The intrinsic plasticity of medial vestibular nucleus neurons during vestibular compensation: a systematic review and meta-analysis

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For Nora.

The unintended inaccuracies and omissions are my own.
Declaration of originality

This is to certify that, to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for acceptance into any other degree.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

I understand that my thesis will be lodged with the Director of University Libraries and made available for immediate use.

Rajiv Wijesinghe

Contributions

Aaron Camp acted as a second reviewer, independently assessing articles for inclusion in the systematic review.
List of abbreviations

4-AP – 4-aminopyridine
AHP – afterhyperpolarisation
AP – action potential, synonymous with spike
BPPV – benign paroxysmal positional vertigo
CI – confidence interval
EPSP – excitatory post synaptic potential
GABA – γ-aminobutyric acid
IPSP – inhibitory post synaptic potential
IVN – inferior vestibular nucleus
LTD – long term depression
LTP – long term potentiation
LTS – low-threshold spike
LVN – lateral vestibular nucleus, synonymous with Deiter’s nucleus
MLF – medial longitudinal fasciculus
MVN – medial vestibular nucleus
NMDA – N-methyl-D-aspartate
RMD – raw mean difference
SEM – standard error of the mean
SN – spontaneous nystagmus
SVN – superior vestibular nucleus
TEA – tetraethylammonium
TTX – tetrodotoxin
UVD – unilateral vestibular deafferentation
VNC – vestibular nuclear complex
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I — ABSTRACT

The diversity of activity displayed by neurons of the central nervous system is unmatched by any other cell in the body. Each neuron displays a characteristic, stereotypic pattern of firing which often defines its functional role (Llinas, 1988). Some neurons are spontaneously active at rest, displaying pacemaker-like properties, while others are very quiescent until stimulated by synaptic inputs. Some neurons fire rapid, regular action potential trains which show little deterioration in frequency over time. Others fire only short bursts of action potentials and reduce their rate of firing quickly, producing very little response to even large inputs (Bean, 2007). These discharge characteristics are fundamentally determined by two main features: the intrinsic membrane properties of the neuron and the nature of the synaptic inputs the neuron receives. Intrinsic properties are those relating to the architecture of the neuronal membrane, intracellular ionic buffers that regular electrolyte concentrations and the types of ion channels expressed on the membrane and their pattern of distribution (Wijesinghe & Camp, 2011). Meanwhile, synaptic properties are determined by the types of transmitters arriving at the neuronal surface, the distribution of these synapses and their density over various functionally specialised regions of the neuron (Spruston, 2008). From the various permutations of these different properties emerges the vast array of different firing characteristics observed of individual neurons from different regions of the brain (Llinas, 2014).

Despite the prevalent stereotypy observed across different subtypes of neurons, alterations in the local environment and external stimuli can induce changes in these basic properties. This phenomenon, known as neuronal plasticity, has been observed in normal physiological states and is believed to underlie experience-dependent changes in neural activity such as learning and memory (Mayford, Siegelbaum & Kandel, 2012; Sweatt, 2016). It has also been observed in various disease states and may act as a homeostatic mechanism to downregulate...
excitotoxicity or restore lost functional capacities (Beck & Yaari, 2008; Camp, 2012; Vitureira, Letellier & Goda, 2012; Yin & Yuan, 2014). These changes were first observed to occur in synapses, where high intensity stimuli induced changes that altered the likelihood of signal transmission at a particular synapse. Since then, the stimuli that induce synaptic plasticity and the cellular mechanisms that maintain these changes have been widely investigated (Bailey, Kandel & Harris, 2015; Kandel, 2001). However, it has now been recognised that intrinsic neuronal properties themselves are plastic and may contribute to some of the processes previously attributed to synaptic mechanisms alone (Desai, 2003; Hanse, 2008; Mozzachiodi & Byrne, 2010; Titley, Brunel & Hansel, 2017). A number of studies in the past 30 years have demonstrated important activity-dependent changes in firing dynamics that appear to act along multiple timescales and influence network activity in a variety of ways. These changes, termed intrinsic plasticity, are manifest in the patterns and frequency of action potential discharge of individual neurons. This dynamism is primarily driven by alterations in ion channel expression, excitatory neurotransmitter receptor expression and intracellular buffering protein concentrations (Beraneck & Idoux, 2012; Camp & Wijesinghe, 2009).

I am interested in the studying the basic intrinsic properties of individual neurons, how they determine discharge dynamics in networks, and the conditions that modulate these properties (for example see previous work in Camp & Wijesinghe, 2009; Wijesinghe & Camp, 2011; Wijesinghe, Solomon & Camp, 2013; Wijesinghe et al., 2015). In particular, I am interested in how pathological changes might influence the firing properties of downstream neurons. Typically, animal models with a simple neuronal circuit, an easily lesioned peripheral sensory organ and observable behaviours have been chosen for such studies. One such model system is the vestibular system, which maintains our sense of equilibrium. It is composed of an easily accessible neuronal circuit within the brainstem which is homologous between a number of species (Goldberg et al., 2012). It mediates basic reflexes that maintain gaze stability during head movement and stabilises dynamic posture (Bronstein, Patel & Arshad,
This sensory modality also has a unique property of near immediate recovery following damage to the components that mediate it, a process known as vestibular compensation (Curthoys & Halmagyi, 1995). This process occurs in humans and can be reliably reproduced experimentally, making it a convenient model to bridge *in vitro* findings to clinical observations (Straka, Zwergal & Cullen, 2016). Recent studies have suggested that vestibular compensation may be a behavioral correlate of a form of experience-dependent plasticity occurring within the vestibular nuclei of the brainstem (Dutia, 2010; Lacour & Tighilet, 2010; Macdougall & Curthoys, 2012). More interestingly, part of the recovery may be mediated by changes in the intrinsic properties of vestibular nucleus neurons in a way that is necessary for the process to occur.

In the thesis that follows, I present the first comprehensive systematic review of the scientific literature searching for evidence to investigate the following hypothesis: intrinsic plasticity mediates changes observed during the acute phase of vestibular compensation. To determine the methodological quality of studies discovered through searches of electronic databases, I independently developed tools to assess the precision, validity and bias of each study. Based on a total of 17 studies which met pre-determined inclusion and exclusion criteria, I conclude that there is evidence in favor of the hypothesis. Then, pooling quantitative data from this evidence, I performed a meta-analysis which demonstrates a moderate, statistically significant increase in the intrinsic excitability of medial vestibular nucleus neurons following unilateral vestibular deafferentation. Specifically, their spontaneous discharge rate increases by 4 spikes/sec on average and their sensitivity (or gain) in response to current stimuli increases. Using this novel approach, I demonstrate that the methodology of systematic review and meta-analysis is a useful tool in the summation of data across experimental studies with similar aims. I also identify a number of areas in which the reporting of experimentation in field of vestibular research can be improved to strengthen the quality and validity of future work.
II – INTRODUCTION

1. The vestibular system

Our sense of equilibrium is created by a complex sensorimotor system distributed throughout the central and peripheral nervous system (Angelaki & Cullen, 2008). It is sensitive enough to detect subtle perturbations of both body position and our environment independently to maintain orientation unconsciously. The sensory information used by this system is derived from the paired vestibular organs, visual inputs and sensory and proprioceptive feedback from limbs (afferents from skin, joints and muscles). These signals are received by components of the vestibular system and distributed to brainstem oculomotor and spinal locomotor effector circuits. This integrated neural network mediates postural control when stationary, maintains gaze stability to create a stable visual world during movement and generates our perception of orientation and motion in space (Goldberg et al., 2012).

During periods of vestibular dysfunction these capacities breakdown, resulting in the illusory sense of motion while stationary (known as vertigo), postural imbalance and slip of the visual image with loss of acuity (Kerber & Baloh, 2015). These symptoms appear most dramatically during acute unilateral vestibular dysfunction, most commonly caused by peripheral vestibular disorders such as vestibular neuritis, benign positional paroxysmal vertigo (BPPV) and Meniere’s disease (Ludman, 2014; Strupp & Magnusson, 2015). Further, acute and chronic vestibular dysfunction has been linked to more complex deficits such as impairments in spatial navigation (Borel et al., 2008; Borel et al., 2014; Panichi et al., 2017), memory tasks (Brandt et al., 2005; Smith, 1997) cognition (Smith, 2017), bodily self-consciousness (Deroualle & Lopez, 2014) and out-of-body experiences (Lopez & Elziere, 2017).
The vestibular system is composed primarily of five paired components – the vestibular organs (or labyrinth), the vestibular nerve containing vestibular afferents, the vestibular brainstem nuclei (or vestibular nuclear complex (VNC)), the vestibulocerebellum and the vestibular cortex. The following sections will summarise the anatomy and physiology of the vestibular system, with a particular focus on the characteristics of the medial vestibular nucleus (MVN).

1.1 Peripheral vestibular organs

The peripheral vestibular sense organs are paired structures situated in the temporal bones on either side of the skull, enclosed such that they move in concert with the head (Champney, 2016). Each organ consists of an outer bony labyrinth that encases a membranous labyrinth filled with a continuous column of viscous endolymph. The inner membranous labyrinth has three specialised functional regions: the cochlea, semicircular canals and the vestibule, the latter two of which form the vestibular part of the labyrinth (Figure 1). The vestibule contains the two roughly spherical otolith organs, the utricle and the saccule, while the semicircular canals each end in a dilated portion called the ampulla (Figure 1A-C). The semicircular canals are arranged orthogonally and are stimulated by angular accelerations, while the otolith organs (utricle and saccule) are sensitive to linear accelerations. Therefore, each direction of movement will result in some combination of signals from each paired organ to unambiguously encode the direction of movement. Within the 5 dilated portions of the labyrinth (utricle, saccule and 3 ampullae) lie sensory epithelia that transduce movement. The ability to detect tilt, rotation and translation is determined solely by the specific orientation of each sensory epithelium and the anatomical differences of each section (Figure 1E).
**Figure 1** – The peripheral vestibular organs and their internal anatomy.  

