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Evidence for a reference frame transformation of vestibular contributions to voluntary reaching movements

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RÉSUMÉ

Les estimations des mouvements de soi provenant des signaux vestibulaires contribuent à la planification et l'exécution des mouvements volontaires du bras lorsque le corps se déplace. Cependant, comme les senseurs vestibulaires sont fixés à la tête alors que le bras est fixé au corps, les signaux vestibulaires doivent être transformés d'un système de référence centré sur la tête à un système centré sur le corps pour pouvoir contribuer de façon appropriée au contrôle moteur du bras. Le but premier de ce travail était d'étudier l'évidence d'une telle transformation. La stimulation galvanique vestibulaire (SGV) a été utilisée pour activer les afférences vestibulaires et simuler une rotation autour d'un axe naso-occipital fixe pendant que des sujets humains faisaient des mouvements du bras dans le plan horizontal, avec la tête dans différentes orientations. Une transformation des signaux vestibulaires implique que la SVG devrait simuler une rotation autour d'un axe horizontal lorsque la tête est droite et autour d'un axe vertical lorsque la tête est en flexion antérieure. La SGV devrait ainsi perturber les mouvements du bras en fonction de l'orientation de la tête. Nos résultats démontrent que les signaux vestibulaires contribuant aux mouvements d'atteinte sont effectivement transformés en un système de référence centrée sur le corps. Le deuxième but de ce travail était d'explorer les mécanismes utilisant ces signaux vestibulaires transformés. En comparant les effets de la SGV appliquée avant ou pendant les mouvements d'atteinte nous avons montré que les signaux vestibulaires transformés contribuent à des mécanismes de compensation distincts durant la planification des mouvements d'atteinte comparativement à l'exécution.

Mots clés : transformation de système de référence, mouvements d'atteinte, vestibulaire, stimulation galvanique

ABSTRACT

Vestibular signals provide self-motion estimates that contribute to the planning and execution of voluntary reaching movements during body motion. However, because the vestibular sensors are fixed in the head whereas the arm is fixed to the trunk vestibular signals must be transformed from a head-centered to a body-centered reference frame to contribute appropriately to limb motor control. The first goal of the current work was to investigate the evidence for such a transformation. To do so we used galvanic vestibular stimulation (GVS) to selectively activate vestibular afferents and simulate rotation about a fixed roughly naso-occipital axis as human subjects performed reaching movements with the head in different orientations. If vestibular signals that contribute to reaching are transformed to body-centered coordinates, then with the head upright GVS should simulate mainly tilt about an earth-horizontal axis (roll), whereas with the head pitched forward the same stimulus should simulate rotation about an earth-vertical axis (yaw). We therefore predicted that GVS should perturb horizontal-plane reach trajectories in a head-orientation dependent manner. Our results demonstrate that vestibular signals which contribute to reaching are indeed transformed to a body-centered reference frame. The second goal of this work was to explore the mechanisms that use these transformed vestibular signals. By comparing the effect of GVS applied during versus prior to reaching we also provide evidence that transformed vestibular signals contribute to distinct compensation mechanisms for body motion during reach planning versus execution.

Key words: reference frame transformation, reaching, vestibular, galvanic stimulation

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LIST OF SYMBOLS AND ABBREVIATIONS

Symbols

COM_A= Center of mass along the directions axial to the link
COM_P= Center of mass along the directions perpendicular to the link
I= Inertia about the center of mass
m, M= Mass
r= Radius
v= Linear velocity
ω= Angular velocity

Abbreviations

III= Oculomotor nuclei
VI= Abducens nuclei
EMG= Electromyographic
GVS= Galvanic vestibular stimulation
LIP= Lateral intraparietal area
LVST= Lateral vestibulospinal tract
M1= Primary motor cortex
MIP= Medial intraparietal area
MST= Medial superior temporal cortex
MVST= Medial vestibulospinal tract
PIVC= Parieto-insular vestibular cortex
PMd= Dorsal premotor cortex
PMv= Ventral premotor cortex
Pre-SMA= Pre-supplementary motor area
PRR= Parietal reach region
PPC= Posterior parietal cortex
rFN= Rostral fastigial nucleus
RST= Reticulospinal tracts
SMA= Supplementary motor area
VCR= Vestibulocollic reflex
VIP= Ventral intraparietal cortex
VN= Vestibular nuclei
VOR= Vestibulo-ocular reflex
VSR= Vestibulospinal reflexes

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CONTRIBUTIONS OF AUTHORS

Chapter 2 contains a manuscript submitted for publication to the Journal of Neurophysiology: Moreau-Debord I., Martin C., Landry M., and Green A. M. *Evidence for a reference frame transformation of vestibular signal contributions to voluntary reaching.* For this article, the nature of my contribution is as follows: It was my responsibility to recruit the subjects, perform the experiments, and analyze the collected behavioral data. In addition I also contributed to the programming of the experimental task and writing additional analysis code as necessary. Furthermore I prepared a first draft of the manuscript (text and figures). My colleague Christophe Martin created the biomechanical model of the limb that figures in the article and compared the experimental data with the predictions of the model. He also assisted in collecting and analyzing the data for the second experiment. Marianne Landry was involved in the early piloting work that eventually led to the first experiment. My supervisor, Dr. Andrea Green provided guidance and instruction throughout the study, including data collection, data analysis and interpretation, and the preparation of the final manuscript.

Chapter 1

General introduction and literature review

1.1 General introduction

When reaching to an object in the environment, the motor plan for the reach must take into account the spatial relationship between the arm and the object of interest as well as the dynamic properties of the limb and of the environment within which the reach is executed (Lackner and Dizio, 1994, Kalaska, 2009, Medendorp, 2011). However motion of the body during or immediately prior to reach execution can change the spatial relationship between the arm and the object of interest (Medendorp et al., 1999, Bresciani et al., 2002b, 2005, Van Pelt and Medendorp, 2007, Medendorp, 2011). In addition, reaching during body motion also causes additional dynamic forces to act on the limb due to motion of the body (Lackner and Dizio, 1994, Pigeon et al., 2003, Bockisch and Haslwanter, 2007, Bortolami et al., 2008b). As a consequence, in order to preserve reach accuracy the brain must take into account the effects of the body motion on the kinematics and the dynamics of the arm movement. This requires the brain to either adjust the arm motor plan before the reach is executed or modulate arm motor commands online depending on whether the body motion occurred prior to or during reach execution respectively. To do so the brain depends critically on estimates of self-motion to determine how the body has moved or is moving and the consequences of that movement on the reach.

The vestibular organs, as head-fixed motion detectors, provide information about head movement that can be used in the creation of self-motion estimates (Angelaki and Cullen, 2008, Green and Angelaki, 2010a, Cullen, 2012). While the contribution of self-motion signals from the vestibular sensors to a variety of behaviours such as oculomotor control (Fuchs and Kimm, 1975, Keller and Kamath, 1975, Chubb et al., 1984, McCrea et al., 1987, Scudder and Fuchs, 1992, Cullen et al., 1993, Cullen and McCrea, 1993, Minor et al., 1999, Huterer and Cullen, 2002, Roy and Cullen, 2003, Angelaki, 2004) and postural control (Inglis and Macpherson, 1995, Deliagina et al., 1997, Massion, 1998, Deliagina et al., 2000, Horak et al., 2001, Beloozerova et al., 2003, Goldberg and Cullen, 2011, Hsu et al., 2012) have been well studied, it is only recently that studies have begun to explore vestibular contributions to voluntary limb motor control (Lackner and Dizio, 1994, Bresciani et al., 2002a, 2002b, 2005, Mars et al., 2003, Tunik et al., 2003, Bockisch and Haslwanter, 2007, Guillaud et al., 2011). These studies have provided behavioural evidence for vestibular contributions to spatial and dynamic compensations for body motion during reaching. However, little is known about how vestibular signals are processed appropriately to contribute to reaching. In particular, there is a general problem when considering any contribution of the vestibular system to the planning and execution of reaching movements. Because the vestibular sensors are fixed in the head whereas the arm is attached to the trunk, a given body movement will result in different patterns of vestibular stimulation depending on how the head is oriented relative to the body. In order to contribute appropriately to the kinematics and dynamics of reaching movements, vestibular signals must first be transformed from a head-centered to a body-centered reference frame.

The main goal of this work was to provide evidence that the vestibular signals which contribute to reach planning and execution indeed reflect such a transformation from a head-centered to body-centered reference frame. One technique that can be used in order to study such transformations of vestibular signals is known as galvanic vestibular stimulation. This technique involves the electrical stimulation of the vestibular afferents by passing current through surface electrodes placed behind the ears on the mastoid processes. This technique is particularly useful for studying the contribution of vestibular signals to behaviours such as reaching as it selectively activates the vestibular afferents making it possible to isolate their contributions from other potential sources of motion information including motion cues such as proprioceptive or somatosensory inputs.

In this introductory chapter, several broad areas of research that involve the vestibular system will be discussed. To start, I will begin with a description of the vestibular periphery, followed by an overview of several important behaviours and computations that central vestibular processing is known to contribute to, including reaching movements. In addition, as the experiments presented in this thesis involve the use of galvanic vestibular stimulation, this technique and its behavioural effects will also be reviewed along with its particular advantages for the study of reference frame transformations of vestibular signals. Finally, this introductory chapter will be concluded with a description of the motivations and specific goals of the present work.

1.2 The peripheral vestibular system

1.2.1 The vestibular organs

The vestibular system is comprised of two symmetrical vestibular labyrinths that are located within the inner ears (Fig. 1.1A). Each labyrinth contains three semicircular canals, known as the anterior, posterior, and horizontal semicircular canals (Fig. 1.1B) and two otolith organs, the utricle and saccule (Fig. 1.1C). Over the frequency range of natural head movements, the semicircular canals provide the brain with information about angular velocity of the head while the two otolith organs sense linear accelerations due to either translation of the head or reorientation of the head relative to gravity (Goldberg and Fernandez, 1971b, Fernandez and Goldberg, 1976a).

1.2.1.1 Spatial properties of the vestibular organs

The respective spatial tuning properties of a given vestibular organ depend on how it is positioned in the head and on how the sensory hair cells, which are responsible for the mechano-electrical transduction process, are oriented in the organ (Goldberg et al., 2012). In brief, rotation is sensed by the canals as follows. Each canal is shaped as a circular tube filled with a fluid known as endolymph. At one end of each semi-circular canal there is an enlargement of the canal called the ampulla that contains the sense organ known as the crista (Goldberg et al., 2012). The crista contains hair cells whose cilia are embedded in a gelatinous membrane known as the cupula, which spans the diameter of the canal. The hair bundles of vestibular hair cells are made of numerous small cilia and one long and rigid cilium known as

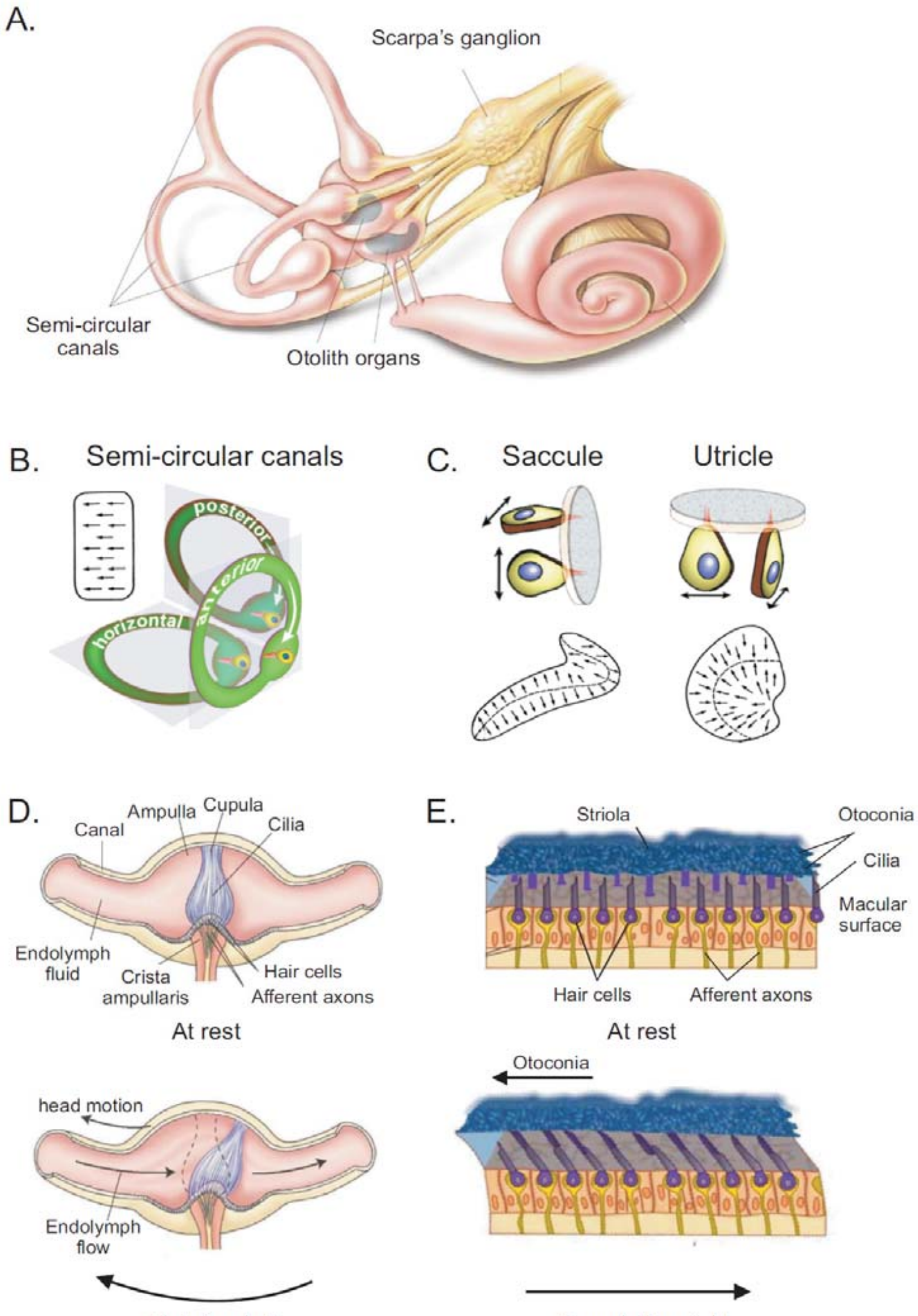

Figure 1.1. **The vestibular periphery.** A) The vestibular labyrinth. B) The semicircular canals sense rotations of the head in three dimensions. Whereas the horizontal canal senses yaw rotation of the head, the anterior and posterior canals sense pitch and roll of the head. For a given canal, all sensory hair cells respond similarly to rotation about an axis perpendicular to the plane of the canal. C) The otolith organs sense linear accelerations of the head. The saccule senses accelerations in the saggital plane,

and the utricle in the horizontal plane (top). The spatial tuning sensitivity of a given otolith organ is spread across the surface of the macula. The striola (dashed black line in figure) separates the population of sensory cells into two groups, with oppositely-directed tuning responses (bottom). D) How the semi-circular canals sense rotational motion of the head. Rotation of the head causes endolymph fluid to lag behind due to its inertia, deflecting the cupula which bends the cilia of the sensory hair cells, causing them to respond. E) How the otolith organs sense acceleration of the head. Translation of the head causes the otoconia crystals to lag behind due to their inertia, bending the cilia of the sensory hair cells and causing them to respond. Similarly, tilting the head will also deflect the cilia and lead to a response, as the otoconia will be accelerated by the force of gravity (Illustrations for A and D from Siegel and Sapru (2007). Illustrations for B and C from Day and Fitzpatrick (2005a) and Lindeman (1969). Illustration for E from Writer and Arora (2012)).

the kinocilium located at one end of the bundle. When the cilia are moved towards the kinocilium due to bending of the cupular membrane, mechanically gated transduction ionic channels located at the tips of the stereocilia open and depolarize the hair cell. In contrast, stereocilia movement away from the kinocilium closes those channels, hyperpolarizing the hair cell (Eatock and Lysakowski, 2006). Because the canals are tethered to the skull, when the head moves the canals move with it. This motion generates an inertial force within the endolymph fluid, displacing it relative to the canal walls in the opposite direction to the head movement. The endolymph displacement produces a viscous drag force on the canal walls and a buildup of pressure on the cupula that deflects the cupular membrane (and by extension the cilia embedded within), activating the hair cells (Fig. 1.1D) (Highstein et al., 1996, Rabbitt et al., 1996, 2009, Goldberg et al., 2012).

In the crista, all the hair cell bundles are aligned in the same direction such that fluid displacement bends the cilia of each hair cell either towards or away from the kinocilium, giving rise to a depolarization or hyperpolarization of the whole population of hair cells during rotation in the plane of a canal (Fig. 1.1B) (Wersall, 1956, Goldberg and Fernandez, 1971b, 1975, Flock and Goldstein, 1978, Highstein et al., 1996, Rabbitt et al., 2010). The horizontal canals are mainly oriented in the horizontal plane of the head making them preferentially sensitive to rotation about an axis that is mainly aligned with a head-vertical axis (i.e. yaw). The anterior and posterior canals are oriented approximately +/– 45 degrees from the saggital plane of the head making them preferentially sensitive to rotations of the head in the vertical plane about combined pitch and roll axes. In addition, since the whole canal structure is tilted slightly backwards in the head by approximately 30 degrees relative to the horizontal plane (Della Santina et al., 2005), the horizontal canals also display a small sensitivity to roll rotations and the anterior and posterior canals display some sensitivity to yaw rotations. The three semi-circular canals are roughly oriented in three orthogonal planes centered in the head, allowing them to sense head rotation in three dimensions (Blanks et al., 1975, Della Santina et al., 2005).

For the utricle and saccule, the sensory organ is a planar structure called the macula that is covered in a gelatinous membrane whose top-most layer is filled with calcium carbonate crystals known as otoconia (Fig. 1.1E) (Goldberg et al., 2012). These otoconia make this membrane (referred to as the otoconial membrane) denser than the surrounding endolymph. The hair bundles of the hair cells located on the macula protrude into the overlying otoconial membrane (Flock, 1964). When the head is linearly accelerated in space, the denser otoconial membrane lags behind due to its inertia leading to a shear displacement of the membrane relative to the skull (and therefore relative to the macula surface) in the opposite direction to the acceleration. This bends the cilia that are embedded in the membrane and hyperpolarizes or depolarizes the hair cells of the macula (Fig. 1.1E bottom). Similarly, tilting the head relative to gravity will cause the force of gravity to “pull” on the denser otoconial membrane, producing a shear displacement in the direction of gravity which also bends the cilia, hyperpolarizing or depolarizing the hair cells (Flock, 1964, Fernandez and Goldberg, 1976a).

Unlike in the canals, the orientation of the hair cell bundles are distributed in all directions across the macula, allowing a spread of preferred response directions such that the otolith organs respond to acceleration of the head in all directions in the plane in which they reside (Fig. 1.1C) (Lindeman, 1969, Fernandez et al., 1972, Fernandez and Goldberg, 1976b, Fitzpatrick and Day, 2004).The saccule is roughly oriented in the saggital plane, making it sensitive to accelerations in this plane (i.e. up-down and forward-backward movements of the head), whereas the utricle is roughly oriented in the horizontal plane, making it sensitive to lateral and forward-backward movements of the head (Naganuma et al., 2001, 2003). The utricle is also tilted slightly backwards such that it has some sensitivity to up-down motion in the sagittal plane. Together, the two organs are roughly oriented in two orthogonal planes to sense linear acceleration in 3D.

1.2.1.2 Dynamic properties of the vestibular organs

The canals and the otolith organs have particular dynamic properties that determine how their sensory cells respond to motions of the head. For the semi-circular canals, since the hair cells respond to deflections of the cupula, the output signals of the hair cells depend on the relationship between head movement and displacement of the cupula membrane. In turn, this relationship depends on the viscosity of the endolymph fluid, the diameter of the canals and the elasticity of the cupula (Oman et al., 1987, Selva et al., 2009, Goldberg et al., 2012). At low frequencies of head rotation under .04 Hz, the cupular displacement is proportional to angular acceleration of the head, such that the output of the hair cells should reflect angular acceleration. This is not surprising considering that it is angular accelerations of the head that produce the inertial forces that act on the endolymph and lead to fluid displacement relative to the canal walls. Above frequencies of .04 Hz, the cupular displacement becomes proportional to angular velocity of the head as the "canal-cupula system" (i.e. the interaction between the small canal diameter, the high viscosity of endolymph, and the elasticity of the cupula) acts like a low-pass filter, such that the output of the hair cells should reflect angular velocity. This means that functionally, over the normal frequency range of movements (~2-20 Hz) (Hullar and Minor, 1999) the semi-circular canals serve as velocity transducers and the canal sensory cells signal angular velocity of the head (Jones and Milsum, 1971). However, because at very low frequencies the hair cells are instead sensitive to angular acceleration, with sustained rotation of the head at constant velocity they stop signalling head rotation despite ongoing movement as the displaced cupula returns to its resting position. The return of the cupula to its resting position has been estimated to have a time constant of about 4-7 seconds (Oman et al., 1987, Dai et al., 1999, Rabbitt et al., 2009, Selva et al., 2009).

With regards to the otolith organs, the saccule and utricle respond to linear accelerations due to translations of the head in space and due to reorientation of the head relative to gravity (Goldberg and Fernandez, 1975, Fernandez and Goldberg, 1976a). Since the hair cells of the otolith organs respond to shear displacement of the otolithic membrane on the macula surface, the output signals of the hair cells depend on the relationship between net gravitoinertial force (i.e., the sum of the gravitational force and linear accelerations of the head acting on the membrane) and shear displacement of the otolithic membrane. One of the factors influencing this relationship is the viscoelastic properties of the otolithic membrane that are suggested to dampen the effect of the gravitoinertial force on shear displacement (Goldberg et al., 2012). For frequencies of gravitoinertial force under 10 Hz, the shear displacement is proportional to this force, such that the output of the hair cells should reflect net linear acceleration (i.e. the gravitoinertial force) (Fernandez and Goldberg, 1976c, Goldberg et al., 2012). As frequencies increase above 10 Hz, the gain between gravitoinertial force and shear displacement starts to decrease as the viscoelastic properties of the membrane become important. Therefore above 10 Hz the output of the hair cells no longer veridically signal net linear acceleration (Fernandez and Goldberg, 1976c, Goldberg et al., 2012). However, it has recently been suggested that the 10 Hz frequency cutoff point might be too low, and that otolith organs may continue to serve as acceleration transducers even at very high frequencies (Dunlap et al., 2012, Goldberg et al., 2012).

1.2.2 The vestibular afferents

The vestibular afferents are bipolar cells with their somas located in Scarpa`s ganglion which travel along the VIII cranial nerve to carry signals of head motion to the vestibular nuclei in the brainstem (Gacek, 1969, Goldberg and Fernandez, 1980) and to the posterior cerebellum (Barmack, 2003). Individual afferent fibers innervate the sensory neuroepithelium of either the canals or otoliths. A given afferent innervates several hair cells with similar spatial tuning properties, such that afferents display directional selectivity in their responses

(Fernandez and Goldberg, 1976b, Baird et al., 1988). The vestibular afferents in the squirrel monkey display a resting firing rate of about 90 spikes/sec for canal afferents and 60 spikes/sec for otolith afferents (Goldberg and Fernandez, 1971b, Fernandez and Goldberg, 1976a). The afferents respond to head motion by modulating their firing rate about this baseline with the rate increasing or decreasing depending on the amplitude and direction of the movement of the head. In some afferents the action potentials of the resting discharge rate have a regular and consistent spacing, whereas in others the spacing of action potentials can be very irregular (Goldberg and Fernandez, 1971b, 1975, Goldberg, 2000). Irregular afferents display more phasic responses with greater sensitivity to natural and electrical stimulations than regular afferents (Goldberg and Fernandez, 1971a, Fernandez and Goldberg, 1976c, Goldberg et al., 1984, Goldberg, 2000).

1.3 The central vestibular system

Central vestibular processing first occurs in the vestibular nuclei (VN), which include the descending, lateral (also known as Dieter's), medial and superior vestibular nuclei (Barmack, 2003), as well as parts of the cerebellum including the rostral fastigial nuclei (Shimazu and Smith, 1971, Batton et al., 1977, Carleton and Carpenter, 1984, Homma et al., 1995), the nodulus and uvula (Xiong and Matsushita, 2000a, b), the anterior vermis (Voogd et al., 1991) and the flocculus (Langer et al., 1985, Bukowska, 1995, Tan et al., 1995) which receive either direct vestibular afferent inputs or indirect vestibular projections via the VN. In addition to receiving afferent inputs from the semicircular canals and the otolith organs, there is a strong convergence of sensory information from other senses onto VN neurons (Angelaki and Cullen, 2008). For example, VN receives neck proprioceptive inputs from the external cuneate and central cervical nuclei (Pompeiano, 1972, Boyle and Pompeiano, 1981, Carleton and Carpenter, 1983, Matsushita et al., 1995, Gdowski and McCrea, 2000, Sadeghi et al., 2007) as well as oculomotor inputs from several areas including the nucleus of the optic tract, the superior colliculus and the cerebellar nucleus prepositus (Cazin et al., 1982, Magnin et al., 1983). In addition, VN receives cortical inputs from several different regions of the cortex, such as the parieto-insular vestibular cortex, premotor cortex 6/6pa, anterior cingulate cortex, somatosensory cortex 3a, intraparietal sulcus area 3v, and superior temporal cortex (Ventre and Faugier-Grimaud, 1988, Faugier-Grimaud and Ventre, 1989, Akbarian et al., 1994, Fukushima, 1997). Below I provide a brief overview of how vestibular signals contribute to oculomotor control, postural control, and to the computation of self-motion estimates. Finally, this section will be concluded with an overview of how vestibular signals contribute to reaching, which is the topic of this work.

1.3.1 Vestibular contributions to oculomotor control

One of the best studied contributions of the vestibular system is to oculomotor control. In particular, the vestibulo-ocular reflex (VOR) serves to stabilize gaze during motion of the head by producing eye movements in the direction opposite to the head in order to stabilize images on the retina (Lorente de No, 1933, Angelaki, 2004). Since both the eyes and the vestibular organs are located in the head, vestibular signals are in the appropriate reference frame to drive such compensatory eye movements, making the VOR a computationally simple reflex. Indeed, the most direct pathway that mediates the rotational VOR is a tri-synaptic pathway known as the “three neuron arc” (Fig. 1.2A) (Angelaki, 2004). Taking the horizontal VOR as an example, in this arc during leftward rotation vestibular afferents from the left canal excite secondary neurons in the ipsilateral vestibular nuclei. The vestibular nuclei neurons then send direct excitatory projections to the contralateral abducens motor neurons (the third neurons in the three-neuron arc) that innervate the lateral rectus muscle of the right eye. Internuclear neurons in the contralateral abducens also project to motor neurons in the left oculomotor nucleus that control the medial rectus muscle of the left eye. Consequently for a leftward rotation both eyes move to the right. This tri-synaptic pathway allows the rotational VOR to be extremely fast, having a latency of only about 6-7 ms for rotations of the head (Minor et al., 1999, Huterer and Cullen, 2002). However, the tri-synaptic pathway is not sufficient on its own to fully drive the reflex, as a signal proportional to eye position must also be sent to extraocular motor neurons to compensate for the dynamic properties of the eye plant. In order to do so, this position signal is computed using a neural integrator that has been found in the prepositus hypoglossi in the medulla for horizontal eye positions (Cannon and Robinson, 1987) and in the interstitial nucleus of Cajal in the midbrain for vertical and torsional eye positions (Crawford et al., 1991, Fukushima, 1991). Collectively, these velocity and position signals allow the brain to stabilize gaze regardless of how the head is rotating in space. Tri-synaptic pathways also exist for the translational VOR that carry vestibular information from the otolith afferents to motor neurons in the abducens and oculomotor nuclei that control the extraocular muscles (Fig. 1.2B) (Angelaki, 2004). However, latencies for the translational VOR are slightly longer (~10-12 ms), suggesting that other longer pathways play a dominant role in the translational VOR (Angelaki, 2004).

