 in the region of the intraparietal sulcus (IPS) (Herwig et al., 2003).

Figure 8.5

The 20-10 EEG electrode placement system

P3 and P4 were used in identifying left and right area 7a in the parietal cortex.

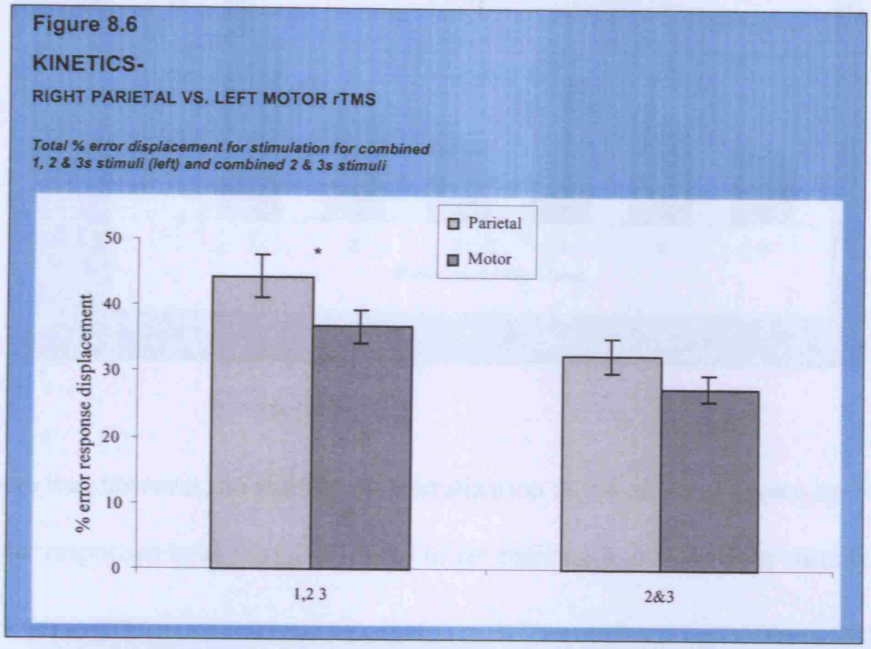


STUDY 2A - Kinematic encoding: right parietal vs. left motor cortex

Six healthy right-handed subjects (one female and five male; average age 35 years) subjects took part in Study 2A. Three of the male subjects had previously participated in Study 1. Subjects were explicitly told to try to recover the kinetics of rotation with as little thought to displacement as possible. Subjects underwent the usual period of practice with the joystick (see Chapter 5, Methods, for details) prior to starting the experiment. The order of motor cortex and occipital cortex stimulation was balanced across the 6 subjects.

Results

The average total % error displacement for all stimuli (i.e. right & left; 1, 2, 3s) showed a significantly worse performance for the right area 7a TMS vs. left motor cortex (Figure8.6; 44.3% vs. 36.8%; P <0.05; n = 288). There was however, no significant

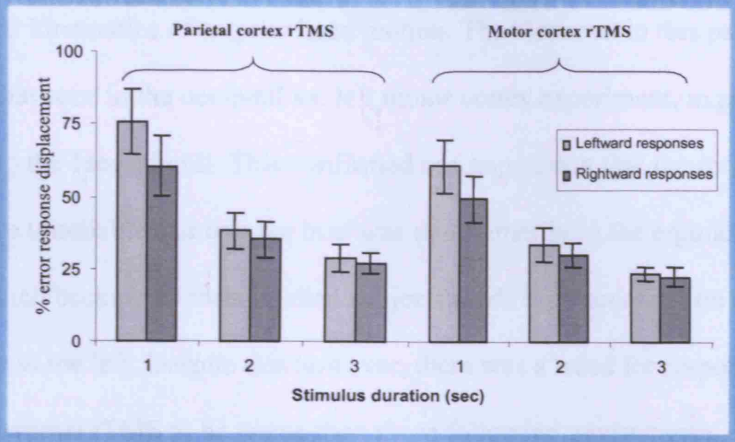


difference between total % error of response displacement between left parietal and left motor stimulation for combined responses to 2 and 3s stimuli. The result obtained for combined responses to 1,2, and 3s stimuli appear to be biased by the large variability in the responses to the 1s rotations which also show consistently worse % error of response displacement leftward as demonstrated in Figure 8.7. The bias was in the same direction as that seen in study 1, i.e. worse leftward responses. Significantly, subjects in Study 1 were allowed free choice of strategy including kinetic matching.

Figure 8.7

KINETICS - Rt PPC vs. Lt Motor cortex

Total % error displacement for stimulation for 1, 2 & 3s stimuli



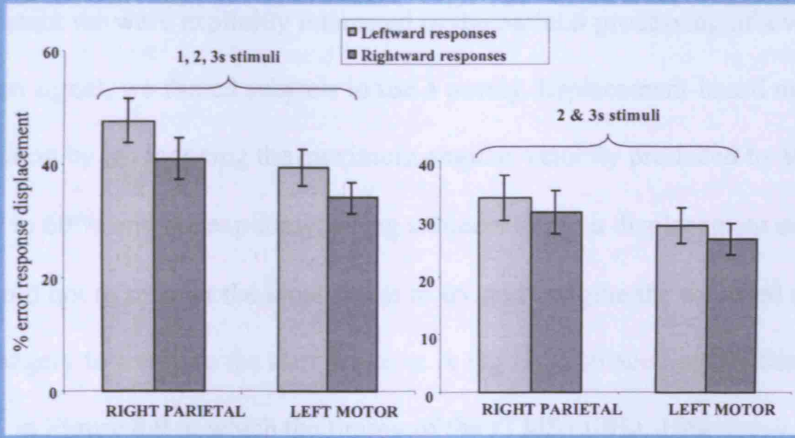
There was however, no significant lateralization in the effect as shown by Figure 8.8, for either responses to all stimuli (1,2,3s) or for responses to 2 and 3sec stimuli.

Figure 8.8

KINETICS-

RIGHT PARIETAL VS. LEFT MOTOR rTMS

Total % error displacement for Right Parietal and Left Motor Cortex comparing left vs rightward responses



Conclusions

These results suggest that rTMS to the right IPS had no significant effect on the encoding of vestibular kinematics of angular head motion. The bias seen in this paradigm was similar to that seen in the occipital vs. left motor cortex experiment, in particular for responses to the 1sec stimuli. This confirmed our impression that the responses to 1sec stimuli were unreliable and that the bias was due primarily to the ergonomics of the joystick which became important when subjects made high acceleration responses particularly to the left. Despite this however, there was a trend for responses made following parietal rTMS to be worse than those following motor cortex rTMS.