**A** The bony labyrinth (left) with cross sections of the semicircular canal (middle) and otolith organs (right).  

**B** Internal structure of the cupula of the semicircular ampulla.  

**C** Internal structure of the otolithic membrane.  

**D** Cross section of hair cells. Solid cilium is the kinocilium.  

**E** A schematic of the sensory epithelia of the (from left to right) ampulla, saccule and utricle with arrows indicating the polarity of each hair cell. Figures A-C adapted from Champney, 2016.  

Figures D and E adapted from Goldberg, 2012.
The sensory epithelia are lined by specialised vestibular hair cells which contain mechanosensitive elements that generate electrical signals to send through the vestibular nerve to the brainstem (Gillespie & Muller, 2009). Each hair cell is composed of a cell body, lined by rigid stereocilia of differing heights attached to each other at their tips to form a bundle that moves in concert (Vollrath, Kwan & Corey, 2007, Figure 1D). The stereocilia project into a gelatinous elastic mass, which is displaced by movement of the endolymph when the head moves. The longest of these stereocilia, the kinocilium, determines the polarity of the hair cell. If stereocilia are tilted towards the kinocilium, the hair cell becomes more hyperpolarised and inhibits afferent nerve firing. In contrast, stereocilia movement away from the kinocilium causes hair cell depolarisation and increases vestibular afferent firing (Lowenstein & Wersäll, 1954).

The anatomy of the otolith organs and ampullae differ in a way that dictates their ability to detect specific types of movement. In the otoliths, the irregularly shaped sensory epithelium, the macula, contains a central ridge, the striola, toward which kinocilia are oriented (Figure 1E). In the horizontally orientated utricle, kinocilia are oriented towards the striola, while in the vertically orientated saccule kinocilia are directed away (Lindeman, 1969). Stereocilia project upwards into a gelatinous elastic mass composed of glycoprotein, atop of which lie calcium carbonate crystals called otoconia (Figure 1C). This structural unit, the otoconial membrane, creates significant inertia such that it tends to lag during linear head movements. The relative movement of the membrane to the bony labyrinth fixed in the head displaces the stereocilia triggering changes in afferent firing. Because of the variety of orientations of stereocilia on the macula, movements of the otoconial membrane in any linear direction can be signalled. However, the movement of the otolith membrane is restricted to the linear plane such that otoliths are unable to independently distinguish between tilt, rotation and translation.
In contrast, the ampullae of the semicircular canals contain a gelatinous mass, the cupula, that generates an occlusive membrane across the opening of each canal (Figure 1B). This restricts the flow of endolymph out of the canal, such that movements of endolymph within the canal during head movement displace the cupula back and forth. The cupula sits above the sensory epithelium, called the crista ampullaris, which is a saddle shaped structure that comes to a crest at its centre. In a similar mechanism to that seen in the otolith organs, movement of the cupula deflects stereocilia and subsequently generates changes in afferent neuron firing rates. However, in contrast to the otolithic membranes, hair cells are orientated in one direction that maximises responses to movement in the orientation of flow within the canal. Endolymph is only able to move if the direction of the rotation is in a plane orthogonal to the canal\(^1\). Therefore, the directionality of the signal produced by the canals is inherent in the structure of the canal, rather than the orientation of hair cells.

Movement is coupled to the generation of electrical signals within the vestibular nerve by an elegant cascade of events. When the kinocilium is deflected, mechanoelectrical transducer channels within all the stereocilia are opened such that the hair cell membrane changes. This so called receptor potential of the hair cell is depolarised by stereocilia bending along the polarisation axis towards the kinocilium and hyperpolarised by bending in the opposite direction (Shotwell, Jacobs & Hudspeth, 1981). Membrane potential changes generate inward potassium and calcium currents on the basolateral membrane of the hair cell, which differ in their characteristics between type I and II hair cells\(^2\) (Goldberg & Brichta, 2002). In particular, the increase in intracellular calcium facilitates the fusion and subsequent exocytosis of synaptic vesicles (Beutner et al., 2001; Keen & Hudspeth, 2006) containing the excitatory neurotransmitter glutamate (Bonsacquet et al., 2006; Matsubara et al., 1999). The

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\(^1\) This is known as Ewald’s 1\(^{st}\) law
\(^2\) There are two distinct hair cells – tall type I cells are innervated by a calyx synapse, while round type II cells are innervated by a bouton shaped synapse. Type I cells are only found in vestibular epithelia, while type II cells are found in all hair-cell containing organs. See Lysakowski, A 1996, ‘Synaptic organization of the crista ampullaris in vertebrates’, Ann N Y Acad Sci, vol. 781, pp. 164-82.
hair cell-afferent synapses contain ribbon-style elements that allow for the continuous exocytosis of neurotransmitter (Zanazzi & Matthews, 2009; Zenisek et al., 2003), which can facilitate the transduction of repetitive stereocilia movements. This process in turn results in depolarisation of the postsynaptic membrane of the vestibular afferent, generating postsynaptic conductances that can modulate the resting spontaneous discharge of the afferent (Holt et al., 2006; Rennie & Streeter, 2006).

1.2 Primary vestibular afferents

Vestibular afferents are spontaneously active at rest (Lowenstein & Sand, 1936), a property which confers two important characteristics. Firstly, it allows each afferent to respond to movements bidirectionally, by increasing firing in one direction and disfacilitating firing in the opposite direction (Fernandez & Goldberg, 1976). Secondly, there is no discontinuity between discharge rate and movement, eliminating a sensory threshold for perception (Fernandez & Goldberg, 1971). This activity is present across most studied species, including rats (Curthoys, 1982), cats (Tomko et al., 1981) and monkeys (Lysakowski et al., 1995), in both awake and anaesthetised in vivo circumstances (Ramachandran & Lisberger, 2006).

There are two main types of vestibular afferent which can be distinguished by the nature of their synapse with hair cells, the sensitivity to particular movements and their action potential (AP, or spike) discharge dynamics (Table 1). The most interesting aspect of this distinction is the way in which it determines the sensitivity of afferents to synaptic and external current inputs. Modelling studies (Smith & Goldberg, 1986) and in vitro experiments (Baird et al., 1988) have demonstrated that the time course of the afterhyperpolarisation (AHP) plays a deterministic role in the interspike voltage trajectory and therefore the temporal dynamics of discharge activity. In regular spiking afferents, the AHP is deep and slow, but rises above a critical firing threshold such that firing occurs even in the absence of
superimposed synaptic currents. This type of firing is also referred to as deterministic, as synaptic potentials are sufficient but not necessary for firing. In contrast in irregular afferents, the AHP is fast and shallow, such that the only way in which the potential reaches firing threshold is by the imposition of synaptic current noise. Therefore, irregularly firing afferents display non-deterministic firing characteristics and their activity is more reflective of the random timing of synaptic quantal release. Further, current (or galvanic) stimulation increases firing rates more robustly in irregular than regular afferents (Marlinski, Plotnik & Goldberg, 2004; McCue & Guinan, 1994), in a way that is likely due to properties of the afferent neuron, as opposed to the hair cell itself.

| Irregularly discharging                      | Regularly discharging                                      |
|----------------------------------------------|-----------------------------------------------------------|
| Thick and medium-sized axons ending as calyx and dimorphic terminals in the striola, synapse with type I hair cells | Medium-sized and thin axons ending as bouton terminals in the extrastriolar zone, synapse with type II hair cells |
| Phasic-tonic response dynamics               | Tonic response dynamics                                    |
| High sensitivity to angular or linear forces | Low sensitivity to angular or linear forces.               |
| Large responses to electrical stimulation of efferent fibres | Small responses to electrical stimulation of efferent fibres |
| Low thresholds to short shocks and large responses to constant galvanic currents | High thresholds and small responses to the same galvanic stimuli |

*Table 1 – The differential properties of vestibular afferents. Adapted from Goldberg, 2012.*

### 1.3 The vestibular nuclei

Each signal from the otoliths and canals is complementary, such that a composite of these signals is integrated to generate information about head position. This process occurs in the brainstem VNC, where afferent nerve fibres projecting from the vestibular organ synapse with second order vestibular neurons (Figure 2A). The VNC is a group of nuclei located on the floor of the fourth ventricle at the pontomedullary junction of the brainstem. It is
subdivided along anatomical lines into four intimately related subnuclei, each denoted by their relative location to the others (Figure 2B). Afferent fibres conveying information from different parts of the vestibular organ are distributed amongst these four nuclei in a topographic manner (Cullen, 2016). This organisation is highlighted by the physiology of second order vestibular neurons. The rostral MVN and LVN contain neurons responsive to yaw-axis rotations (Cullen & McCrea, 1993; Scudder & Fuchs, 1992), while neurons in the MVN and SVN are responsive to pitch and roll movements (Dickman & Angelaki, 2004; Tomlinson & Robinson, 1984). Similarly, VNC outputs are well organised, as fibres projecting from the LVN travel down to peripheral musculature via the lateral vestibulospinal tract, while the remaining three nuclei project to the cerebellum via the vestibulocerebellar pathways (Figure 2B, right). This wide interconnectivity with other regions of the central nervous system establishes the machinery for multimodal sensory integration in creating the sense of balance (Angelaki & Cullen, 2008).