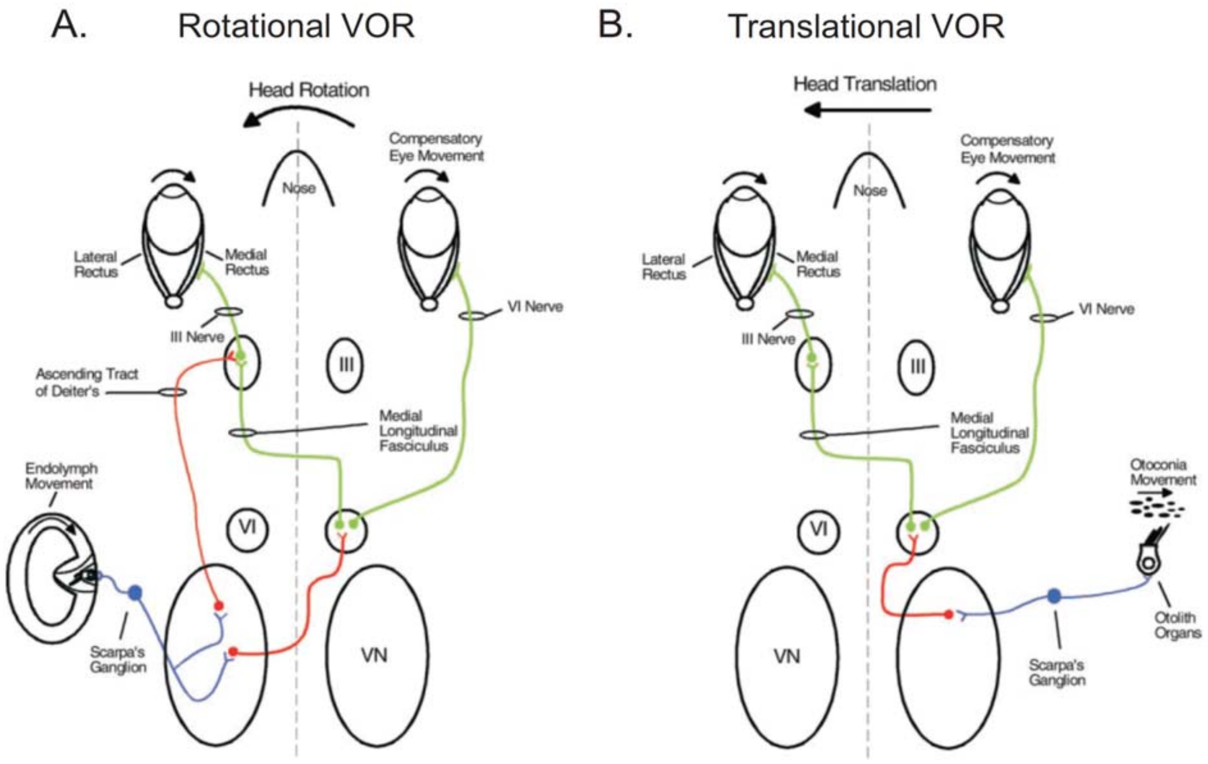

Figure 1.2. **Tri-synaptic pathways in the vestibulo-ocular reflex.** A) Schematic of the "three-neuron arc" mediating the horizontal rotational VOR. B) Schematic of the most direct pathways involved in the translational VOR. Blue lines represent vestibular afferent projections, the red lines represent the second-order projections, and the green lines represent extraocular motor neuron projections. While only excitatory pathways are shown, inhibitory pathways exist that complement these excitatory parhways by inhibiting antagonist muscles. VN, vestibular nuclei; VI, abducens nuclei; III, oculomotor nuclei. (From Angelaki, 2004).

The principal neurons involved in the VORs combine head (vestibular) and eye movement signals to various extents. They include several cell types known as "eye-head" (McFarland and Fuchs, 1992, Cullen et al., 1993, Roy and Cullen, 2003, Angelaki, 2004), "position-vestibular-pause" (McCrea et al., 1987, Scudder and Fuchs, 1992, Cullen and McCrea, 1993, Angelaki, 2004), and "burst-tonic" neurons (Fuchs and Kimm, 1975, Keller and Kamath, 1975, King et al., 1976, Chubb et al., 1984, McFarland and Fuchs, 1992, Angelaki, 2004) based on their response characteristics to head and eye movements. In particular, these neurons responsible for VOR generation (eye-head, position-vestibular-pause, and burst-tonic) are located in the medial, lateral, and superior vestibular nuclei (McFarland and Fuchs, 1992, Cullen et al., 1993, Cullen and McCrea, 1993, Scudder and Fuchs, 1992) as well as in the prepositus hypoglossi (McFaland and Fuchs, 1992, Cullen et al., 1993) and interstitial nucleus of Cajal (Fukushima et al., 1991) where many cells with primarily tonic or burst-tonic activity are found. Finally, extraocular motor neurons that display characteristic burst-tonic activity are found in the abducens, oculomotor, and trochlear nuclei (Baker and Berthoz, 1974, Fuchs et al., 1988, Cullen et al., 1993, Das and Mustari, 2007).

1.3.2 Vestibular contributions to postural control

The contribution of the vestibular system to postural control mechanisms has also been well studied (Inglis and Macpherson, 1995, Deliagina et al., 1997, 2000, Massion, 1998, Horak et al., 2001, Beloozerova et al., 2003, Hsu et al., 2012). In general, the postural system serves to stabilize the head and body by producing corrective motor behaviour that returns the head and body to a stabilized position when deviation from this position is detected (Beloozerova et al., 2003). Vestibular information play a particular role in helping stabilize the head in space through the vestibulocollic reflex (VCR), which activates the neck musculature in response to vestibular stimulation to move the head in the opposite direction to the sensed head motion (Goldberg and Cullen, 2011). While there are direct, tri-synaptic pathways connecting semi-circular canal afferents with motor neurons of the neck (forming a three-neuron arc), indirect pathways appear to play a dominant role in the VCR (Wilson and Yoshida, 1969a, Wilson and Maeda, 1974, Shinoda et al., 1992, 2006, Goldberg and Cullen, 2011).

The vestibulospinal reflexes (VSR) use information provided from the vestibular organs and muscle proprioceptors in order to maintain balance, posture, and stability of the body against gravity (Goldberg et al., 2012). For example, roll of the head produces a reflexive extension of the limbs ipsilateral to the direction of the roll and flexion of the contralateral limbs. While corrective motor responses are mainly generated using somatosensory information from limb mechanoreceptors (Inglis and Macpherson, 1995, Beloozerova et al., 2003, Stapley and Drew, 2009, Hsu et al., 2012), inputs from the vestibular afferents have been shown to be very important for the normal functioning of postural mechanisms as unilateral or bilateral labyrinthectomies can lead to short and long-term effects on postural control (e.g. body twisting and persistent head roll tilt in rodents) (Deliagina et al., 1997, Stapley et al., 2006, Macpherson et al., 2007) . In addition, descending inputs from the vestibulospinal tract provide a high tonus in the extensor limb muscles during standing by providing a high level of excitability to the extensor motor neurons of the limbs, which is critical in order to support the body when standing (Duysens et al., 2000). Furthermore, studies using human patients with vestibular deficits or labyrinthectomized cats have shown that vestibular inputs from the labyrinths are important for modulating the amplitude of automatic postural responses and scaling their magnitude to that of the postural disturbance (Keshner et al., 1987, Horak et al., 1990, Macpherson and Inglis, 1993, Allum et al., 1994, Inglis and Macpherson, 1995).

The vestibulospinal reflexes are mediated by the lateral and medial vestibulospinal tracts (LVST and MVST) and the lateral and medial reticulospinal tracts (Fig. 1.3). The MVST originates in the rostral part of the descending vestibular nucleus as well as the bordering regions of the lateral and medial vestibular nuclei (Akaike, 1973, Akaike et al., 1973, Rapoport et al., 1977) and descends to the spinal cord through the medial longitudinal fasciculus to influence neck and trunk (but not limb) musculature (Wilson and Maeda, 1974, Fukushima et al., 1979, Shinoda et al., 1994, 1997, Uchino et al., 1997, 2005). The LVST originates principally from the lateral vestibular nucleus with some contribution from the descending vestibular nucleus (Shinoda et al., 2006). The LVST is involved not only in the control of the neck and trunk but of limb musculature as well (Wilson and Yoshida, 1969b, Grillner et al., 1970, Shinoda et al., 1986). The reticulospinal tracts originate in the pontomedullary reticular formation (Nyberg-Hansen, 1965, Petras, 1967). Vestibular information is sent to the reticular formation either directly via the vestibular nuclei (Peterson and Abzug, 1975, Peterson et al., 1975) or more indirectly via the cerebellar cortex and fastigial nucleus (Walberg et al., 1962, Batton et al., 1977, Asanuma et al., 1983, Homma et al., 1995) before being sent down the spinal cord. The vestibulospinal and reticulospinal tracts can act reciprocally on the extensor and flexor muscles of certain joints such as the knee or elbow in some circumstances. In particular, direct electrical stimulation of the LVST has been shown to excite extensor motor neurons and inhibit flexor motor neurons, whereas direct electrical stimulation of reticulospinal axons has been shown to excite flexor motor neurons and inhibit extensor motor neurons (Wilson and Yoshida, 1969b, Grillner et al., 1971).

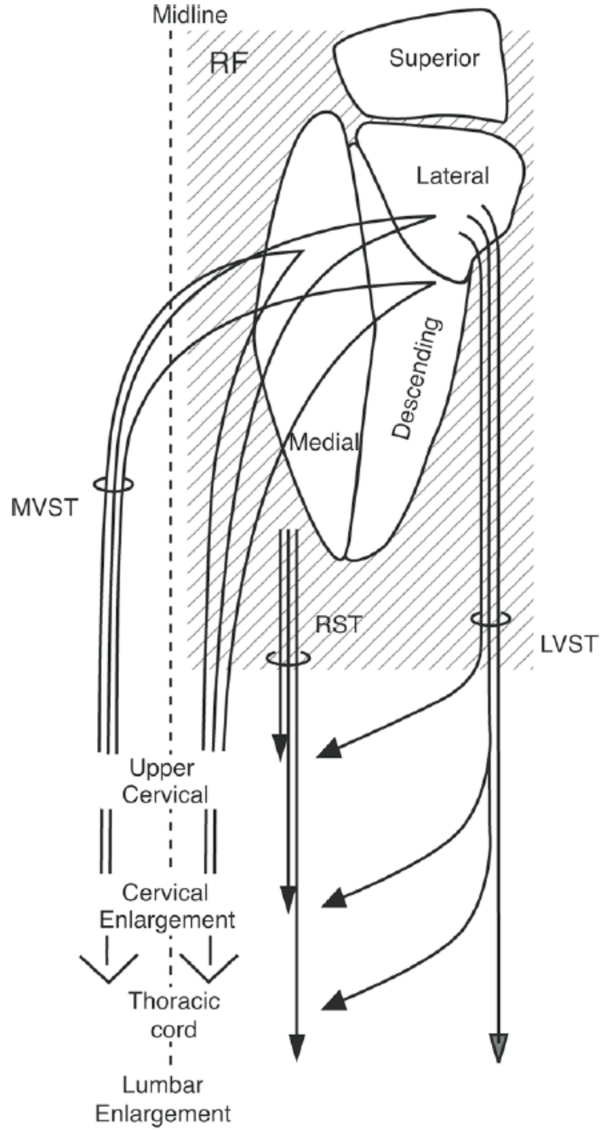

Figure 1.3. **Pathways mediating the vestibulospinal reflexes.** Schematic showing the origins of the vestibulospinal tracts in the vestibular nuclei and their projections to the spinal cord. The projections of the reticulospinal tracts are also shown. Superior, lateral, medial and descending represent the four vestibular nuclei. LVST, lateral vestibulo-spinal tract; MVST, medial vestibulo-spinal tract; RST, reticulospinal tracts. (From Wilson and Melvill Jones, 1979).

1.3.3 Vestibular contributions to self-motion estimation

In order to provide behaviourally relevant self-motion estimates and drive motor behaviour accordingly, vestibular inputs must undergo substantial processing in the brain. While for some behaviours the computational requirements are rather simple, such as the VOR where both head and eye signals are in head-centered coordinates, for other behaviours vestibular information must undergo further transformations. Historically, evidence for a self-motion estimation network involving vestibular information came from the "velocity storage" mechanism, described as performing an integration of vestibular signals in order to partially compensate for the high-pass dynamic properties of the semicircular canals and store an improved estimate of angular velocity of the head at lower frequencies of vestibular stimulation (<0.04 Hz; see Section 1.2.1.2) (Cohen et al., 1977, 1981, Robinson, 1977, Raphan et al., 1979, Katz et al., 1991, Reisine and Raphan, 1992, Yokota et al., 1992). However, velocity storage was later found to display complex spatial properties that were dependent on the spatial orientation of the head relative to gravity (Raphan et al., 1981, Harris, 1987, Raphan and Cohen, 1988, Dai et al., 1991, Merfeld et al., 1993, Angelaki and Hess, 1994, 1995, Wearne et al., 1997, 1998). For example, these studies demonstrated that if, following constant velocity rotation about an axis aligned with the direction of gravity, head orientation is changed, the 3-D eye velocity vector associated with the VOR will realign with the gravity vector. These puzzling spatial characteristics suggested that the neural network responsible for the phenomenon of velocity storage plays a broader computational role in constructing estimates of self- motion (Angelaki and Hess, 1994, 1995, Angelaki et al., 1995, Green and Angelaki, 2010a). In particular, this network for self-motion estimation appears to be involved in using vestibular signals for a variety of computations essential for determining how the head and body are moving. These computational problems include resolving what is known as the tilt-translation ambiguity (Green and Angelaki, 2003, 2004, 2010a, b, Green et al., 2005, Shaikh et al., 2005, Yakusheva et al., 2007, Angelaki and Cullen, 2008), distinguishing passively from actively generated motion (Roy and Cullen, 2001, 2004, Cullen and Minor, 2002, Cullen and Roy, 2004, Sadeghi et al., 2007), and estimating motion of the body (Manzoni et al., 1993, Kleine et al., 2004, Shaikh et al., 2004, Brooks and Cullen, 2009, Green and Angelaki, 2010a, b).

Of particular relevance to the current study is the problem of computing body motion. While the vestibular sensors encode head motion in head-centered coordinates, making them an ideal source of movement information for behaviours such as the VOR (Angelaki, 2004), other behaviours such as postural control or voluntary reaching require estimates of body motion. Vestibular signals alone are not sufficient to determine body motion, since the vestibular organs can be similarly activated whether the head moves alone or if the head and body move together. Instead, to distinguish motion of the body from motion of the head on the body vestibular signals must be combined with proprioceptive signals. It has been suggested that the appropriate integration of vestibular signals and proprioceptive signals for computing body motion would require two computational steps (Fig. 1.4) (Green and Angelaki, 2010b, a). First, because a given body motion will stimulate the vestibular sensors differently depending on head orientation vestibular signals must be transformed from a head- to a body-centered reference frame. This involves combining vestibular estimates of head motion nonlinearly with static neck proprioceptive estimates of the orientation of the head on the body (Manzoni et al., 1993, Kleine et al., 2004, Shaikh et al., 2004, Green and Angelaki, 2010a, b). However, just transforming the vestibular signals into body-centered coordinates is not sufficient to determine body motion. Motion of the body needs to be dissociated from motion of the head on the body. In a second computational step, the dynamic vestibular signals that have been transformed into body-centered coordinates need to be integrated with dynamic neck proprioceptive estimates of the change in head position relative to the body (Brooks and Cullen, 2009, Green and Angelaki, 2010a, b). The output of this second computational step would provide the brain with an estimate of body motion. Recent studies have made progress in determining the neural correlates for these two computational steps (see Section 3.4.1) (Manzoni et al., 1999, Kleine et al., 2004, Shaikh et al., 2004, Brooks and Cullen, 2009). The goal of the current work is to provide evidence for the first of these steps in vestibular contributions to reaching.

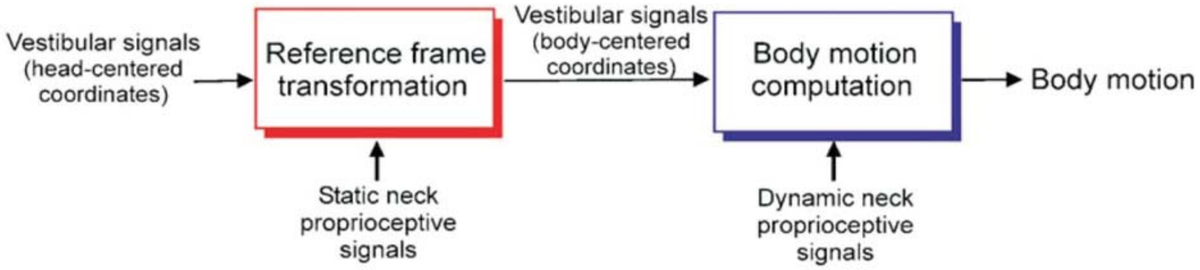

Figure 1.4. **Estimating body motion.** There are two computational steps required. First, head-centered vestibular signals need to undergo a reference-frame transformation to a body-centered reference frame through the use of static neck proprioceptive signals (red box). Second, the transformed vestibular signals need to be combined with dynamic neck proprioceptive signals to generate an estimate of the motion of the body (blue box). (From Green and Angelaki, 2010b).

1.3.4 Vestibular contributions to voluntary reaching movements

In many situations, reaches are performed during motion of the body. Consequently accurate reaching requires keeping track of the spatial location of targets relative to the limb as the body moves (Medendorp et al., 1999, Bresciani et al., 2002b, 2005, Medendorp and Crawford, 2002, Guillaud et al., 2006, Van Pelt and Medendorp, 2007, Medendorp, 2011) as well as compensating for additional dynamic forces that act on the limb due to the motion of the body (Lackner and Dizio, 1994, 1998a, b, 2005, Dizio and Lackner, 1995, 2000, 2001, Pigeon et al., 2003, Bockisch and Haslwanter, 2007, Bortolami et al., 2008b, Guillaud et al., 2011). While vestibular contributions to gaze and postural control have been well characterized (see Sections 1.3.1 and 1.3.2), less is known about how the vestibular system contributes to the estimates of self-motion that are involved in voluntary motor behaviours such as reaching. However, in recent years a number of studies have provided direct evidence for a vestibular contribution to both spatial and dynamic compensations for body motion in the planning and control of reaching (Lackner and Dizio, 1994, Bresciani et al., 2002a, 2002b, 2005, Mars et al., 2003, Tunik et al., 2003, Bockisch and Haslwanter, 2007, Guillaud et al., 2011). Notably, different studies have emphasized distinct mechanisms by which vestibular signals contribute. Below, I briefly review the evidence for these different mechanisms and the contributions that vestibular signals make to them.

1.3.4.1 Vestibular contributions to spatial updating

In order to interact with objects in the environment, we must be able to represent their location relative to ourselves. Because our movements continuously change the spatial relationship between objects of interest and different motor effectors, these representations must be updated in a process known as spatial updating (Klier and Angelaki, 2008, Medendorp, 2011). Spatial updating has been most extensively studied for saccades, where it has been demonstrated that subjects are able to accurately update the location of a previously-flashed visual target relative to the eye despite intervening eye movements (Hallett and Lightstone, 1976, Mays and Sparks, 1980, Schiller and Sandell, 1983, Sparks and Mays, 1983, Sparks et al., 1987, Tehovnik and Sommer, 1996).

A number of recent behavioural studies have also explored the accuracy with which eye and arm movements can be updated to compensate spatially for body motion. In such a paradigm, a visual target is typically shown that serves as the goal of the task. The target is then extinguished, and subjects are asked to remember the spatial location of the target for a memory period during which the body is displaced in space. The subject is finally cued to make an eye or arm movement to the remembered target location. Vestibular contributions to the updating of eye movements for body motion have been demonstrated in a number of studies using such a paradigm (Medendorp et al., 2002, 2003, Klier et al., 2005, 2006). In particular, these studies have demonstrated that while spatial updating does occur, under certain circumstances this updating is more or less accurate depending on the information available. For actively-generated movements in darkness, where vestibular, proprioceptive and efference copy signals are available, spatial updating of eye movements is accurate (Medendorp et al., 2002, 2003). For passive movements, where only vestibular cues are available, the picture is different. After passive torsional roll movements of the head about a naso-occipital axis, eye movements to a remembered target were accurate (Klier et al., 2005). However, placing subjects in a supine position such that a roll movement of the head now causes rotation in the horizontal plane (and therefore no head reorientation relative to gravity) led to poor spatial updating performance (Klier et al., 2005). This demonstrates that gravity signals from the vestibular system play an important role in the ability to update for roll rotations. In contrast to updating for passive roll rotations, updating for passive yaw rotation of the head was associated with larger systematic errors (Klier et al., 2006). Reorienting the body in pitch such that the yaw rotation of the head is now in a vertical plane did not improve the ability of subjects to update spatially, demonstrating that gravity cues do not seem to make an important contribution to yaw spatial updating (Klier et al., 2006). Rather, since yaw updating is accurate for actively-generated head movements, efference copies likely play a more important role in updating for yaw movements. Nonetheless, it is certain that vestibular signals are among the signals which contribute to spatial updating for passive yaw rotation because labyrinthectomized monkeys display compromised spatial updating immediately after vestibular loss for both rotation and translation in the horizontal plane (Li and Angelaki, 2005, Wei et al., 2006).

In contrast to eye movements, less is known about how spatial updating contributes to reaching movements. For spatial updating following active translations of the body in darkness, pointing movements to the memorized location of previously flashed targets are quite accurate (Medendorp et al., 1999, Admiraal et al., 2004, Van Pelt and Medendorp, 2007). Spatial updating has also been shown for passive yaw rotations of the whole body. In a study by Bresciani and colleagues (2002b), subjects seated in a mechanically rotatable chair made reaches in darkness to the memorized spatial location of previously flashed targets after being rotated in the horizontal plane about an axis that passed through the long axis of the body (i.e. yaw rotation about a vertical body axis). In such a situation subjects were able to perform reaches that were generally accurate with small errors, as trajectory endpoints were deviated from controls by only about 4.5 degrees for a 40 degree whole-body yaw rotation. Therefore, these studies have shown that spatial updating for reaching movements is effective both when body movements are actively generated and motor efference copies about trunk movement are available as well as in situations of passive movement in darkness where vestibular signals are presumably used to estimate the effect of body motion on the spatial relationship between the arm and the target.

At present the accuracy of spatial updating to compensate for body motion during reaching and the extent to which vestibular versus other signals contribute to these compensations has not been well characterized. Nonetheless, it is known that performance is less accurate in such a spatial updating task than when compensating for the spatial displacement of the limb and body when reaching during ongoing body motion (see Section 1.3.4.3 below).

1.3.4.2 Vestibular contributions to dynamic compensations for body motion during reaching

When reaching during rotation of the body, there are additional forces that act on the limb due to the body motion. In a rotating frame of reference any linear movement that has a component perpendicular to the axis of rotation is subject to Coriolis and centrifugal forces (Lackner and Dizio, 1994, Bockisch and Haslwanter, 2007, Bortolami et al., 2008b). Coriolis forces are a function of the angular velocity of the reference frame, the linear velocity of the arm, and the mass of the arm ($F_{coriolis} = -2m(\omega \times v)$, where m is the mass of the arm, v the linear velocity of the limb, and ω the angular velocity of the rotation). Centrifugal forces are proportional to the angular velocity of the rotation and the squared distance of the limb from the axis of rotation ($F_{centrifugal} = \omega r^2$, where r is the distance of the limb from the center of rotation and ω is the angular velocity of the rotation). Reach paths during active turn-and-reach movements suggest that the brain can anticipate the effects of these forces as well as the inertial properties of the limb on limb trajectory and adjust motor commands accordingly (Pigeon et al., 2003, Bortolami et al., 2008b). The nature of how these forces are predicted is not fully known. During active movements efference copy signals may provide a source of information for these predictions. However during passive movements information for these predictions must come from other sources such as the vestibular sensors.

Evidence for a contribution of vestibular signals to dynamic compensations for body motion during reaching has been provided by studies where subjects were placed in the center of a rotating room that rotated at constant velocity and asked to perform reaching movements in darkness to a target fixed relative to the body (i.e., an egocentric target) (Fig. 1.5A) (Lackner and Dizio, 1994, 1998a, 2005, Dizio and Lackner, 1995, 2000, 2001). In this situation dynamic compensation for Coriolis and centrifugal forces is necessary but spatial compensation is not. Because of the dynamic properties of the vestibular canals, they no longer signal rotation after about 30-60 seconds of being exposed to constant angular velocity (see Section 1.2.1.2). Thus in this experiment subjects felt stationary even though they were turning. Importantly, when reaching in this situation, arm movements were deviated by Coriolis forces acting on the limb during rotation (Lackner and Dizio, 1994, 1998a, 2005, Dizio and Lackner, 1995, 2000, 2001). This is in contrast to the normal situation when reaching while turning where reach trajectories are made straight to the target (Bresciani et al., 2002b, Pigeon et al., 2003, Bortolami et al., 2008b). Thus, this experiment demonstrated that

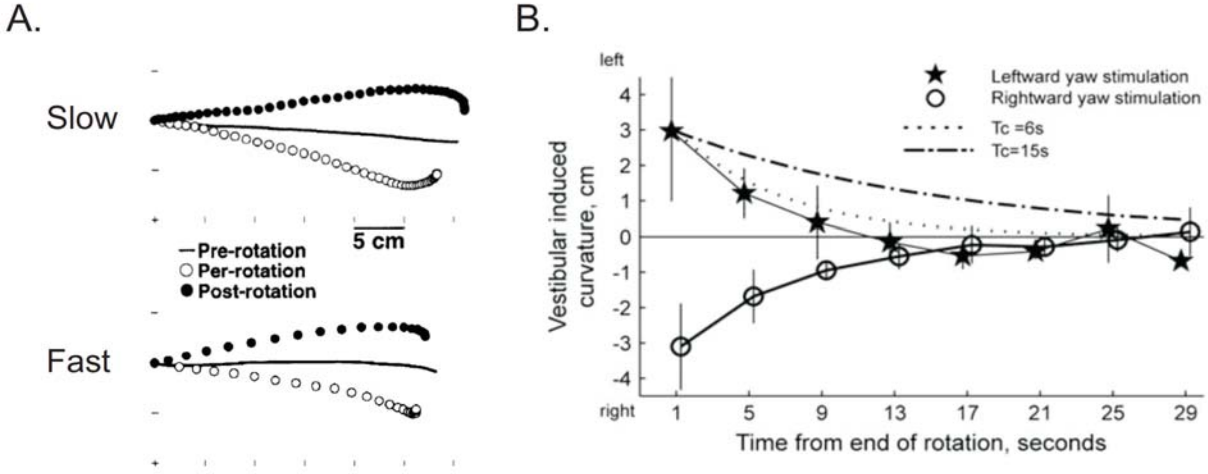

Figure 1.5. **Vestibular contributions to dynamic compensations for body motion during reaching.** A) Average reach trajectories viewed from above (i.e. in the horizontal plane) for slow (~700ms movement duration) and fast (~400ms movement duration) reaches performed in a room rotating counterclockwise at constant velocity (see text). Trajectories shown are for initial reaches only (i.e., the first reach performed) in each condition. Pre-rotation: initial reaches performed when the room was stationary such that no dynamic forces act on the limb (i.e. no Coriolis and centrifugal forces). Per-rotation: reaches performed when the room was rotating but subjects did not have any vestibular sense of rotation. Note that trajectories are deviated by Coriolis forces acting on the limb that have not been compensated for in the absence of vestibular rotation cues. Post-rotation: reaches performed after the slow rotating room came to a full stop. Initial reaches are deviated in the opposite direction to those in the per-rotation condition, demonstrating that subjects reached as if they were trying to compensate for the dynamic forces that were acting on the limb when reaching during rotation but that were no longer present (From Lackner and DiZio, 1994). B) Trajectory deviations compared to controls when subjects performed reaching movements to a remembered target immediately after rotating for two minutes at constant velocity and coming to an abrupt stop. In this situation subjects were stationary but their vestibular sensors signalled rotation (see text). Initial reaches were substantially deviated in the horizontal plane, but became similar to controls as the vestibular signal decayed across time. Also shown is the expected decline in curvature for the leftward yaw stimulation condition if the decay was due to the return of the displaced cupula to its resting position that has a time constant of 6s (Tc=6s; see Section 1.2.1.2), or if the decay included "velocity storage" which extends this time constant to 15s (Tc=15s; see Section 1.3.3) (From Bockisch and Haslwanter, 2007).

when vestibular cues were absent subjects failed to predict and compensate for the additional forces imposed on the limb by the rotation. More recently, the reverse has been demonstrated in a study by Bockisch and Haslwanter (2007) (Fig. 1.5B) . Seated subjects in darkness were rotated in yaw about an axis that passed through the center of the body for 2 minutes before being abruptly decelerated to a stop. Due to the dynamic characteristics of the vestibular sensors, the sudden deceleration is interpreted as rotation in the opposite direction such that subjects, now stationary, experienced a strong vestibular signal of rotation in the opposite direction. When reaching to the location of a remembered egocentric target, reach trajectories were deviated in the direction appropriate to compensate for the Coriolis and centrifugal forces that would have been present if reaching during rotation (Bockish and Haslwanter, 2007). Therefore, it appears that vestibular signals are used by the brain to predict the effects of these forces on limb trajectory and to adjust motor commands accordingly.

1.3.4.3 Vestibular contributions to online compensations for unexpected body motion

In the studies described above subjects either reached after body rotation or in a situation where the body rotation had already begun prior to reaching and could act as a contextual cue for predicting the dynamic characteristics of the environment. In these situations the effects of the body motion on the trajectory of the limb could be taken into account during reach planning to generate appropriate motor commands. A number of other studies have considered the ability of vestibular signals to contribute to online compensations for actual or simulated body motion during reaching applied as a passive unpredictable perturbation after the reach had been initiated (Bresciani et al., 2002a, Mars et al., 2003, Guillaud et al., 2011). In such a situation both spatial and dynamic compensations are required for the unexpected body motion, but the brain could not pre-plan them. Instead, the motor commands need to be modified during the ongoing movement in order to preserve reach accuracy.