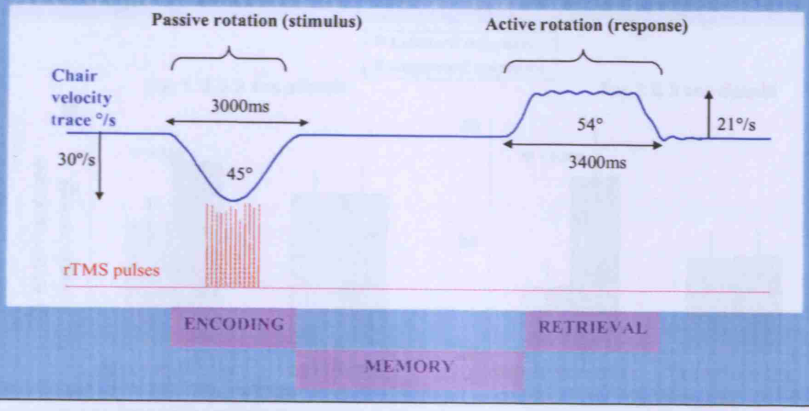
STUDY 2B - Spatial encoding: right parietal vs. left motor cortex

We decided to focus the analysis on responses to 2 and 3sec stimuli since responses to 1sec stimuli appeared to be highly variable as well as showing a directional performance bias (worse with leftward responses). This variability and bias was exaggerated when subjects set out to recapitulate the kinetics of head motion. In addition, since in this experiment we were explicitly interested in the parietal processing of a vestibular-derived position signal, we forced subjects to use a purely displacement-based mode of angular orientation by (a) reducing the maximum angular velocity produced by the joystick from 140°/s to 60°/s and (b) explicitly telling subjects to use a displacement strategy; subjects were told not to recover the kinetics but to try and imagine the travelled angle and to use this imagery to return to the start position. A typical displacement-matching trace is shown in Figure 8.9 in which the timing of the rTMS (10Hz, 10% above MT as for Study

2A) relative to the chair rotation is displayed. We included 1s stimuli but were mindful of the asymmetrical responses engendered by 1s stimuli since subjects tended to reproduce some of the stimulus acceleration characteristics with higher frequency rotations. The same 6 subjects who participated in the Study 2A took part in Study 2B.

Figure 8.9

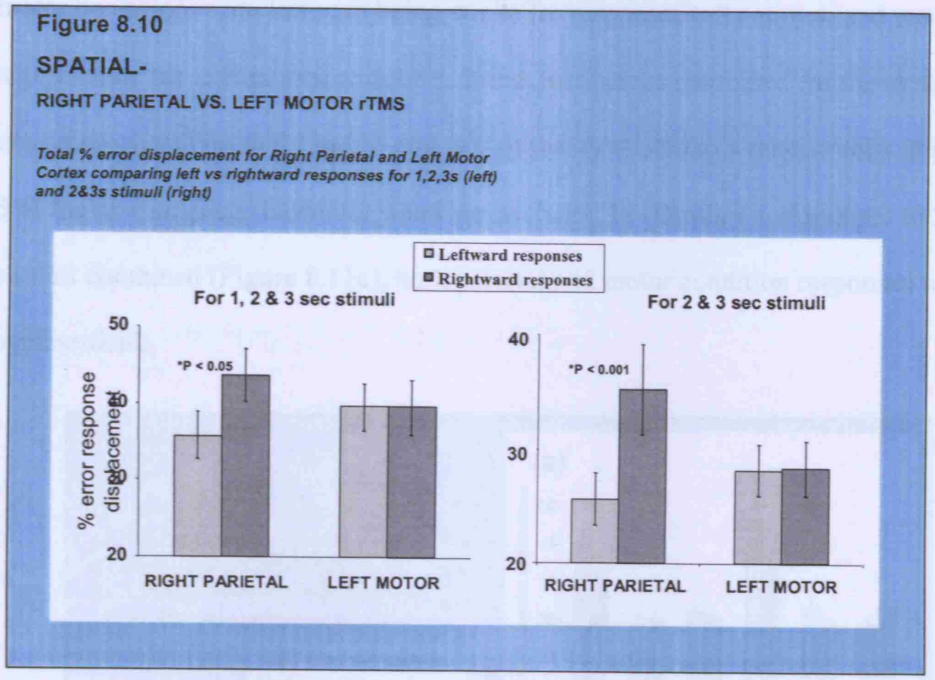
Chair velocity response during enforced spatial strategy. *(compare with Figure 8.2.)*



Results

The total % error of response displacement (right and left responses combined) was not significantly different between the two conditions (right parietal rTMS: 39.75% vs. left motor cortex: 39.58; $P > 0.05$). There was however a significant response asymmetry with rTMS of the right parietal but not left motor cortex for all responses (Figure 8.10). When responses to 1s stimuli were excluded the asymmetry in the parietal condition became even more pronounced whilst the motor cortex condition responses remained highly symmetrical. Note that that asymmetry was in the opposite direction to that

previously observed (in Study 1 and 2A) which we had ascribed to subjects' manual coordination when trying to recapitulate high acceleration stimuli. In addition the subjects had become proficient at the task, particularly when asked to recover displacement and made even easier with the lower peak velocity joystick setting.

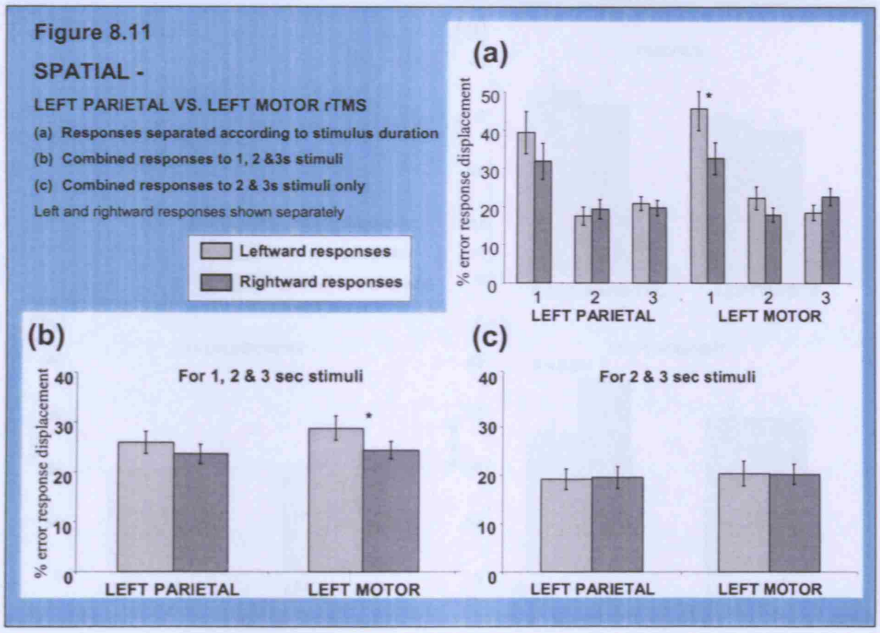


STUDY 2C – Spatial encoding: left parietal vs. left motor cortex

We tested 6 right-handed subjects, 3 of whom participated in both Study 2A and B. The average age of this group (5 male) was 32 years. The task and conditions were identical to Study 2B except for the side of parietal rTMS, in this case left parietal.