There is a significant redundancy in these projections, as nerve fibres from canals and otoliths can be found throughout the VNC (John Leigh & Zee, 2015). As a population, vestibular neurons that are responsive to rotations can be classified based on their physiological and functional specialisation. The designations position-vestibular-pause (PVP), eye-head (EH) or vestibular-only (VO) label neurons by their responses to specific types of eye and head movements (Cullen, 2016). Neurons can be further classified as type I or II neurons based on whether they are activated by ipsilateral or contralateral rotations respectively (Duensing & Schaefer, 1958). Generally, type I PVP and EH neurons mediate the angular vestibuloocular reflex (VOR, Figure 2C), while type I VO neurons encode posture and self-motion. Based on the responses to sinusoidal head movements and current stimuli, vestibular encoding is thought to be a largely linear process (Sadeghi et al., 2007). Vestibular neurons typically show a linear change in firing frequency over a wide physiologically relevant range of frequencies (Massot, Chacron & Cullen, 2011) and are capable of transducing synaptic inputs into changes in firing frequency (McElvain et al., 2015).
**Figure 2** (opposite page) - The VNC and its connections. **A** The VNC receives multiple inputs from primary sensory organs and widely distributed regions of the brain. **B** The VNC is divided into 4 distinct nuclei. Vestibular nerve afferents synapse in all subregions of the VNC (left). There are also strong connections between the paired VNC’s (centre) and the cerebellum (right). **C** The VOR is a polysynaptic reflex arc which connected head movements such as translation (left) and tilt (right). Movements are detected by the vestibular organs and signals are ultimately distributed to the oculomotor nuclei (III, IV, and VI). Figures **A** and **B** adapted from Cullen 2016. Figure **C** adapted from John Leigh and Zee, 2015.

### 1.4 The medial vestibular nucleus

The MVN is the largest of the vestibular nuclei. It plays a central role in brainstem mediated oculomotor reflexes and there is a correlate of this region in most studied species. It is also the nucleus in which most studies of vestibular compensation have been conducted. Therefore, the remainder my thesis will focus on the specific properties of the MVN and its second order vestibular neurons.

#### 1.4.1 Organisation and cytoarchitecture

MVN neurons have been generally described as small, round, pear or triangular shaped (Highstein & Holstein, 2006). There are a mixture of projection neurons that have been observed to send axons to the contralateral vestibular nucleus (known as commissural projections) (Epema, Gerrits & Voogd, 1988), oculomotor nuclei (Langer et al., 1986; McCrea et al., 1987), spinal cord (Holstege, 1988; Shinoda et al., 2006), cerebellum (Purcell & Perachio, 2001) and thalamus (Wijesinghe, Protti & Camp, 2015). In addition, there are intervestibular neurons (similar but distinct to interneurons found in other regions of the brain) which connect regions between different nuclei in the VNC (Epema, Gerrits & Voogd, 1988). There is a gradual increase in the size of MVN neurons in the caudorostral direction.
In particular, larger cells appear to populate the rostrolateral region of the MVN, while the smaller cells are located primarily in the caudomedial MVN. Based on this apparent distribution, it has been suggested that the MVN neurons can be divided into magnocellular and parvocellular groups respectively (Epema, Gerrits & Voogd, 1988). Interestingly, the magnocellular region receives strong inputs from the semicircular canals and the flocculus of the cerebellum and project to the oculomotor brainstem nuclei. Meanwhile the parvocellular region tends to receive inputs from the otolith organs and spinal cord and projects to targets within the nucleus, as well as back to the spinal cord and the cerebellum (Buttner-Ennever, 1992).

1.4.2 Classification

In developed adult animal models, there are at least two physiologically distinct subtypes of MVN neurons (Figure 3). In vitro in acute brainstem slices of rats (Gallagher, Lewis & Gallagher, 1985) and guinea pigs (Serafin et al., 1991a), MVN neurons can be distinguished by the width of the action potential and the character of the afterhyperpolarisation (AHP). A third intermediate type not readily distinguishable based on the above properties may also exist (see section 2.3.4 below). In the original studies by Gallagher and colleagues and Serafin and colleagues, most observed neurons displayed tonic firing properties, however a minority of type B neurons displayed burst-type low threshold spikes and subthreshold plateau potentials (Figures 3B, C). A third group, designated type C neurons, displayed no characteristic features and were not analysed in their studies. The observed proportions of each subtype were roughly similar (32% type A, 47% type B, 21% type C) and the passive membrane properties of these neurons (such as membrane potential, capacitance and input resistance) were not significantly different between the three classes. A binary classification system has subsequently been reproduced using an automated algorithm that presupposes no
thresholds or number of classes (Beraneck et al., 2003) and confirmed with an expectation-maximisation algorithm (Idoux et al., 2008)\(^3\).

\(^3\) However, see section 2.4.3 for a discussion of this issue
Figure 3 (opposite page) – MVN neurons can be classified by their electrophysiological characteristics.

A Traces of spontaneous discharge recorded in two different MVN neurons in the guinea pig. B Plateau potentials seen in response to subthreshold current steps in a subset of type B neurons. C Low threshold spiking activity seen following release from hyperpolarisation in a subset of type B neurons. D The trajectory of the action potential and AHP define type A and B subtypes. Type A neurons have a deep monophasic AHP, while type B neurons have a biphasic AHP. E Relative proportions of type A and B neurons plotted against their spontaneous discharge rates in vitro. A-C Traces taken adapted from Serafin et al 1991. D AHP traces adapted from Camp et al. 2006. E Graph adapted from Johnston et al. 1994.

In addition to their distinct electrophysiological features, MVN neuron subtypes appear to differ in their anatomical location, projections, synaptic inputs and neurotransmitter outputs (Table 2). Both subtypes receive direct vestibular afferent inputs, as well as commissural inputs from the opposite nucleus (Babalian et al., 1997; Babalian & Vidal, 2000). Type A neurons tend to be located in the parvocellular part of the MVN, while type B neurons populate the magnocellular part (Sekirnjak & du Lac, 2006). Type A neurons also receive primarily γ-aminobutyric acid (GABA)-ergic inputs, while type B neurons receive both GABA-ergic and glycinergic inputs (Camp, Callister & Brichta, 2006). Consistent with these properties, type A neurons are primarily inhibitory GABAergic neurons which project in local circuits within the vestibular nuclei, while type B neurons are glutamatergic and glycinergic neurons projecting to spinal cord and oculomotor nuclei (Bagnall, Stevens & du Lac, 2007; Saito, Takazawa & Ozawa, 2008; Sekirnjak & du Lac, 2006; Sekirnjak et al., 2003; Takazawa et al., 2004).
|                     | Type A                          | Type B                          |
|---------------------|--------------------------------|---------------------------------|
| Anatomical location | Parvocellular MVN              | Magnocellular MVN               |
| Synaptic inputs     | GABA                           | GABA and glycine                |
| Neurotransmitter output | GABA                      | Glutamate, glycine              |
| Projections         | Local vestibular circuits      | Spinal cord Oculomotor nuclei   |
| AHP                 | Large amplitude, monophasic    | Small amplitude, biphasic        |
| AP                  | Broad                          | Narrow                          |
| A-like rectification | Strong                        | Absent or weak                  |
| Special features    | Occasional plateau potentials  | Many plateau potentials, 15-20% show LTS |
| Sensitivity to current | Low                      | High                            |
| Dynamic behaviour   | Tonic                          | Phasic-tonic                    |
| Functional role     | Possible correlate of *in vivo* tonic neurons | Possible correlate of *in vivo* kinetic neurons |

*Table 2 - Properties of MVN neuron subtypes. Adapted from Straka et al. 2005 and Eugene et al. 2011.*

Despite this clear distinction, the electrophysiological properties of MVN neurons as a population appear to change in response to specific circumstances. This plasticity appears to be influenced very strongly by changes in the intrinsic properties that dictate the discharge profiles of these neurons. Below, I discuss the determinants of intrinsic excitability, with a focus on MVN neurons, and show how these properties are altered in response normal and pathological variations in sensory inputs and network activity.


2. Intrinsic excitability

Neuronal discharge patterns are determined by the nature and frequency of the synaptic inputs neurons receive, as well as the intrinsic membrane properties of the individual neuron. Intrinsic properties can be active properties, such as ion channel mediated conductances or intracellular electrolyte concentrations controlled by buffers, or passive properties, such as the input resistance generated by variations in the structure of the neuronal membrane (Wijesinghe & Camp, 2011). The unique combination of these properties establishes a specific repertoire of firing patterns for each neuron that dictates how it encodes the afferent signals it receives. This responsiveness of neurons to incoming inputs is termed intrinsic excitability. The potential repertoire for outputs is wide given the variety of ionic channels which can be expressed (Hille, 2001) and the permutations by which they are distributed across the neuronal membrane.

2.1 Ionic conductances

MVN neurons display a range of action potential firing dynamics that are dependent on their unique intrinsic properties. Specifically, particular potassium (K\(^+\)), sodium (Na\(^+\)) and calcium (Ca\(^{2+}\)) conductances appear to shape the action potential and its afterhyperpolarisation in a way that determines neuronal subtype and intrinsic excitability.

2.1.1 Potassium channels

Potassium channels typically generate an outward current to repolarise the neuron following the rapid depolarising phase of the action potential. They act to attenuate the impact of depolarisation by shifting the membrane potential towards the potassium equilibrium
potential and away from spike threshold. Further, this generates a relative refractory period\(^4\) which prevents further spike firing until equilibrium (i.e. the resting membrane potential) is re-established. Therefore, the activation-inactivation dynamics of the particular potassium channels expressed can determine the duration of the relative refractory period and limit the maximal firing rate of neurons.

There are a number of potassium conductances that shape the repolarisation and AHP of MVN neurons in a subtype-specific manner (Figure 3D). Type A neurons are characterised by a deep monophasic AHP, which slows after a distinct inflection point. In contrast, Type B neurons display a biphasic AHP, composed of an initial fast shallow component followed by a delayed slow component with no rectifying quality (Serafin et al., 1991b). Using selective potassium channel blockers, Johnston and colleagues (1994) demonstrated that potassium currents with early or delayed inactivation profiles generate the distinct profiles of the AHP in each neuronal subtype. In both neurons, the first rapid component is mediated by a voltage-gated A-type tetraethylammonium (TEA)-sensitive $K^+$ current ($I_A$). In type A neurons, there is a second $I_A$-like component generating the slight inflection in the AHP, which acts to dampen firing rates. Further, both neurons have calcium-sensitive potassium conductances that generate the delayed component of the AHP. In type A neurons, this is mediated by the large conductance potassium (BK) channel, while in the type B neuron, repolarisation is mediated by the small conductance potassium (SK) channel (Johnston, MacLeod & Dutia, 1994). These conductances may act to control firing rate and maintain the tonic firing pattern, as application of the SK channel antagonist apamin or low calcium recording solutions increase the excitability of these neurons and can induce the burst firing pattern (Johnston, MacLeod & Dutia, 1994).