In a study by Bresciani and colleagues (2002b) seated subjects in darkness were asked to perform reach movements to the remembered location of a previously flashed target that was fixed in space (Fig. 1.6A). During reach execution, a platform passively rotated the whole-body of subjects in the horizontal plane about a vertical body axis in an unpredictable fashion in either the clockwise or counterclockwise direction and for different rotation amplitudes. In this situation, reach trajectory end-points were only deviated by about 4 degrees for a 40 degree whole-body rotation (the largest rotation amplitude used) relative to the actual position of the reach target. This result suggested that subjects were able to use vestibular cues to perform reach movements that were quite accurate despite the displacement of the limb and body due to the passive whole-body rotation (Bresciani et al., 2002b).

Another study attempted to dissociate the contribution of vestibular cues from other potential contributions such as somatosensory or proprioceptive cues by using galvanic vestibular stimulation to selectively stimulate vestibular afferents. Of particular relevance to the current work is a study by Bresciani and colleagues (2002a) (Fig. 1.6B). Standing subjects whose head was held in place by a bite-bar performed reaching movements in darkness to the memorized spatial locations of previously-flashed targets using a pointer connected to the ground by telescoping rods that allowed arm movement in the horizontal plane. In half of the trials, the movement onset triggered an electrical stimulation (3mA square pulse) of the

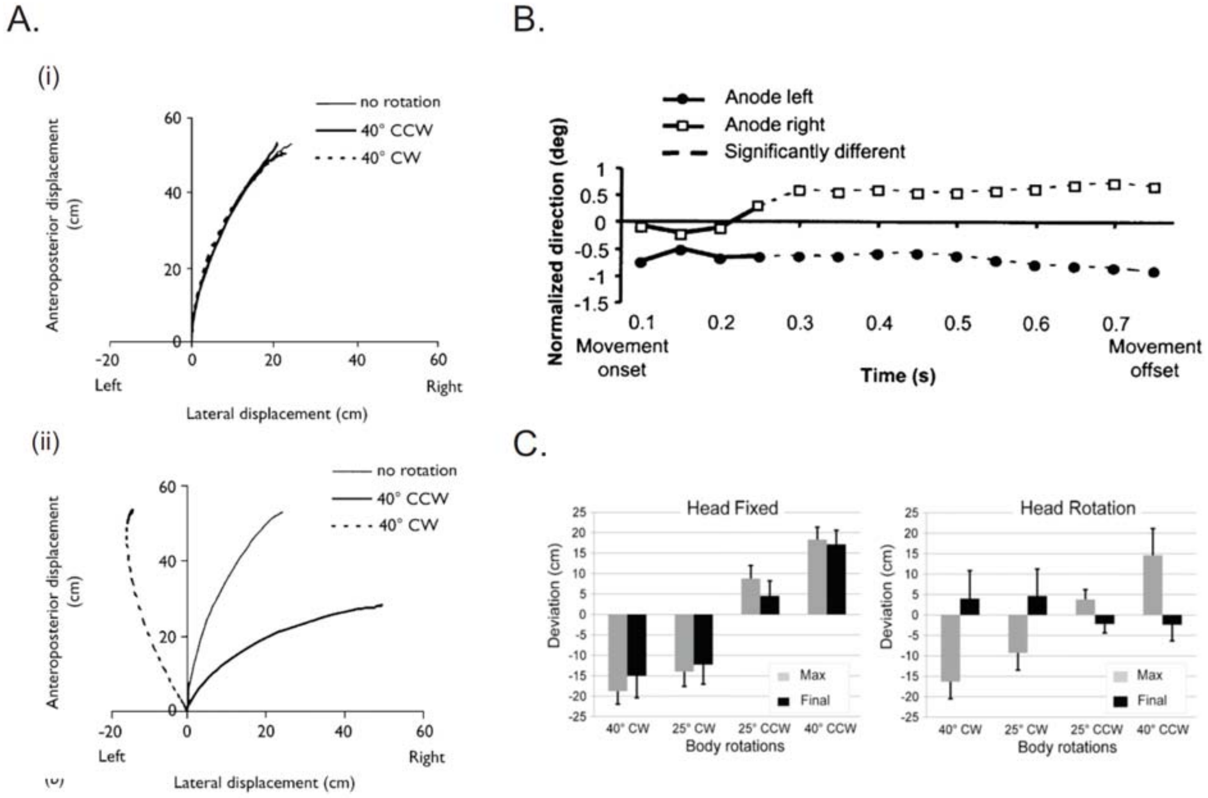

Figure 1.6. Vestibular contributions to online compensations for unexpected body motion. A) Reach trajectories of a subject when reaching to a remembered target while stationary (no rotation), or during 40 degree clockwise (CW) or counterclockwise (CCW) passive whole-body yaw rotation illustrated in world coordinates (i) and in trunk-centered coordinates (ii). Note that in (i) even though the trunk was displaced by 40 degrees, the subject was able to perform reaching movements that were very similar to controls. (From Bresciani et al. 2002b). B) Reach trajectory deviations in the horizontal plane evoked by galvanic vestibular stimulation when reaching to a remembered target. Positive values on the x-axis indicate rightward lateral deviations and negative values leftward lateral deviations relative to controls. Note that trajectories were always deviated towards the anode. (From Bresciani et al. 2002a). C) The maximum lateral deviations during the reach (max) and final lateral end-point deviations (final) of reach trajectories of a proprioceptively deafferented subject reaching to a body-fixed target during body rotation with either the head fixed in space (head fixed) or rotating with the body (head rotation) for different rotation directions and amplitudes. Note that only when the head moved with the body such that vestibular information about the body rotation was available was the subject able to reach to the location of the body-fixed target with minimal errors. (From Guillaud et al., 2011).

vestibular afferents using a technique known as bipolar binaural galvanic vestibular stimulation (GVS; see Section 1.4 below). The subjects could not predict on what trials the stimulation would occur nor the stimulation polarity. Galvanic vestibular stimulation excites afferents on the side of the cathodal electrode and thus simulates motion towards the cathode (see Section 1.4 below). When the vestibular perturbation was present during the arm movement, reach trajectories in the horizontal plane were deviated, demonstrating that vestibular signals can influence arm motor commands online. These trajectory deviations were always directed towards the anode consistent with the suggestion that subjects were trying to compensate spatially for a simulated body motion towards the cathode.

GVS has also been used to explore vestibular contributions to the online coordination of arm and trunk motion. In a study by Mars and colleagues (2003), seated subjects performed reaches with simultaneous forward trunk movement in darkness to the remembered location of a space-fixed target. On some trials an unexpected bipolar binaural GVS pulse of unpredictable polarity (1.5 mA square pulse for 1.5 s) was delivered during ongoing movement. Application of the GVS resulted in trunk and hand deviations towards the anode, demonstrating that vestibular signals can influence arm and trunk coordination during ongoing movement. These deviations were suggested to be due to two different effects of the vestibular perturbation on the movement, a modification in the trajectory of the trunk and a superimposed modification of the position of the arm relative to the trunk. Furthermore, similar to the study of Bresciani and colleagues (2002a), these deviations were in the direction consistent with spatial compensation for simulated motion towards the cathode.

Another study which attempted to dissociate vestibular from proprioceptive contributions to reaching investigated a subject with complete loss of proprioceptive and somatosensory sense from the nose downwards (Fig. 1.6C) (Guillaud et al., 2011). In this study, the subject performed reaching movements in darkness to the remembered location of a briefly-flashed egocentric target while seated in a mechanically rotatable chair. In this situation dynamic compensation for body rotation is necessary but spatial compensation is not. Immediately following the onset of the reach, either the head and body were passively rotated together or the body was rotated alone in a pseudo-randomly chosen direction about the body-vertical axis (i.e. yaw rotation). When the head was held stationary such that no vestibular signal of motion was present, the subject did not compensate for the dynamic forces acting on the limb and made large end-point errors when reaching. In contrast, reach end-point errors were much smaller when the head and the body were rotated together, suggesting that vestibular signals may have been used online to adjust the reach motor command and compensate for the dynamic forces acting on the limb.

In summary, while it is only recently that studies have begun to explore vestibular contributions to reaching movements, evidence has been provided to suggest that they contribute to spatial and dynamic compensations for body motion during reaching under a variety of different behavioural conditions. However, the specific mechanisms by which vestibular signals contribute to reaching and the neural correlates for these mechanisms have yet to be determined, and will need to be explored in future research.

1.4 Galvanic vestibular stimulation

Different techniques have been used to test vestibular contributions to a variety of behaviours, including asking subjects to actively move or rotate themselves in space (Medendorp et al., 2002, Van Pelt and Medendorp, 2007, 2008) and using motion systems to passively rotate or translate subjects (Lackner and Dizio, 1994, Bresciani et al., 2005, Bockisch and Haslwanter, 2007). In the current study, another technique known as galvanic vestibular stimulation was used to electrically stimulate the vestibular sensors. This technique, in which an electrical stimulation is applied to excite vestibular afferents, has previously been used to investigate vestibular contributions to a range of behaviours including postural responses, vestibularly-driven perceptual processes, and eye movements (St George and Fitzpatrick, 2011). Below I describe this technique with its advantages and disadvantages and provide an overview of how it has been used previously to study the vestibular system.

1.4.1 The galvanic vestibular stimulation technique and its effects on the vestibular periphery

1.4.1.1 The galvanic vestibular stimulation technique

In the galvanic vestibular stimulation technique (GVS), surface stimulation electrodes are placed behind the ears on the mastoid processes in order to electrically activate the vestibular afferents. For experimental situations, GVS is typically delivered using a controlled current source with current amplitudes in the range of ~1-3 mA (Fitzpatrick et al., 1994, Wardman et al., 2003), although in a few studies higher currents up to 10 mA have been used

(Aw et al., 2006). The stimulus that has been most often applied is a DC pulse of current with a duration that is usually from .5 s to 5 s (Fitzpatrick et al., 1994, Bresciani et al., 2002a, Wardman et al., 2003), although GVS has also been applied using high frequency trains of pulses (Schneider et al., 2000). In general, GVS has been most commonly delivered with an anodal electrode behind one ear and a cathodal electrode behind the other ear, known as bilateral bipolar GVS (Fitzpatrick et al., 1994, 2002, 2006, Day et al., 1997, Fitzpatrick and Day, 2004). Other configurations that have been used include bilateral monopolar GVS, where electrodes of same polarity are placed behind both ears (Severac Cauquil et al., 1998, 2000), and unilateral monopolar GVS, where only one stimulation electrode is placed behind one ear and the other electrode is placed elsewhere such as on the clavicle (Severac Cauquil et al., 2000, Kennedy et al., 2004).

1.4.1.2 The site of action of galvanic vestibular stimulation

Galvanic vestibular stimulation selectively activates the vestibular system through its action on vestibular afferents. In particular, GVS directly affects the spike trigger site of the primary afferents innervating the hair cells of the canals and otoliths by modulating the polarization of the neuroepithelium in the crista and macula of the vestibular organs (Goldberg et al., 1984). This polarization by GVS leads to increases or decreases in afferent firing rate depending on whether the current hyperpolarizes (anode) or depolarizes (cathode) the trigger site, such that the cathodal electrode will cause an excitatory response and the anodal electrode will cause an inhibitory response in vestibular afferents (Goldberg et al., 1984). Since natural motions of the head such as rotations activate the canal ipsilateral to the direction of rotation and inhibit the canal contralateral to the direction of rotation, binaural bipolar GVS simulates motion of the head towards the cathodal ear.

1.4.1.3 Advantages and disadvantages of using galvanic vestibular stimulation

A strong advantage of using the GVS technique is that it allows a selective stimulation of the vestibular sensors in the absence of an actual movement that could also activate other senses such as proprioceptive or somatosensory inputs (Fitzpatrick and Day, 2004). Therefore, any observed behavioural response to GVS must be due to the vestibular perturbation alone. This has made GVS an attractive tool in order to probe the contribution of the vestibular system to a wide range of behaviours, including postural, oculomotor and perceptual processes (St George and Fitzpatrick, 2011). However, it is important to note that GVS is an unnatural stimulus. GVS simultaneously activates all afferents in a similar fashion regardless of directional tuning and bypasses the hair cell transduction mechanisms to directly affect the spike trigger site (Goldberg et al., 1984). There is no natural movement that could create the same afferent activation pattern as produced by GVS (Fitzpatrick and Day, 2004). Nonetheless, GVS has been shown to evoke a consistent and predictable response that can be interpreted in the context of a model of the net afferent signal evoked by GVS (see Section 1.4.3) (Fitzpatrick and Day, 2004). Of particular relevance to the current work is the use of GVS to study reference-frame transformations of vestibular signals, as the afferent activity induced by GVS is the same regardless of how the head is oriented relative to the body and the external space (see Section 1.4.3.2).

1.4.2 Behavioural effects of galvanic vestibular stimulation

Galvanic vestibular stimulation has been used to study vestibular contributions to a range of behaviours. Much research using this technique has looked at the behavioural responses to GVS in the context of postural control (Nashner and Wolfson, 1974, Britton et al., 1993, Pastor et al., 1993, Fitzpatrick et al., 1994, Inglis et al., 1995, Day et al., 1997, Day and Cole, 2002, Wardman et al., 2003, Cathers et al., 2005, Mian et al., 2010, St George and Fitzpatrick, 2011). A few studies have also examined eye movement responses (Schneider et al., 2000, 2002, MacDougall et al., 2002, Aw et al., 2006) and perceptual responses to GVS (Fitzpatrick et al., 1994, 2002, Wardman et al., 2003, St George and Fitzpatrick, 2011). Below I summarize the behavioural responses typically observed for bipolar binaural GVS and its relationship to interpreting the net GVS signal.

1.4.2.1 Postural effects of galvanic vestibular stimulation

One of the most clearly observed behavioural responses to GVS is its effect on posture. Binaural bipolar GVS elicits a consistent postural response in upright standing subjects that involves a whole-body sway in the direction of the anodal ear (Fig. 1.7A) (Nashner and Wolfson, 1974, Britton et al., 1993, Pastor et al., 1993, Inglis et al., 1995, Day et al., 1997, St George and Fitzpatrick, 2011). This response involves the legs, trunk, and neck, producing a consistent tilt to the anodal side until a maximal static position is reached that becomes larger with greater stimulation intensity. The behavioural response is what would be expected if the brain was compensating for simulated body tilt towards the cathode. The amplitude of the sway response can depend on a number of factors, such as the distance of the feet from one

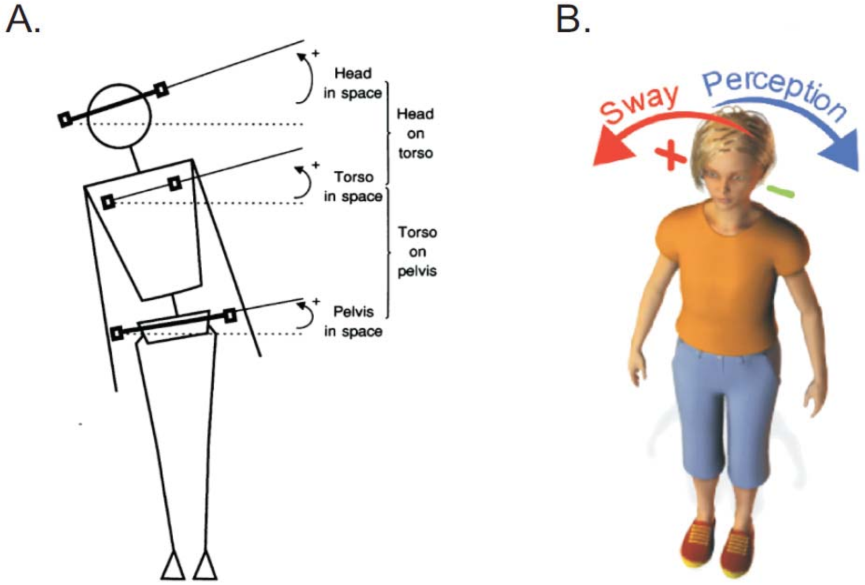

Figure 1.7. **The effects of bipolar binaural galvanic vestibular stimulation on posture and motion perception.** A), bipolar binaural GVS evokes a whole-body postural sway response that is directed towards the anode. (From Day et al., 1997). B) The postural sway response that is directed towards the anode (+) is in the appropriate direction to compensate for a perceived whole-body sway towards the cathode (-). (From Day and Fitzpatrick, 2006).

another, with the response becoming more attenuated the further apart the feet are placed (Day et al., 1997) or if visual information is available (Britton et al., 1993, Fitzpatrick et al., 1994). In addition, adopting a sitting posture rather than standing further reduces the observed tilt through the reduction of upper body segment movement (Day and Cole, 2002).

Several studies have looked at the muscle responses evoked by GVS (Britton et al., 1993, Fitzpatrick et al., 1994, Cathers et al., 2005, Mian et al., 2010). The effects of GVS on electromyographic (EMG) responses can be seen as early as 40 ms in the arm and 60 ms in the leg (Britton et al., 1993, Fitzpatrick et al., 1994). There are two components to the EMG response evoked by GVS. First, there is a small early component (~60-70 ms latency in the leg) followed by a larger response that arrives later (~110 ms latency in the leg) and overrides the early component (Britton et al., 1993, Fitzpatrick et al., 1994, Cathers et al., 2005). The early response, known as the short latency response, activates muscles in the appropriate fashion to elicit body movement towards the cathodal side (Britton et al., 1993). The origins and role of the short latency response remains uncertain and is a source of debate (Cathers et al., 2005, Mian et al., 2010). In contrast the later component, known as the medium-latency response, activates muscles in a distal to proximal order in the appropriate fashion to elicit body movement towards the anodal side (Britton et al., 1993), reflecting the observed postural sway response evoked by the GVS (Britton et al., 1993, Fitzpatrick et al., 1994, Cathers et al., 2005).

1.4.2.2 Eye movement responses to galvanic vestibular stimulation

A number of studies have investigated the oculomotor responses evoked by GVS (Schneider et al., 2000, 2002, MacDougall et al., 2002, Aw et al., 2006). The administration of GVS evokes stereotypical and repeatable VOR responses at a latency of about 9 ms (Aw et al., 2006) that are always the same regardless of how the head is oriented in space (Schneider et al., 2000) with the response magnitude increasing linearly with current intensity (Aw et al., 2006).The main oculomotor effect of GVS is one of conjugate torsional eye rotation away from the cathodal side and towards the anodal side (Schneider et al., 2000, 2002, Aw et al., 2006). In addition, there is also a much smaller component of conjugate horizontal eye rotation away from the cathode and towards the anode, and some vertical divergence of the eyes. The torsional components of the eye movement which are nearly fourfold larger than the other components (Aw et al., 2006) include a large tonic ocular torsion of both eyes and a superimposed torsional nystagmus (Schneider et al., 2002). These ocular responses are directed so as to compensate for a simulated motion of the head towards the cathode (Schneider et al., 2002) with the torsional and vertical divergence responses appropriate for compensating for head rotation in roll (about a head naso-occipital axis), and the horizontal responses appropriate for compensating for a much smaller head rotation component in yaw (about a head vertical axis). This is consistent with the GVS being interpreted as a net rotation about a head-fixed axis elevated slightly from the naso-occipital axis (Schneider et al., 2002).

1.4.2.3 Perceptual effects of galvanic vestibular stimulation

In many situations GVS can be accompanied by sensations of body motion (Fitzpatrick et al., 1994). In unrestrained upright standing subjects, GVS at intensities that evoke a sway response towards the anode (~0.5-2 mA for about 1 s) are accompanied by a clear percept of body sway towards the anodal side (Fitzpatrick et al., 1994, Wardman et al., 2003). Thus, in this case the percept is consistent with the actual evoked movement of the body. Larger stimulations are more likely to induce stronger percepts of motion than smaller stimulations (e.g. 4 mA vs. 1 mA), and the same is true for stimulus duration, with longer stimulus durations (e.g. 5 s vs. 1 s vs. 0.4 s) producing clearer percepts of movement (Fitzpatrick et al., 1994, Wardman et al., 2003). However the perceptual effect of GVS is strongly dependent on the conditions of stimulus delivery. When subjects are strapped in place such that the sway response towards the anode is prevented from developing, subjects will instead report a GVS-induced perception of motion that is directed towards the cathode (Fitzpatrick et al., 1994, Wardman et al., 2003). In addition, in subjects lying in a supine position such that there is no need for any postural responses, 1-2 mA GVS for around 4 s evokes sensations of spinning in the horizontal plane towards the cathode about an axis that passes through the head (Fitzpatrick et al., 2002). Collectively, these results suggest that GVS induces a percept of movement that is directed towards the cathode (Fig. 1.7B). However this percept is overwhelmed by the much more salient percept of sway in the opposite direction when behavioural postural compensations are evoked.

1.4.3 Fitzpatrick and Day's summation model

Overall, the perceptual (Fitzpatrick et al., 1994, 2002, Wardman et al., 2003) and motor (Nashner and Wolfson, 1974, Pastor et al., 1993, Fitzpatrick et al., 1994, Inglis et al., 1995, Day et al., 1997, Schneider et al., 2000, 2002, Day and Cole, 2002, Wardman et al., 2003, Cathers et al., 2005, Aw et al., 2006, Mian et al., 2010, St George and Fitzpatrick, 2011) responses to GVS are consistent with GVS simulating motion that is interpreted by the brain as a rotation towards the cathode about a head-centered axis that is mainly aligned with but slightly elevated from the head naso-occipital axis. In light of these observations, Fitzpatrick and Day (2004) developed a model to more precisely determine how the GVS-evoked vestibular signal is being interpreted by the brain. In the model, the brain is assumed to perform a summation of the GVS-evoked responses across the afferent population of the vestibular organs to compute a net unified representation of simulated movement. As will be discussed in the following sections, the model makes different predictions for the net stimulation of semi-circular canal afferents and for those of otolith afferents. These predictions have been tested and are supported by evidence from several studies investigating the effects of GVS on posture, self-motion perception and locomotion.

1.4.3.1 Interpretation of the net vestibular signal

An actual rotation only activates afferents that innervate canals that lie at least partially in the plane of rotation with all afferents associated with a given canal activated in a similar manner, either increasing or decreasing firing rate (Fitzpatrick and Day, 2004). In contrast the galvanic stimulus simultaneously activates the afferents associated with all canals regardless of their orientation relative to the axis of rotation (Goldberg et al., 1984). The assumption of the Fitzpatrick and Day (2004) model is that despite the unnatural activation pattern, the brain interprets the GVS as the net vector of rotation obtained by summing the contribution of all afferents across all canals. If we assume the canals are oriented in orthogonal planes, for the horizontal canal the stimulation simulates a natural yaw rotation towards the cathodal ear. For the anterior and posterior canals of a given labyrinth, since they are oriented + or – 45 degrees from the saggital plane, stimulation will simulate both a component of rotation in roll and in pitch (Fig. 1.8A). The roll component is in the same direction for both canals (towards the cathodal ear) such that they will add together. In contrast, the pitch component is in opposite directions such that that they cancel each other out completely. Therefore summing the rotation signals across the three canals on one side leads to a net signal of rotation having both roll and yaw components with the roll component being much larger than the yaw component

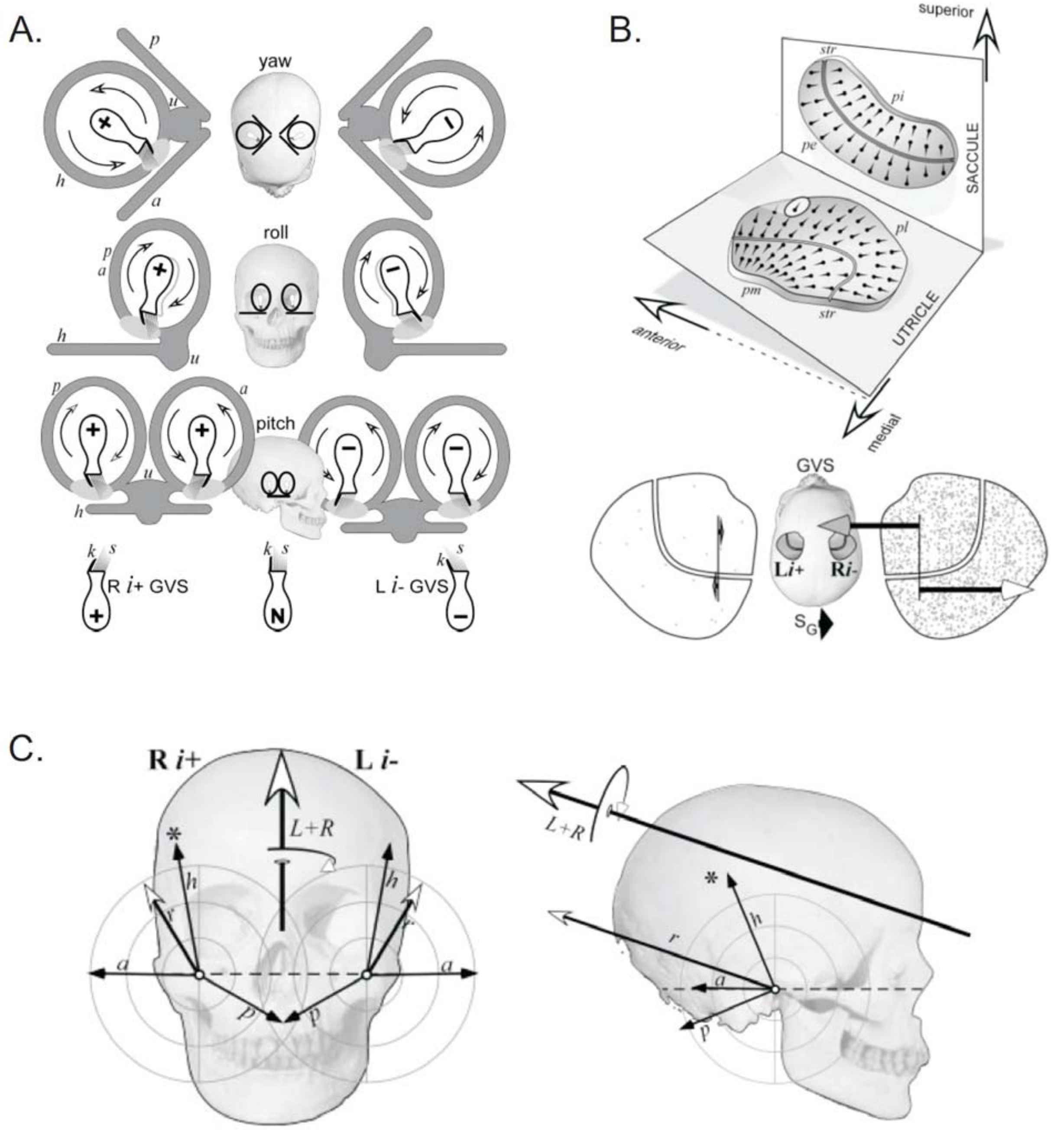

Figure 1.8. **Predictions of the Fitzpatrick and Day (2004) summation model.** A) Predictions of the model for the net effect of semicircular canal afferent stimulation. The directions of the yaw, roll and pitch signals evoked by GVS are illustrated. Since all hair cells of a given canal respond in a similar manner, a single hair cell is used to illustrate the direction of rotation evoked by GVS. Here, the anodal electrode is on the right side of the head (R i+ GVS, left side of figure) and the cathodal electrode is on the left side of the head (L i- GVS, right side of figure). While the GVS-evoked yaw and roll rotation

signals are additive on each side of the head, pitch signals should cancel out. Symbols: p, posterior canal; h, horizontal canal; a, anterior canal; u, utricle. B) Top, Illustration of the spread in hair cell spatial tuning directions (the pointed dots in the figure) in the otolith organs. Tuning directions are oppositely directed on each side of the striola, such that GVS will preferentially activate afferents innervating one side of the striola and inhibit the other. Bottom, illustration of the GVS evoked responses in the utricle. The cathode on the right (Ri-) increases firing of the entire population, while the anode on the left (Li+) decreases it. On each side of the head the oppositely-directed tuning of the hair cells in the pars medialis and pars lateralis cause the signals to almost cancel each other out. The amplitude and direction of the response to GVS in each portion of the macula is shown by arrows. Since there is a slight imbalance in the populations of hair cells between the pars medialis and lateralis, a small GVS-evoked signal of net acceleration (Sg) towards the cathode is expected. C) The GVS-evoked axis of simulated motion. The net vector of motion evoked by GVS is dominated by the semi-circular canal inputs. Vectors for each canal are shown as black arrows and plotted orthogonal to the plane of the canal (a, anterior; p, posterior; h, horizontal) with Reid's plane (dashed line) shown for reference. For each labyrinth, the vector summation of the three canals is shown with small white arrows (r, resultant). The large white arrow represents the vector summation of both labyrinths (L+R). The lateral and vertical components of the vectors are shown in the front view, and the sagittal and vertical components are shown in the lateral view (From Fitzpatrick and Day, 2004).

due to both vertical canals signalling roll (Fitzpatrick and Day, 2004). Summing the canal signals across both labyrinths, bilateral bipolar GVS will produce a signal of rotation about an axis inclined slightly upward from a naso-occipital axis (Fig. 1.8C). Fitzpatrick and Day (2004) estimated that this net rotation axis is inclined upwards by about 18.8 degrees relative to Reid's line, a stereotaxic reference line that is roughly in the horizontal plane when the head is upright facing straight ahead (Blanks et al., 1975).