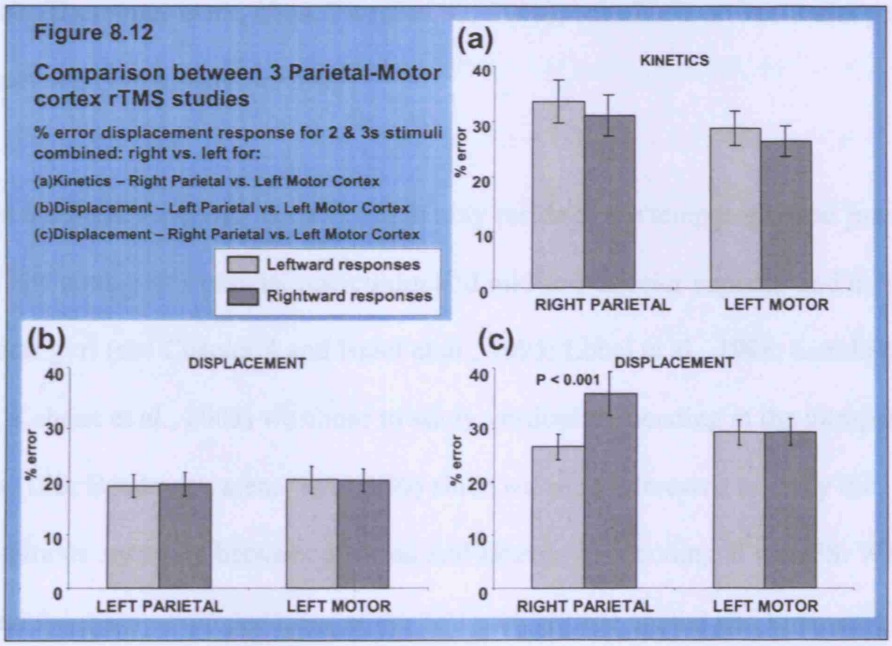
Results

As in part 2B, there was no significant difference in the total % error of response displacement (right parietal rTMS: 27.71% vs. left motor cortex: 26.58%). Again, as previously seen, there was a trend for an asymmetry in response for both parietal and motor conditions with leftward being worse for responses to 1s stimuli and reached significance for 1s rotations and for 1, 2 and 3s rotations combined for the motor condition only (Figure 8.11a&b) and was probably related to a relative lack of practice in 3 of the new subjects. However when we excluded 1s stimuli, i.e. responses to 2 & 3s stimuli combined (Figure 8.11c), both parietal and motor condition responses were highly symmetrical.



Finally, Figure 8.12 compares the results from the three parietal tests for 2 and 3s stimuli. Essentially this shows no effect of rTMS except for a significantly worse performance for rightward versus leftward responses for right parietal rTMS. Note the motor cortex

results show a high degree of symmetry. Direct comparison in terms of absolute magnitude of % error of responses between different conditions is not valid since the studies were not done in the same session. Previous data obtained from pilot experiments during the development of the GBS experiment (Chapter 5) demonstrated that for a given subject, path reversal vestibular navigation performance remained stable within a given session but may vary between sessions. Despite this, the combined % displacement errors for the rTMS studies ranged between approximately 20 – 35% which compares to that in the GBS task (Chapter 5) of 26.40% for 12 sighted subjects (without rTMS) for 288 responses to 1, 2 and 3s stimuli (note: this value incorporates subjects' preferred strategy from position-matching to highly kinetic-matching).



Discussion

Repetitive TMS applied over the right IPS in the region of Brodmann areas (BA) 7/40, during the encoding phase of passive leftward rotations, resulted in a significantly worse navigational performance as compared to that for passive rightward rotations and to the motor cortex rTMS control condition (Figure 8.12c). Repetitive TMS applied to the left parietal cortex had no significant effect on response symmetry and in addition there was no difference from control (Figure 8.12b). Our data also shows that right PPC rTMS had no effect on the encoding of movement kinematics. The disruption of contralateral visuospatial function in normals has been demonstrated by rTMS to the right PPC in normals (Bjoertomt et al., 2004; Fierro et al., 2000), but effects on vestibular perception have not been previously reported.

Whilst the main vestibular cortex in man may reside in the temporoparietal junction (TPJ) and contiguous parietal operculum and mid-to-posterior superior and middle temporal gyri (see Chapter 4 and Israel et al., 1995; Lobel et al., 1998; Suzuki et al., 2001; Kahane et al., 2003) we chose to study vestibular encoding at the intraparietal sulcus (IPS; Brodmann areas 'BA' 7/40) since we were interested to study the dichotomous encoding between position and kinematic encoding at the IPS. Whilst both IPS and the main vestibular locus at the TPJ both encode spatial and kinematic parameters (Grusser et al., 1990; Klam & Graf, 2003a,b), we hypothesised that the IPS may be more biased towards spatial rather than kinematic encoding given its pivotal role in visuospatial function (Andersen et al., 1999). The evidence for vestibular encoding at

the IPS comes from animal single neuron studies (Fredrickson et al., 1966; Snyder et al., 1998; Klam & Graf, 2003a), human neuroimaging (Bottini et al., 1994; Lobel et al., 1998; Dieterich et al., 2003; Bense et al., 2000) and human electrical cortical stimulation (ECS) studies (Foerster, 1936; Blanke et al., 2000). Foerster (1936) reported two patients who sensed whole-body rotation and motion of the environment with ECS in the IPS. Blanke et al. (2000) reported a patient who sensed rightward whole-body rotation without rotation of environment with ECS in the left IPS.

The above finding from Blanke et al. (2000) suggesting a contralateral vestibular cortical encoding, is supported by human neuroimaging studies albeit with a bias for increased activation in the non-dominant hemisphere (Bense et al., 2000; Dietrich et al., 2003). Dieterich et al. (2003) observed maximal activation in the right hemisphere of right handers to vestibular stimuli producing a leftward slow phase eye movement (i.e. sensed self-motion to the left). Vestibular stimuli inducing sensed self-motion to the right in right handers resulted in a increased left hemisphere activity compared to right but was still of lesser activation than that in the right hemisphere with stimuli inducing sensed left motion. The converse was observed for left handers.