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\(^4\) This follows the absolute refractory period, which is determined by the duration of inactivation of sodium channels that generate the inward current during the rapid depolarisation phase of an action potential.
Such changes have also been observed in GIN and YFP-16 transgenic mice, which divide the MVN neuron population into GABAergic and non-GABAergic neurons. Non-GABAergic neurons typically fire with higher rates and display a more rapid action potential rise and fall. In this model, the application of TEA increases action potential width in both groups and negates the intrinsic differences in repolarisation rates (Gittis & du Lac, 2007). Further, the ability to sustain rapid firing rates is dependent on the relative density of BK and Kv3 currents. In rapidly firing neurons, Kv3 currents dominate, preventing Na\(^+\) channel inactivation by a rapid transition from the open to closed state. In slower firing neurons, BK currents dominate and dynamically reduce Na\(^+\) channel availability (Gittis, Moghadam & du Lac, 2010). These differences are not clearly explained by differences in Na\(^+\) conductances (Gittis & du Lac, 2008). Therefore, differences in the density of diverse potassium currents may account for the diversity of firing rates seen in MVN neurons (Gittis, Moghadam & du Lac, 2010).

2.1.2 Sodium channels

In most mammalian neurons, voltage gated sodium channels provide the initial explosive burst to generate the all-or-nothing action potential. All MVN neurons display a tetrodotoxin (TTX)-sensitive Na\(^+\) current that generates the action potential. In addition to this, most (90%) type B and a smaller proportion (40%) of type A neurons display a non-inactivating, relatively TTX-insensitive persistent sodium current (Straka et al., 2005). This mediates a subthreshold plateau potential that can last for hundreds of milliseconds and trigger conventional action potentials. This potential can be triggered by depolarising current stimuli delivered at potentials below firing threshold, or direct stimulation of afferent nerve fibres (Babalian et al., 1997; Beraneck et al., 2003; Johnston, MacLeod & Dutia, 1994; Serafin et al., 1991a). It is thought to assist in the integration and amplification of dendritic synaptic inputs by elevating membrane potentials closer to action potential firing thresholds (Ceballos, Roque & Leao, 2017; Crill, 1996).
2.1.3 Calcium channels

As noted above, the type A/B distinction depends primarily on calcium sensitive potassium channels that determine the profile of the AHP. Adding Ca\(^{2+}\) buffer to the recording pipette skewed the proportion of neurons towards type A characteristics (Eugene et al., 2007). In addition, an increase in intracellular Ca\(^{2+}\) concentrations is associated with reduced excitability (Nelson, Gittis & du Lac, 2005; Smith, Nelson & Du Lac, 2002). In addition to their effect on the AHP, Ca\(^{2+}\) channels can shape the phase of firing output. A small subset (10-15\%) of type B neurons display low-threshold spiking (LTS) activity mediated by low threshold Ca\(^{2+}\) currents activated at relatively hyperpolarised potentials (Figure 3C). These spikes can trigger rapid Na\(^{+}\) action potential firing known as burst firing and are typically seen following release from hyperpolarising current steps (Babalian et al., 1997; Serafin et al., 1991b). High-threshold Ca\(^{2+}\) channels have been observed in both type A and B neurons however their role may primarily be in shaping the action potential during development and less so during resting discharge (Sansom, Smith & Darlington, 1993).

2.2 Discharge properties

MVN neurons are spontaneously active in vivo (Newlands & Perachio, 1990b; Smith & Curthoys, 1988a; Smith & Curthoys, 1988b) and in vitro (Babalian et al., 1997; Vibert et al., 1999). In various in vitro preparations, they typically fire with a pacemaker like quality, discharging regular spikes at rates with a mean between 5-40 Hz (Darlington, Gallagher & Smith, 1995; Him et al., 2001; Ris & Godaux, 2001; Sun et al., 2002), a rate slightly lower than that seen in vivo (Figure 3E) This activity persists in the absence of synaptic input, as seen in conditions of synaptic uncoupling (Lin & Carpenter, 1993) and neurotransmitter antagonism (de Waele et al., 1993). This implies that the basic observed discharge properties are mediated largely by intrinsic membrane properties.
In vivo recordings show at least two distinct populations of neurons that can be characterised by the pattern of their spontaneous activity. A group of neurons display a very regular action potential discharge pattern and are termed tonic neurons. In contrast, a smaller group display an irregular pattern and are termed phasic- tonic or kinetic neurons (Shimazu & Precht, 1965). In vitro, this division is also seen between the MVN subtypes, such that type A neurons are typically regular with coefficients of variation of spiking activity < 0.25, while type B neurons are more irregular (Babalian et al., 1997). Regularity here appears to be positively correlated with the size of the AHP, highlighting that AHP shape may influence the sensitivity of MVN neurons to synaptic inputs.

Patch clamp recordings have further elucidated the input-output profile of MVN neurons (Figure 4). In response to graded current ramps, type B neurons display an overshoot in discharge rate that slowly plateaus to a lower baseline, while type A neurons display a more linear response (Ris et al., 2001b) (Figure 4A). When held at more hyperpolarised potentials, the response to small amplitude sinusoidal stimuli is relatively linear in both subtypes and mirrors the change in the underlying membrane potential induced (Beraneck et al., 2003; Ris et al., 2001b). The resonant frequency of type A neurons is lower than that of type B neurons (Figure 4B), suggesting that the longer AHP limits action potential production at high frequencies. However, type B neurons experience more firing rate modulation in response to such stimuli, suggesting a higher sensitivity to small membrane potential fluctuations such as those induced by synaptic currents (Beraneck et al., 2003). These characteristics suggest that type A neurons may act as low-pass filters acting to maintain

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5 This distinction is most readily seen in the whole brain preparation. Acute brain slice preparations suffer from a relative paucity of network connections which may alter the balance of inhibitory activity that influences discharge dynamics. (Camp, AJ, Callister, RJ & Brichta, AM 2006, 'Inhibitory synaptic transmission differs in mouse type A and B medial vestibular nucleus neurons in vitro', J Neurophysiol, vol. 95, no. 5, pp. 3208-18.)

6 The frequency at which the neuron is most able to convert current inputs into action potentials in a linear fashion. This frequency is different for each individual neuron.
resting activity, while type B neurons are able to encode high frequency modulations, possibly creating frequency tuned channels within the MVN (Straka et al., 2009; Straka et al., 2005).

**Figure 4** - Firing responses to graded ramp and sinusoidal current stimuli. **A Upper** Current-clamp traces in response to prolonged ramp and plateau depolarising currents in type A (left) and type B (right) neurons. **A Lower** Plots of instantaneous firing rates against time demonstrate relatively linear dynamics in type A neurons, compared to a non-linear profile with a temporary ‘overshoot’ in type B neurons. **B** Firing rate modulation observed to sinusoidal inputs before (closed circles) and after (open circles) labyrinthectomy in type A (left) and type B (right) neurons. Firing rate modulation is defined by the mean amplitude of the response divided by the magnitude of the injected current. Dashed lines indicate the median peak resonant frequency obtained for each subtype, which is higher in type B neurons following labyrinthectomy. Figures adapted from Beraneck et al. 2003.
A further demonstration that intrinsic properties dictate firing dynamics is seen in response to depolarising and hyperpolarising current steps. In response to prolonged depolarising stimuli across all MVN neurons, there is a decrement in firing rate, termed firing rate adaptation (FRA), which increases with initial firing rate (Figure 5). This feature is probably dependent on potassium conductances as lower extracellular potassium concentrations, which increase the driving force on outward currents, also increase the rate of adaptation. Upon release from hyperpolarised potentials, they display a robust increase in firing rates\(^7\) over baseline spontaneous discharge rate which progressively adapts to back to the baseline over time (Sekirnjak & du Lac, 2002) (Figure 5A). This post-inhibitory rebound firing (PRF) activity ranges along a continuum from weak to strong, where weak PRF neurons respond with an increase in firing rate of 10 spikes/sec over baseline, while strong PRF neurons show rates over 30 spikes/sec. This feature is dependent at least in part on the hyperpolarisation-activated potassium (I\(_{H}\)) current. Interestingly, these PRF and FRA are correlated, such that stronger FRA is seen in neurons with strong PRF (Figure 5B and C). The correlation of these differential properties and the previously identified subtypes based on AHP is yet to be clarified.

\(^7\) A small number of neurons show a decrement in rate following release from hyperpolarisation, however this population was not further characterised.
Figure 5 - Firing rate adaptation (FRA) and post-inhibitory rebound firing (PRF) dynamics of MVN neuron discharge. A Upper Current-clamp traces in response to 1 second long negative current steps with amplitudes large enough to induce at least 30mV of hyperpolarisation. Traces on the left indicate strong PRF, while traces on the right indicate a lack of PRF. A Lower A plot of instantaneous frequency against time.

The frequency of PRF is highest immediately following hyperpolarisation (peak PRF). B The degree of adaptation is correlated with degree of PRF. The adaptation ratio is calculated by dividing the discharge rate in the 1st 100msec following a hyperpolarising pulse by the last 100msec. C Absolute adaption varies with firing rate at stimulus onset, while adaption ration only varies in a subgroup with high PRF. Adapted from Sekirnjak and du Lac 2002.
2.3 Intrinsic plasticity

Neuronal plasticity refers to changes in the properties of neurons that are altered in response to external stimuli or changes in the local environment. The first forms of neuronal plasticity were described in the *Aplysia* sea snail (Kandel, 2001). A number of groups observed that the efficacy of synaptic transmission in a simple motor reflex circuit could either be reduced or enhanced by repetitive stimulation of a presynaptic neuron (Hughes & Tauc, 1963). These changes were observed either by delivering noxious stimuli to a different part of the body or by directly repetitively stimulating the presynaptic neuron (Castellucci et al., 1970). This demonstrated that neuronal activity could change the properties of connections at a cellular level and has been put forward as one of the neural correlates of experience-dependent phenomena such as learning and memory (Kandel, 2001). The mechanisms mediating synaptic plasticity have now been extensively investigated and we have a solid understanding of the molecular changes that occur during this process.