Unlike in the canals, in the otoliths the preferred directions of the hair cells are spread out in an orderly fashion across the macula of the saccule and utricle (Fig. 1.8B top; see also Fig. 1.1C) (Fernandez and Goldberg, 1976b, Naganuma et al., 2001, 2003). In addition, the striola of the macula that runs from one end of the organ to the other separates the hair cell population in two, with the spatial tuning of the hair cells being oppositely directed on each side (Flock, 1964, Fernandez et al., 1972). Consequently, activation of all afferents by GVS results in the simultaneous signaling of motion in all directions in the plane of each sensor. Due to this fanlike spread of direction preferences and the antagonistic organization of hair cell responses between the two sides of the striola (see Section 1.2.1.1), the afferent responses of a given otolith organ should largely cancel each other out (Fitzpatrick and Day, 2004). In particular, any residual signal that is left after summation would have to be due to differences in the relative population of hair cells on each side of the striola. For the utricle, it has been estimated that the difference in the proportion of total hair cells between the pars medialis (the inner part of the macula relative to the striola) and the pars lateralis (the outer part of the macula) is about 47% to 53% with the majority going to the pars lateralis (Tribukait and Rosenhall, 2001). As a consequence, the net vector response produced by GVS of the utricles will be a small and close to negligible signal indicating translation towards the cathodal side or a tilt of the head towards the anodal side (Fig. 1.8B bottom) (Fitzpatrick and Day, 2004). For the saccule, a recent study has estimated that the difference in the proportion of total hair cells between the pars superior and the pars inferior to be about 56% to 44% with the majority going to the pars superior (Tribukait et al., 2005). Therefore the net vector response produced by GVS in the saccules should be a small and close to negligible signal indicating downward and forward translation on the cathodal side and upward and backward translation on the anodal side. As a consequence, vector summation across both saccules is likely to completely cancel out the signal (Mian et al., 2010).

Overall, the predictions of the Fitzpatrick and Day (2004) model suggest that the simulated motion evoked by bilateral bipolar GVS is dominated by the net semi-circular canal afferent signal of rotation that is directed towards the cathode about an axis that is oriented in the sagittal plane toward the back of the head and inclined upwards by 18.8 degrees relative to Reid's plane (Fig. 1.8C) (Fitzpatrick and Day, 2004). The orientation of this predicted axis of simulated movement is in agreement with the postural, oculomotor and perceptual responses to GVS described above (Britton et al., 1993, Fitzpatrick et al., 1994, 2002, Schneider et al., 2000, 2002, Wardman et al., 2003, Aw et al., 2006). As will be discussed below, the predictions of this model have been confirmed by studies that have used bilateral bipolar GVS to directly test if vestibular signals are transformed from a head-centered to a world-centered frame of reference.

1.4.3.2 Evidence for a head- to world-centered reference-frame transformation of vestibular signals and support for the summation model

The Fitzpatrick and Day (2004) model has been directly used to explore whether vestibular signals are transformed to a world-centered frame of reference for postural control (Cathers et al., 2005, Mian et al., 2010), self-motion perception (Day and Fitzpatrick, 2005b) and locomotion (Fitzpatrick et al., 2006, Osler and Reynolds, 2012). These studies in turn have confirmed the validity of the model's predicted axis of simulated rotation. The basic paradigm used in all of these investigations involves applying GVS with the head in different orientations and observing the behavioural responses to the stimulations. For example with the head upright the GVS axis is roughly aligned with the earth (or body) horizontal whereas with the head forward the same axis is roughly aligned with the earth (or body) vertical. If vestibular signals are transformed from a head-centered to a world- (or body) centered frame of reference, then changing the orientation of the head in space (or relative to the body) should result in the same GVS signal being interpreted as a rotation about a different spatial (or body) axis. Behavioural responses to the GVS should thus vary as a function of head orientation.

The first studies of this type considered postural compensations in upright standing subjects when the head was reoriented in the horizontal plane (Nashner and Wolfson, 1974, Lund and Broberg, 1983, Pastor et al., 1993). In particular, the whole-body postural sway response was directed laterally to the side when the head was facing straight ahead. However, turning the head to the right or left on the body such that the GVS axis was now close to aligned with the sagittal plane of the body instead led to forward and backward whole-body sway. This head-orientation dependent effect of the postural sway response provides evidence for a head- to body-centered transformation of vestibular signals that contribute to postural control. Fitzpatrick, Day, and colleagues (Cathers et al., 2005, Fitzpatrick et al., 2006, Mian et al., 2010) have extended these observations by exploring the effect of reorienting the head in pitch on postural sway and the medium-latency EMG responses to determine whether vestibular signals are transformed from a head-centered to a world-centered reference frame. Whereas with the head upright the stimulation simulates rotation in the vertical plane, with the head pitched forward the stimulation should simulate rotation in the horizontal plane (Fig. 1.9A). If vestibular signals are transformed to a world-centered reference frame, then with the head pitched forward the stimulation should no longer evoke postural compensations as it no longer signals reorientation relative to gravity. In these studies, pitching the head forward abolished the large sway and the medium-latency EMG response that is seen with the head

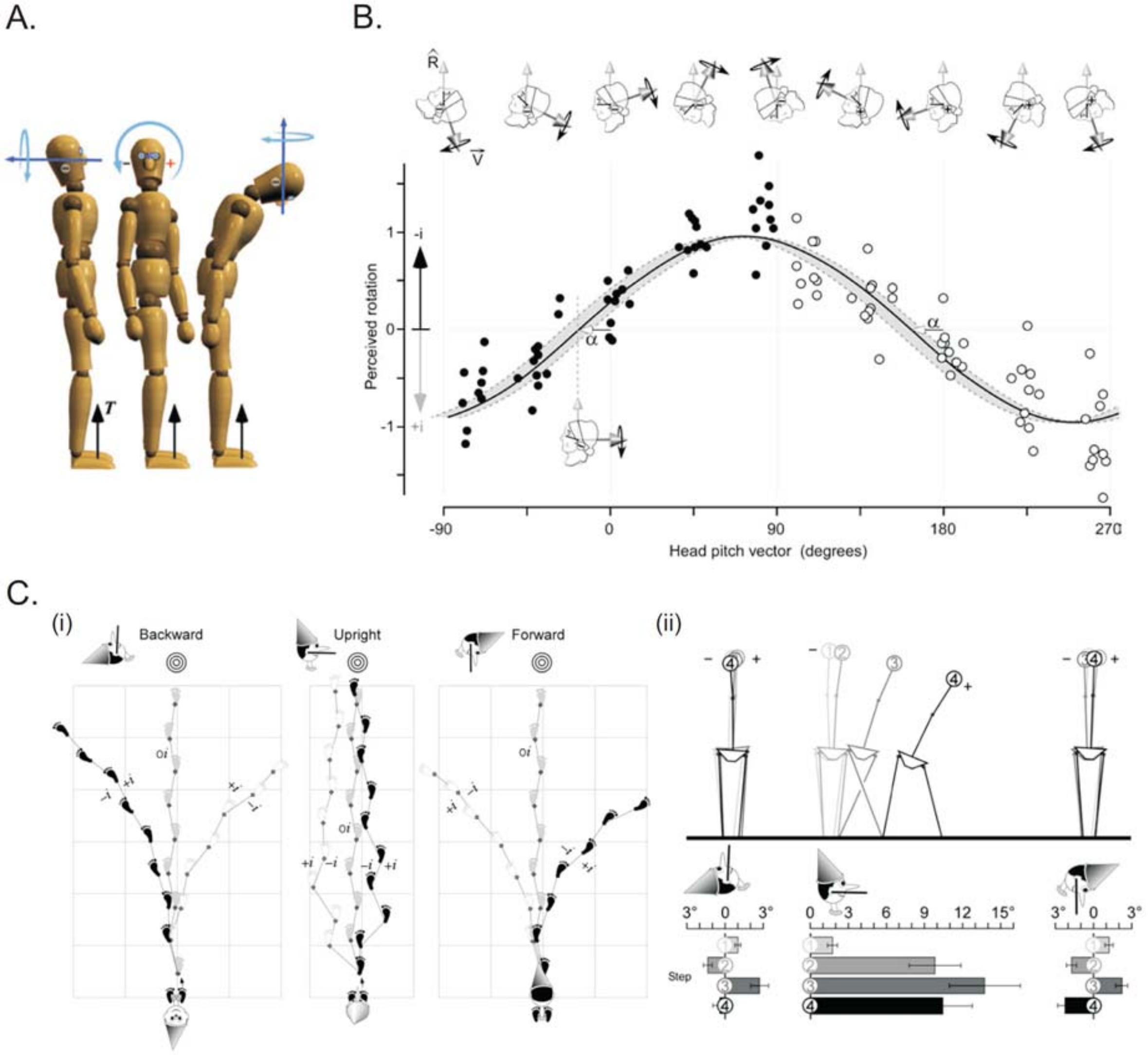

Figure 1.9. **Confirmation of the summation model and use of GVS to study reference-frame transformations of vestibular signals.** A) With the head upright, GVS simulates rotation in the vertical plane. With the head titled forward, GVS simulates rotation in the horizontal plane. (From St. George and Fitzpatrick, 2011). B) The perceived GVS-evoked body rotation based on head orientation. The black points represent anode right stimulation, and the white points represent anode left stimulation. The grey arrow (always oriented up) represents the axis about which GVS-evoked motion percepts were evaluated. Perceived rotation in the horizontal plane towards the cathodal electrode is positive, while perceived rotation towards the anode is negative. A head pitch angle of 0 (and 180) means that Reid's plane was aligned with the horizontal plane (black line on face). The angle denoted by α represents the head angle at which no motion in the horizontal plane was reported, (when Reid's plane was tilted backwards by 16.4 degrees). The continuous line is a least-squares fit, and the shaded

area represents the 95% confidence limit of the model's predicted rotation vector (V, dark arrow) (From Day and Fitzpatrick 2005). C) A reference-frame transformation of vestibular signals for locomotion. (i), the foot placements of a subject are shown as they walked to a target (target in figure) with the head in different orientations (pitched backwards, upright, and pitched forwards). Walked trajectories with the anode on the left are shown in white, with the anode on the right in black, and without stimulation in grey. While the trajectories that were walked with the head upright were not deviated, pitching the head caused trajectories to be deviated to the right or left depending on stimulus polarity. Furthermore, reversing the pitch direction of the head led to trajectory deviations in opposite directions for the same GVS polarity. (ii), the alignment of the body relative to the vertical is shown for the first four steps (labelled 1-4) across subjects. The top part depicts a typical postural pattern observed during those first steps in different head orientations. The bottom graphs display the tilt of the trunk segment for anodal right stimulation. While stimulation with the head upright lead to important whole-body tilts towards the anode, posture was minimally affected when the head was pitched forward or backward (From Fitzpatrick et al., 2006).

upright (Cathers et al., 2005, Mian et al., 2010). This result was interpreted as evidence that vestibular signals were transformed to a world-centered frame of reference to contribute to postural control.

In addition to postural control, Fitzpatrick and Day decided to test the contributions of transformed vestibular signals to other spatially-dependent behaviours such as self-motion perception (Day and Fitzpatrick, 2005b) and locomotion (Fitzpatrick et al., 2006). To explore the contribution of vestibular signals to spatial perception, Day and Fitzpatrick (2005b) administered bilateral bipolar GVS to restrained seated subjects when their head assumed different orientations in space. For the same stimulus polarity, when the head was pitched forward subjects perceived whole-body yaw rotation in one direction, and with the head pitched backwards subjects reported whole-body yaw rotation in the opposite direction (Fig. 1.9B). Therefore, by simulating a rotation about a head-fixed axis and measuring the perception of subjects about an earth-fixed axis, Day and Fitzpatrick (2005b) demonstrated that vestibular signals are transformed to world-centered coordinates to contribute to the perception of self-motion in space. Furthermore, they estimated that the GVS-evoked perception of rotation is about an axis aligned in the sagittal plane of the head (a naso-occipital axis) and elevated upwards by approximately 16.4 degrees relative to Reid's plane, which corresponds very well with the theoretical GVS-evoked rotation axis of the Fitzpatrick and Day (2004) summation model (i.e. elevated 18.8 degrees relative to Reid's plane).

To explore whether world-centered transformed vestibular signals contribute to locomotion, Fitzpatrick and colleagues (2006) examined the walking paths and sway responses of blindfolded subjects during the administration of bilateral bipolar GVS with the head in different orientations relative to gravity (Fig. 1.9C). With the cathode behind the right ear, walked trajectories were deviated towards the left when the head was pitched forward and towards the right when the head was pitched backwards with little to no sway of the body. In contrast, with the head upright there was a substantial sway response of the body but subjects continued walking straight ahead and did not deviate significantly from a straight line (Fitzpatrick et al., 2006). Along the same vein, Osler and Reynolds (2012) investigated the turning behaviour of blindfolded standing subjects marching on the spot during the administration of bilateral bipolar GVS with the head in several different orientations. The stimulation induced turning behaviour when stepping in place that was maximal with the head tilted forward, minimal with the head upright, and reversed direction with the head titled backwards, in a similar fashion to what was observed by Fitzpatrick and colleagues (2006). In both of these studies it was suggested that vestibular signals are transformed to a world-centered frame of reference to contribute to locomotion. In addition, by studying the strength of the relationship between head orientation and turning behaviour, Osler and Reynolds (2012) concluded that the GVS axis of simulated rotation is elevated 22 degrees from Reid's plane. This estimate, derived from motor output, is statistically indistinguishable from the theoretically predicted orientation of the GVS axis of simulated motion (Fitzpatrick and Day, 2004) and from the estimate derived from perceptual reports (Day and Fitzpatrick, 2005b) providing further support for the Fitzpatrick and Day model (2004).

1.5 Motivation for the current study

The general goal of the current work is to further our understanding of how vestibular signals contribute to the planning and execution of reaching movements during body motion. While previous studies have provided evidence for vestibular contributions to spatial and dynamic aspects of reaching during body motion (Lackner and Dizio, 1994, Bresciani et al., 2002a, 2002b, Mars et al., 2003, Bockisch and Haslwanter, 2007, Guillaud et al., 2011) (see Section 1.3.4), little is known about how vestibular signals are processed appropriately to contribute to reaching. Notably, an essential computation relevant for any vestibular contribution to reaching arises because the vestibular sensors are fixed in the head whereas the arm is attached to the trunk. Therefore, a given body movement will result in different patterns of vestibular stimulation depending on how the head is oriented relative to the body (Fig. 1.10A). In order to contribute appropriately to the planning and execution of reaching movements, vestibular signals must first be transformed from a head- to a body-centered reference frame. In this work, we set out to demonstrate that such a reference frame

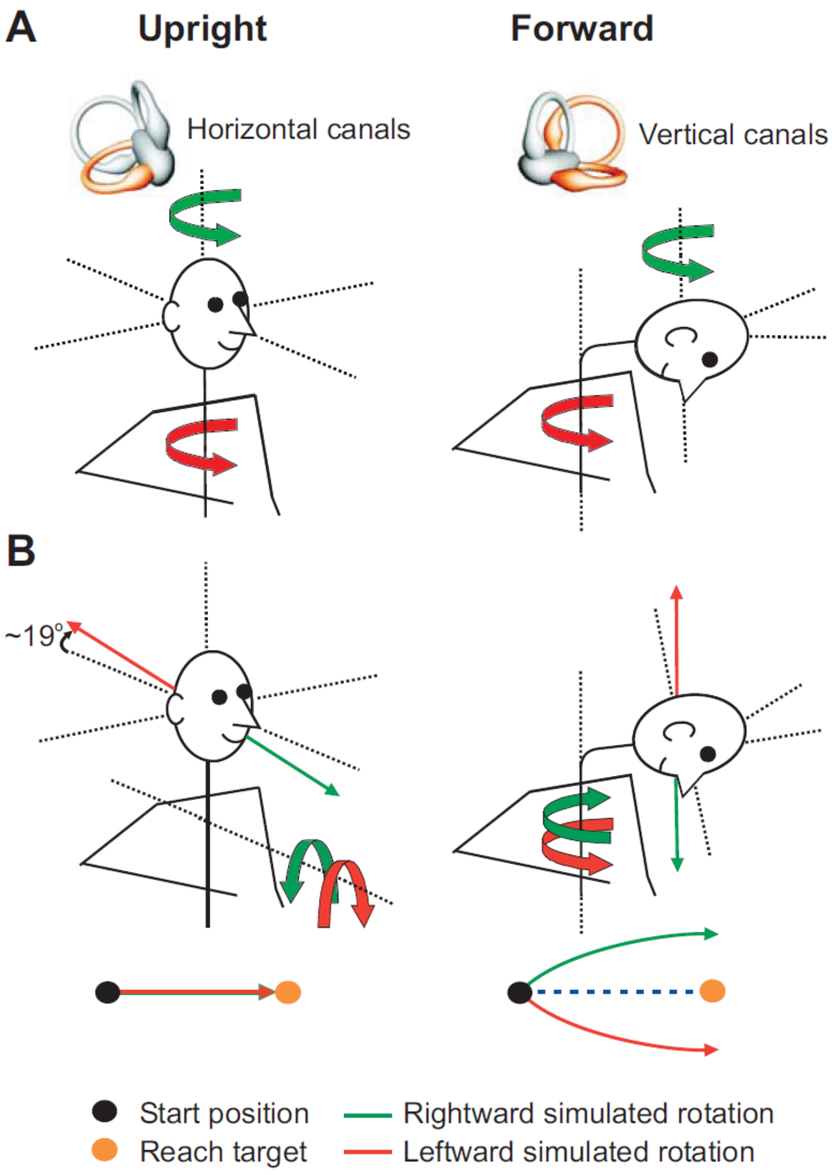

Figure 1.10. **Experimental rationale and predictions.** A) Rotation about a given body axis (e.g. vertical; red arrow) stimulates different sets of semicircular canals in different head-re-body orientations. To correctly interpret body motion vestibular signals must be interpreted in a head-orientation-dependent way (i.e., they must be transformed from a head- to a body-centered reference frame) B) Binaural bipolar GVS stimulates vestibular afferents so as to simulate net rotation about an axis that is inclined roughly 19 degrees upwards from the naso-occipital head axis (Fitzpatrick and Day, 2004). If the vestibular signals which contribute to reaching are transformed from a head to a body-centered reference frame then the same stimulation should be interpreted mainly as body tilt with the head upright, but as body vertical-axis (yaw) rotation with the head tilted forward by 71 degrees.

The stimulation is therefore predicted to evoke only minimal horizontal plane trajectory deviations with the head upright (bottom, left) but much larger ones with the head inclined forward (bottom, right). Arrows and axes indicate simulated rotation direction for cathode right (rightward stimulation; green) and cathode left (leftward stimulation; red) stimulation polarities. Black circle: start position; Orange circle: reach target.

transformation of vestibular signals does occur for the vestibular signals which contribute to the planning and execution of voluntary reaching movements.

To test this hypothesis we drew on the work of Fitzpatrick and Day (Fitzpatrick and Day, 2004, Cathers et al., 2005, Day and Fitzpatrick, 2005b, a, Fitzpatrick et al., 2006, Mian et al., 2010, St George and Fitzpatrick, 2011) in GVS which has been used to provide evidence for a head- to world-centered reference frame transformation of vestibular signals for postural control (Cathers et al., 2005, Mian et al., 2010), locomotion (Fitzpatrick et al., 2006) and self-motion percepts (Day and Fitzpatrick, 2005b) (see Section 1.4.3.2). In the current study we used GVS to selectively activate the vestibular afferents of human subjects as they performed horizontal-plane reaching movements to space-fixed targets with the head in different orientations with respect to the trunk. With the head upright, the axis of simulated rotation is roughly aligned with a body-horizontal axis. In contrast, with the head in a pitched-forward orientation the same axis of simulated rotation becomes aligned with a body-vertical axis (Fig. 1.10B). Therefore, if the vestibular signals that contribute to reaching undergo a transformation from a head-centered to a body-centered reference frame, the same galvanic vestibular stimulation should elicit reach trajectory deviations that depend on the orientation of the head relative to the body. More specifically, with the head upright reach trajectories to a remembered target location should be minimally deviated in the horizontal plane by the stimulation as the simulated rotational motion is mostly in the vertical plane (i.e. a whole-body roll tilt) and would be expected to elicit primarily a postural response. In contrast, with the head pitched forward the same stimulation should now be interpreted as rotational motion about a body-vertical axis (i.e. a whole-body yaw rotation) and larger horizontal-plane reach trajectory deviations should be observed to compensate for a GVS-evoked simulated displacement of the body and limb relative to the target in the horizontal plane (Fig. 1.10B).

The reference-frame transformation of vestibular signals from a head- to body-centered coordinate reference frame for reaching movements was tested in two experiments. In the first experiment, the stimulation was delivered during the execution of a reach movement to test whether vestibular information that contributes to online reach execution undergoes a transformation to a body-centered reference frame. In the second experiment, the stimulation was delivered prior to the execution of a reach movement to test whether vestibular information that contributes to motor planning also undergoes a transformation from head- to body-centered coordinates. In addition, the results of both experiments were compared in order to determine if vestibular signals contributed to similar or distinct mechanisms during reach planning versus execution.

Chapter 2

Evidence for a reference frame transformation of vestibular signal contributions to voluntary reaching

2.1 ABSTRACT

Recent studies have shown that vestibular signals contribute to the planning and execution of voluntary reaching during body motion. However, to contribute appropriately they must be transformed from a head-centered to a body-centered reference frame. To investigate the evidence for this transformation we used galvanic vestibular stimulation (GVS) to simulate rotation about a head-fixed, roughly naso-occipital axis as human subjects made planar reaching movements with their head in different orientations. If vestibular signals that contribute to reaching have been transformed from a head- to a body-centered reference frame, the same stimulation should be interpreted as body tilt about an earth-horizontal axis with the head upright and as rotation about an earth-vertical axis with the head inclined forward. We

thus predicted that GVS would perturb reach trajectories in a head-orientation-dependent way. In keeping with this prediction, GVS applied during reach execution induced trajectory deviations that were significantly larger with the head forward as compared to upright. Only with the head forward were trajectories and endpoints consistently deviated in opposite directions for rightward versus leftward simulated rotation, as appropriate to compensate for body rotation about a vertical axis. These results directly demonstrate for the first time that vestibular signals contributing to reach execution have indeed been transformed from a head- to a body-centered reference frame. By comparing the effects of GVS applied before versus during reach execution we also provide evidence that spatially transformed vestibular signals contribute to distinct compensation mechanisms for body motion during reach planning versus execution.

2.2 INTRODUCTION

Whether running to catch a baseball, turning to pick up a coffee cup or reaching for the handrail as the bus turns a corner, the execution of voluntary motor control tasks, such as reaching, relies critically on estimates of our self-motion and orientation. In particular, accurate reach planning and control must take into account both the spatial relationship between the limb and a reach goal as well as physical properties of the limb and the environment in which movement is executed (Lackner and DiZio, 2005, Kalaska, 2009, Medendorp, 2011). Body motion typically impacts on both of these kinematic and dynamic aspects of motor planning and execution. To preserve reach accuracy, estimates of planned or ongoing body motion are essential both to compensate for spatial displacements of the limb relative to a reach goal (Medendorp et al., 1999, Bresciani et al., 2002b, 2005, Van Pelt and Medendorp, 2007) as well as to plan and coordinate dynamic aspects of motor execution, including compensating for additional forces that act on the arm during body motion (e.g., Coriolis and centrifugal forces; interaction torques) (Lackner and Dizio, 1994, Pigeon et al., 2003, Bockisch and Haslwanter, 2007, Bortolami et al., 2008b, a).

The vestibular sensors (semicircular canals and otolith organs) are among the most important sources of self-motion signals. However, while their contributions to gaze stabilization (i.e., VOR Angelaki, 2004, Green and Angelaki, 2010a, Cullen, 2012) and postural control (Inglis et al., 1995, Horak et al., 2001, Cathers et al., 2005, Stapley et al., 2006, Macpherson et al., 2007) have been extensively studied, less is known about the mechanisms by which vestibular signals contribute to voluntary limb control. A complication in studying their influence is that the self-motion estimates used for reach planning and execution are likely to be derived from a variety of sensory signals (e.g., visual, vestibular, proprioceptive) as well as motor efference copies. Because vestibular signals are integrated with such sensory and motor sources of movement information at the earliest central processing stages (Waespe and Henn, 1977, Boyle and Pompeiano, 1981, Wilson et al., 1990, Buttner et al., 1991, Gdowski and McCrea, 2000, Cullen, 2004, Cullen and Roy, 2004), it is difficult to isolate their specific contributions. Nonetheless, in recent years a number of studies have provided convincing evidence that vestibular signals play a direct role in several different aspects of the planning and execution of voluntary limb movements (Lackner and Dizio, 1994, DiZio and Lackner, 2001, Bresciani et al., 2002a, 2002b, 2005, Mars et al., 2003, Tunik et al., 2003, Bockisch and Haslwanter, 2007, Blouin et al., 2010, Guillaud et al., 2011).

In particular, vestibular signals have been implicated in the kinematic aspects of reach planning through their contribution to a "spatial updating" mechanism presumed to involve updating or remapping a central representation of the egocentric spatial location of the reach goal to compensate for a prior passive displacement of the body (Bresciani et al., 2002b, 2005). Other investigations have emphasized the importance of vestibular signals as contextual cues for selecting appropriate motor commands by providing information about the dynamic characteristics of the environment. In particular, studies by Lackner and colleagues showed that when the body is passively rotated at constant velocity so that the semicircular canals no longer signal body motion because of their high-pass dynamic properties (Fernandez and Goldberg, 1971), initial reach trajectories are perturbed by the failure to compensate for coriolis and centripetal forces acting on the limb (Lackner and Dizio, 1994, DiZio and Lackner, 2001). Conversely, a recent study by Bockisch and Haslwanter (2007) examined reach trajectories executed immediately after constant velocity trunk rotation was stopped. During the several seconds in which the body was stationary but the canals incorrectly signaled rotation in the opposite direction to the original rotation (i.e., again, due to their dynamic properties; Fernandez and Goldberg, 1971), reaching movements were deviated in the direction appropriate to compensate for the coriolis forces that would be predicted if the body had actually been turning (Bockisch and Haslwanter, 2007).

The above studies provide support for a role for vestibular cues in both the kinematic and dynamic aspects of motor planning. Evidence that vestibular signals contribute directly to online reach execution has been provided by experiments showing that when subjects make reaching movements during unpredictable passive body rotations in darkness, trajectories in space are virtually identical to those elicited when stationary (Bresciani et al., 2002b, 2005). In principle, vestibular and proprioceptive signals as well as limb inertia could all potentially contribute to the required online spatial and dynamic compensations for body motion. Importantly, however, the direct influence of vestibular signals has been confirmed by experiments showing that when vestibular afferents are selectively activated by galvanic vestibular stimulation, reach trajectories and endpoints are perturbed (Bresciani et al., 2002a, Mars et al., 2003). Further evidence has also been provided by studies demonstrating the importance of vestibular signals for reaching in the absence of proprioception (Tunik et al., 2003, Guillaud et al., 2011).

Collectively, such studies have established an important role for vestibular signals in reach planning and execution and pointed to several different mechanisms by which vestibular signals may contribute. However, the actual transformations they must undergo to do so have only begun to be explored. The most evident of these, required for any vestibular contribution to reaching, arises because the vestibular sensors are fixed in the head whereas the arm is fixed to the trunk. A given body movement will thus induce different patterns of vestibular stimulation depending on head-re-body orientation (Fig. 1.10A). Consequently, to correctly interpret vestibular signals so that they may contribute appropriately to reaching, the CNS must first transform these signals from a head-centered to a body-centered reference frame.

To provide evidence for this transformation, in the current study we used small transmastoidal currents (galvanic vestibular stimulation, GVS) to selectively stimulate the vestibular sensors as human subjects made horizontal plane reaching movements. Although GVS simultaneously activates all vestibular afferents, a model of the net afferent activation during bipolar GVS that is well supported by experimental results (Cathers et al., 2005, Day and Fitzpatrick, 2005b, Fitzpatrick et al., 2006, Mian et al., 2010) has shown that the stimulation signals a virtual rotation about an axis inclined slightly upward (~19 degrees) from the head naso-occipital axis (Fitzpatrick and Day, 2004). With the head upright (Fig. 1.10B, left) this axis is close to aligned with the earth-horizontal, consistent with the observation that galvanic stimulation during upright stance elicits whole-body tilt responses (Lund and Broberg, 1983, Pastor et al., 1993, Fitzpatrick et al., 1994, Inglis et al., 1995, Day et al., 1997). However, with the head statically pitched 71 degrees forward (Fig. 1.10B, right), the same stimulation corresponds to rotation about an earth-vertical axis. Thus, if vestibular signals are transformed from a head-centered to a world (or body-centered) reference frame, the same stimulation should elicit rotation estimates and behavioural responses that depend on head orientation. Recent studies have used this observation to demonstrate that vestibular signals which contribute to perceptual estimates of the route travelled and to steering and postural compensations during locomotion have been transformed from a head-centered into a world-centered reference frame (Day and Fitzpatrick, 2005b, Fitzpatrick et al., 2006, St George and Fitzpatrick, 2011).