Given the above data, we were thus surprised when we did not obtain a positive effect with rTMS at the left IPS following our result from right PPC rTMS in our right handed subjects. Why might this be? The data from Kahane et al.s' large ECS study (>200 patients and 10,000 ECS sites) showed that 10 out of 12 right hemisphere ECS stimuli resulted in perceived rotations to the left but 2 out of 3 left-sided stimuli also resulted in

leftward rotations. The small number of left-sided stimulus loci make the degree of left hemisphere contra- or ipsilateral encoding difficult to comment upon however, is the discrepancy in numbers between right and left cortex indicative of an asymmetry in allocation of resources to vestibular encoding between hemispheres? The larger number of right sided ECS locations make the interpretation here more robust regarding laterality and suggests that the right vestibular cortex is highly lateralised albeit with a similar absolute allocation of resources as compared to the left hemisphere regarding encoding right-directed vestibular motion signals.

Congruent with human neuro-imaging and ECS studies, animal studies report a predominantly contralateral representation of vestibular signals (Klam & Graf, 2003a,b). Unfortunately the animal data does not fully clarify the issue because Klam and Graf (2003a,b) as well as Grusser et al. (1990a) all recorded neurones in the left hemisphere so a left-right comparison, unlike the neuroimaging studies, is lacking. Their observations from the left hemisphere are however pertinent. Grusser et al. (1990a) found a left cortical contralateral preponderance for vestibular velocity signals of 53% for posterior insular vestibular cortex (PIVC) units using a phase shift analysis (i.e. comparing sinusoidal rotation profile with time-locked neuronal response). Using a similar analysis Klam and Graf (2003a) found that 68% of vestibular-sensitive IPS neurones encoded contralateral rotation. Klam and Graf (2003a) however also used a random stimulation experiment to decorrelate position, velocity and acceleration stimulus parameters and then performed a multi-regression analysis to assess the parameters to which neurones were responding to. Angular velocity encoding was found in 100% of units with 50% of

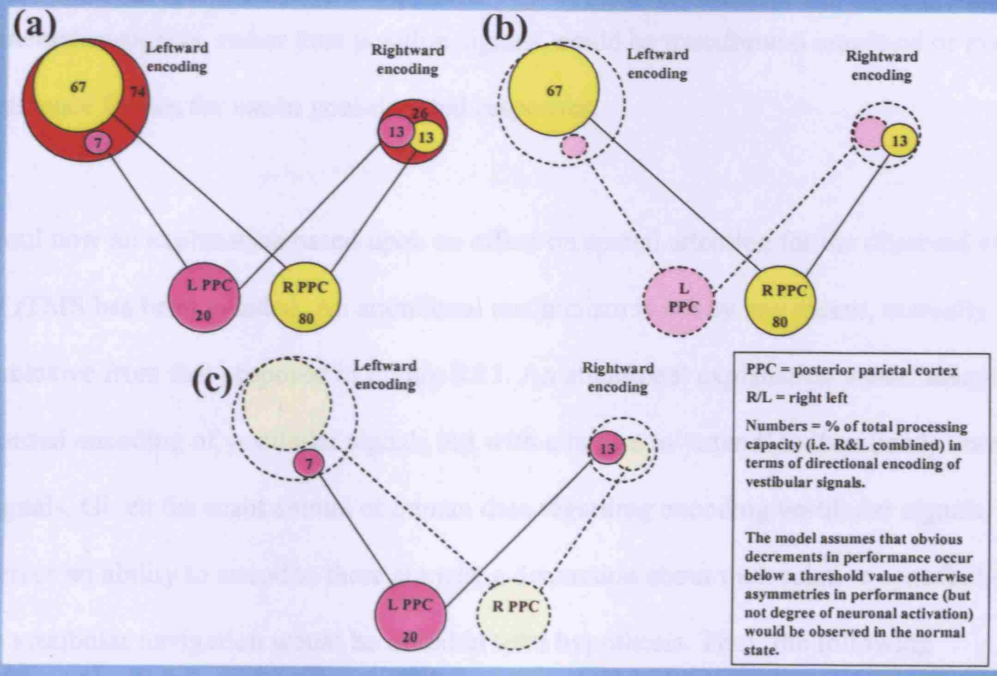
neurones encoding contralateral motion using a linear multi-regression fit (53% using a non-linear fit). These data thus suggests that left posterior parietal cortex vestibular encoding, when compared to the human data (i.e. Kahane et al., 2003; circa. 85% right ECS sites showed contralateral encoding) is less asymmetrical than the right.

The model shown in Figure 8.13 attempts to combine the animal and human data discussed above based upon an asymmetrical allocation of resources and 'degree of contralaterality', between right and left hemispheres in terms of direction of vestibular motion processing. Since the proportions of directional encoding for units in animal IPS and PIVC in the left hemisphere are similar (Grusser et al., 1990; Klam & Graf, 2003), it is assumed that a similar relationship exists between the human analogues of PIVC (i.e. primarily the TPJ and associated areas; see Chapter 4 and Kahane et al., 2003) and the IPS. Extrapolating from Kahane et al.s' data (2003) would suggest that the right PPC has 80% of the total resources allocated to vestibular motion processing in the PPC and this is partitioned into 67% and 13% for encoding leftward and rightward vestibular inertial signals respectively. For the left hemisphere, Kahane et al.s' (2003) data suggests an ipsilateral bias (2 versus 1 ECS locations), however, given the small numbers we have inverted the proportions, i.e. contralateral bias (2:1), in keeping with the left hemisphere data from Grusser et al. (1990a) and Klam and Graf (2003a,b). The model also assumes that there is a threshold value in terms of resource allocation above which performance in terms of vestibular encoding is normal. In the model, a threshold of e.g. 10% would mean that in 8.13a or 8.13b, no deficit is apparent, even when the left PPC is lesioned since the right PPC provides sufficient resources to encode rightward vestibular signals. In 8.13c,

however, following a right PPC lesion, the ipsilateral encoding provided by the left PPC is insufficient to maintain adequate performance. The presence of a threshold to performance predicts that following a left PPC lesion, vestibular encoding should show a performance decrement if the residual functional capacity is challenged. Experiments to test this have not been performed although right hemifield visuospatial function is impaired with left PPC lesions (Han et al., 2004).

Fig 8.13 Model of asymmetric vestibular cortical resources between hemispheres.

Proposed model showing relative allocation of resources between hemispheres in terms of directional encoding of vestibular derived motion signals: (a) shows the normal state (b) left PPC lesion (c) right PPC lesion.