Electrophysiologically, synaptic plasticity manifests itself as an increase in synaptic transmission in response to strong correlated presynaptic inputs, known as long term potentiation (LTP), or a decrease in transmission, known as long term depression (LTD). For example, during LTP, repeated inputs to the presynaptic neuron generate an increase in the amplitude and frequency of excitatory post-synaptic potentials (EPSPs). However, whether an EPSP triggers action potential generation in the postsynaptic neuron depends on whether this neuron is sensitive enough to the delivered stimulus. The probability of firing and the character of the output is dependent primarily on the intrinsic properties of the neuron. These properties have been observed to be plastic in an activity-dependent manner in both normal and pathological states and the importance of this phenomenon is becoming increasingly recognised (Turrigiano, Abbott & Marder, 1994). Underlying these changes are alterations in the density and pattern of ion channel expression and intracellular ion buffers.
Often in healthy states the mechanisms that drive these processes act to maintain homeostasis (Desai, 2003), however at times can facilitate the development of aberrant behaviours in various disease states (Beck & Yaari, 2008; Wijesinghe & Camp, 2011). In the following section, I discuss some of the ion channel conductances that mediate intrinsic neuronal plasticity.

2.3.1 Potassium channels

SK channels are a family of calcium-activated potassium channels that mediate a small inward conductance. It is primarily responsible for the medium afterhyperpolarisation (mAHP), which activates rapidly and decays over a period of several hundreds of milliseconds (Faber, 2009). This time scale allows the conductance to limit the maximal firing potential and switch between tonic and burst firing in vestibular neurons (de Waele et al., 1993). Behavioural paradigms such as operant learning have been shown to change the intrinsic excitability of neurons within neuronal ensembles in a manner that is dependent on SK2 channel activity (Whitaker et al., 2017). The type of activity-dependent changes that can be induced by these channels also depend on their anatomical location. For example, SK2 modulation within the dendritic compartment has been observed to mediate a robust amplification of multiple dendritic responses to synaptic and non-synaptic tetanisation patterns in cerebellar Purkinje cells (Ohtsuki et al., 2012). Some of the molecular (Chen et al., 2016) and genetic (Meadows et al., 2016) mechanisms that may underlie these alterations have also been elucidated and provide a promising link to the pathophysiology of neurodevelopmental conditions such as autism (Shen et al., 2016). SK channels are expressed on type B MVN neurons (see Table 2), however whether they play a role in the intrinsic plasticity of these neurons is yet to be elucidated.

$I_A$, or A-type $K^+$ current, is a fast, transient current mediated by the $K_v4$ subgroup of potassium channels. The membrane potential activation range of this current is below that
required to generate spikes. Therefore, it appears to play a role in attenuating EPSPs (Ramakers & Storm, 2002) and back-propagating spikes (Hoffman et al., 1997) primarily on dendritic spines (Johnston et al., 2000). In hippocampal neurons, LTP protocols have been shown to induce internalisation of Kv4.2 channels (Kim et al., 2007). Further, increasing expression of Kv4.2 channels in neurons decreases N-methyl-D-aspartate (NMDA) receptor subunit expression and prevents the induction of LTP, while decreasing Kv4.2 channel expression enhances the ability to induce LTP (Jung, Kim & Hoffman, 2008). This bidirectional plasticity may be dependent on or modulated by protein kinase activity, as channel phosphorylation appears to shift the voltage dependence in I_A (Hoffman & Johnston, 1998) such that preventing dephosphorylation can reduce intrinsic excitability (Lin et al., 2011). A lack of control over dendritic excitability in an animal model of temporal lobe epilepsy has been related to the decreased availability of Kv4 channels (Bernard et al., 2004).

Interestingly, sustained seizures have been shown to inhibit phasic firing within thalamocortical neurons due to an increase in A-type currents, a homeostatic mechanism that aims to reduce neuronal excitability. This mechanism is blunted in transgenic mice with a mutant leucine-rich glioma-inactivated-1 (LGI1) protein (Smith et al., 2012), which has been linked to autoimmune encephalitis (Lai et al., 2010) and forms of human epilepsy (Kalachikov et al., 2002). The I_A current plays a central role in shaping the action potential of MVN neurons (see Section 2.1.1) and changes in this current may mediate intrinsic plasticity changes, particularly in the type A subtype.

Hyperpolarization-activated cyclic nucleotide-gated (HCN) potassium channels mediate the so-called ‘H’ current (I_H). It is a slow conductance active at resting membrane potential which does not inactivate and is augmented by hyperpolarisation (He et al., 2014). The current acts to reduce EPSP summation (Berger, Larkum & Luscher, 2001; Williams & Stuart, 2000) and tetanic stimulation has been shown to increase the hyperpolarisation amplitude required for activation. Increased HCN conductances have been observed in dentate granule cells from human patients with temporal lobe epilepsy, suggesting a homeostatic form of intrinsic
plasticity which acts to reduce excitability (Stegen et al., 2012). Similar homeostatic forms of intrinsic plasticity have also been observed in response to hypoxia and ischaemia, where Kv2.1 channel expression and dephosphorylation increased to suppress excitability and confer neuroprotection (Misonou et al., 2005). Kv2.1 channel alterations have also been observed in a commonly used transgenic mouse model of Alzheimer's disease, in which functional channel expression is reduced, increasing neuronal excitability (Frazzini et al., 2016).

2.3.2 Sodium channels

The most important of the nine subtypes of voltage-gated sodium channels is the Na\(_{1.6}\) channel, which is expressed abundantly at the axon initial segment (Royeck et al., 2008). The features of this current often determine the action potential threshold of a neuron and modulation of this conductance has significant implications for intrinsic excitability (Child & Benarroch, 2014; Dumenieu et al., 2017). Classical LTP induces changes intrinsic excitability in CA1 hippocampal neurons by shifting the activation curve of sodium channels towards more hyperpolarised potentials, reducing spike thresholds (Xu et al., 2005). In contrast, abnormal activity-dependent facilitation, a phenomenon known as kindling, increases Na\(_{1.6}\) conductances persistently in CA3 neurons assisting in epileptogenesis (Blumenfeld et al., 2009). This deleterious form of intrinsic plasticity may play a role in normal hippocampal function as well as certain forms of severe epilepsy (Barker et al., 2017; Hargus et al., 2013; Zhu et al., 2016) and encephalopathy (Lopez-Santiago et al., 2017; Ottolini et al., 2017) and has significant implications for potential therapeutic interventions (Mantegazza et al., 2010; Marini & Mantegazza, 2010).

Sensory and behavioural stimuli are also potent triggers for intrinsic plasticity modifications mediated by sodium currents. Cocaine-induced changes in intrinsic plasticity in circuits mediating addictive behaviours are dependent on a slowly inactivating sodium current (Kamii et al., 2015). Persistent visual stimulation increases the excitability of optic tectal neurons of
the tadpole through an increase in sodium currents (Aizenman et al., 2003). These changes can be mediated by translational repressor proteins such that bind ion channel protein subunits and reduce their expression (Driscoll et al., 2013). These observations highlight the variety of channels and the mechanisms by which they can alter intrinsic neuronal properties. Such changes are likely to contribute to the plasticity observed in MVN neurons following vestibular lesions and the evidence for such changes will be the focus of this thesis.

2.3.3 Homeostatic mechanisms

Intrinsic plasticity can act to protect the status quo that maintains activity in neuronal circuits. This is termed homeostatic plasticity. In the vestibular system, the tuning characteristics of vestibular neurons must undergo changes during alterations in head structure during development and in the face of conflicts from other sensory modalities to maintain oculomotor and spinal reflexes. In vitro studies suggest that these forms of plasticity may be dependent on the intrinsic properties of vestibular neurons. For example, the subtype of MVN neurons may change in response to alterations in synaptic network activity. Experiments by Camp and colleagues studied the effect of chronic deprivation of inhibitory transmission in the vestibular nuclei using transgenic mice with dysfunctional glycine receptor mutations. They found that the proportion of type C (see section 1.4.2 above) neurons is higher in mutants than in wildtype animals. Further, these neurons appear to have lower firing response gains compared to type B neurons\(^8\), suggestive of a protective reduction in neuronal excitability (Camp et al., 2010). This was proposed to be a shift from a type B to C profile, a mechanism where intrinsic properties themselves can mediate protective changes in neural circuits. One other clear demonstration of homeostasis in the vestibular system is an activity-dependent recovery of vestibular function following damage to the labyrinth or vestibular nerve termed vestibular compensation.

\(^8\) Only type B neurons receive glycinergic inputs. See Table 2 for details.
3. Vestibular Compensation

If either of the vestibular organs malfunctions, there is a period of disequilibrium which can be prohibitively disabling. This is evidenced by reduced workplace productivity, increased healthcare professional visits and inpatient hospital stays in those suffering from common peripheral vestibular disorders (Benecke et al., 2013; Neuhauser, 2016). Fortunately, the perceptual disturbance and its behavioural consequences are short lived and there appears to be a spontaneous recovery of vestibular function. This phenomenon of resolution is termed vestibular compensation and the mechanisms behind this apparent recovery of function have been debated for a number of years (Beraneck & Idoux, 2012; Cullen et al., 2009; Curthoys & Halmagyi, 1992; Curthoys & Halmagyi, 1995; Curthoys & Halmagyi, 1999; Darlington, Dutia & Smith, 2002; Darlington & Smith, 1996; Dutia, 2010; Gliddon, Darlington & Smith, 2005; Mathews, Camp & Murray, 2017; McCall & Yates, 2011; Peusner et al., 2009; Yates & Miller, 2009). The methods of treatment and rehabilitation following recovery from vestibular disorders aim to manipulate and enhance the process of compensation (Balaban, Hoffer & Gottshall, 2012; Deveze et al., 2014; Halmagyi, Weber & Curthoys, 2010; Lacour et al., 2009; Lacour, Helmchen & Vidal, 2016; Lacour & Tighilet, 2010; Lewis, 2016). Therefore, understanding the mechanisms that govern this process is of paramount importance.