In the current study, we used a similar approach to provide evidence for such a transformation in vestibular contributions to reaching. Specifically, we predicted that if vestibular signals that contribute to reaching have been transformed from a head- to a body-centered reference frame, the same stimulation should perturb horizontal-plane reach trajectories in a head-orientation-dependent way. With the head upright (simulating mainly tilt) the stimulation should elicit mainly postural compensations but only small horizontal-plane trajectory deviations (Fig. 1.10B, bottom left). In contrast, with the head pitched forward much larger trajectory deviations should be evoked to compensate for a simulated earth-vertical-axis body rotation (Fig. 1.10B, bottom right). We evaluated these predictions in the context of two experiments designed to 1) provide evidence for a reference frame transformation of vestibular signal contributions to reaching and 2) explore the nature of the vestibular-driven self-motion compensation mechanisms involved by comparing the effects of GVS on reach execution versus planning.

2.3 METHODS

2.3.1 Subjects

Forty right-handed subjects aged 18-47 years (19 males and 21 females) with no reported history of vestibular dysfunction, neurological problems or sensorimotor anomalies participated in the study (18 in Experiment 1 and 22 in Experiment 2). All subjects provided written informed consent before their inclusion and were naïve as to the goals of the experiment and the hypotheses to be tested. The study was approved by the Human Research Ethics Committee of the Faculté de Médecine, Université de Montréal.

2.3.2 Experimental set-up

During each experiment subjects were comfortably seated facing a projection system with their right arm supported in the horizontal plane by a robotic exoskeleton (KINARM, BKIN Tech) and with their head secured firmly in place by a custom-built adjustable, padded head support system (Fig. 2.1A). Subjects performed voluntary reaching movements to the visual or remembered location of targets displayed by the projection system in the plane of the

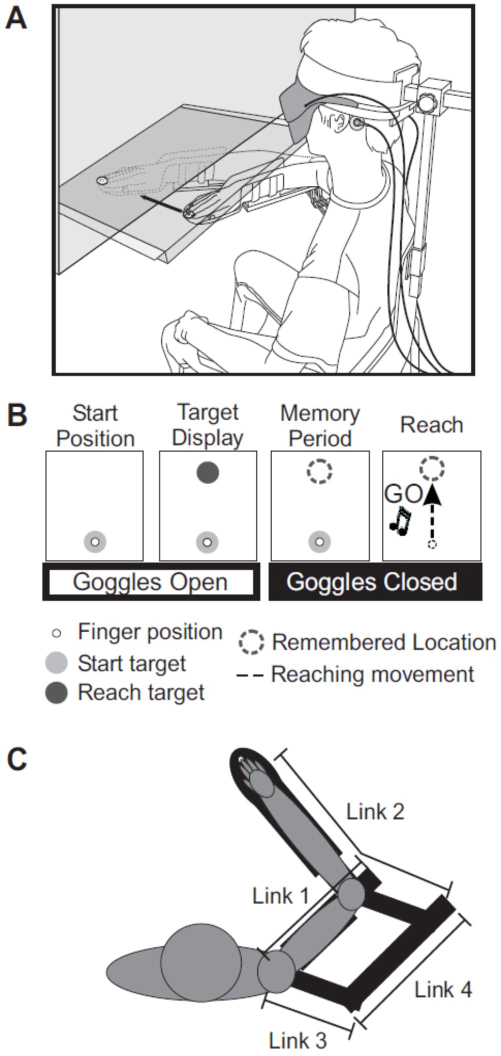

Figure 2.1. **Experimental procedure.** A) Experimental setup. The subject's right arm was supported in the horizontal plane by a robotic exoskeleton (KINARM). Visual targets were projected onto the plane of movement. During most trials vision was blocked by occlusion goggles. The subject's head was secured firmly in place by an adjustable head support system. Bipolar GVS was delivered via carbon rubber electrodes placed behind each ear on the mastoid process. B) Task Protocol. Subjects placed the cursor representing their middle finger in the start target and a reach target was displayed for a brief duration before the target was extinguished and occlusion goggles simultaneously closed. Subjects remembered the target's spatial location for a variable memory period until a "GO" tone signalled to them to reach to the remembered target location. GVS was delivered either during the reaching movement (Experiment 1) or in the memory period just prior to reaching (Experiment 2). C) KINARM linkage.

subject’s arm through a semitransparent mirror. The KINARM exoskeleton provided gravitational support to the limb and was used to constrain and precisely measure horizontal-plane arm movements, but did not otherwise assist subjects in completing the task. A black fabric tunic placed in front of the subject’s body and a sliding metal barrier located between the subject’s arm and the projection screen completely blocked vision of the subject’s trunk and arm during the experiment. Information about starting hand position (on all trials) as well as reach trajectory and final hand position (on visual feedback trials only) was provided on the projection screen by a small circular cursor 1 cm in diameter which overlaid the subject's middle fingertip location and tracked its position. To eliminate visual cues during trials in which movements were made to a remembered target location, the study was performed in a darkened room and subjects wore electrically-controlled visual occlusion goggles (PLATO, Transluctent Tech) that became opaque to completely block vision throughout the reaching movement. A speaker centered beneath the subject’s chair was used to provide auditory cues during the task.

2.3.3 Galvanic stimulation

Bipolar, binaural galvanic vestibular stimulation (GVS) was delivered by a stimulator (Grass Technologies, Model S88X) via a constant current source to carbon rubber electrodes (1.5”x1.75”, Pro Carbon) placed over the mastoid processes and secured with adhesive medical tape. Conductive gel was used to minimize resistance between the skin and the electrodes. The stimulus consisted of a short duration (750 ms or 2000 ms) 3 mA square pulse delivered either during or immediately prior to reach execution. Stimulus polarity was varied throughout each experiment to excite vestibular afferents on the left (cathode left) or right (cathode right), simulating a net rotation towards the left or right ear, respectively (Fitzpatrick and Day, 2004). Before commencing each experiment, individual responses to the stimulation were tested. Briefly, subjects stood with their eyes closed and feet together and the stimulus intensity was gradually increased to 3 mA starting from 0.5 mA. We noted the stimulus amplitude at which upper body movement was first observed toward the anode side with the head upright. Subjects were also asked to confirm that they were comfortable with the 3 mA stimulus amplitude used in the experiments and to provide subjective impressions of the stimulation both with the head upright and inclined forward.

2.3.4 Procedure

We conducted two experiments in this study. The goal of the first experiment was to provide evidence that the vestibular signals which contribute to reach execution have undergone a reference frame transformation from a head-centered to a body-centered reference frame. To further explore the compensation mechanisms underlyling the GVS-induced trajectory deviations we observed in Experiment 1 we performed a variant of the task in Experiment 2 in which the stimulation was applied just prior to reach onset instead of during the arm movement.

For both experiments the sequence of events in a trial was similar (Fig. 2.1B). At the beginning of each trial a start target appeared and subjects were asked to place the cursor representing the tip of their middle finger in the start target (2 cm diameter circle). The end target (2 cm diameter circle) was then presented 20 cm in front of the starting point for 1 s.

The subjects were instructed to memorize the allocentric spatial location of the end target. The end target was then extinguished and the occlusion goggles became opaque to remove any visual cues. After a variable delay period (see below) an auditory tone ("go signal") indicated that subjects should execute an arm movement to the remembered spatial location of the end target. Because the ideal spatial and dynamic compensations for body rotation during reaching depend on hand velocity and displacement, to ensure similar velocity profiles across trials and subjects a second auditory tone was used to provide feedback about movement speed. Specifically, after each movement was completed a high-pitched tone indicated if the arm movement was too fast, whereas a low-pitched tone signalled a movement that was too slow. The absence of auditory feedback indicated to subjects that they had executed their reaching movement within the appropriate time frame (800 +/- 200 ms; average peak velocity of ≈ 47cm/s). Subjects were explicitly informed that the auditory tone only provided feedback about their movement speed but provided no information about the accuracy of their reaching movement.

Galvanic stimulation was delivered in 16% of trials chosen pseudo-randomly. The polarity of the stimulation was also pseudo-randomly chosen such that 50% of the stimulation trials simulated rotation towards the right ear (cathode right) and 50% simulated rotation towards the left ear (cathode left) with no more than two subsequent GVS trials having the same polarity. Thus, subjects could neither predict on which trials the stimulation would occur, nor its polarity. To minimize the possibility of a given stimulation trial influencing the results of subsequent stimulus or control trials, trial sequences were chosen so that each stimulation trial was followed by a randomly-chosen minimum of 4-7 "no-stimulation" trials. Consequently, stimulation trials were separated from each other by a minimum of 32-56 s.

Only those no-stimulation trials immediately preceding stimulation trials (i.e., the last trial in each set of no-stimulation trials) served as “control trials”. In addition, to help maintain movement accuracy, 8% of the no-stimulation trials that were not control trials were “visual feedback trials” in which the visual occlusion goggles remained transparent and the end target and finger cursor remained visible throughout the movement.

In each experiment, subjects performed reaching movements in blocks of 250 trials that were each preceded by a practice session of 20-40 trials. A given block was performed with the head in either the upright position or with the head tilted forward. The forward pitch angle varied on an individual basis between 35.5 and 58 degrees (mean 51 degrees) depending on the comfort level of the subject and their capacity to clearly see the targets. Throughout each block the head was secured comfortably but firmly in place. The order of head orientation blocks was counterbalanced across subjects.

2.3.5 Experiment 1

The goal of this experiment was to investigate whether GVS perturbed reach trajectories in a head-orientation-dependent way, consistent with a transformation of vestibular signal contributions to reaching from a head- to a body-centered reference frame. In a single session, subjects performed two blocks of 250 trials (one with the head upright and one with the head tilted forward) in which, after a variable memory period (1000-1800 ms), the stimulation was administered *during the movement* for 750 ms following the time at which exit of the finger from the start target was first detected (approximately 100 ms after true movement onset). The stimulation thus lasted approximately throughout the duration of the reaching movement.

2.3.6 Experiment 2

The goal of Experiment 2 was to further explore the compensation mechanisms underlying GVS-induced trajectory perturbations by delivering the stimulation during the delay period immediately *before movement onset* instead of during the reach. Twenty-two new subjects performed two blocks of 250 trials (one with the head upright and one with the head tilted forward) in which the stimulation was provided for either 750 ms (Group A; 10 subjects) or 2000 ms (Group B; 12 subjects) during the memory period (750-1550 ms, Group A; 2000-2800 ms, Group B) immediately preceding the "go" sound.

2.3.7 Data analysis

Shoulder and elbow joint angles of the KINARM were sampled at 1000 Hz, converted to finger positions by the KINARM data acquisition system and stored on a computer. All data were analyzed offline using MATLAB (Mathworks Inc. Natick, MA). Hand velocity was computed numerically using a five-point differentiation routine written in Matlab and low-pass Butterworth filtered at 20 Hz using a digital filter with zero delay. Movement onset and offset times were defined as the time at which hand velocity reached or dropped below 5% of the peak velocity on that trial. All movements were further inspected manually and in cases where there was a clear misidentification of movement onset or offset the appropriate time was manually corrected. To quantify the extent to which galvanic stimulation perturbed reach trajectories we calculated the perpendicular (lateral) distance between actual hand position and a straight line connecting the start and end targets at each time point during the reach. The difference in perpendicular displacements between stimulation and control trials was used as a measure of the stimulation-induced perpendicular trajectory change. Statistical comparisons were based on t-tests and analyses of variance (ANOVA) using Matlab and the SPSS statistics package (Version 20, IBM).

2.3.8 Computational model

We used model simulations to predict how reach trajectories would be perturbed if subjects used vestibular signals to compensate ideally for the expected spatial displacement of the arm and/or additional forces that would be imposed on the limb by the rotation simulated by GVS. The models were built using the SimMechanics package within the SIMULINK simulation environment in Matlab and included simple biomechanical models of: 1) the limb ("arm only model"); 2) the limb combined with the full KINARM linkage ("full arm/KINARM model"); 3) the limb combined with a simplified two-joint equivalent of the KINARM linkage ("simplified arm/KINARM model").

2.3.8.1 Model description and parameters

In all models, the upper arm and forearm-hand limb segments were modelled as a system of two thin rods with uniform mass distribution and lengths based on measurements taken for each subject. Limb segment masses were estimated based on average values for adult males (upper arm: 2.1 kg; forearm: 1.7 kg) and females (upper arm: 1.7 kg; forearm: 1 kg) (Nikolova and Toshev, 2007). Limb or combined limb/KINARM segments (see below) were connected to each other and to a cylindrical body element via single degree of freedom rotational joints to simulate simple shoulder and elbow articulations in the horizontal plane. Body diameter was based on the measured distance from the body midline to the shoulder for each subject.

The full KINARM exoskeleton was modeled as a four-bar mechanical linkage (Fig. 2.1C) including two links which support the limb (Links 1 and 2) and two additional links used to apply a load/torque directly to the elbow joint (Links 3 and 4; see Scott, 1999 for details). Information about each link's mass (M), center of mass along the directions axial to the link (COM_A, measured from proximal to distal) and perpendicular to the link (COM_P, positive medial and negative lateral) and inertia (I, about the COM) were obtained from the KINARM documentation accompanying the system (Link 1: M = 3.86 kg , COM_A = 0.0294 m , COM_P = -0.0124 m, I = 0.0209 kg m^2; Link 2: M = 0.5510 kg , COM_A = -0.0110 m, COM_P = -0.0139 m, I = 0.0090 kg m^2; Link 3: M = 2.93 kg , COM_A = 0.0331 m, COM_P = 0 m, I = 0.0136 kg m^2; Link 4: M = 0.34 kg , COM_A = 0.1225 m, COM_P = 0 m, I = 0.0047 kg m^2). In addition, the supplied parameters for Link 2 were adjusted on an individual subject basis to take into account the added properties of the forearm support trough (M = 0.36 kg , COM_A = 0.162 m , COM_P = 0 m, I = 0.0036 kg m^2) whose position relative to the elbow joint varied as a function of the forearm length of each subject (mean adjusted Link 2 parameters: M = 0.911 kg , COM_A = 0.0670 m, COM_P = -0.0084 m; I = 0.0213 kg m^2). For simplicity, the small inertia contributed by the KINARM shoulder and elbow joint motors and friction at the KINARM joints were not modelled. To complete the combined arm/KINARM model, the physical properties of the two KINARM links which support the upper arm and forearm (Links 1 and 2) were combined with those of each limb segment to calculate a total mass, center of mass and inertia for each arm/KINARM segment.

Although reaching with the KINARM adds only a small load to the limb, to reach accurately motor commands must nonetheless take into account and compensate for its biomechanical properties. After the first few practice trials subjects were consistently able to reach accurately to the end target and thus we assumed that subjects incorporated the physical properties of the KINARM into their "internal model" of the arm/KINARM reaching environment when generating motor commands. Importantly, however, whereas in a stationary environment the combined arm/KINARM linkage performs similarly to a two-joint shoulder-elbow system with added mass and inertia, in a rotating environment the additional eccentrically-mounted linkage and joints (i.e., those associated with Links 3 and 4) would introduce additional interaction torques as compared to a simple two-joint arm. Subjects only actually experienced the KINARM in a stationary environment. Thus, such additional torques were never generated and subjects never learned to compensate for them. For this reason, to simulate the ideal torques subjects should produce to compensate for body rotation when reaching with the KINARM we used a simplified two-joint approximation to the full KINARM model. This model assumes that subjects treat the KINARM as if it were indeed a simple two-joint system that adds an inertial load to the limb. The simplified two joint arm/KINARM model was identical to the full arm/KINARM model except that Links 3 and 4 were removed and the inertia of Links 1 and 2 were increased to compensate. In particular, the inertia that should be added to Links 1 and 2 was estimated for each subject using an iterative least squares minimization procedure in which the shoulder and elbow torque profiles required to execute the average control trajectory using the simplified arm/KINARM model were matched to be close to identical to those required to generate the same trajectory with the full arm/KINARM model. The results of this matching procedure yielded average values of I=0.030 and I=0.045 for Links 1 and 2 (with arm trough), respectively, in the simplified two-joint KINARM approximation. These values were found to be in excellent agreement with those predicted theoretically using dynamic equations for the KINARM which were simplified by considering the contribution of Link 4 to interaction torques to be negligible.

2.3.8.2 GVS stimulus

Although there is considerable reported variability in individual sensitivities to GVS under different experimental conditions (Day and Cole, 2002, MacDougall et al., 2002, Fitzpatrick and Day, 2004) we assumed that the 3 mA GVS stimulus pulse used in our experiments simulated a rotation step with a constant velocity of 10.5 deg/s, based on a 2-6 deg/s/mA (mean 3.5 deg/s/mA) sensitivity estimated from oculomotor responses to galvanic stimulation (Schneider et al., 2002). The rotation axis was assumed to be elevated by 19 degrees from the head naso-occipital axis (i.e., relative to Reid's line; Fitzpatrick and Day, 2004). For simulation purposes, the component of the rotation velocity about the body vertical axis was calculated for each subject based on their measured head angle when reaching in the head tilted forward position.

2.3.8.3 Model simulations

We simulated the expected limb deviations of individual subjects for three conditions, assuming that vestibular signals are appropriately transformed from a head- to a body-centered reference frame. The first condition corresponds to a purely spatial (kinematic) compensation for the predicted displacement of the limb relative to the target ("spatial only") during the simulated body motion. In this case, reach trajectories were predicted for each subject on the basis of purely kinematic considerations (i.e., no biomechanical model) simply by updating each subject's average unstimulated control trajectory in joint coordinates (i.e., shoulder and elbow joint angles across time) to compensate for the simulated angular deviation of the body at each time point throughout the reach. That is, we predicted the trajectories in joint coordinates that would be necessary to replicate the control trajectory in world coordinates if the body were rotating. The updated trajectories in joint coordinates were then used to compute the world-centered trajectories in hand coordinates that would be predicted if the body actually remained stationary (i.e., as in our experiment). For comparison, we also calculated the ideal predicted trajectories for the situation where a body turn is followed subsequently by a reach (i.e., the situation simulated in Experiment 2 by applying GVS prior to movement onset). This differs from the case of reaching during body rotation because the reach is initiated only after body movement and thus from a new initial position in space relative to the target.

The second condition corresponds to the trajectory deviations expected when GVS is applied throughout the reaching movement and subjects compensate not only for the spatial displacement of the limb relative to the target but also dynamically for the additional forces that would be imposed on the limb if the body was actually rotating. These correspond to the ideal compensations required for accurate reaching during body rotation (i.e., the situation simulated in Experiment 1) when taking into account limb biomechanics. To simulate the expected trajectory deviations in this “spatial+dynamic” compensation case we used a two-step process. First, subject control trajectories in joint coordinates that were updated kinematically to compensate spatially for the body rotation (i.e., same trajectories as in Condition 1) were used as the “desired trajectory” input to an inverse dynamic representation of the biomechanical model of the arm. This was used to determine the torques at the elbow and shoulder that would be necessary to generate the desired trajectory if the body were rotating throughout the reach. In the second step, the torques generated in the first step were used as inputs to a forward dynamics limb representation to predict the expected arm trajectory that would result from those torques if the body was in fact stationary (i.e., as in our experiments). That is, we assumed that vestibular signals (stimulated by GVS) are used by the CNS to generate the torques necessary to provide ideal compensation for the simulated rotation and predicted what the impact would be on reach trajectories if those “ideal” torques were generated under conditions where the body was in fact stationary.

The “spatial+dynamic” condition simulates the ideal reach trajectories predicted when moving only the limb. However, in the current study reaching movements also involved moving the KINARM exoskeleton which has its own dynamical properties. To investigate the predictions for the “spatial+dynamic” case when the KINARM properties were also taken into account, the same procedure was repeated using an inverse dynamic representation of the “simplified arm/KINARM” model (i.e., two-joint KINARM approximation) in the first step to compute the ideal torques the subject should supply during an actual body rotation. The torques were then fed into a forward model of the “full arm/KINARM” model (i.e., full KINARM linkage) to predict how the arm would be deviated under conditions where the body was actually stationary. Using the “simplified arm/KINARM” forward model instead of the “full arm/KINARM” forward model in the second step produced similar predictions. Note that an assumption in generating these predictions is that subjects’ motor commands take into account the dynamics of the simplified 2-joint KINARM both when planning a stationary reach and when applying the additional torques necessary to compensate for simulated body rotation. Alternatively, however, because subjects have no actual experience with the KINARM in a rotating environment, it is possible that they only take into account its properties when planning reach trajectories in a stationary environment. The additional corrective torques applied to compensate for body motion might reflect mainly the dynamic properties of the arm alone. To simulate the predicted trajectories for this case we used the “full arm/KINARM” inverse model to predict the torques necessary to execute the control reach trajectory when stationary and the “arm only” inverse model to estimate the added torque required to compensate for the simulated rotation. The sum of the two was then fed into a forward model of the “full arm/KINARM” to predict the arm trajectory when the body was stationary.

To dissociate dynamic compensations for body motion during reaching from spatial ones, the third and last condition we considered was the trajectory deviations that would be predicted if GVS was applied during reaching to an egocentric (i.e., body-fixed) rather than an allocentric (world-fixed) target. In this case, subjects must compensate for additional forces imposed on the limb by the rotation but no spatial correction is required (“dynamic only” compensation). The procedures in this case were the same as those for the “spatial+dynamic” compensation case described above except that because subjects reached to a body-fixed target, no spatial correction was applied and the desired trajectories used were simply the subject control trajectories.

The simulations described above were used to generate predictions for how rotation simulated by GVS would be expected to perturb reach trajectories under conditions where the body was actually stationary. In a final set of simulations we also examined the converse. That is, to confirm that the actual GVS-induced trajectory deviations we observed were consistent with playing a functional role in correcting reach trajectories for body rotation, we simulated what the impact of the observed deviations would have been if the subject had actually been rotating. In this case, we used the full inverse model of the arm/KINARM to obtain an estimate of the average shoulder and elbow torques required to generate the observed trajectories. The torques were subsequently fed into a forward model of the arm only or simplified arm/KINARM to estimate the trajectories that would have been produced by those torques if the subject had been rotating.

2.4 RESULTS

2.4.1 Experiment 1

2.4.1.1 Average reach trajectories

The first experiment was designed to test the hypothesis that vestibular signals contributing to the execution of voluntary reach movements have been transformed from a head-centered to a body-centered reference frame. In particular, if such a reference frame transformation does occur, then the same galvanic stimulation should perturb reach trajectories in a head-orientation-dependent way (Fig. 1.10B). Figure 2.2 illustrates average reach trajectories and velocities for an example subject during no-stimulation control trials (blue) and stimulation trials simulating rotation towards either the right ear (green; cathode right) or the left ear (red; cathode left) with the head upright (Fig. 2.2A) or inclined forward by 50 degrees (Fig. 2.2B). The subject made stereotyped movements with similar bell-shaped velocity amplitude profiles (Morasso, 1981) across all conditions with an average peak velocity of approximately 47 cm/s. While reach trajectories under all stimulus conditions closely superimposed with the head upright (Fig. 2.2A) small but significant differences between stimulation and control trials were clearly evident with the head inclined forward, particularly toward the end of the reaching movement. With the head forward, GVS simulating leftward rotation deviated hand trajectories to the right of control trajectories whereas stimulation simulating rightward rotation deviated trajectories to the left.

Despite inter-subject variability in the extent to which GVS perturbed individual reach trajectories, a similar pattern of stimulation-induced reach deviations was observed across most subjects as reflected in the mean trajectory plots for all subjects illustrated in Figure 2.3. With the head upright, on average galvanic stimulation induced small but observable trajectory deviations (Fig. 2.3A), reflecting the fact that, unlike the subject in Figure 2.2, the trajectories of several subjects were at least transiently perturbed by the stimulation, particularly for simulated leftward rotation. Notably, however, the changes were most prominent in the middle of the movement but had largely disappeared by movement end. On average, simulated rightward and leftward rotation both deviated trajectories toward similar end-points slightly to the right of control trajectories by 0.24 cm and 0.16 cm, respectively. In

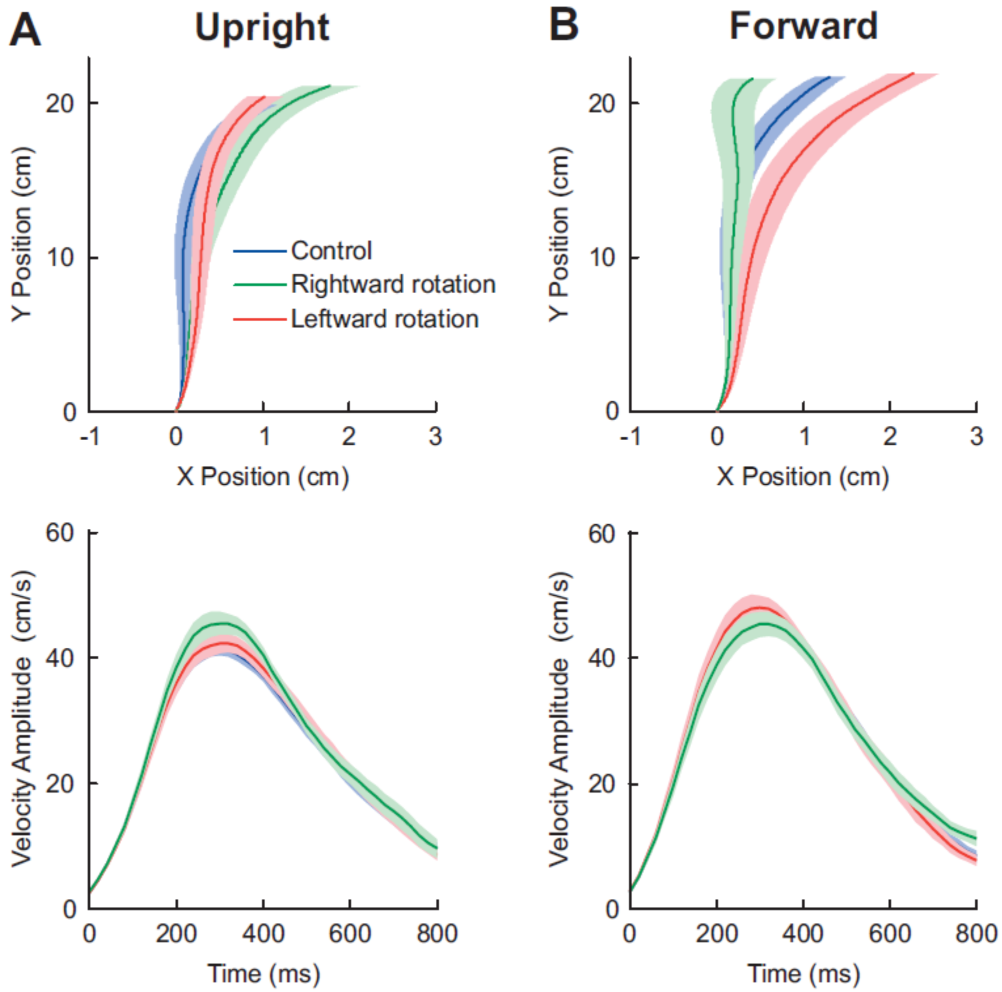

Figure 2.2. **Reach trajectories for an individual subject.** Average reach trajectories (top) and velocity amplitudes (bottom) for an individual subject in Experiment 1 for (A) the head upright and (B) the head forward. Control trials: blue; GVS trials simulating leftward rotation (cathode left): red; GVS trials simulating rightward rotation (cathode right): green. Shaded regions indicate standard error. Time 0s = movement onset.