Previous vestibular navigation experiments in patients with right parietal lesions have been inconclusive either showing no effect or a decrement in performance compared to controls or other brain damaged patients (Tropper et al., 1991; Israel et al., 1995; Farrell & Roberson, 2000; Philbeck et al., 2001). Of these experiments, our task was the only

pure vestibular navigation task in which stimulus and response phases were under vestibular guidance. Other tasks for example, required the use of pointing (Philbeck et al., 2001) or saccades (Israel et al., 1995). The transformation of vestibular signals into a visual or arm spatial reference frames could occur at a different locus to that for a task requiring a purely vestibular spatial reference frame. For example, visually-guided versus proprioceptively-guided reaching is known to involve different reference frames and neuronal substrates (Battaglia-Mayer & Caminiti, 2002). In addition our demonstration of the use of different strategies (Chapter 5) in vestibular navigation is pertinent since kinematics signals, rather than position signals, could be transformed into hand or eye reference frames for use in goal-directed responses.

Until now an explanation based upon an effect on spatial attention for the observed effect of rTMS has been avoided. An attentional mechanism is not by any means, mutually exclusive from that proposed in Figure 8.13. An attentional explanation would assume a normal encoding of vestibular signals but with a failure to 'attend' to the already encoded signals. Given the scant animal or human data regarding encoding vestibular signals versus an ability to attend to these signals, a discussion about their relative contributions to vestibular navigation would be mired in total hypothesis. Thus, the following discussion, for purposes of clarity, will not differentiate between encoding or attentional mechanisms *per se* as an explanation for our findings, although most of the references are from the attentional field.

Thus the model (Figure 8.13) regarding a right parietal lobe bias for spatial processing, albeit visuospatial (as opposed to vestibulospatial), is not new (Vallar et al., 1996; Mesulam, 1998; Driver and Vuilleumier, 2001). In addition, the idea of a bilateral but unbalanced distribution of PPC resources as described in Figure 8.13 for spatial processing is supported by several studies. Sack et al. (2002) found bilateral IPS activation via fMRI (functional MRI) during a visuospatial task whose performance was disrupted by rTMS applied to the right and not left PPC. Functional imaging evidence from healthy and brain lesion subjects, suggest that whilst there is a contralateral predominance in PPC contribution to visuospatial function, there is indeed an asymmetrical contribution to visuospatial function since right PPC also appeared to contribute to both visual hemifields (Corbetta et al., 1993, Martinez et al., 2001; Han et al. 2004). In addition, left parietal damage is associated with mild but definite deficits in engaging attention in the right visual field (Han et al. 2004). It may be that the PPC either provides the spatial maps to or engages the appropriate maps in, occipital and frontal areas during visuospatially coordinated motor tasks (Sereno et al., 2001; Han et al., 2004). The PPC could subserve a similar role in vestibular perception, in this case engaging areas such as MST (medial superior temporal cortex) that signal whole-body motion from optic flow (Froehler & Duffy, 2002) and the main vestibular cortical areas in the TPJ and superior temporal gyrus. Indeed the ability to toggle attention between different modalities is important for the perception of self-motion. That such a process does occur is suggested by the reciprocal-inhibition between primary vestibular and visual cortices (Brandt et al., 1998) and it would be interesting to see the modulatory effect of PPC inactivation on this temporo-occipital interaction. An experiment using

combined PET (or fMRI) and rTMS could be specifically designed to explore this question. However, neuro-imaging techniques suffer from their inability to measure brain activity during natural vestibular stimulation. rTMS by itself is offers a tool with which we can further tease out the role of the PPC and other brain areas in modulating attention, encoding, memory and updating of vestibular signals during natural vestibular stimulation.

Chapter 9

Cortico-brainstem dissociation during whole-body angular rotation in yaw

Introduction

In Chapter 8 we looked at where vestibular signals may be encoded in the cortex. Chapter 7 looked at how such signals may be encoded at perceptual level and also touched on the issue of correlating signals, arising at brainstem level, which eventually ascend to perceptual, presumably cortical level. In this final experimental chapter, a new method to simultaneously assess and thus to compare, perceptual and VOR thresholds to angular acceleration, is described.

The idea for this experiment was derived from the unpublished clinical observation that some elderly patients do not experience a sensation of vertigo despite clear vestibular-induced nystagmus (e.g. during a caloric test). The reason for this cortico-brainstem vestibular dissociation is speculative but may be related to diffuse degeneration of cortical areas (e.g. from small-vessel vascular disease or neurodegenerative diseases) subserving vestibular perception given the extensive vestibular cortical representation. Thus dizziness is not a consequence of brainstem activation *per se*, it is the result of the

activation of higher order centres including cerebral cortex as confirmed by human electrical cortical studies in which vestibular sensations are elicited without any oculomotor response (See Chapters 4 and 8 as well as Blanke et al., 2000; 2002; 2004 and Kahane et al., 2003).

We hypothesised that a failure to perceive vestibular sensations may contribute to dizziness via visuo-vestibular mismatch in the light and to gait disorders in the dark due to a failure to perceive low frequency body oscillations in the absence of vision. We devised a semi-automated simple test to investigate the magnitudes of the physical thresholds of perceptual and VOR nystagmic responses to natural semicircular canal stimulation.

Although the natural stimulus of the semi-circular canals is angular acceleration of the skull, the obtained values at which human subjects can detect rotational acceleration, has varied considerably when one reviews the attempts to measure this over the past century (See Chapter 3 and Guedry, 1974). Apart from the differences in the mechanical devices used to accelerate human subjects, differences in the dynamics of rotational stimuli used may explain the wide variability in estimated angular acceleration perceptual thresholds. Further variability in thresholds studies results may come from comparisons between studies in which thresholds are defined either as a conscious perception of rotation, by the emergence of a nystagmic response or the use of oculogyral illusion thresholds. The oculogyral illusion, which is the illusion of a fixed small target in the dark moving in the

opposite direction to the rotation of the observer, is probably caused by suppression of the VOR nystagmic response (Evanoff & Lackner, 1987). Concurrent input to motion perception from vestibular and visual stimuli may thus explain previously reported oculogyral thresholds which were lower than nystagmic thresholds (Clark & Stewart, 1969). However, even studies carried out in total darkness suggest discrepancies between perceptual and nystagmic thresholds. For instance, Okada et al (1999) noticed that, at the end of a rotational response elicited by suprathreshold angular velocity steps, subjects normally cease to report a rotational sensation before the slow phase ocular response ends. This finding was interpreted as being due to a difference between perceptual (cortical) and nystagmic (brainstem) vestibular thresholds. This interpretation was in turn based on informal reports in the literature (Benson, 1968; Hood, 1984) but there are scant quantitative data to substantiate this presumed threshold dissociation. We addressed this issue directly by simultaneously measuring perceptual and nystagmic vestibular thresholds in the same individuals. Furthermore, we preliminarily compare data in young and older subjects since absolute or relative changes in these two thresholds could partly account for the high prevalence of balance problems in the elderly population (Colledge et al., 1994; Davis, 1994).