This phenomenon can be reliably induced experimentally. Animals subjected to peripheral unilateral vestibular lesions, either by labyrinthectomy or vestibular neurectomy, suffer from profound behavioural changes such as postural instability, locomotor and oculomotor deficits. Electrophysiologically, this manifests as a progressive rebalancing of activity between the paired vestibular nuclei (Fetter, 2016). Below, I will review the behavioural manifestations

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9 In a minority of patients, this process does not completely ameliorate the neurological deficits sustained following vestibular damage. Further, this process is dependent on the presence of some residual vestibular function and may not occur in cases of bilateral vestibular failure (e.g. Aminoglycoside ototoxicity).
of vestibular dysfunction and recovery, the physiological correlates of compensation and possible cellular mechanisms underlying observed changes.

3.1 Behavioural recovery

3.1.1 Static deficits

Immediately following unilateral vestibular deafferentation (UVD), there are a number of oculomotor and postural deficits which can be seen in human subjects (Fetter, 2016) and induced experimentally (Straka, Zwergal & Cullen, 2016). These deficits can arbitrarily be defined as static (present when there is no applied stimulus apart from gravity) or dynamic (revealed by movement). Static deficits observed in humans include the symptom of vertigo, a postural bias towards the lesioned side, spontaneous nystagmus with a slow phase to the affected side and the ocular tilt reaction. A couple of days after UVD, the intensity of these deficits abates, such that they may only be revealed in certain circumstances (Figure 6). For example, spontaneous nystagmus (SN) typically disappears after one day in guinea pigs (Figure 6A) and rodents (Curthoys, Smith & Darlington, 1988; Hamann & Lannou, 1987), around 2 days in cats and monkeys (Fetter & Zee, 1988; Maioli & Precht, 1985; Maioli, Precht & Ried, 1983) and up to 1 week in humans (Cass, Kartush & Graham, 1992; Pulec, 1974). Static deficits have been shown to recover in the absence of visual (Fetter, Zee & Proctor, 1988) and cerebellar (Haddad, Friendlich & Robinson, 1977) inputs, consistent with the idea that SN is a purely vestibular phenomenon. However, these extra-vestibular regions have been shown to influence the recovery process (Johnston, Seckl & Dutia, 2002; Nelson et al., 2017) in a way that may modulate the degree or speed of compensation. Further, SN

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10 The ocular tilt reaction consists of three components – a persistent head tilt towards the lesioned side, a conjugate ocular torsion away from the pre-lesion ocular torsional position and skew deviation (vertical misalignment of eyes in the orbits) whereby the eye on the affected side sits lower in the orbit compared to its partner. See Halmagyi, GM, Curthoys, IS, Brandt, T & Dieterich, M 1991, 'Ocular tilt reaction: clinical sign of vestibular lesion', Acta Otolaryngol Suppl, vol. 481, pp. 47-50.
may still be detected in the dark (which negates ocular fixation), suggesting that the extent of this recovery may never be complete (Fisch, 1973).

Figure 6 - Static deficits and physiological changes in vivo during vestibular compensation. A Spontaneous nystagmus observed at different time points following unilateral labyrinthectomy in the guinea pig. B Changes in resting activity recorded in type I neurons following unilateral labyrinthectomy in the guinea pig. Figures adapted from Curthoys and Halmagyi 1995.
3.1.2 Dynamic deficits

In contrast, dynamic deficits include impairments of dynamic postural control (or ataxia), scaling of the gain of the vestibular ocular reflex (VOR) and alterations the degree of response to caloric stimulation. Dynamic changes appear to follow a longer time course of recovery and there may be permanent deficits in specific aspects of vestibular function (Curthoys, 2000). For example, for a given angular head acceleration, the speed of the VOR diminishes following UVD, indicating a reduction in the gain of the reflex (Figure 7). In the next 2 post-operative days, the gain increases, however does not reach pre-operative values (Fetter & Zee, 1988). Further, around the yaw axis, this reduction in VOR gain is more apparent towards the lesioned side (Halmagyi et al., 1990; Paige, 1989). The reduction and asymmetry is persistent over a number of months and has been seen in most studied models (Baarsma & Collewijn, 1975; Baloh et al., 1984; Cass & Goshgarian, 1991; Chapuis et al., 1992; Olson & Wolfe, 1984; Takahashi, Uemura & Fujishiro, 1984), suggesting incomplete recovery of this particular vestibular function. Similarly, asymmetric ataxia recovers over time courses slightly longer than a month (Baloh et al., 1984; Black & Nashner, 1984; Black et al., 1989; Igarashi et al., 1970; Igarashi et al., 1978; Igarashi et al., 1979; Jensen, 1979a; Jensen, 1979b), but may remain impaired for much longer.
**Figure 7** – Dynamic changes in VOR gain before (left) and after (right) unilateral labyrinthectomy. **A** Eye and head velocities plotted as a function of time during angular rotations **B** Eye velocity plotted as a function of head velocity to indicate the gain of the VOR. At high head velocities, VOR gain is significantly reduced.

Figure adapted from Curthoys and Halmagyi 1995.
3.2 Mechanisms of compensation

The recovery of these behaviours could be due to either a restoration of vestibular function, or a substitution of analogous non-vestibular sensory information. It has been argued that static changes may be partly due to restoration, while dynamic changes may be due primarily to substitution (Curthoys & Halmagyi, 1995). Early physiological changes appear to be insufficient to reconstitute dynamic vestibular function, which remains asymmetrical and ineffective (Gilchrist et al., 1998) without extra-vestibular substitutions (Curthoys, 2000; Halmagyi et al., 1990). However, the basic function of the VOR is a useful tool to understand the physiological changes that occur during vestibular compensation to restore static deficits. The VOR is dependent on the equal balance of activity between the paired vestibular nuclei, as head movement is encoded by changes in tonic afferent discharge depending on the direction of movement. Therefore, one would expect that for vestibular function to be restored to normal, discharge in the deafferented nucleus would remain tonically active, even if not at baseline levels.

3.2.1 Rebalancing act

Immediately following UVD, in vivo recordings demonstrate a decrease in the proportion of spontaneously active type I neurons, as well as a reduction in their spontaneous discharge rate (Newlands & Perachio, 1990a; Newlands & Perachio, 1990b; Ried, Maioli & Precht, 1984; Smith & Curthoys, 1988b). This is accompanied by an increase in the discharge of type I neurons in the contralateral nucleus (Markham, 1968; Markham, Yagi & Curthoys, 1977; Smith & Curthoys, 1988a), explained by a loss of commissural inhibition from the lesioned side. However, within hours to days for most studied models, the number of recordable type I neurons increases and their discharge rate increases (Figure 6B). This occurs despite the presence of inhibitory projections from the intact side, as spontaneous activity is observed.
even following transection of commissural fibres in the brainstem and cerebellum (Smith & Curthoys, 1988b) and following bilateral labyrinthectomy (Ris & Godaux, 1998). This re-emergence of activity parallels the amelioration of behavioural symptoms such as spontaneous nystagmus (Ris et al., 1995; Smith, Darlington & Curthoys, 1986; Yagi & Markham, 1984). These observations suggest that despite being deprived of a large amount of afferent input, MVN neurons rebalance spontaneous activity to such a level that allows for the re-emergence of at least basic vestibular function.

3.2.2 Neurochemical and synaptic changes

What drives the return in spontaneous neuronal activity? The vestibular nerve does not undergo any substantial recovery following neurectomy, such that ipsilateral afferent vestibular inputs to central vestibular neurons are permanently abolished. Bilateral UVD results in a smaller reduction in spontaneous activity when compared to the ipsilateral nucleus in unilateral UVD, suggesting that commissural inputs do not account for these changes either. There are however some changes in synaptic and neurotransmitter sensitivities that may contribute. There does appear to be a substantial reorganisation of synaptic inputs to vestibular neurons following deafferentation (Goto, Straka & Dieringer, 2000; Goto, Straka & Dieringer, 2001), however this appears outside of the time period during which early changes are seen. There are also a number of changes in protein expression and phosphorylation (Kerr et al., 2000; Sansom et al., 1997), the expression of early gene proteins (Horii et al., 2003; Kitahara et al., 2007; Kitahara et al., 2012; Kitahara et al., 2002; Kitahara et al., 1995), neurotrophic factors (Bolger et al., 1999; Smith et al., 1998) and stress related proteins (Alice et al., 1998; Guilding, Seckl & Dutia, 2004) following labyrinthectomy, however their causality in the return of neuronal activity is unclear (Darlington & Smith, 2000).
3.2.3 The intrinsic mechanism hypothesis

The intrinsic pacemaker activity observed in MVN neurons in vitro under normal conditions seems to remain following labyrinthectomy (Darlington, Dutia & Smith, 2002; Dutia, 2010; Straka et al., 2005). In particular, this activity persists in the context of synaptic uncoupling and antagonism in acute brain slices in vitro (Figure 8). This growing body of evidence suggests that external influences may be insufficient to explain the return of spontaneous neural activity, leading to the development of the intrinsic mechanism hypothesis (Darlington & Smith, 1996). This hypothesis posits that the mechanism by which vestibular neuron activity returns may be intrinsic to the neuron. In other words, at least part of the process of vestibular compensation is a manifestation of experience dependent intrinsic plasticity. The evidence behind this hypothesis will be the focus of this thesis and the systematic review presented in Chapter IV.
**Figure 8** - Changes in intrinsic membrane properties during vestibular compensation. **A** The number of spontaneously active neurons is decreased in the presence of synaptic antagonists. The number of active neurons increases 2 days, and lasts for at least 1 week, following labyrinthectomy. **B** The spontaneous discharge rates in neurons before (grey) and after (black) labyrinthectomy increase immediately. **C** Firing rate potentiation (FRP) following a long hyperpolarising pulse. Dots indicate spontaneous firing rates. **D** The input-output function for a single neuron before (open circles) and after (closed circles) hyperpolarisation. This demonstrates that FRP is evident as an increase in spontaneous discharge and gain. Figure **A** adapted from Ris et al. 2001. Figure **B** adapted from Cameron et al. 1997. Figure **C** and **D** adapted from Nelson et al. 2017.
III – AIMS

The thesis that follows is motivated by gaps in our knowledge of the mechanisms that govern the process of vestibular compensation. I am most interested in the role that intrinsic plasticity plays in this process. Therefore, I aim to:

1. Survey the evidence behind the intrinsic mechanism hypothesis of vestibular compensation. I will use the systematic review methodology to comprehensively explore the basic experimental data which assess acute changes in intrinsic membrane properties of MVN neurons following unilateral labyrinthectomy.