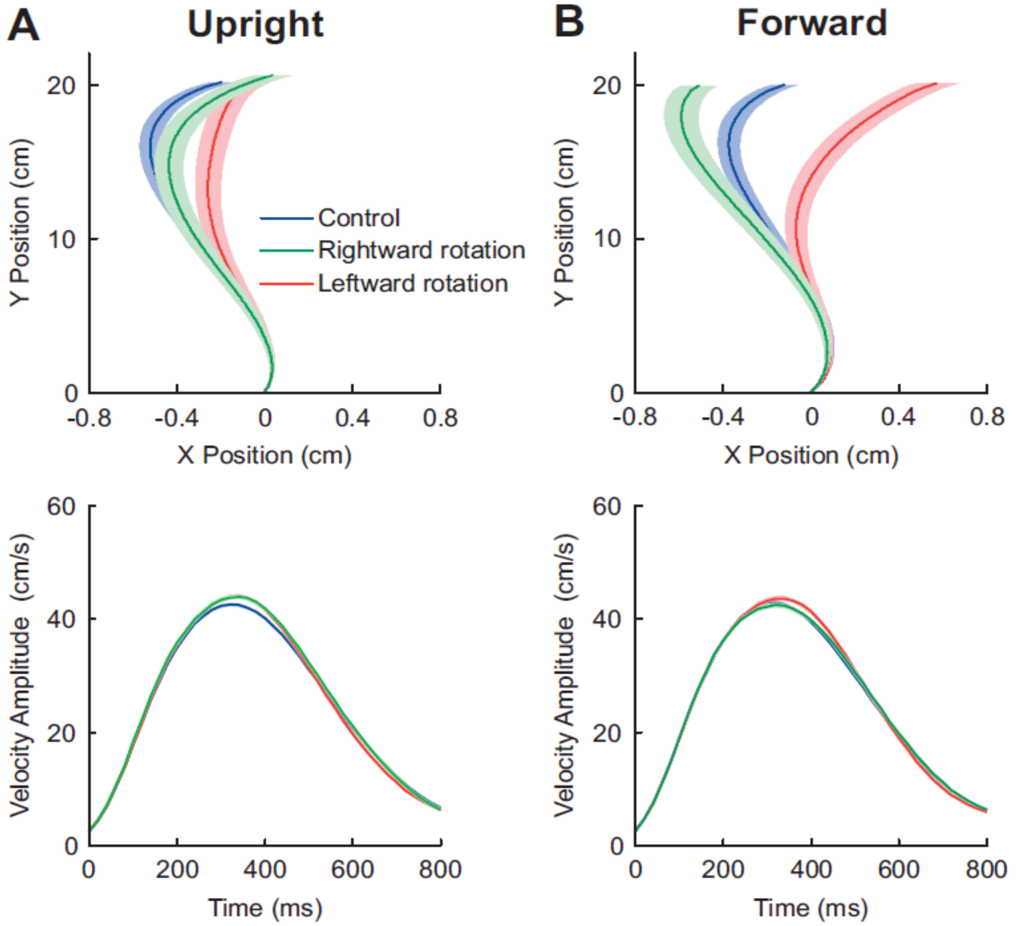

Figure 2.3. **Reach trajectories across all subjects.** Average reach trajectories (top) and velocity amplitudes (bottom) across all subjects in Experiment 1 (N=18) for (A) the head upright and (B) the head forward. Control trials: blue; GVS trials simulating leftward rotation (cathode left): red; GVS trials simulating rightward rotation (cathode right): green. Shaded regions indicate standard error.

contrast, with the head tilted forward (mean 51 degrees) movement trajectories progressively deviated from one another in opposite directions, reaching significantly different end-points for leftward versus rightward stimulation that were displaced 0.69 cm to the right and 0.39 cm to the left of the average control trajectory, respectively (Fig. 2.3B). Thus, consistent with the predictions for a reference frame transformation of vestibular signal contributions to reaching, the same stimulation altered reach trajectories in a head-orientation-dependent fashion. Specifically, with the head forward trajectory changes were not only on average larger than with the head upright but progressively increased in the opposite directions for each stimulus polarity over the course of the reach, as appropriate to provide spatial compensation for displacement of the limb relative to the target during simulated rotation about the vertical body axis.

2.4.1.2 Stimulation-induced trajectory changes

To better quantify the observed stimulation-induced reach trajectory perturbations and their variability across subjects we calculated the extent to which trajectories were deviated laterally by the stimulation in each head orientation (i.e., the stimulation-induced perpendicular displacement from control trajectories). Figure 2.4 illustrates these average perpendicular displacements and corresponding velocities across all subjects as a function of time relative to movement onset. Statistically significant stimulation-induced deviations (t-test, $p<0.05$) were observed as early as approximately 272 ms after stimulation onset in reach trajectories and 176 ms after stimulation onset in reach velocities, similar to previously reported latencies for the effects of GVS on reaching (Bresciani et al., 2002a). However, with

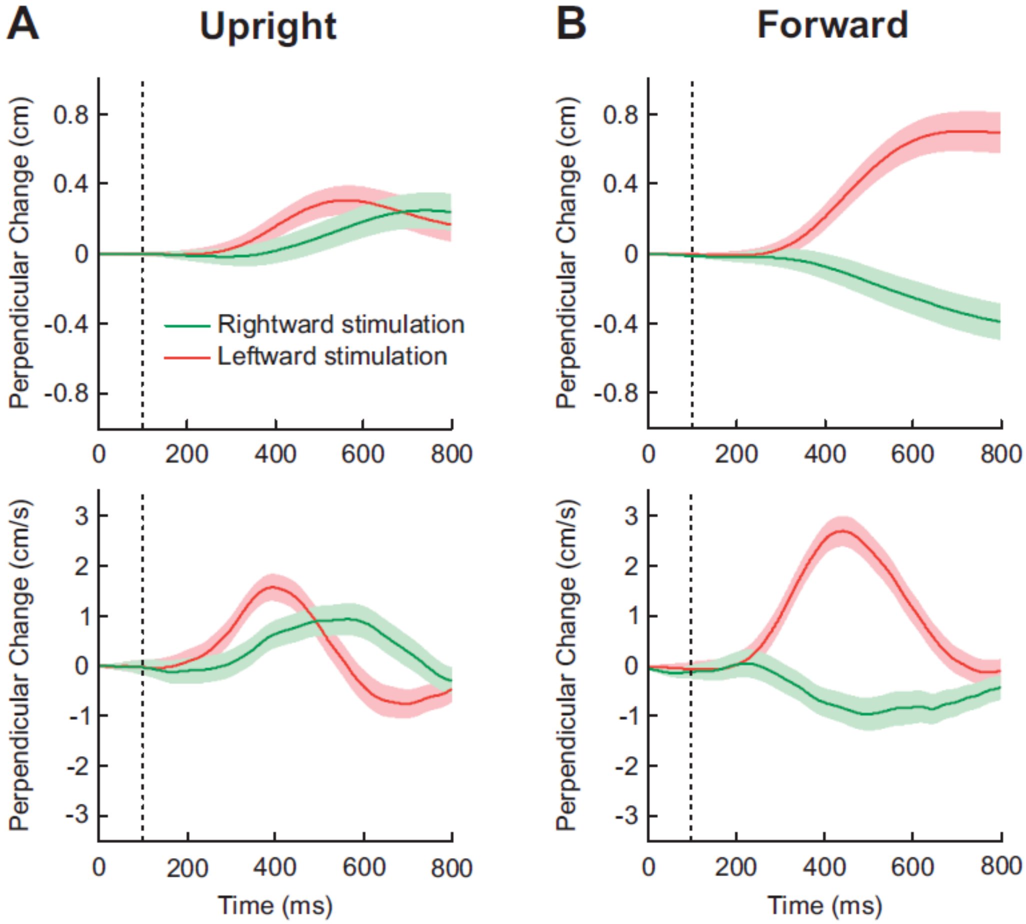

Figure 2.4. **Stimulation-induced perpendicular changes across all subjects.** Average stimulation-induced perpendicular changes relative to control in reach trajectory (top) and velocity (bottom) across all subjects in Experiment 1 (N=18) for (A) the head upright and (B) the head forward. GVS trials simulating leftward rotation (cathode left): red; GVS trials simulating rightward rotation (cathode right): green. Trajectory deviations to the right/left of controls are positive/negative. Dotted vertical line: stimulation onset. Shaded regions indicate standard error.

the head upright (Fig. 2.4A), trajectory deviations for rightward and leftward stimulation were similar, differing significantly only transiently for 70 ms between 443 and 513 ms after movement onset (t-test, $p<0.05$). In contrast, with the head inclined forward (Fig. 2.4B) trajectory changes were oppositely directed for opposite stimulation polarities and were significantly different from 352 ms onwards (t-test, $p<0.05$). These oppositely-directed displacements increased progressively in amplitude over the course of the reach, compatible with spatial compensation for displacement of the limb relative to the target during simulated rotation about a body-vertical axis. Importantly, although stimulation-induced deviations were observed in both head orientations, the average amplitudes of the deviations observed with the head forward became significantly larger than those with the head upright starting at about 465 ms from movement onset for rightward simulated rotation and 506 ms for leftward simulated rotation (t-test, $p<0.05$), consistent with the hypothesis of a reference frame transformation of vestibular signal contributions to reaching.

To illustrate the extent to which these average trends were reflected in the responses of individual subjects, the difference in perpendicular displacements for leftward versus rightward simulated rotation ("left-right change") with the head forward as compared to the head upright were plotted at different times relative to movement onset for each subject (Fig. 2.5). Whereas the data points are clustered around the origin at 200 ms post movement onset, at longer latencies (600 ms, 800 ms) most data points fall above the unity slope line indicating that, despite considerable variability in the amplitude of the changes across individual subjects, larger deviations were typically observed with the head forward as compared to upright. Notice also that for the head forward these changes were typically positive indicating that deviations were to the right for leftward and to the left for rightward stimulation. In keeping with these observations, 15 out of 18 subjects showed left-right changes that were statistically significant at 600 and/or 800 ms post movement onset with the head either upright or forward (t-test, $p<0.05$). Of these, 12 showed changes that were larger in amplitude with the head forward as compared to upright with the difference in amplitude reaching significance in 7 subjects (one-tailed t-test, $p<0.05$). In all these cases the changes were positive, consistent with spatial compensation for simulated rotation about the vertical body axis. Only one subject showed larger positive changes at reach endpoint with the head upright as compared to forward. Thus, the head-orientation-dependent effect of GVS on reach trajectories could be observed for most individual subjects in this experiment.

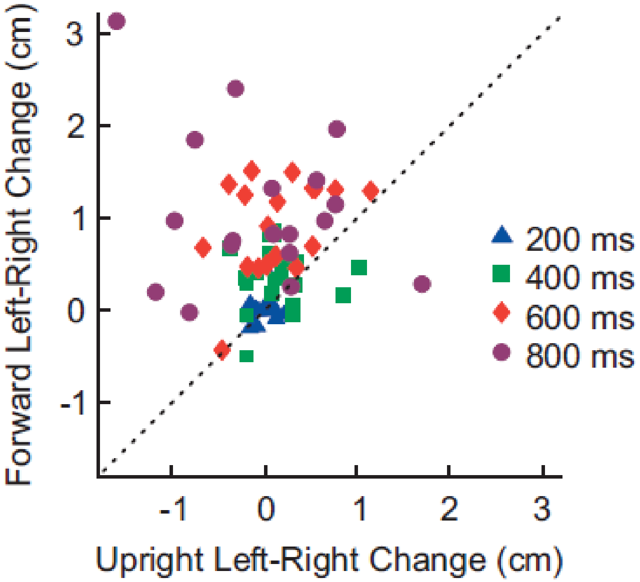

Figure 2.5. **Stimulation-induced perpendicular changes for individual subjects.** Difference in stimulation-induced perpendicular trajectory displacements for leftward versus rightward simulated rotation (“left-right change”) with head forward versus head upright for individual subjects (N=18). Data points indicate left-right change at 200 ms (blue triangles), 400 ms (green squares), 600 ms (red diamonds) and 800 ms (purple circles) post movement onset. Unity slope line: dashed black.

2.4.1.3 Comparison with theoretically predicted displacements

The above results illustrate a head-orientation-dependent effect of GVS on reach trajectories that was quite consistent across subjects and on average highly statistically significant. Although deviations were small in amplitude (on average < 1 cm) this was not unexpected given the small rotation velocities simulated by a 3 mA galvanic pulse (see Section 2.3.8.2) and multiple salient cues that the subject's body was in fact stationary (i.e., subject seated in a stationary chair with the arm supported in a large robotic exoskeleton). Indeed, subjects reported that when seated during the experiment the short 750 ms stimulus evoked no clear percept of rotation and that they were unable to tell whether a given stimulation pulse simulated rotation to the right versus the left.

To better assess how the GVS-induced trajectory deviations we observed with the head forward compared with those that would be theoretically predicted if subjects attempted to compensate ideally for a simulated (but nonexistent) body rotation about the earth-vertical axis, we compared our experimental results with the predictions of biomechanical models of the limb and combined limb/KINARM. The short 3 mA GVS pulse we delivered was assumed to simulate a constant rotation step of 10.5 deg/s (see Section 2.3.8.2). Fig. 2.6A illustrates the trajectory deviations predicted during simulated body rotation for three conditions: 1) Subjects compensate only for the expected spatial displacement of the hand relative to an allocentric target ("spatial only", thick dotted lines); 2) Subjects compensate both for the expected spatial displacement of the hand relative to the target and dynamically for the forces that would be imposed on the limb by body rotation when reaching to an allocentric target ("spatial + dynamic", dashed lines); 3) Subjects compensate only dynamically for the forces predicted to

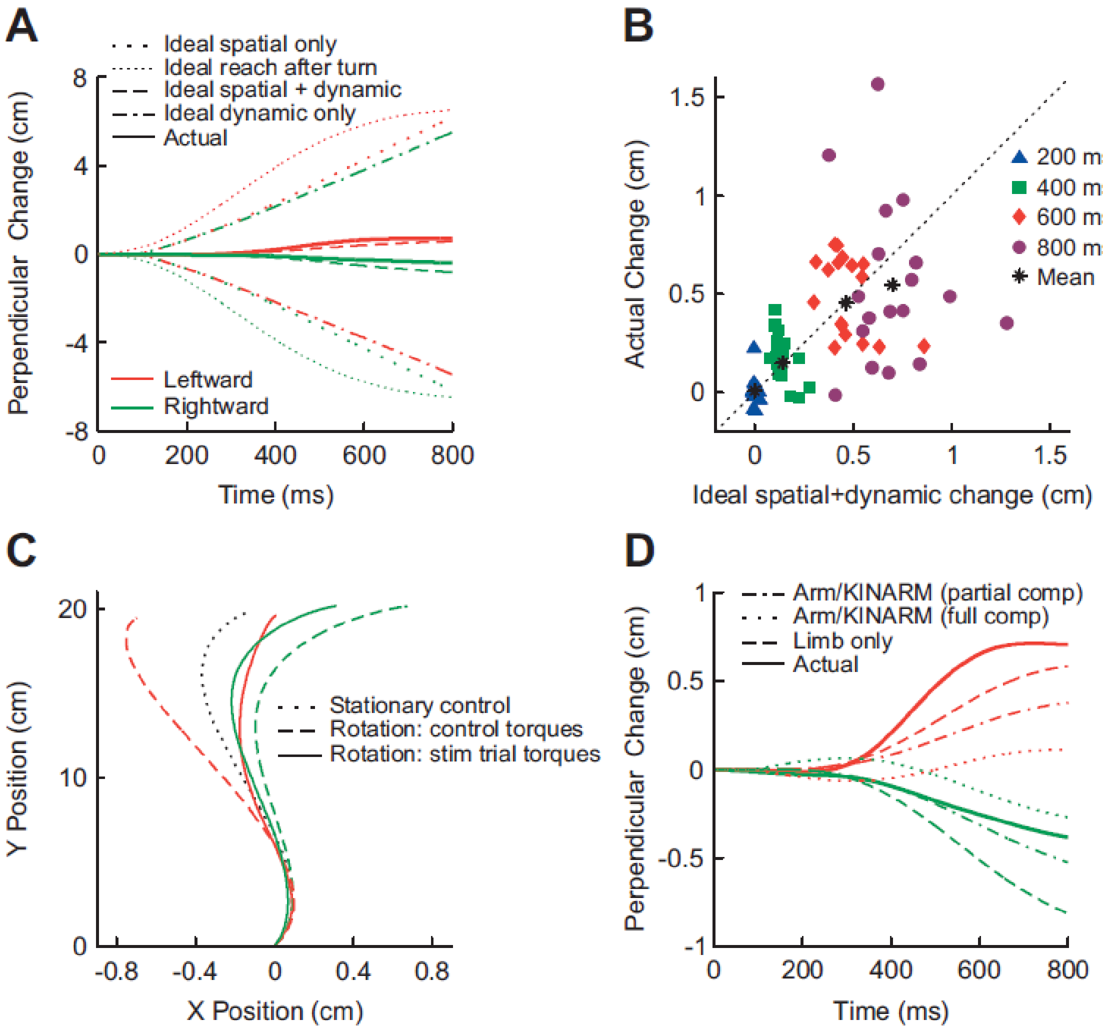

Figure 2.6. **Actual GVS-induced trajectory changes compared with those predicted by model simulation.** A) Average stimulation-induced perpendicular trajectory changes relative to control across subjects for rightward (green) and leftward (red) simulated rotation are superimposed on those predicted if subjects compensated ideally during body rotation only for the spatial displacement of the limb relative to the reach target ("spatial only"; large dotted lines) or for both the spatial displacement and additional forces imposed on the limb by the rotation ("spatial + dynamic"; dashed lines). Also shown are the predictions for the purely dynamic compensations required when reaching during body rotation to a body-fixed (egocentric) rather than a world-fixed (allocentric) target ("dynamic only"; dash-dot lines) as well as the predictions for spatial updating when reaching to a remembered location after a body rotation ("reach after turn"; small dotted lines). Predictions for the "spatial +dynamic" and "dynamic only" cases were made using a biomechanical model of the limb only ("arm only" model). Trajectory deviations to the right/left of controls are positive/negative. B) Average of actual

stimulation-induced changes for rightward and leftward rotation plotted as a function of the ideal "spatial+dynamic" change for individual subjects predicted using the "arm only" model. Data points indicate 200 ms (blue triangles), 400 ms (green squares), 600 ms (red diamonds) and 800 ms (purple circles) relative to movement onset. Asterisks indicate mean values. Unity slope line: dashed black. C) GVS trial trajectories in world coordinates that would be predicted during an actual leftward (solid red) or rightward (solid green) body rotation compared with the trajectories predicted if no compensation was applied and the control trajectory (dotted black) torques were instead executed during leftward (dashed red) or rightward (dashed green) rotation. D) Predictions for the "spatial + dynamic" condition when subjects are assumed to take into account the combined arm/KINARM biomechanical properties either only when planning a stationary reach ("arm/KINARM (partial comp)"; dash-dot lines) or both when planning a stationary reach and when applying additional compensation for simulated rotation ("arm/KINARM (full comp)"; dotted lines). "Arm only" model predictions: dashed lines. Actual deviations: solid lines.

be imposed on the limb by body rotation when reaching to an egocentric (body-fixed) target ("dynamic only", dash-dot lines).

An examination of the predictions across conditions shows that when only the spatial displacement of the limb relative to the target is taken into account during allocentric reaching, as expected the predicted deviations are in the opposite direction to the simulated rotation (Fig. 2.6A, "spatial only", dotted lines). Conversely, because coriolis forces and limb inertia will tend to push the limb (in body-centered coordinates) in the opposite direction to body rotation, the dynamic compensation that must be applied to overcome these factors to reach egocentrically results in predicted deviations in the same direction as the simulated rotation (e.g., "dynamic only" case, Fig. 2.6A, dash-dot lines). Finally, most relevant to the current experiment is the case of reaching to an allocentric target during body rotation and appropriately considering both spatial and dynamic compensations (i.e., "spatial + dynamic" case; Fig. 2.6A, dashed lines). In this case, rotation-induced forces and limb inertia aid in stabilizing the limb in space, reducing the applied torque necessary to compensate for the spatial displacement of the limb relative to the target. Consequently, the predicted trajectory deviations are significantly smaller than those estimated on the basis of purely kinematic considerations.

The experimentally observed average deviations across subjects for rightward and leftward simulated rotation are superimposed on the predictions in Figure 2.6A for comparison (solid traces). In Figure 2.6B, the average of leftward and rightward deviations for individual subjects are plotted as a function of the ideal "spatial + dynamic" displacement (i.e., the ideal displacement for the conditions in Experiment 1) estimated using the "arm only" model at different times post movement onset. While the experimentally observed displacements were larger than ideal for leftward simulated rotation and smaller than ideal for rightward simulated rotation, on average for both directions the observed deviations were remarkably close to the theoretical predictions (Figs. 2.6A and 2.6B). As a further test of the functional significance of the observed trajectory deviations during GVS, Figure 2.6C illustrates a simulation of what the average stimulation trial trajectories would have looked like if they had been executed during an actual rotation (Fig. 2.6C, solid traces). Notice that during an actual rotation the trajectories for each rotation direction are predicted to be similar and much closer to the average control trajectory (Fig. 2.6C, dotted traces) than those that would be predicted if no compensation had been applied (Fig. 2.6C, dashed traces).

Finally, because reaching movements in this experiment were actually executed using the KINARM which adds an inertial load to the limb, we considered how taking into account the KINARM biomechanical properties would influence the predicted trajectory deviations. As illustrated in Figure 2.6D, taking into account the biomechanical properties of the KINARM in addition to the limb further reduces the size of the predicted deviations to an extent that depends on whether subjects are assumed to compensate for the added inertial load of the KINARM only during stationary control reaching (dash-dot lines) or during both stationary control reaching and when compensating for the GVS-simulated rotation (dotted lines). Comparison of both the profile and amplitude of these predictions with the GVS-induced deviations that were observed experimentally suggests that the KINARM compensation subjects applied was likely to be a partial one, appropriate only for a stationary environment (dash-dot lines).

In summary, the deviations we observed, while small, were on average remarkably close in amplitude to those predicted theoretically despite the unnatural stimulus and multiple cues that the subjects were stationary. The results of Experiment 1 thus show that galvanic stimulation reliably perturbs reach trajectories in a head-orientation-dependent manner, consistent with the predictions for a transformation of vestibular cues from a head-centered to a body-centered reference frame. Furthermore, the observation of robust stimulation-induced deviations despite the absence of a clear motion percept provides support for a substantial involuntary contribution of vestibular cues to the control of voluntary reaching.

2.4.2 Experiment 2

The results of Experiment 1 showed that with the head forward, GVS elicited deviations in reach trajectories that were appropriately directed to help compensate for simulated rotation about the body vertical axis. However, as noted above, reaching accurately to an allocentric target during whole-body rotation requires the CNS to compensate spatially for the body displacement relative to the target, while at the same time taking into account the additional forces acting on the arm during body motion and its inertial properties. To further explore which mechanisms might underlie the GVS evoked trajectory perturbations we observed in Experiment 1, in Experiment 2 GVS was instead administered to subjects prior to reach movement onset. In this case, compensating for the simulated rotation requires reaching towards a new spatial goal without the need for dynamic compensations.

2.4.2.1 Reach trajectories

Figure 2.7 illustrates average reach trajectories for two different subject groups (Group A, 750 ms pulse duration; Group B, 2000 ms pulse duration) when GVS was administered during the memory period immediately prior to the “go” cue. Stimulation duration for Group A (N=10) was the same as for the subjects in Experiment 1 (750 ms) but because reaching took place only after the stimulation had ended, the appropriate compensation was a purely spatial one (i.e., based on kinematic considerations only). Consequently, the GVS should ideally have elicited trajectory deviations that were substantially larger than those observed in Experiment 1 (Fig. 2.7A; compare small dotted and dashed traces). In contrast to these predictions and the results of Experiment 1, however, average subject trajectories across conditions superimposed both with the head upright as well as with the head tilted forward (Fig. 2.7A). Thus, when applied prior to reach execution GVS had no effect on reach trajectories. This was true both on average as well as for most individual subjects

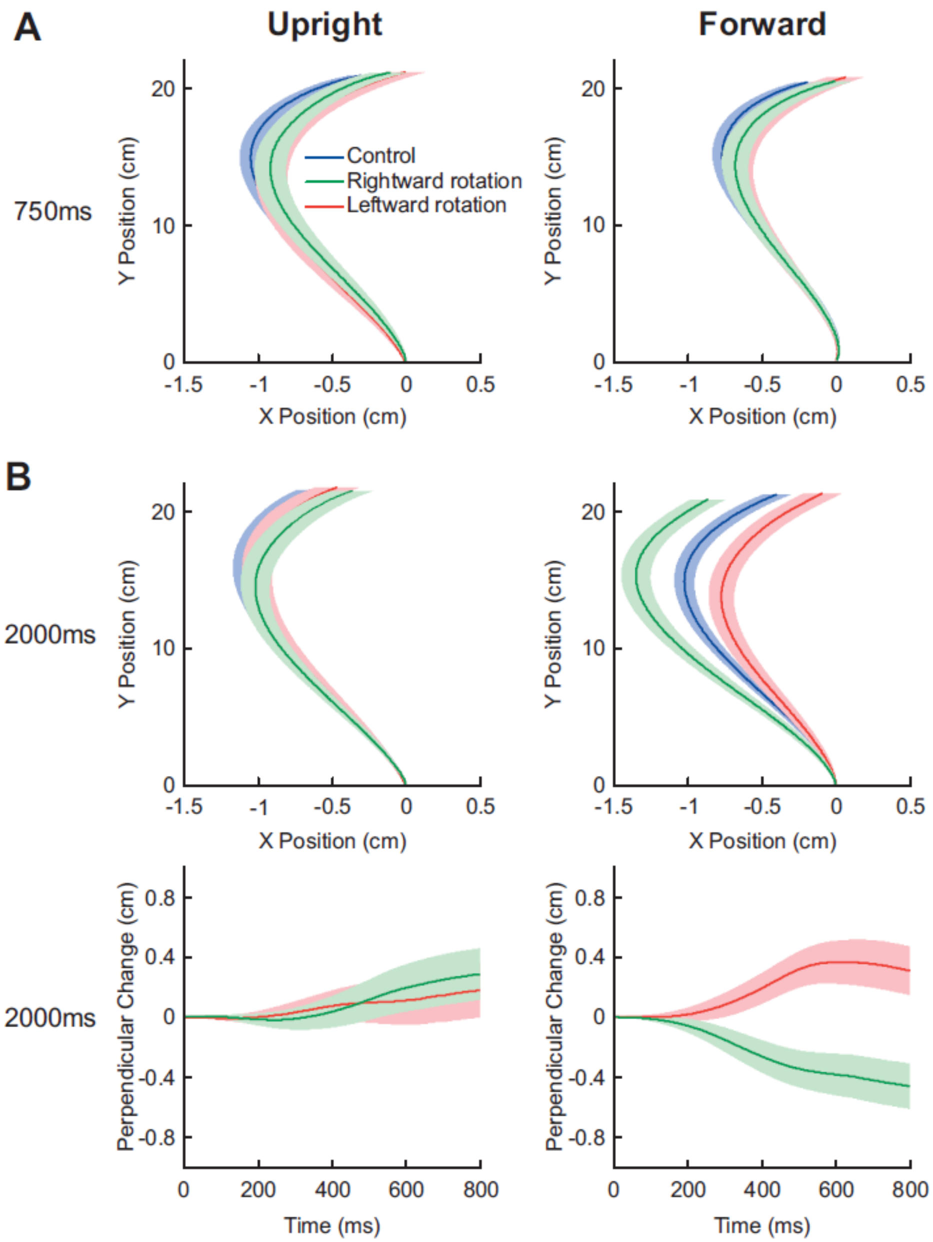

Figure 2.7. **Average reach trajectories across subjects in Experiment 2 when GVS was applied during the memory period prior to reach onset.** A) Reach trajectories with the head upright (left) and head pitched forward (right) when GVS was applied for 750 ms (Group A; N=10). B) Reach trajectories (top) and stimulation-induced perpendicular displacements (bottom) with the head upright (left) and inclined forward (right) when GVS was applied for 2000 ms (Group B; N=12). Control trials: blue; GVS trials simulating leftward rotation (cathode left): red; GVS trials simulating rightward rotation (cathode right): green. Shaded regions indicate standard error.

(t-test, p>0.05). Specifically, only 3 out of 10 subjects exhibited statistically significant end-point deviations for either head upright or head forward and in no subject was there a significant interaction between head orientation and stimulus type (2x2 ANOVA, p>0.05). These observations suggest that the vestibular stimulation-induced deviations we observed in Experiment 1 were mediated by an online compensatory mechanism that acts specifically *during* reach execution.

Nonetheless, a number of studies have provided evidence for a vestibular contribution to spatial updating when the body is passively displaced prior to movement execution both in the case of saccades (Blouin et al., 1998, Klier et al., 2005, Li and Angelaki, 2005, Wei et al., 2006, Klier and Angelaki, 2008) and reaching (Bresciani et al., 2002b, 2005). To further explore whether GVS could be used to drive such a spatial updating mechanism we examined the effects of applying a longer 2000 ms duration stimulation in subject group B (N=12). With the head upright, average trajectories remained unperturbed (Fig. 2.7B, left). However, in contrast to group A, with the head forward the longer stimulation employed in Group B elicited clear trajectory deviations that were oppositely directed to the simulated rotation direction (Fig. 2.7B, right). Similar to the results of Experiment 1, these deviations increased in amplitude over the course of the reach, becoming significantly different for rightward versus leftward simulated rotation starting at 258 ms post movement onset. Interestingly, however, leftward versus rightward deviation differences were not only observed slightly earlier than those in Experiment 1 (i.e., 258 vs 352 ms for position deviations and 173 vs 272 ms for velocity deviations) but the deviations were also more symmetric for leftward versus rightward stimulation. In addition, a comparison of the amplitudes of the deviations observed in Experiment 1 versus those for Experiment 2, Group B showed that after normalization for stimulus duration (i.e., the fact that a longer stimulation simulates a larger angular body displacement), GVS applied prior to movement onset was approximately four times less effective at eliciting a vestibularly-driven trajectory deviation than GVS applied during movement (Fig. 2.8). Collectively these observations suggest that the deviations observed for Group B in Experiment 2 are likely to reflect a spatial compensation mechanism that is distinct from that observed in Experiment 1. Importantly, because the observed deviations were again head-orientation-dependent, the vestibular cues which contribute to this distinct mechanism have also been appropriately transformed from a head- to a body-centered reference frame.