Methods

Subjects

Participants belonged to a young (n=14, range 19-37, mean 23yrs) or older (n=9, range 56-75, mean 63yrs) group. All subjects were healthy and not taking any regular medication.

Apparatus

Subjects were seated in a motorized chair which rotated about an earth-vertical axis. The head was in the normal upright position and supported by semi-circular rest which stabilized both the neck and head. The chair was driven by a DC-motor under velocity servo-control using tachometric feedback. Velocity commands to the servo were provided by a 16 bit DA output from a PC. Chair velocity was obtained by via an off-axis, directly-geared tachometer. The outputted velocity signal was associated with a noise level that allowed a velocity resolution of 0.024°/s, thus giving a 0.005°/s^2 acceleration resolution over a 5s time period. Chair angular acceleration was obtained off-line by differentiating the recorded angular velocity. Horizontal eye movements were recorded from the right eye using infrared oculography (Iris, Skalar, Delft, NL). Ocular movements, chair velocity and responses for perception of left and right motion were digitised at 200Hz. A chair-mounted bi-directional joystick was used to by subjects to signal perceived rightward or leftward motion.

Experimental procedure

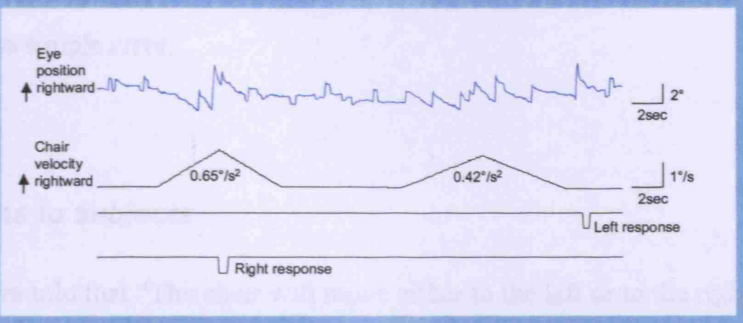
Experiments were conducted in the dark. The task of the subject was to indicate the perceived direction of motion, left or right, using a bi-directional joystick. A computerised staircase algorithm (see MOBS procedure below and 13) was used to determine subjects' perceived angular acceleration. Chair motion in either direction was associated with a vibration that was felt by most subjects. For chair velocities above 2.5°/s this was a 3 Hz vibration, measured with an angular rate sensor (gyroscope; Silicon

Sensing Systems, Plymouth UK), whose RMS amplitude was 0.21°/s; for chair velocities below 2.5°/s the vibration RMS was less than 0.035°/s. This confound was obviated, however, by asking subjects to indicate the direction of motion rather than when they first felt any motion. The directional response also allowed us to assess any intra-individual vestibular asymmetries. White noise at 60dB was transmitted through earphones. Following a single practice trial (in which the MOBS procedure was run until a perceptual threshold was obtained), three further thresholds were obtained via the MOBS procedure. Subjects were exposed to triangular velocity profiles lasting 10 seconds (5 s acceleration, 5 s deceleration). There was a 5 s 'window of opportunity', commencing with the start of the chair rotation, in which subjects were required to indicate the perceived direction of motion. Following a correct response, the chair would immediately start to decelerate. For the chair rotations used, a randomised inter-stimulus delay of between 5-7 seconds was sufficient to allow any postrotatory vestibular effects to decay as confirmed by the eye-movement trace. Motion direction was randomised.

Fig 9.1

Raw traces of eye position, chair velocity and perceptual responses.

The first stimulus, a rightwards acceleration 0.65°/s², elicits an accurate perceptual response following which the chair immediately decelerates. The second chair rotation, of acceleration 0.42°/s² , does not illicit a correct response within the 5s window, i.e. it is sub-perceptual. In this case the chair continues to rotate at constant angular acceleration for the full 5s and then decelerates.



MOBS procedure

Perceptual angular acceleration thresholds were obtained via a Modified Binary Search (MOBS) algorithm (Tyrell & Owens). This algorithm was designed to combine the efficiency of a binary search with the capability to capture fluctuating targets. The series of rotations derived from a given computerised MOBS staircase procedure would determine a threshold value from the mean value of the lowest perceived (suprathreshold) and highest non-perceived (subthreshold) value following 5 stimuli reversals (i.e. 5 consecutive response-no response pairs to the last upper and lower angular acceleration limits). The computer program that ran the MOBS program, considered a late (i.e. more

than 5s from chair rotation onset) response or a wrong response (e.g. right instead of left) as non-responses. Importantly, the program was able to backtrack and repeat stimuli since it held in memory, the last two previous upper and lower boundaries (in addition to the current upper and lower boundaries under test) of the test variable. This ability to backtrack ensured that wrong or non-responses were indeed due to sub-threshold stimuli rather than to simple error.

Instructions to subjects

Subjects were told that "The chair will move either to the left or to the right. As soon as you feel that you are moving in one direction, push the joystick in the direction you perceive the motion and then back to the central position. From the start of each movement you have 5 seconds to respond. If you cannot decide on the direction of movement leave the joystick in its central position. Between each movement there will be a 5-7 second pause. Throughout each test try to look straight ahead with your eyes open". If no direction was indicated within 5 seconds, a wrong response was noted.

Criteria for nystagmic threshold

The non-perceptual (VOR – or nystagmic) threshold was defined as the lowest acceleration required to elicit appropriately directed both slow and fast phases of vestibular nystagmus with at least two fast phases. In the rare event of ambiguity in differentiating a nystagmic response from noise we employed the following criteria for detecting a saccadic response viz. a deflection of amplitude greater than 1deg, peak

velocity 40deg/s and duration 40ms. Eye-movement recordings were visually examined on and off acceleration periods to ensure that the nystagmus was stimulus evoked. For each participant, the VOR threshold was defined when nystagmus was evident on 3 or more separate occasions.

Results

Qualitative assessment of VOR vs. perceptual thresholds.

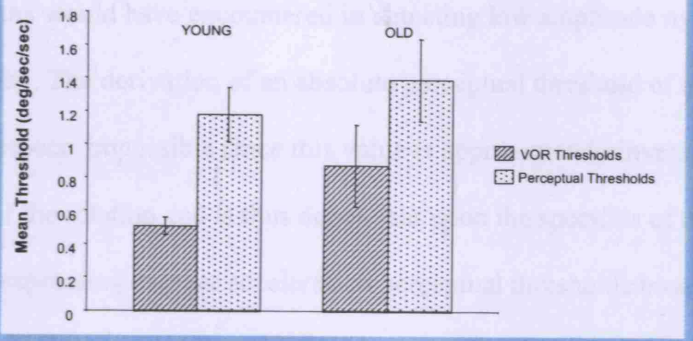
All 14 young subjects had observable rotationally-induced nystagmic beats at lower levels of acceleration than their perceptual thresholds. In the older group, this was apparent in 7 out of the 9 subjects. The remaining two subjects had noisy eye movement recordings that made it difficult to discern low amplitude eye movements.