2. Quantify the magnitude of intrinsic plasticity changes seen following UVD in vitro. I will use the method of meta-analysis to pool data across studies to estimate a summary effect based on this data set.

3. Demonstrate the utility of systematic review and meta-analysis techniques in pre-clinical or experimental work. I will develop methods of assessing the methodological quality of such work, in a similar fashion to techniques that have been applied successfully in human trial research.

4. Determine the suitability of UVD as a model of lesion-induced intrinsic plasticity.
A systematic review integrates different sources and types of evidence to generate a summary estimate of the effect of a particular intervention or technology (Gough, Oliver & Thomas, 2017). It derives its evidentiary power over the commonly used narrative review from its transparent and rigid methodology, designed to critically appraise included data and reduce sources of systematic bias. In particular, many narrative reviews suffer from a number of potential biases that risk polluting the quality of the scientific conclusions. These problems include:

- The lack of an explicit statement of a research question as the subject of the review. Therefore, irrelevant sources of evidence may be included inappropriately
- An incomplete attempt to identify all the relevant literature adequately
- No clear definition of the scope of the review using explicit inclusion and exclusion criteria
- No consistent assessment of the quality, precision or validity of the experimental data reproduced as evidence
- Conduct of reviews by authors with a strong professional interest in the field, possibly skewing the presentation of their own research over alternative viewpoints or contradictory data

In contrast, systematic reviews set out to answer a pre-specified research question, determine eligibility for including evidence based on explicit inclusion and exclusion criteria and assess the quality of the evidence based on the methods used to obtain data. The results of the review are then reported using a transparent template to avoid bias. Because of this rigour, it is held to be one of the highest standards of evidence in medicine (Cook, Mulrow &
Haynes, 1997). Therefore, it has been used widely to assist progress in vast areas of research (Petticrew, 2001), including medicine, allied health and psychology to name a few.

Despite this high standard of evidence, systematic reviews have only rarely been conducted in the analysis of primary data obtained from laboratory-based research studies. However, it is becoming increasingly recognised that this form of analysis may play a strong role in improving the quality of evidence used to guide the advancement of laboratory and pre-clinical research (de Vries et al., 2014). In addition to the descriptive qualitative review, of particular interest is the role of meta-analysis, which allows the pooling of quantitative data to compare the effects of a particular intervention across studies. This is performed using a complex statistical method that combines the effect sizes from studies to generate an average estimate of effect (Cheung et al., 2012). It has the advantage of generating a pooled estimate across different data sets that improves the statistical power behind a particular scientific conclusion. Further, it provides a convenient method of determining the accuracy and precision of studies regarding the question at hand.

To survey the evidence behind the intrinsic mechanism hypothesis, I structured the following research question: “What are the effects of unilateral vestibular deafferentation on the intrinsic membrane properties of medial vestibular nucleus neurons during the acute period of vestibular compensation”. Expressed in the PICO\textsuperscript{11} format:

\begin{itemize}
  \item \textbf{P} – medial vestibular nucleus neurons
  \item \textbf{I} – unilateral vestibular damage
  \item \textbf{C} – normal subjects
  \item \textbf{O} – changes in characteristics of intrinsic membrane properties
\end{itemize}

\textsuperscript{11} Population, Intervention, Comparator/Control, Outcome
1. Methods

To reduce the risk of bias, the Cochrane Collaboration guidelines were used to perform literature searches for the systematic review (Higgins & Green, 2011). The results of the systematic review are reported using criteria adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009).

1.1 Definitions

*Intrinsic excitability* refers to the neuronal activity that is determined by structural features of the cell membrane, ion channel expression and intracellular buffering proteins that control concentrations of ions. I will restrict my analysis to active membrane properties that shape incoming inputs and maintain activity in the absence of synaptic input. It can be measured as the rate of spontaneous firing, or by the response to graded current stimuli (also known as the gain).

*Vestibular compensation* is the gradual restoration of vestibular function following damage to the vestibular system. In animal models, the behaviours observed are changes in posturing, spontaneous nystagmus and abnormal turning and rolling behaviours. This may be acute (less than 2 weeks) or chronic (greater than 2 weeks)\(^\text{12}\). The model widely used to study vestibular compensation is UVD.

1.2 Inclusion and exclusion criteria

\(^\text{12}\) This distinction is made as static deficits tend to resolve by 1 week, while chronic deficits persist beyond this time period. By choosing 2 weeks as the period for acute compensation, this allows for some degree of variability.
Studies were included if they presented original research examining intrinsic neuronal properties during the process of vestibular compensation. Reviews, abstracts, conference proceedings, commentaries and non-English articles were excluded. Analysis was restricted to adult (i.e. mature) animal models as changes seen in younger animals may represent developmental modifications as opposed to plastic changes that may occur at maturity. Vestibular lesions could be performed by any method, including physical or chemical disruption of the vestibular labyrinth, vestibular nerve transection or focal ototoxic drug administration. From herein UVD will refer to these lesions. Ideally, the success of the deafferentation procedure was confirmed with behavioural or anatomical observations, however this was not a prerequisite for inclusion. The effects of chronic lesions (>2 weeks) were excluded, as changes after this time period may not reflect the early behavioural recovery of static deficits. Also, alternative complex network processes are believed to govern this chronic period of compensation (Beraneck & Idoux, 2012; Darlington, Dutia & Smith, 2002). Intrinsic properties could be studied using direct intracellular patch-clamp or extracellular whole-cell recordings of visually identified MVN neurons in vitro. Studies that inferred intrinsic properties through protein expression changes of ion channels or intracellular electrolyte buffers were also included.

For the meta-analysis, studies were restricted to intracellular patch clamp recordings taken from MVN neurons. Extracellular whole cell recordings were also included if, within the study itself, differences between intracellular recordings were justified to be similar. Studies presenting gain measurements were included if, within the presented data, information regarding the raw spontaneous firing rates was explicit or able to be easily calculated. Studies which performed electrophysiological recordings but did not appropriately account for blockade of synaptic currents were excluded\(^\text{13}\).

\(^{13}\) This could be achieved either using a high magnesium, low calcium intracellular electrode solution or an external bath solution containing an appropriately diverse cocktail of specific synaptic receptor antagonists
| Included | Excluded |
|----------|----------|
| Population | MVN neurons | Other vestibular nuclei |
| Intervention | Labyrinthectomy, Vestibular nerve transection | Chronic lesions (more than 2 weeks) |
| Outcome | Spontaneous discharge rates, Change in gain, Ion channel expression patterns | Synaptic modifications |
| Study designs | Original research, In vitro preparations | Reviews, non-English articles, Abstracts and conference proceedings, In vivo preparations |

**Table 3 - Inclusion and exclusion criteria for the systematic review**

### 1.3 Outcome measures

The primary outcome measure for this work was the raw mean difference in spontaneous discharge rate of MVN neurons following vestibular labyrinthectomy. Secondary outcomes included changes in MVN neuronal gain, variation in ion channel expression on the MVN neuron cell membrane and modulation of sensitivity to neurotransmitters.

### 1.4 Literature searches

In order to compile a comprehensive database of studies, I generated a wide range of terms with appropriate synonyms (listed in Appendix 2) to capture any relevant data. The following electronic databases were searched for relevant studies relating to the study question:

- Medline (OvidSP) - 01/01/1946 - 01/10/2017
- Pubmed (Internet) – up to 01/10/2017
- Embase (Internet) – up to 01/10/2017
Searches were not limited by publication date, language or publication status at the time of search. The references within all included studies or narrative reviews were hand searched to identify any further studies that may have satisfied the inclusion criteria.

1.5 Selection of studies and data extraction

Titles and abstracts from the final search were pooled into an Endnote\textsuperscript{(R)} database and duplicates were removed. Each reference was subjected to the above inclusion criteria by two assessors independently and any conflicts were mediated through discussion. Following this, the full texts of articles were obtained and assessed rigorously to ensure they satisfied the inclusion criteria. At this stage, articles re-presenting previously published data were removed. Studies were identified by the surname of the first author and the year of publication.

1.6 Quality assessment

Due to the recognition of the value of the systematic review, a number of tools have been developed to assist their conduct in basic animal research. These include collaborative groups such as the CAMARADES\textsuperscript{14} collaboration, the SYRCLE risk of bias tool (Hooijmans et al., 2014), the ARRIVE guidelines for reporting animal research (Kilkenny et al., 2010)\textsuperscript{15} and examples of methods of assessing validity and precision (Collins, Ross & Lang, 2017).

\textsuperscript{14} Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies. See http://www.dcn.ed.ac.uk/camarades/ default.htm.

\textsuperscript{15} This is analogous to the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) criteria used in reporting reviews in medical fields. Moher, D, Liberati, A, Tetzlaff, J, Altman, DG & Group, P 2009, 'Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement', BMJ, vol. 339, pp. b2535.
Each study in this review was assessed for scientific precision, criterion validity (of the model) and risk of bias. The risk of bias for each study was assessed using the SYRCLE tool which has been validated for use in animal studies (Hooijmans et al., 2014). For the assessment of validity and prevision, published tools were not strictly applicable. Therefore, I developed a novel set of criteria to assess these methodological domains. For each included study, questions were used by the reviewers to assign a rating based on how well the criterion was satisfied. If the answer was unequivocal, the relevant criterion was scored either yes or no. If it was unclear, then the criterion was scored unclear. Often the last rating was assigned due to a lack of explicit statement of necessary detail to answer the question, or ambiguous and vague descriptions within the published report. The responses to questions were integrated to establish an overall rating for each domain.