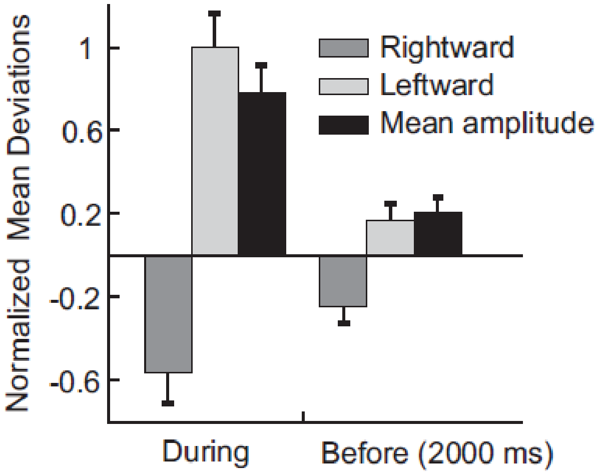

Figure 2.8. **Comparison of the effect of GVS applied during versus prior to reaching.** Normalized average perpendicular trajectory displacements at 800 ms post movement onset when GVS was applied during reaching (Experiment 1) compared with those when stimulation was applied for 2000 ms immediately prior to reaching (Experiment 2, Group B). Displacements were normalized relative to the largest average deviations observed in Experiment 1 (i.e., for leftward simulated rotation). Deviations for Experiment 2, Group B were also scaled for stimulus duration to account for the fact that the longer 2000ms stimulation pulse simulates a larger angular displacement than the 750 ms stimulation pulse. Simulated rightward rotation: dark gray; Simulated leftward rotation: pale gray; Average amplitude (unsigned) for rightward and leftward rotation: black.

2.5 DISCUSSION

The capacity to reach accurately as we move depends on estimates of planned or ongoing self-motion to compensate both kinematically and dynamically for body motion. Recent studies have provided evidence that sensory signals from the vestibular organs are important contributors to such self-motion estimates (Lackner and Dizio, 1994, DiZio and Lackner, 2001, Bresciani et al., 2002a, 2002b, 2005, Mars et al., 2003, Tunik et al., 2003, Bockisch and Haslwanter, 2007, Blouin et al., 2010, Guillaud et al., 2011). However, because the arm is fixed to the trunk whereas the vestibular sensors are fixed in the skull, to contribute appropriately vestibular signals must first be transformed from a head-centered to a body-centered reference frame. Here we have provided direct evidence for this transformation by using bipolar GVS to selectively stimulate vestibular afferents as subjects made horizontal plane reaching movements with their head either upright or inclined forward by about 50 degrees. If the vestibular signals which contribute to reaching have been appropriately transformed into body-centered coordinates then the same GVS stimulus should be interpreted as rotation about a different body axis in each head orientation. Consequently, we predicted that horizontal-plane reach trajectories should be perturbed in a head-orientation-dependent way. In keeping with this prediction, GVS-induced trajectory displacements were on average significantly larger with the head forward than with the head upright, particularly at reach endpoints. Furthermore, only with the head forward were trajectory perturbations consistently oppositely-directed for each stimulation polarity and in the direction that would provide compensation for a spatial displacement of the limb relative to the target during simulated rotation about a body-vertical axis (i.e., yaw body rotation). Both observations are consistent with the net vestibular afferent activation by GVS being interpreted mainly as rotation about an earth-horizontal axis with the head upright but mainly as rotation about an earth-vertical axis with the head forward, providing direct evidence that a reference frame transformation of vestibular contributions to reaching has indeed taken place.

Whereas Experiment 1 examined the evidence for such a transformation during reach execution, in Experiment 2 we instead applied GVS in the memory period just prior to reaching. When the stimulation was provided for the same duration as in Experiment 1 (750ms) but prior to reach onset, trajectories remained undeviated regardless of head orientation. This suggests that the trajectory deviations observed in Experiment 1 reflect compensation mechanisms for body motion that are specific to online reaching execution and likely distinct from those involved in updating an internal spatial representation of the reach goal during reach planning. However, when GVS was applied for a longer duration (2000 ms) deviations in reach trajectories were again observed. As discussed further below, we postulate that these reflect a distinct "spatial updating" process that is slower, less effectively activated by vestibular signals, or more affected by the multiple cues that subjects were actually stationary than the online compensation mechanisms responsible for the trajectory deviations in Experiment 1. Importantly, the deviations associated with this presumed spatial updating mechanism were observed only with the head inclined forward but not with the head upright, providing evidence that the vestibular signals contributing to this distinct mechanism have also been appropriately transformed from a head- to a body-centered reference frame. Below we discuss these findings in the context of previous studies and the potential underlying neural mechanisms for vestibular contributions to reaching.

2.5.1 Reference frame transformation of vestibular signals for reaching

To our knowledge this is the first study to provide direct behavioural evidence that vestibular signals contributing to reaching have been transformed from head-centered to body-centered coordinates. Our results build on and complement those of a number of previous studies which have used GVS to provide evidence either for vestibular contributions to reaching or for spatially transformed vestibular signals. In particular, Bresciani et al. (2002a) previously showed that the application of GVS perturbs reach trajectories in upright standing subjects, providing a direct demonstration of the contribution of vestibular signals to reach execution. Here we have extended those results by examining GVS-induced reach trajectory perturbations in different head orientations to provide evidence for the required vestibular signal reference frame transformation.

Our results are compatible with those of the Bresciani et al. (2002a) study in several respects, including the finding that the earliest effects of GVS on movement trajectories are observed at significantly longer latency (275 ms in our study versus 240ms in Bresciani et al., 2002a) than those reported previously for body sway responses (e.g., 185 ms after movement onset; Nashner and Wolfson, 1974) or for the earliest GVS-evoked EMG responses in leg muscles (~65 ms; Britton et al., 1993, Fitzpatrick et al., 1994, Watson and Colebatch, 1997) and arm muscles (~40 ms; Baldissera et al., 1990, Britton et al., 1993) engaged in postural control. In addition, in both studies GVS elicited trajectory deviations that were oppositely directed to the simulated rotation direction, compatible with spatial compensation for rotation about a body-vertical axis. Such deviations were observed by Bresciani et al (2002a) even with the head upright, in keeping with the small body-vertical rotation component predicted for a GVS net rotation vector slightly elevated by about 19 degrees from the horizontal head plane. In contrast to these results, however, we observed progressive and consistently oppositely-directed deviations only with the head inclined forward (e.g., Fig. 2.4).

While the reason for this difference in observations during upright reaching is unclear, a methodological difference is that in the current study subjects were seated with their head fixed in space and arm trajectories constrained to and supported in the horizontal plane by the KINARM. In contrast, subjects in the Bresciani et al (2002a) study were standing and made arm movements while holding onto a rod that acted as a pointer and constrained reaching movements to the horizontal plane. Although the head was secured by a bite-bar, the GVS applied during upright standing nonetheless induced postural adjustments including small lateral translations and roll rotation of the trunk. It was concluded that the lateral body translations were not directly responsible for the reach trajectory deviations because the two were in opposite directions. Nonetheless it remains possible that the physical body movement, while very small, enhanced subjects' percept of whole body motion and resulted in larger "compensatory" deviations with the head upright than were observed in the current experiments.

In contrast, the KINARM setup in the current study minimized GVS-evoked trunk or limb postural compensations (Britton et al., 1993, Fitzpatrick et al., 1994). However, it may also have minimized the effect of GVS stimulation on reaching by providing multiple cues that the subject was not in fact moving. Such cues may have reduced the effect of an already small body-vertical virtual rotation component with the head upright, such that no consistent trajectory deviations were elicited. If true, we might expect that if the effect of GVS on reach trajectories were reexamined in standing subjects with the head tilted forward, not only would trajectory deviations be much larger than those observed with head upright by Bresciani et al (2002a) but the head forward deviations would also be significantly larger than those observed in the current study.

Alternatively, our model simulations suggest that despite the unnatural stimulus and multiple cues that subjects were stationary, the small deviations we observed were close to appropriate in amplitude. This observation alone is not sufficient to prove that subjects used vestibular signals and knowledge of limb biomechanics to correct online in a close to ideal fashion for the simulated rotation. For example, we could not distinguish in this experiment between such an ideal compensation and a purely spatial correction (i.e., a correction based on kinematics only) that was significantly undercompensatory. Furthermore, the exact amplitude of the ideal correction is dependent on a number of factors including the assumptions that went into the model, how the GVS stimulus was actually interpreted by individual subjects and how they compensated for the KINARM dynamics. Nonetheless, the simulations show that the appropriate deviations are substantially smaller than those that would be predicted on the basis of spatial considerations alone and are of the same order of magnitude as those observed. This observation, combined with evidence for an appropriate spatial transformation of vestibular signals, further strengthens the support for a contribution of vestibular signals to a robust involuntary compensation mechanism for body motion.

Our results are also similar to those of a number of recent studies which have used GVS to provide evidence for a reference frame transformation of vestibular signals contributing to postural responses (Lund and Broberg, 1983, Cathers et al., 2005, Fitzpatrick et al., 2006) and spatial navigation during locomotion (Fitzpatrick et al., 2006). In particular, the current investigation was inspired by the recent studies of Fitzpatrick, Day and colleagues (Day and Fitzpatrick, 2005b, Fitzpatrick et al., 2006) who used GVS to demonstrate head-orientation-dependent effects of vestibular stimulation on perceptual estimates of the route travelled as well as on postural sway and steering during locomotion. During locomotion, GVS applied with the head upright resulted in postural sway but minimal path deviations, consistent with the GVS being interpreted as tilt about an earth-horizontal axis. In contrast, with the head inclined forward, GVS elicited little postural sway but subject walking paths deviated to the right or left of controls for leftward versus rightward simulated rotation, compatible with the same stimulation now being interpreted as rotation about an earth-vertical axis. These observations were interpreted as evidence for a transformation of vestibular signals into a world-centered reference frame (Fitzpatrick et al., 2006).

The current study complements and extends these prior investigations by demonstrating a head-orientation-dependent contribution of vestibular signals to reaching. However, while similar experimental approaches were used to demonstrate head-orientation-dependent responses, this does not necessarily imply that the same self-motion representations contributed to the behaviours. In particular, Fitzpatrick, Day and colleagues interpreted their observations as evidence for a transformation of vestibular signals into a world-centered reference frame, as seemingly appropriate for postural control and spatial navigation (Fitzpatrick et al., 2006). In contrast, because the arm is attached to the body, here we have interpreted our observations as evidence that vestibular signals have been transformed into body-centered coordinates with the ultimate goal of being used to help estimate body motion. Neither interpretation can be confirmed without examining behavioural responses over a range of both head and body orientations. Furthermore, assuming any one representation for vestibular cues (e.g., body-centered) is likely an oversimplification. For example, there is evidence that the motor commands for arm movements along the earth-vertical take into account gravitational (i.e., world-fixed) constraints (Papaxanthis et al., 2003, Gentili et al., 2007, Crevecoeur et al., 2009, Gaveau and Papaxanthis, 2011). This suggests that vestibular signals which have been transformed into body-centered coordinates to help compute body motion for reaching may still need to be further "interpreted" or modulated as a function of body orientation in space. A critical next step in understanding how vestibular cues are processed and used for different behavioural purposes will thus be to identify the neural correlates for these transformations and to characterize the nature of the representations that are encoded.

A number of studies have begun to address this question by examining the types of self-motion representations encoded within brainstem-cerebellar circuits and providing evidence for both world- and body-centered motion representations. In particular, the transformation of semicircular canal signals into world-centered estimates of reorientation relative to gravity is an essential part of the theoretical computations involved in dissociating ambiguous otolith signals into estimates of tilt versus translational motion (Green and Angelaki, 2004, 2007, 2010b). Recent studies investigating how and where these computations are performed have provided evidence that, for the limited range of whole-body orientations considered, the firing rates of Purkinje cells in the posterior cerebellar vermis (nodulus and ventral uvula) reflect such spatially-transformed canal signals (Yakusheva et al., 2007, Angelaki et al., 2010). Other studies that compared neural responses to rotation and translation across different head-re-body orientations in the horizontal plane have provided evidence that deep cerebellar neurons in the rostral fastigial nucleus and Purkinje cells in the anterior vermis carry vestibular signals that have been at least partially transformed into a body-centered reference frame (Manzoni et al., 1999, Kleine et al., 2004, Shaikh et al., 2004). Furthermore, a recent study has explicitly shown that, for movements in the horizontal plane, many neurons in the rostral fastigial nuclei combine vestibular and neck proprioceptive signals precisely as required to compute body motion (Brooks and Cullen, 2009).

At present, the transformations of vestibular signals performed by brainstem-cerebellar circuits have only begun to be investigated and it is still unclear to what extent the various motion representations encoded in specific regions (e.g., the rostral fastigial nuclei) contribute to specific behaviours, such as postural control versus reaching. Nonetheless this circuitry appears as a promising candidate for computing and distributing the types of body- or world-centered self-motion signals for which evidence has been provided here and in other recent studies (e.g., Day and Fitzpatrick, 2005b, Fitzpatrick et al., 2006).

2.5.2 Distinct mechanisms for self-motion contributions to reaching

The contribution of self-motion estimates to reaching has now been demonstrated in a variety of different behavioural conditions. In particular, at the reach planning stage, self-motion signals have been implicated in updating an internal representation of the relative spatial locations of the reach goal and limb to compensate for an intervening body movement executed prior to reaching (i.e., "spatial updating" Medendorp et al., 1999, Bresciani et al., 2002b, 2005, Van Pelt and Medendorp, 2007). A number of studies have also established a role for self-motion estimates as contextual cues for selecting appropriate motor commands by providing information about the current or planned dynamic characteristics of the reaching environment (Lackner and Dizio, 1994, DiZio and Lackner, 2001, Pigeon et al., 2003, Bockisch and Haslwanter, 2007). Still other studies have emphasized their contribution to online spatial and dynamic compensations for unexpected or passive body motion (Bresciani et al., 2002b, 2005, Guillaud et al., 2011). However, whether each of the various spatial and dynamic compensations for body motion during reach execution and/or planning are mediated by similar versus distinct mechanisms remains poorly understood. Similarly, little is known about the extent to which different mechanisms may rely preferentially on particular sensory (e.g., vestibular, visual, proprioceptive) and/or motor (e.g., efference copy) information about ongoing or planned movement.

Our current results point to a distinction in the mechanisms underlying vestibular contributions to spatial compensation for body motion during reach planning versus execution. In particular, in Experiment 1 we showed that, with the head forward, GVS applied during reach execution resulted in reach trajectory deviations that were appropriately directed to compensate spatially for simulated rotation about a body-vertical axis. In Experiment 2 we instead applied GVS just prior to reaching, simulating a “turn and then reach” paradigm in which accurate reaching depends on updating the motor plan to compensate spatially for the intervening body motion. Comparisons of the results of the two experiments revealed several differences that suggest that the spatial compensation mechanisms to which vestibular signals contribute during online reach execution are likely to be distinct from those during reach planning. In particular, GVS applied for the same duration (750 ms) as in Experiment 1 but prior to reach onset had no effect on reach trajectories in either head orientation. This suggests that the GVS-induced deviations we observed in Experiment 1 were produced by an online correction mechanism that acts specifically when reaching is executed during ongoing body motion.

Importantly, we found that when GVS was applied prior to reach onset, trajectory deviations could nonetheless be elicited if the stimulation was applied for a longer time period (2000 ms). Similar to the results of Experiment 1, the deviations were head-orientation-dependent. Only with the head forward did they deviate progressively in opposite directions to the simulated rotation direction, consistent with spatial compensation for rotation about a body-vertical axis. However, despite the longer stimulation duration, reach trajectories were on average less perturbed than in Experiment 1. After normalization for stimulus duration, GVS applied prior to movement onset was estimated to be approximately 4 times less effective at eliciting a vestibularly-driven trajectory deviation than GVS applied during movement (Fig. 2.8). Furthermore, whereas in Experiment 1 the rightward trajectory deviations elicited for leftward simulated rotation were much larger than the leftward deviations observed for simulated rightward rotation, those observed in Experiment 2 were far more symmetric (compare Figs. 2.3, 2.4 and 2.7B). Although we cannot fully explain these differences and they were not predicted by our model simulations, we can nonetheless speculate that such a distinction may exist because the deviations observed in Experiment 2 reflect purely spatial compensations whereas those in Experiment 1 reflect a combination of spatial and biomechanical factors involved in compensating for reaching during body motion. Finally, it is relevant to note that while subjects typically experienced no clear percept of rotation during the experiment when exposed to the 750 ms stimulation pulse, those exposed to GVS for 2000 ms had a clearer rotation percept and could often indicate in which direction they felt they had turned.

Collectively, these observations support the suggestion that the deviations observed in Experiment 2 (for 2000 ms GVS) reflect the contribution of spatially-transformed vestibular signals to a mechanism which is distinct from that responsible for the deviations in Experiment 1. In particular, we suggest they reflect a spatial updating process that is likely to be slower than the online compensation mechanism activated in Experiment 1, and which either may be less effectively activated by vestibular stimuli or rely on stronger rotation percepts. Indeed, several studies have shown that while spatial updating of eye or arm movements accurately compensates for actively generated body motion (Blouin et al., 1998, Medendorp et al., 1999, Admiraal et al., 2004, Van Pelt and Medendorp, 2007), it is often significantly less accurate for passive body rotation, particularly for rotations about an earth-vertical axis that involve no reorientation relative to gravity (Blouin et al., 1998, Klier et al., 2005, 2006). This suggests that although vestibular canal signals contribute to spatial updating, the estimate of spatial displacement they provide may be somewhat crude, with efference copy signals and other cues (e.g., gravitational) playing an important role in improving that estimate under typical behavioural conditions.

Importantly, these results are consistent with the conclusions of Bresciani et al. (2002b, 2005) who showed that when reaching to the remembered location of an earth-fixed target, subjects were more accurate if the reach took place during rather than directly after passive whole-body rotation (Bresciani et al., 2002b). Furthermore, when visual stimuli were used to adapt subject behavioural responses so that they systematically underestimated and undercompensated for the rotation, the effects of adaptation were specific to the context in which reaching was executed (Bresciani et al., 2005). Adaptation of reach trajectories in a spatial updating task (i.e., reaching to a remembered target location after rotation) had no effect on the accuracy with which subjects reached during ongoing body motion. In contrast, adaptation of the motor commands to stabilize the limb in space during rotation also altered reaching movements made during ongoing body rotation. On this basis it was concluded that the preservation of accurate reach trajectories during body motion is not mediated by a "spatial updating" process (i.e., a process in which an internal representation of the reach goal is updated) but rather by a distinct sensorimotor process that maps vestibular signals more directly onto motor responses (Bresciani et al., 2005). Our current results are consistent with and provide further support for these conclusions.

Ultimately, understanding how self-motion signals contribute to voluntary motor control will depend on an investigation of the underlying neural mechanisms. The posterior parietal cortex is believed to be a key structure involved in spatial updating with specialized regions being implicated in processing the spatial goals for saccades and reaching movements (Colby and Duhamel, 1996, Andersen et al., 1998, Andersen and Buneo, 2002). Although the mechanisms underlying spatial updating to compensate for body motion have not yet been established, vestibular projections into parietal regions such as the parieto-insular vestibular cortex (PIVC), the medial superior temporal cortex (MST), the ventral intraparietal cortex (VIP), and parietal area 7a (Shinder and Taube, 2010, Lopez and Blanke, 2011) may play a role.

In contrast, the mechanisms involved in compensating online for body motion during reach execution likely involve more direct projections to spinal arm circuitry via vestibulospinal and reticulospinal tracts that aid in stabilizing the limb in space. However, reaching during body motion also involves compensating for additional forces such as Coriolis forces that depend in a predictable way on a number of factors including trunk angular velocity, limb linear velocity and the spatial relationship between the two (e.g., Lackner and Dizio, 1994). Thus, it seems likely that accurate reaching during body motion must involve more sophisticated computations performed by supraspinal motor circuits including cortical regions such as the primary motor cortex (M1) and its interactions with the cerebellum. Indeed, studies investigating how we learn to compensate for Coriolis forces (Lackner and Dizio, 1994, Shadmehr and Mussa-Ivaldi, 1994) have provided support for the notion that such circuits build “internal models” of the dynamical properties of the motor plant (e.g., arm) and the environment (e.g., external forces) which are used to compute motor commands (Wolpert and Kawato, 1998, Kawato, 1999, Shadmehr, 2004, Shadmehr et al., 2010). Contextual cues play an important role in distinguishing between different dynamic environments (Lackner and Dizio, 1994, 2005, Gandolfo et al., 1996, Cothros et al., 2006, Imamizu et al., 2007, Kluzik et al., 2008). Thus, when reaching takes place during ongoing or planned body motion vestibular, proprioceptive and/or efference copy signals presumably provide these contextual cues, ensuring computation of motor commands appropriate to compensate for the additional forces imposed on the limb (Lackner and Dizio, 1994, 2005, Pigeon et al., 2003, Bockisch and Haslwanter, 2007).

Importantly, these internal models are presumed to exist within feedback circuits that mediate online correction for any performance errors (Kawato et al., 1987, Wolpert and Kawato, 1998, Bhushan and Shadmehr, 1999, Shadmehr and Krakauer, 2008, Wagner and Smith, 2008). Thus, even when body motion is unpredictable, this same circuitry may be at least partially responsible for the online compensations for body motion observed in this and previous studies (Bresciani et al., 2002a, 2002b, 2005, Mars et al., 2003, Tunik et al., 2003).

While the neural correlates for vestibular contributions to these compensations remain unknown, a region of area 3a which receives a convergence of vestibular and somatosensory inputs from the arm and hand (Odkvist et al., 1974, Guldin and Grusser, 1998), is likely of particular relevance given the strong connections between area 3a and the primary motor cortex (Huffman and Krubitzer, 2001). Experiments which further investigate the nature of the vestibular contributions to this area (e.g., whether they have been transformed into body-centered coordinates) are thus likely to be important for understanding vestibular contributions to reaching.

2.6 CONCLUSION

The current study shows explicitly for the first time that the vestibular signals which contribute to reach execution and planning have been transformed into body-centered coordinates, consistent with their role in helping to estimate and compensate for body motion. However, the important questions of how and where these transformations are performed and the nature of the distinct mechanisms by which vestibular signals contribute to voluntary reaching have only begun to be addressed. Elucidating the neural mechanisms for these computations represents a challenging and exciting area of future investigation that promises to yield new insights into both vestibular system function and the control of goal-directed movement.

Chapter 3

General summary and discussion

3.1 General summary

In recent years, a number of studies exploring vestibular influences on reaching behaviours have provided evidence that vestibular signals can contribute to both spatial (Medendorp et al., 1999, Bresciani et al., 2002b, 2005, Medendorp and Crawford, 2002, Guillaud et al., 2006, Van Pelt and Medendorp, 2007, Medendorp, 2011) and dynamic compensations (Lackner and Dizio, 1994, 1998a, b, 2005, Dizio and Lackner, 1995, 2000, 2001, Pigeon et al., 2003, Bockisch and Haslwanter, 2007, Bortolami et al., 2008b, Guillaud et al., 2011) for the effects of body motion on reach trajectories. However, since the arm is fixed to the trunk whereas the vestibular sensors are fixed in the head, in order for vestibular signals to contribute appropriately to reaching they must be transformed from a head-centered to a body-centered reference frame. The primary goal of this work was to investigate whether vestibular signals that contribute to reaching do undergo such a reference frame transformation. The second goal of this thesis was to explore the underlying mechanisms that use these transformed vestibular signals during reach execution and reach planning. The results presented herein show that the vestibular signals that contribute to reaching indeed undergo a transformation from a head-centered to a body-centered reference frame. In addition we provided evidence that vestibular signals contribute to a sensorimotor compensation mechanism during reach execution that is distinct from their contribution to compensating for a displacement of the limb relative to the target during motor planning. Below I briefly summarize these experimental results in context of previous work, discuss the potential neural correlates for these different mechanisms and the reference-frame transformation of vestibular signals and finally provide an overview of the future directions which are of interest to pursue.

3.2 Reference frame transformation of vestibular signals that contribute to reaching

The first goal of this work was to investigate whether vestibular signals which contribute to reaching undergo a transformation from a head-centered to a body-centered reference frame. While head- to world-centered reference frame transformations of vestibular signals have been shown for postural control (Cathers et al., 2005, Mian et al., 2010), self-motion perception (Day and Fitzpatrick, 2005b), and locomotion (Fitzpatrick et al., 2006, Osler and Reynolds, 2012), no study prior to the present work has demonstrated a head- to body-centered reference frame transformation of vestibular signals contributing to reaching movements. To provide evidence for such a transformation seated subjects in darkness were asked to perform horizontal-plane reaching movements to the remembered location of a space-fixed target with their head either upright or pitched forward while bipolar binaural GVS was used to selectively stimulate the vestibular afferents. Our predictions were that if vestibular signals that contribute to reaching are transformed from a head- to body-centered reference frame, then the same vestibular stimulus should be interpreted as rotation about a different body axis for different orientations of the head on the body. Consequently we should observe head-orientation dependent effects of the stimulation on reaching movements. More precisely, we predicted that when the head is upright and the axis of simulated rotation is roughly aligned with the body-horizontal axis minimal deviations in horizontal plane reach trajectories should be observed. In contrast, with the head forward and the axis of simulated rotation aligned with the body-vertical axis GVS should elicit larger deviations in horizontal plane reach trajectories trajectories. In agreement with our predictions trajectory deviations were larger with the head forward than upright, and only with the head forward were trajectories deviated in a direction consistent with compensating spatially for rotation of the body about a vertical axis. These results provided evidence that vestibular signals which contribute to reaching were transformed from a head- to body-centered reference frame.

An important aspect of this work is that it also provides particularly convincing evidence for a robust vestibular contribution to the online control of reaching movements. A general difficulty in studying how vestibular information is used in the control of reaching during an actual physical rotation is that it is difficult to dissociate the relative contributions of vestibular information from proprioceptive or perceptual contributions to limb motor control. For example, in the study by Bresciani and colleagues (2002b) subjects were able to perform accurate reaching movements to the remembered spatial location of a previously-viewed target despite an unexpected passive whole-body rotational perturbation suggesting a role for vestibular signals in online reach control. However, proprioceptive contributions could not be completely dissociated from vestibular contributions. Other studies have tried to get around this problem by using GVS or examining reach behaviour in patients with substantial proprioceptive and somatosensory loss (Bresciani et al., 2002a, Mars et al., 2003, Guillaud et al., 2011), but even in these studies there were still nonetheless some complications in interpreting the data in each case. For example, in another study by Bresciani and colleagues (2002a) GVS was used to selectively stimulate the vestibular sensors while upright standing subjects performed reaching movements. However, it is uncertain whether the observed GVS-induced trajectory deviations were entirely directly vestibular driven or whether they also reflected additional connections driven by proprioceptive signals and/or perceptual processes to compensate for GVS-elicited trunk displacement (see Section 2.5.1). Furthermore, Guillaud and colleagues (2011) dissociated proprioceptive from vestibular contributions to reaching by examining the responses of a subject with severe proprioceptive and somatosensory loss from the nose downwards. They provided evidence that vestibular signals can be used by the brain to predict and compensate for the inertial properties of the limb and the dynamic forces acting on the limb when reaching occurs during body rotation (see Section 1.3.4.3). However while they provided convincing evidence for a role for vestibular signals in the absence of proprioceptive information, it is also possible that healthy subjects who do not suffer from such a sensory loss may not use vestibular signals in the same manner.

In contrast, we believe the current work provides particularly convincing evidence for a robust vestibular contribution to online motor control. Specifically, by using the GVS technique in seated subjects with the arm supported by the KINARM and a short stimulus duration (750 ms) that did not evoke motion percepts, we managed to avoid some of the above confounds. Furthermore and importantly, while a number of other sensory signals can contribute to self-motion estimates in the absence of visual and auditory cues, of these only the vestibular sensors are fixed in the head. Therefore, reach trajectories would not have been expected to be deviated by GVS in a head-orientation dependent manner consistent with a head- to body-centered reference frame transformation if vestibular information did not make a contribution to online motor control that extends beyond the activation of some kind of non-specific reflexive movement. In addition, the absence of clear motion percepts when GVS was applied during reach execution demonstrated the involuntary nature of these vestibular contributions to limb motor control. Finally, we found that the amplitude of the trajectory deviations we observed were comparable to those predicted by a biomechanical model of the limb suggesting the brain can use vestibular signals and knowledge of the properties of the limb to determine the dynamics of the reach environment and to correct motor commands online accordingly. Collectively these observations argue for a robust involuntary vestibular contribution to the online control of reaching movements.