Quantitative assessment of VOR vs. perceptual thresholds.

Figure 1 shows the data in the 8 young and 7 older subjects who met our criteria for VOR threshold quantification, i.e. three separate directionally congruent VOR responses, together with their corresponding perceptual thresholds. VOR thresholds were lower than perceptual thresholds both in the young (0.51°/s/s SD 0.14 and 1.18°/s/s SD 0.46 respectively) and older group (0.87°/s/s SD 0.65 and 1.39°/s/s SD 0.65 respectively). Despite data inspection (Figure 1) suggesting that VOR thresholds were lower in the younger group, a repeated measures ANOVA showed a significant main effect of test (VOR vs. Perceptual, f=20.427, p=0.001) but no significant overall age effect (f=3.019, p = 0.106).). The two thresholds (all subjects pooled) were not significantly correlated (Spearman's Rank Correlation Coefficient = 0.258; p = 0.354).

Fig 9.2
VOR and Perceptual Thresholds in Young Vs Old subjects

Mean (+/- SEM) nystagmic (VOR) and perceptual thresholds in the young and older subject group. All averages differed significantly, except for the "old" and "young" perceptual thresholds.



Discussion

The primary aim of this study was to compare simultaneously obtained perceptual and nystagmic vestibular thresholds. In particular, we wished to validate a technique which could then be applied to patients (particularly older patients) with dizziness and gait disturbance. The main result was that perceptual thresholds were significantly higher than nystagmic VOR thresholds.

Very little data comparing ocular and perceptual vestibular thresholds with the same technique are available. Our results agree with previous informal observations in the literature, that is brainstem thresholds of vestibular activation are lower than perceptual

thresholds (Benson, 1968; Hood, 1984; Okada et al., 1999). However, reports from the days preceding oculography (with the technique known as cupulometry) are in stark contrast to ours with nystagmic thresholds considerably higher than perceptual (Hulk & Jongkees, 1948). This difference is almost certainly due to the difficulty that earlier investigators would have encountered in detecting low amplitude nystagmus without oculography. The derivation of an absolute perceptual threshold of angular acceleration is in some respects impossible since this value is approximately inversely related to the duration of the rotation and is thus dependent upon the specifics of the stimuli used. One means of expressing angular acceleration perceptual thresholds however is in terms of the minimum angular acceleration-time product viz. Mulder's constant (Guedry, 1974), the units of which are those of velocity (i.e. °/s) since it is the product of acceleration and time. It simply reflects the fact that the higher the acceleration and/or the longer the duration of rotation, then the higher the probability of detecting motion from vestibular input. Mulder's constant is however, relatively stable at approximately 2°/s for rotations of duration 5s (as used here) or less. Since our main aim was to obtain simultaneous measures for nystagmic and perceptual angular acceleration thresholds, the validity of absolute acceleration thresholds was of lesser importance although our obtained values are within the range of previous reports (Guedry, 1974).

Our finding that perceptual thresholds were higher than nystagmic thresholds indicates that vestibular brainstem mechanisms are more sensitive to angular acceleration than cortical conscious mechanisms. From a functional point of view, the finding suggests a useful hierarchy whereby evolutionary older reflex responses are prioritized, i.e. the brainstem responds before the cortex perceives. Alternatively, higher level mechanisms

(e.g. thalamocortical) may have developed inhibitory processes in order not to perceive slow, head accelerations, almost certainly trivial such as those encountered in routine postural sway. If such inhibitory processes do exist, they may play a part in suppressing protracted symptoms in vestibular patients and the technique described herewith may be used to test this hypothesis.

A secondary aim of the study was to pilot the notion that older subjects may have higher absolute threshold values and/or relative changes between these two thresholds. Both peripheral and central age-related changes in vestibular anatomy and function have been reported (summarised in Peterka et al., 1990) but most functional vestibular studies reported are however suprathreshold. In contrast to auditory function the issue of age related vestibular thresholds has been neglected. Raised proprioceptive thresholds have been documented in the elderly and, importantly, they are linearly related to increased postural sway (Bergin et al., 1995). It was therefore deemed of potential clinical value to investigate a trend in vestibular thresholds in older subjects. Our results did show somewhat higher vestibular thresholds in the older group, but combined nystagmic and perceptual data, as analysed with ANOVA, showed that this trend was not statistically significant. It must be noted that the reduced number of older subjects, and their relatively speaking young mean age (63 years), does not allow a final conclusion on this issue.

Similarly, differential threshold changes would be of value for the understanding of common problems in the elderly such as dizziness and falls. A relative increase in VOR thresholds could imply a relative deterioration in brainstem mechanisms which, with preserved cortical perception, could increase dizzy or disorientation feelings. The

opposite case, raised perceptual thresholds with normal brainstem mechanism, could make patients not perceive appropriately the early stages of potentially dangerous or balance-challenging situations, and therefore lack appropriate anticipatory or protective postural responses. Our data suggests a preferential increase in nystagmic thresholds in the older group but this trend deserves further study in larger, and wider age range, groups.

In conclusion, a technique for simultaneous measurement of perceptual (cortical) and nystagmic (brainstem) vestibular thresholds is presented. The main finding is the quantitative demonstration of higher perceptual than nystagmic vestibular thresholds. A trend for higher vestibular nystagmic threshold in an older group was detected and this warrants further investigation. Such a finding, if confirmed in a larger series, could have important implications for the investigation of falls in the elderly.

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Chapter 10

Conclusion

Despite the lack of a specific word to describe the sensation of motion that is engendered by vestibular stimulation, it is clearly a separate sense. There is a dedicated organ, the peripheral vestibular apparatus, and although not the purest of senses in the Mullerian sense (Muller, 1826) given the early merging with visual signals at the vestibular nucleus (Henn et al., 1974), the evoked sensation of self-motion is specific and involves cortical loci quite distinct from other sensory areas (Kahane et al., 2003; Blanke et al., 2000; 2002; 2004).

The sense of self-motion, or vestibulation (see Chapter 1), can be qualitative as occurs in dizziness, or it can be precisely calibrated in terms of space, time and motion (Chapters 5 & 7). Calibrated vestibulation may be utilised in accurate spatial navigation akin to a gyroscope in modern navigational systems. Like artificial navigational systems, navigation by vestibulation requires periodic visual landmark calibration.