3.3 Mechanisms involved in reach execution and planning

3.3.1 Vestibular contributions to a spatial updating mechanism during reach planning

The second goal of this study was to explore the underlying mechanisms that use vestibular signals to compensate for body motion in the control of reaching movements. In the first experiment, we observed head-orientation dependent trajectory deviations consistent with a transformation of vestibular signals from a head- to a body-centered reference frame in order to contribute to arm motor control during reach execution. However, different mechanisms could have been responsible for the observed deviations in reach trajectories. In particular, vestibular signals have been suggested to contribute to a spatial updating mechanism during reach planning that compensates for body motion by updating the spatial relationship between the reach goal and the arm to take into account the body displacement (Medendorp et al., 1999, Bresciani et al., 2002b, Admiraal et al., 2004, Van Pelt and Medendorp, 2007). Such a spatial updating mechanism acting online could potentially be responsible at least in part for the observed deviations in the first experiment. Alternatively, the observed deviations could have been due to a more direct online compensation mechanism that is distinct from spatial updating. Such a mechanism might simultaneously provide both spatial and dynamic compensations for body motion, as would be required when reaching during an unexpected movement of the body.

To determine whether a spatial updating mechanism acting online was responsible for the trajectory deviations observed in the first experiment, in a second experiment the GVS was applied just prior to movement onset during the memory period. The goal was to simulate a classic spatial updating paradigm in which a reach to a remembered target location is performed after body rotation. If the deviations observed in the first experiment when GVS was applied for 750 ms during reach execution were due to a spatial updating mechanism, then qualitatively similar but significantly larger end-point deviations should also be observed when stimulation of the same duration was instead presented prior to the movement. However, when we performed this experiment (Experiment 2, Group A) reach trajectories were not significantly affected by a vestibular stimulation that simulated a rotation of the same amplitude as in the first experiment. These results suggest that the mechanism responsible for the deviations observed in the first experiment was specific to reach execution and that this mechanism is likely distinct from spatial updating.

As noted in Chapter 2 (see Section 2.5.2) these results are consistent with those of Bresciani and colleagues (Bresciani et al., 2002b, 2005) who explored whether the online vestibular contributions to reaching involve different mechanisms than those implicated in the vestibular contributions to spatial updating. In the first study (Bresciani et al., 2002b) they demonstrated that reaching movements to the remembered location of a space-fixed target were more accurate when the reach was performed during as compared to after passive whole-body yaw rotation. This suggested that the mechanism underlying online vestibular control of goal-directed arm movements might be specific to reaching during body motion (i.e. a sensorimotor compensation mechanism) rather than due to a spatial updating mechanism (Bresciani et al., 2002b). In the second study, they separately adapted each process (i.e. the suggested sensorimotor compensation mechanism and spatial updating) to induce a systematic underestimation of the rotation of the body (Bresciani et al., 2005). While reaching movements performed after whole-body rotations were sensitive to the spatial updating adaptation, it was only the sensorimotor adaptation that affected reaching movements performed during whole-body rotation. This suggested that the vestibular control of reaching movements performed during body motion is driven by an online sensorimotor compensatory mechanism rather than a spatial updating mechanism (Bresciani et al., 2005). In agreement with the conclusions of Bresciani and colleagues (Bresciani et al., 2002b, 2005), our results suggested that when GVS was present during an ongoing reaching movement the observed trajectory deviations induced by the stimulation were due to a mechanism specific to reach execution that is distinct from spatial updating.

3.3.2 Vestibular contributions to a spatial updating mechanism during reach planning

While we have provided evidence that vestibular contributions during reach execution are likely to be due to a mechanism distinct from a spatial updating mechanism, vestibular signals are known to be able to contribute to such a spatial updating mechanism during reach planning (Medendorp et al., 1999, Bresciani et al., 2002b, Admiraal et al., 2004, Van Pelt and Medendorp, 2007). Indeed, we demonstrated that if GVS for a long enough duration is applied prior to reaching (for 2000 ms; Experiment 2 group B), reaches are deviated in a head-orientation dependent manner similarly to when GVS was applied during reach execution. This result demonstrated that vestibular signals were transformed from a head- to a body-centered reference frame to contribute to what we postulate may be a spatial updating mechanism during reach planning. This mechanism appeared to be distinct from the online mechanism responsible for the deviations observed when GVS was present during reach execution.

Furthermore, as discussed in Chapter 2 (see Section 2.5.2) GVS-evoked vestibular contributions to this spatial updating mechanism were four times less effective at deviating reach trajectories as compared to when GVS was applied during movement. Interestingly, one important difference between the two cases is that vestibular contributions to the presumed spatial updating mechanism only led to reach deviations when GVS was applied for a long enough duration (2000 ms) to evoke percepts of motion. In contrast when GVS was applied prior to reaching but only for a short duration (750 ms; Group A) no trajectory deviations were observed and no motion percept was evoked. This suggests that in contrast to a more direct sensorimotor mechanism, spatial updating may require a perception of motion in order to effectively influence reaching movements.

Nonetheless, even with a percept of motion, trajectory deviations were still undercompensatory for the simulated rotation. More precisely, we estimated that GVS-evoked trajectory deviations in Experiment 2 (Group B) were on average 45 times smaller than what would be ideally predicted if subjects had compensated ideally for the spatial displacement of the limb relative to the target simulated by a 2000 ms GVS stimulation. In contrast, reaches performed after passive whole-body yaw rotation in the study by Bresciani and colleagues (2002b) were updated almost ideally as reach end-points were offset relative to the target by only about 4.5 degrees on average for a 40 degree whole-body rotation. One possibility for the discrepancy between these observations and the current ones is that the unnatural GVS stimulus creates very inaccurate motion percepts. Another possibility is that there were other cues available in the Bresciani and colleagues study (2002b) in addition to vestibular signals such as proprioceptive and somatosensory inputs due to the whole-body motion that could have contributed to self-motion estimates and spatial updating for reaching. Future research will be required to explore to what extent the self-motion estimates that contribute to spatial updating during reaching rely on vestibular versus proprioceptive and somatosensory information.

3.4 Neural correlates for vestibular contributions to reaching

3.4.1 Neural correlates for the reference frame transformation of vestibular signals and the estimation of body motion

Ultimately understanding how vestibular signals are transformed by the brain to generate estimates of body motion and the different mechanisms that use these transformed signals in the planning and control of reaching movements will require an understanding of their underlying neural correlates. Our study provided evidence for a reference frame transformation of vestibular signals that contribute to reaching from a head- to body-centered reference frame. As discussed in Chapter 1 such a reference frame transformation represents the first of two computations presumed to be required to estimate body motion (see Section 1.3.3) (Green and Angelaki, 2010b, a). Potential neural correlates for this computation exist in the rostral fastigial nucleus (rFN) and the anterior cerebellar vermis (Manzoni et al., 1999, Kleine et al., 2004, Shaikh et al., 2004). Neurons in rFN have been shown to encode motion in a reference frame that is intermediate between a head-centered and body-centered reference frame, with many neurons displaying responses that were more consistent with encoding motion in a body-centered frame of reference (Kleine et al., 2004, Shaikh et al., 2004). In addition to rFN, cells in zones A and B of lobules IV and V of the anterior cerebellar vermis appear to encode motion mainly in a body-centered reference frame (Manzoni et al., 1999). Therefore, both rFN and the anterior cerebellar vermis appear to reflect the processing of this first computational step. Nonetheless, while these studies provide neurological evidence for a reference-frame transformation of vestibular signals, this does not mean that these transformed vestibular signals are those that contribute to reaching. Future studies will be required to determine to what extent these signals are involved in reach planning and execution or whether vestibular signals that contribute to reaching are transformed elsewhere.

3.4.2 Neural correlates for the spatial updating mechanism involved in reach planning

While it is important to determine the neural correlates for the reference-frame transformation of vestibular signals that contribute to reaching, the neural mechanisms that use these transformed vestibular signals must also be understood. The posterior parietal cortex (PPC) has been shown to encode spatial goals for both eye and arm movements but in different regions. While the lateral intraparietal area (LIP) has been implicated in the processing of spatial goals for saccades (Colby and Duhamel, 1996, Andersen and Buneo, 2002), the parietal reach region (PRR), which encompasses the medial intraparietal area (MIP) and area V6A has been demonstrated to be involved in the processing of spatial goals for reaching movements (Colby and Duhamel, 1996, Andersen and Buneo, 2002). Furthermore the PPC, and in particular area LIP is known to be involved in updating spatial goals for saccadic eye movements when an intervening saccade displaces the eye from its original position relative to the remembered location of a previously flashed target (Duhamel et al., 1992, Colby et al., 1995, Klier and Angelaki, 2008). However little is known about the neural correlates for spatial updating to compensate for body motion. Nonetheless the fact that the PPC contains regions that encode spatial goals for both eye and arm movements (Colby and Duhamel, 1996, Andersen and Buneo, 2002) suggests that the PPC is likely to play a role in updating saccade and reach goals to compensate for body motion. For example, areas such as

LIP or MIP could be using self-motion estimates computed in other areas (see below) for spatial updating of body movements.

The self-motion signals used for spatial updating during reach planning could be computed in a variety of cortical regions including those that receive vestibular information. These areas include the ventral intraparietal cortex (VIP), the medial superior temporal cortex (MST), area 7a and the parieto-insular vestibular cortex (PIVC) (Shinder and Taube, 2010). For example, VIP contains many neurons showing vestibular responsiveness (Bremmer et al., 2002) as well as visual and somatosensory responses (Duhamel et al., 1998, Avillac et al., 2005, Britten, 2008) and has been suggested to be involved in the analysis and encoding of self-motion (Bremmer et al., 2002, Britten, 2008). VIP appears to be involved in the multisensory encoding of spatial and motion information that is required for goal-directed movements in external space, as it can represent the location of visual targets and differentiate between the motion of objects in space separately from self-motion (Bremmer, 2005). Similar to VIP, area 7a can also encode self-motion and visual targets but these representations appear to be mostly in world-centered coordinates whereas those in VIP are mostly in body-centered coordinates (Snyder et al., 1998). Another area, known as MST, contains neurons sensitive to vestibular stimulation (Duffy and Wurtz, 1991b, a, 1995, Duffy, 1998, Bremmer et al., 1999, Page and Duffy, 2003) and is thought to be implicated in differentiating optic flow due to self-motion from optic flow due to movement of objects in the environment (Duffy, 1998). Finally, PIVC contains neurons that respond to vestibular stimulation (Guldin and Grusser, 1998) as well as neurons that respond to neck proprioceptive signals (Grusser et al., 1990) and preferentially encodes motion of the body rather than motion of the head in space (Grusser et al., 1990). Overall it is possible that one or more of these areas are involved in estimating self-motion relative to the spatial environment. The output of these areas could be providing motion estimates that are used in reach regions for spatial updating across body movements.

3.4.3 Neural correlates for the online sensorimotor compensatory mechanism

In contrast to spatial updating an online sensorimotor compensation mechanism for body movement may involve more direct projections of the vestibular system to arm spinal neurons through the vestibulospinal and reticulospinal tracts. However compensating for the physical properties of the limb and the additional forces that act on the limb such as Coriolis and centrifugal forces requires the brain to perform more complex computations that take into account factors such as the mass of the arm, the linear velocity of the arm, the angular velocity of the trunk and the distance of the arm from the center of the trunk rotation (Lackner and Dizio, 1994, 1998a, 2005, DiZio and Lackner, 2001, Pigeon et al., 2003, Bockisch and Haslwanter, 2007, Guillaud et al., 2011). As discussed in Chapter 2 (see Section 2.5.2) it is likely that performing such computations involves cortical regions such as the primary motor cortex (M1) and its interactions with the cerebellum. Indeed, it has been proposed that these areas are involved in constructing internal models that represent the dynamic properties of the arm and the external environment within which the arm moves (Wolpert and Kawato, 1998, Kawato, 1999, Shadmehr, 2004, Shadmehr et al., 2010). In addition, area 3a may be part of the circuit mediating the online compensatory mechanism as it contains neurons responsive to both vestibular and somatosensory inputs (Guldin et al., 1992) including those from the arm and hand (Guldin and Grusser, 1998), and has strong interconnections with the primary motor cortex (Huffman and Krubitzer, 2001) .

3.5 Future directions

This work leads to several new potential directions for study both at the behavioural and neuronal levels. Several of these directions are described below.

3.5.1 Exploring dynamic compensations for body motion during reach execution

When GVS was delivered during the arm movement (Experiment 1) the observed trajectory deviations due to the stimulation were significantly smaller than those predicted on the basis of purely spatial/kinematic considerations. However, they were remarkably similar in amplitude to the predictions made using a biomechanical model of the limb that took into account both spatial and dynamic factors when compensating for the simulated rotation. This suggested that subjects might be appropriately taking into account limb biomechanics when reaching during a sudden unexpected rotation of the body. However, we cannot differentiate between this possibility and the possibility that reach deviations were simply undercompensatory for a purely spatial correction.

To explore whether subjects could take into account the biomechanics of reaching during body rotation, subjects could be asked to perform reaching movements to a remembered target that remains fixed relative to the body during simulated body motion (i.e. an egocentric rather than an allocentric target) while GVS is delivered. When reaching to an egocentric target, rotation of the body does not change the spatial relationship between the body and the target, so no spatial compensation for body rotation is required. However, dynamic compensations for the velocity-dependent forces that normally act on the limb during rotation are required. If subjects do compensate appropriately when reaching to an egocentric target reach deviations would be predicted to be deviated in the same direction as the simulated rotation (Fig. 2.6A “ideal dynamic only” traces). These predictions contrast from those in Experiment 1 of the current study, where reaches to an allocentric target would be predicted to be deviated in the opposite direction to the simulated rotation. The prediction when reaching egocentrically was actually tested in some piloting experiments that I performed in the laboratory.

To facilitate a distinction between egocentric and allocentric reaching instead of being presented with a point target in the egocentric task subjects were presented with a horizontal line that indicated reach distance. Subjects had to remember the distance between the start position and the line and were instructed to perform straight-ahead reaches that were aligned with the center of their body for that distance. In contrast to our predictions, egocentric reaches were deviated in a similar fashion to the allocentric reaches (i.e. similar to the deviations of Experiment 1 of the current study). That is, egocentric reaches with the head forward were deviated in the direction appropriate for a spatial displacement of the limb relative to the target rather than in the direction consistent with dynamic compensation for Coriolis forces. One explanation for these preliminary results is that, because in this experiment subjects do not have an actual perception of body motion, it would be very difficult to distinguish reaching egocentrically from reaching allocentrically regardless of the visual stimuli used or how subjects were instructed to perform the reach. Furthermore, in contrast to an actual rotation where compensating dynamically during an egocentric reach is required to keep the arm aligned with the center of the body, if subjects tried to apply such a compensation during GVS when the body is actually stationary subjects would have felt the arm move out of its alignment with the center of the body. This conflicting feedback could have played a role in preventing subjects from compensating dynamically for the simulated rotation. In light of this and the absence of an actual perception of body motion, subjects may have resorted to using a default reaching behaviour (i.e. stabilizing the limb in space) under all conditions.

In order to test whether subjects require a stronger percept of body motion to compensate dynamically for the simulated rotation during egocentric reaching, a stronger vestibular cue of motion could be provided by stimulating subjects both during reach execution and during the memory period prior to reach execution. In this situation the vestibular stimulation could provide a cue as to the dynamics of the reaching environment before the arm movement was initiated and allow the brain to plan motor commands that provide dynamic compensation for the expected forces in that environment. However, in contrast to the previous piloting experiments described above, in this situation simulated rotation would begin prior to the onset of reach execution. A consequence of this is that subjects would need to apply very little compensation for the inertial properties of the limb because they would be initiating their reach during simulated ongoing constant velocity rotation rather than during a simulated abrupt acceleration of the body (i.e. a simulated velocity step from 0 to 10.5 deg/sec when GVS occurs unexpectedly during reach execution). Subjects would only need to compensate mainly for the velocity-dependent forces that would be acting on the limb due to body motion (i.e., Coriolis and centrifugal forces). Notably Coriolis forces act in opposite directions for oppositely directed arm movements (Fig. 3.1). That is, reach trajectories are predicted to be deviated in opposite directions when reaching away from the body and toward the body. Thus to examine whether observed trajectory deviations reflect compensation for Coriolis forces in such an experiment subjects could be asked to make both reaches away from their body (as in Experiment 1) and also towards their body.

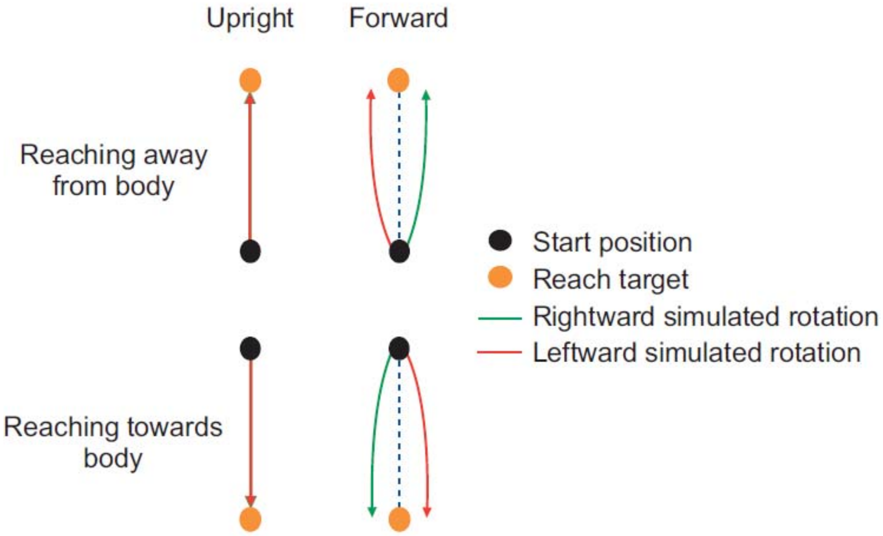

Figure 3.1. **Predictions for the trajectory deviations elicited by GVS to compensate ideally for Coriolis forces during simulated rotation.** A schematic of the reach trajectory deviations predicted when reaching to a body-fixed (egocentric) target during simulated constant velocity rotation with the head upright (left column), with the head pitched forward (right column), during forward (top) and backward (i.e. towards the body; bottom) reaching. Note that with the head forward, the deviations when reaching towards the body are oppositely directed compared to those when reaching away from the body.

Unfortunately, one problem that is likely to arise in the experiment described just above is that any GVS-evoked deviations that reflect Coriolis force compensation are likely to be small and difficult to measure because a comfortable level of applied GVS current (e.g. 3mA) simulates a low rotation velocity (e.g. 10.5 deg/s). Consequently, the resulting velocity-dependent forces that would act upon the limb would be themselves very small and potentially result in trajectory deviations that are too small to clearly distinguish from control trajectories. Thus a final approach to explore vestibular contributions to dynamic compensations for body motion may be to compare trajectory deviations across different reach directions when GVS is applied during reach execution. In particular, the biomechanical model of the limb makes different predictions for the extent to which reach trajectories would be deviated across directions if compensating only spatially for the kinematic aspects of reaching during body rotation versus when contributing to compensations that take into account limb biomechanics.

More precisely, when reaching to targets that are oppositely directed but deviated relative to the body midline by the same amplitude (e.g., 60 degrees vs. -60 degrees from a line passing through the start target and aligned with the center of the body), the extent to which the brain must compensate spatially for only the kinematic aspects of reaching during simulated body rotation are similar for both targets and therefore should lead to reach trajectories being deviated to the same extent in each case (i.e., no difference in the amplitude of trajectory deviations between rightward and leftward simulated rotation for the two reach directions; see Fig. 3.2). In contrast, if subjects do take into account the biomechanics of reaching during body rotation, then reaches should be deviated by GVS to a different extent for oppositely directed reach directions. More precisely, whereas reaching to a target that is shifted relative to the midline by 60 degrees should lead to reaches that are not substantially deviated from each other for opposite GVS polarities, reaching to a target that is shifted by -60 degrees relative to the midline should lead to reach trajectories that are significantly more deviated from each other for opposite GVS polarities (Fig. 3.2) The observation of such a consistent difference in the amplitude of trajectory deviations between the two directions would thus provide support for the idea that limb biomechanics are taken into account in the processing of vestibular contributions to reach execution.

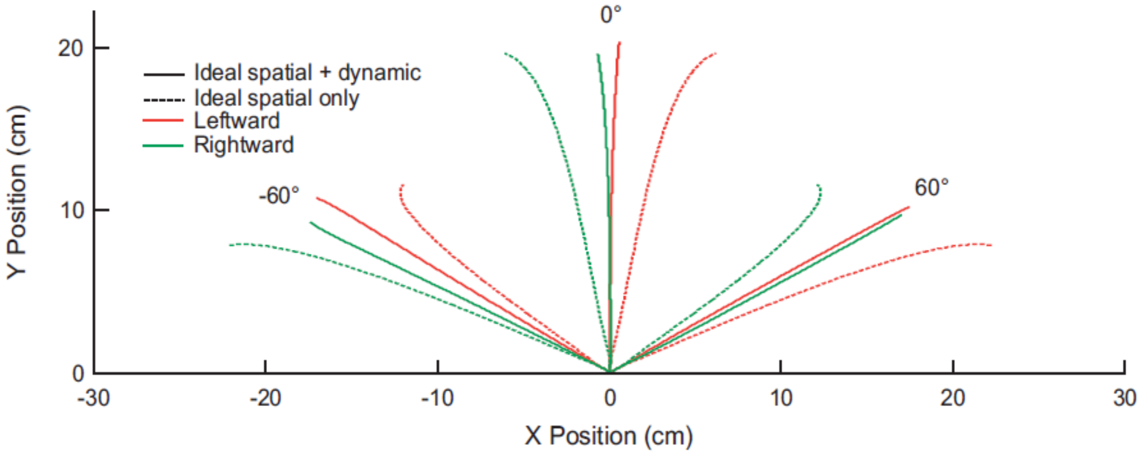

Figure 3.2. **Predictions of a biomechanical model of the limb for the GVS-induced trajectory deviations when reaching in different directions.** Predicted stimulation-induced perpendicular trajectory changes relative to control for rightward (green) and leftward (red) simulated rotation are illustrated for three different target directions (0°, 60°, and -60°) when subjects compensate ideally during body rotation only for the spatial displacement of the limb relative to the reach target ("spatial only"; dotted lines) or for both the spatial displacement and additional forces imposed on the limb by the rotation ("spatial + dynamic"; solid lines). Note that whereas for 60° the ideal "spatial + dynamic" trajectory deviations almost completely overlap for rightward and leftward simulated rotation, for -60° the ideal "spatial + dynamic" trajectory deviations are clearly deviated in opposite directions for opposite GVS polarities. In contrast, the predicted "spatial only" trajectories are deviated to the same extent for 60° and -60°.

3.5.2 Exploring the neural correlates for vestibular contributions to reaching

3.5.2.1 Exploring the neural correlates for a reference frame transformation of vestibular signals

Another potential direction to explore is to identify the neural correlates for the mechanisms underlying vestibular contributions to reaching. As discussed earlier in this chapter (see Section 3.4.1), one area of potential interest is the rostral fastigial nucleus (rFN) of the cerebellum (Kleine et al., 2004, Shaikh et al., 2004). In particular, previous studies of neurons in rFN showed head-orientation dependent spatial tuning properties consistent with a partial transformation of vestibular signals from a head- to a body-centered reference frame. However, this head- to body-centered partial transformation was only demonstrated for head reorientation relative to the body in the horizontal plane. If a true reference frame transformation takes place in 3D then such head-orientation-dependent tuning should also be present for head reorientation in the vertical plane (e.g. reorientations similar to those in the present study). To test the evidence for such a 3D transformation, neural responses in the rFN during whole-body translations or rotations could be examined for motion in 3D and both vertical and horizontal head reorientation relative to the body. However, it is important to note that while the results of such a study may demonstrate that neurons in rFN reflect a transformation of vestibular signals into a body-centered coordinate frame in three dimensions, this does not necessarily mean that these transformed signals are those that contribute to self-motion estimates for reaching movements.

3.5.2.2 Exploring the neural correlates for vestibular contributions to spatial updating

This work has also provided evidence that spatially transformed vestibular signals contribute to a spatial updating mechanism during reach planning. However, the neural correlates for vestibular contributions to this mechanism are not known. As discussed earlier in this chapter (see Section 3.4.2), regions in the posterior parietal cortex are likely to play an important role in updating the location of reach goals during body motion (Colby and Goldberg, 1999, Andersen and Buneo, 2002, Medendorp, 2011). Motor areas implicated in reach planning such as the dorsal premotor cortex (PMd) (Kalaska et al., 1997, Cisek and Kalaska, 2002, 2005) or the supplementary (SMA) and pre-supplementary (pre-SMA) motor areas (Shima and Tanji, 2000, Nachev et al., 2008) might use this updated goal information to plan new reach trajectories. An experiment could be done to explore the relative roles of these different areas in updating or remapping the representations of reach targets during ongoing whole-body motion. The experimental task would be similar to classic spatial updating paradigms. More precisely, a primate subject placed in darkness in a mechanical apparatus that can move the animal in space could be presented with a visual target be flashed in their periphery (while fixating a central target) before being rotated or translated in space. Following the passive motion, the animal would be required to reach to the remembered spatial location of the flashed peripheral target. Recording in regions such as the PMd and area MIP could be performed to explore the relative roles of these areas in encoding and updating reach targets or the relationship between the limb and the target to compensate for the displacement of the body.

3.5.2.3 Exploring the neural correlates for vestibular contributions to reach execution

We have also provided evidence that vestibular signals can contribute more directly online during reach execution where compensating ideally for rotation involves not only keeping track of the relative spatial locations of the limb and target but also compensating dynamically for the additional forces imposed on the limb such as Coriolis forces. An experiment could be designed to explore the neural correlates for such dynamic compensation.

Of relevance to such an experiment would be the results of previous studies that have looked at compensation for Coriolis-like forces during reaching when stationary while holding a robotic manipulandum (Shadmehr and Mussa-Ivaldi, 1994, Brashers-Krug et al., 1996, Thoroughman and Shadmehr, 1999, Gandolfo et al., 2000, Li et al., 2001, Padoa-Schioppa et al., 2002, 2004, Xiao et al., 2006). The robotic manipulandum can apply forces to the hand that are proportional to the hand velocity (i.e. a velocity-dependent force field) but directed perpendicular to the reach direction. A subset of these studies have shown that primates can learn to compensate for these Coriolis-like forces during reaching through repeated exposure to the field and that learning to compensate for the dynamics of the workspace is accompanied by changes in the directional tuning of neurons in M1 (Gandolfo et al., 2000, Li et al., 2001) and other motor areas such as PMd, ventral premotor cortex (PMv) (Xiao et al., 2006) and SMA (Padoa-Schioppa et al., 2002). These changes in neural responses argue for the existence of internal models in these areas that represent the dynamics of the limb and the workspace within which the limb moves (Lackner and Dizio, 1994, Shadmehr and Mussa-Ivaldi, 1994, Brashers-Krug et al., 1996, Wolpert and Kawato, 1998, Thoroughman and Shadmehr, 1999, Shadmehr et al., 2010). However since no actual motion of the whole-body occurred in these manipulandum studies, the contributions of vestibular information to compensating for velocity-dependent forces could not be explored.

In order to study the contributions of vestibular signals to dynamic compensations for body motion during reaching a first step would be to investigate the neural responses in motor areas such as M1 or PMd when a primate reaches to a body-fixed target (i.e. an egocentric target) during an actual passive whole-body rotation at constant velocity where real velocity-dependent forces (Coriolis and centrifugal forces) act on the limb due to the body motion. These responses could then be compared to those obtained from the robotic manipulandum studies outlined above to see how the brain represents compensation for actual Coriolis forces versus those artificially-imposed by a tool (i.e. the robot).

3.6 General conclusions

In the current work we have provided evidence for the first time that vestibular signals which contribute to reaching are transformed from a head- to body-centered reference frame as appropriate to contribute to limb motor control and planning. In addition, we have provided evidence that vestibular signals contribute to distinct compensation mechanisms for body motion during reach execution versus reach planning. Whereas the direct sensorimotor compensatory mechanism implicated in online limb motor control during reach execution appeared to be involuntary, the spatial updating mechanism implicated in reach planning did not appear to be able to use vestibular information as effectively and likely depended on stronger motion percepts. Future studies will be required to further explore the extent to which vestibular information contributes to distinct mechanisms that provide spatial compensation, dynamic compensation or a combination of both when reaching occurs during body motion. In addition, it remains to be seen where in the brain the head- to body-centered reference frame transformation of vestibular signals contributing to reaching is occurring and to identify the neural correlates for the different mechanisms that use these transformed vestibular signals during reach planning and execution.

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