Despite the intimate link with vision, vestibulation is robust to early visual deprivation (Chapter 6). Our finding of an intact vestibular perception in the congenitally blind is consistent with recent animal data which has shown the pre-eminence of the vestibular system in vertebrate CNS navigational systems (Stackman et al., 1997, 2002; Save et al., 1998). Accurate vestibular navigation in congenital blind humans however, is likely to be dependent upon regular co-ordinated motor activity including playing sport and exploring the environment. This is supported by the observation in blind rats, whose hippocampal head direction cells developed coordinated spatial firing only after the animal had actively explored the environment (Save et al., 1998).

Vestibular signals do not supply a measured estimate of space; this must be derived. It may be for this reason that calibrated vestibulation may require an internal clock (Chapter 7), a requirement not alien to ancient mariners. Vestibular encoding of space may be dynamic and may explain why hippocampal spatial systems become dysfunctional when deprived of their vestibular input. Chapter 7 provides evidence for a vestibulo-spatio-kinematic encoding of head motion signals. The reference frame common to visual and vestibular signals at their point of interaction during spatial navigation (i.e. the visual landmark calibration of path integration) is of course space. The hegemony of vestibular signals in vertebrate navigational systems in concert with its primary signal being that of head velocity (Klam & Graf, 2003a) may account for the failure of a visual landmark signal to modulate perceived head velocity. This is in stark contrast to the ability of a moving visual signal, i.e. optic flow, to modulate perceived head velocity (Brandt & Dieterich, 1996).

The localisation and characterisation of the human vestibular cortex is in its infancy (Chapters 4 & 8). Functional neuro-imaging and human electrical cortical stimulation (ECS) studies continue to provide a qualitative database of ***where*** vestibular signals may be cortically represented. They have contributed relatively little thus far in telling us either ***what*** (e.g. velocity? Position? Motion duration? Acceleration?) or ***how*** these signals are represented. It appears that the main human vestibular cortex is centred around the temporoparietal junction (see Chapter 4) but we do not know the functional relevance of the various cortical areas regarding vestibular perception. Blanke and co-workers (Blanke et al., 2000, 2002, 2004) have provided qualitative evidence for a vestibulo-topic representation of whole-body motion. They described using ECS in different cortical loci, patients' symptoms of whole-body motion, from simple uni-directional yaw plane rotation to a bi-directional rocking to even sensations of flying through space (described as out-of-body experience or OBE). Indeed, vestibular signals may elicit a percept of motion in head-based or whole-body-based reference frames (Kahane et al., 2003). Furthermore, the description that some patients undergoing ECS perceived not only self-motion but also motion of objects with which they were in contact (e.g. bed), alludes to inertial encoding in egocentric and allocentric reference frames. Support for an allocentric vestibular-inertial encoding (in addition to an egocentric-based encoding) is provided by ECS elicited OBEs in which patients see themselves moving from an 'out-of-body' perspective (Blanke et al., 2004).

The 3-dimensional cortical encoding suggested by OBEs was anticipated by Grusser's finding in monkey PIVC that the majority of neurones specifically tested showed responses to motion in complex 3-dimensional trajectories (Grusser et al., 1990a,b). Klam and Grafs' (2003a,b) work in monkey area VIP has also alluded to the complexity of the cortical encoding of vestibular signals, in particular an ill-defined non-linear representation of vestibular-derived position signals. Indeed their finding (Klam and Graf, 2003a) of a simultaneous encoding of spatial and kinematic vestibular signals supports our claim that vestibular signals are perceptually encoded via an internal model (Chapter 7). Our findings do not preclude however, a non-linear perceptual encoding of vestibular-derived space as suggested by recordings in animal cortical neurones (Grusser et al., 1990a,b; Klam and Graf, 2003a). Our VVD task in Chapter 7 did not specifically test whether vestibular-spatial encoding was dependent upon a linear perceptual integrator. It is possible that vestibular-derived space may be perceptually encoded in a modular fashion; i.e. each trajectory is encoded by separate internal models which may have little or no influence upon each other in terms of vestibular signal calibration. If there are indeed multiple internal models then their presence would not normally be apparent since in everyday life concurrent visuo-vestibular feedback would simultaneously calibrate all of the internal models in a homogenous fashion. If indeed there is a modular encoding of perceived vestibular signals then it may be possible to adapt vestibular-derived displacement for a specific kinematically-defined trajectory by using the VVD paradigm (Chapter 7) without affecting the perception of trajectories of differing kinematics but same displacement.

In Chapter 8 we demonstrated the utility of rTMS in being able to not only localise vestibular signals in the cortex but also to explore the nature of the signals; e.g. kinematic versus spatial parameters. In Chapter 7 we hypothesised that cortical interval timing mechanisms contributed to the derivation of position signals obtained from vestibular input. Using rTMS one could potentially localise the locus (or loci) of motion duration perception and then separately assess if rTMS in this locus also affected perceived vestibular-derived position. Such a finding would not only explicitly confirm that perceptual timing mechanisms are important for perceived vestibular-derived position but also the location of this supposed cortical neural integration. Repetitive TMS thus offers not only a means to localise vestibular cortex with natural vestibular stimuli but also a functional dissection of these regions. In Chapter 8, we disrupted the encoding phase of vestibular navigation. Equally, we could disrupt the memory and retrieval phases. One could thus map out the cortical network that is involved in this task and thus infer the natural functioning of these areas in vestibular perception.

Finally, we demonstrated in Chapter 9 an objective measure of the dichotomy in function between the brainstem and cortex (perception). This simple test is based upon the concept that many dizzy patients who do not demonstrate abnormalities on standard (i.e. brainstem) vestibular tests, may have a problem at perceptual/cortical level. The hope is to use the new technique to assess the prevalence of cortico-brainstem vestibular dissociation in an elderly population and to also obtain functional measures of gait function and questionnaire data regarding neuro-otological symptoms. Our hypothesis is that patients who show a marked cortico-brainstem disparity may have more symptoms

and/or objective balance deficits. Future work could combine this and other tests of simultaneous brainstem and perceptual function (e.g. Okada et al., 1999) with rTMS to cortical loci. Such an approach may help to differentiate the relative contributions of brainstem and cortex to the functional output of vestibular-related mechanisms.

Early vestibular research in humans was based upon psychophysics (Guedry, 1974). Then came the 'objectivity' of brainstem function as evidenced by vestibulo-ocular reflex recordings. Recent evidence (Chapter 4) has confirmed that the main neuronal substrate of human psychophysics, i.e. the cerebral cortex, also plays an important role in vestibular processing and possibly the most important role in patients since it is where their symptoms are generated (even if the problem is elsewhere). Only now are we beginning to piece together the distributed representation of human vestibular cortex. Further work is required to explore the function of these vestibular cortical loci. Ultimately, a fusion of brainstem, cortical and perceptual aspects of vestibular processing is required in an effort to understand the basic mechanisms of vestibular CNS processing and the myriad of unexplained vestibular symptoms with which patients present to the clinic.

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