### 1.7 Measures of effect

The primary outcome was measured as the raw mean difference in spontaneous discharge rate between the experimental group (UVD) and the control group (either sham-operated or unoperated). This measure was used as the reported mean differences in studies were presented in a scale that was directly comparable between studies (spikes per second). Raw mean difference was calculated using the equation:

\[
y_{RMD} = \bar{X}_E - \bar{X}_C
\]

where \( y_{RMD} \) is the raw mean difference (referred to as the effect size), \( \bar{X}_E \) is the sample mean for the experimental group and \( \bar{X}_C \) is the sample mean for the control group. Outcomes were weighted using a pooled variance, which was calculated from the reported standard error of the mean (SEM) for each experiment. Pooled variance was calculated using the equation:
where \( v \) is the approximate sampling variance, \( s^2_{pooled} \) is the pooled sampling variance across both experimental and control groups and \( n_E \) and \( n_C \) the number of recorded neurons in the experimental and control groups respectively. \( s^2_{pooled} \) is calculated from the equation:

\[
v_{RMD} = s^2_{pooled} \left( \frac{1}{n_E} + \frac{1}{n_C} \right)
\]

The aim of the review is to determine whether UVD has an effect on the MVN neuron population as a whole. To determine an estimate of the mean effect across a population of all possible studies (\( \mu \)), I performed a meta-analysis of the data manually in Microsoft Excel® using a random effects model. When pooling data from multiple experiments, the random effects model assumes that the observed effect in each experiment (\( y \)) is made up of the true effect in that study and some sampling error, which is dependent on a number of factors such as study design and execution. For example, in a pool of experiments, the model assumes that in the \( i^{th} \) experiment:

\[
\theta_i = \mu + \delta_i
\]

where \( \theta_i \) is the true effect in the \( i^{th} \) study, \( \mu \) is the mean effect across a population of all possible studies and \( \delta_i \) is the deviation of the \( i^{th} \) study’s effect from the population mean. Here, the studies that met the inclusion criteria are considered to be a sample from the population of possible evaluations of the effect of UVD on MVN neurons. From this, the mean effect (\( \mu \)) and population variance (\( \Delta^2 \)), which is roughly equivalent to the variance of \( \delta \), can be estimated. Since this estimate is made across studies, there may be variation in the
pool of experiments, termed heterogeneity. The test statistic (Q) can be used to assess the degree of heterogeneity between studies and incorporates the observed treatment effects and an estimate of treatment effect weighted by the observed variance. Q is calculated using the equation:

\[ Q = \sum_{i=1}^{k} w_i(y_i - \bar{y}_w)^2 \]

where \( k \) is the number of observations or studies, \( y_i \) is the \( i^{th} \) observation of the effect of UVD, \( w_i \) is the inverse of the \( i^{th} \) sampling variance:

\[ w_i = \frac{1}{v_{RMD}} \]

and \( \bar{y}_w \) is weighted estimator of treatment effect:

\[ \bar{y}_w = \frac{\sum_i w_i y_i}{\sum_i w_i} \]

The test statistic Q approximates a \( \chi^2 \) statistic with \( k-1 \) degrees of freedom (DerSimonian & Laird, 1986) and can be used to test the null hypothesis \( H_0: \Lambda^2 = 0 \). If \( \Lambda^2 \neq 0 \), Q can be used as an estimate of \( \Lambda^2 \), to yield a new weighted estimator \( w^* \) that accounts for the variability in the population of studies. \( w^* \) is calculated using the equation:

\[ w_i^* = \frac{1}{w_i^{-1} + \Delta_{w}^2} \]
where $\Delta^2_w$ is given by:

$$\Delta^2_w = \frac{Q - (k - 1)}{\sum_i w_i - \sum_i w_i^2 / \sum_i w_i}$$

This new weight is used to calculate an estimate of the average effect ($\mu_w$):

$$\mu_w = \frac{\sum_i w_i^* y_i}{\sum_i w_i^*}$$

and its standard error:

$$s.e. (\mu_w) = \sqrt{\frac{1}{\sum_i w_i^*}}$$

Since some studies distinguished between neuron subtypes and anatomical location, the random effects model was used to account for study specific effects (which are accounted for by the additional random effects variable) and improve the generalisability of the conclusions of the analysis. Confidence intervals (set at 95%) were calculated for each outcome measure and the estimate of the average effect $\mu_w$. Cohen’s D statistics were calculated as a further indication of the magnitude of the effect size (Cohen, 1992). In addition to $Q$, heterogeneity was estimated using the $H$ statistic which describes the relative excess of $Q$ over its degrees of freedom (Higgins & Thompson, 2002) and is calculated by:

$$H^2 = \frac{Q}{k - 1}$$
Further, the inconsistency, $I^2$, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance (Higgins et al., 2003) was calculated by:

$$I^2 = \frac{Q - (k - 1)}{Q}$$
2. Search Results

A search of the published literature yielded 130 references. This was narrowed to 67 references after pooling and elimination of duplicates. Of these, 15 reviews and 5 references not available in English were excluded, leaving 47 relevant references. The abstracts of these references were screened and subjected to pre-specified inclusion and exclusion criteria (see Table 3 in Methods above for details), leaving 22 references relevant to the posed review question. After critiquing the full text (and supplementary materials when available) of each of the remaining references, 5 more studies were excluded, leaving 17 references which were included in the final systematic review. Of these, 6 studies had data that was presented in sufficient detail to be comparable between studies and therefore suitable for meta-analysis (Figure 9).
Many of the included studies present data from multiple experiments. Details relevant to the question of the current thesis are presented below. Asterisked studies were included in the meta-analysis. Details of included studies have also been tabulated with notes used during the systematic review process (see Appendix 1).

2.1 Included studies

**de Waele 1994** used *in situ* hybridisation methods to investigate changes in the relative expression of NMDA and metabotropic glutamate receptors in rat vestibular nuclei before and after UVD. They measured labelling of receptors 5 hours, 3 days and 3 weeks following the lesion and found no significant changes in expression of either channel, except for possibly a weak increase in NMDA receptor expression 5 hours after the lesion.

**Cameron 1997 (*)** performed unilateral labyrinthectomies using surgical disruption and 100% ethanol injections in a rodent model. Animal behaviours were observed following the lesion to confirm the success of the operation. They sacrificed the animals at various time points (4, 6, 24 and 48 hours post procedure) and conducted electrophysiological recordings from acute horizontal brain slices. Slices were bisected to separate the paired vestibular nuclei from their commissural projections. The control was a sham-operated animal, in which the horizontal canal and inner ear were kept intact. The mean resting discharge rate of visually identified MVN neurons was reported. These are presumed to be extracellular whole cell recordings however this is not stated in the report. The authors found that MVN neurons of the ipsilesional nucleus had a significantly higher discharge rate than equivalent cells in the
control group. This effect appeared to be present only at 4, 6 and 24 hours post UVD, not at 2 or 48 hours. Further, it was anatomically restricted to neurons in the rostral third of the nucleus. This was the first report to explicitly examine the time course of acute changes following UVD, reproducing an effect that had been reported *in vitro* in a mixture of acutely and chronically lesioned animals (see Smith 1992 in Excluded studies section below). They suggested that this increase served to counteract the disfacilitation of deafferentation and the increased inhibition from contralateral commissural projections.

**Cameron 1999 (*)** explored the role of stress in vestibular compensation. They studied whether changes in spontaneous firing observed in Cameron 1997 would be altered by: a) a lack of behavioural experience of disequilibrium following UVD or, b) administration of a synthetic glucocorticoid agonist or antagonist. They repeated the experiments performed by Cameron 1997 (i.e. unilateral labyrinthectomy and a sham-operated control in a rodent model) for the purpose of a control. For the first experiment (a) they performed unilateral labyrinthectomies, maintained anaesthesia for 4 or 6 hours following the procedure and then sacrificed the animals without withdrawing sedation. For the second (b) they administered intraperitoneal dexamethasone (or spironolactone or RU38486 as an antagonist) 30 minutes prior to and 2 hours following the operation. For all experimental groups, mean resting discharge rates were recorded using single unit extracellular recordings. They reported that: a) maintaining anaesthesia following labyrinthectomy prevented increases in spontaneous firing, however b) administration of dexamethasone restored the increase in spontaneous firing in these same animals. The control experiment data was used in the meta-analysis.

**Vibert 1999** studied the mechanisms behind ‘Bechterew’s phenomenon’, a postural and oculomotor syndrome which arises when a second vestibular lesion is made following compensation from labyrinthectomy of the opposite side. Using field potential recordings in whole brain preparations, they demonstrated an imbalance between the bilateral MVN’s, such that the initially lesioned, compensated side had a higher resting discharge rate.
Unfortunately, most data (particularly spontaneous discharge rates) was presented graphically and therefore numerical data could not be extracted from the published work with sufficient precision to be included in the meta-analysis.

**Yamanaka 2000 (*)** studied the effects of GABA inhibition on rat vestibular nuclei during vestibular compensation following labyrinthectomy. Consistent with their own previous work, they demonstrated an increase in spontaneous discharge rate ipsilateral to the lesion, restricted to rostral neurons within the MVN. In addition, this subset of neurons was less responsive to both muscimol and baclofen (GABA$_A$ and GABA$_B$ agonists respectively), compared to caudal cells which were significantly more responsive to muscimol. These changes were not observed in animals that had undergone bilateral vestibular lesions, suggesting the deafferentation procedure itself was not responsible for the differences in sensitivity to inhibition.

**Him 2001 (*)** performed labyrinthectomies in a rat model and examined discharge rates after 3 and 7 days of compensation. They furthered previous analyses by looking at the differences between electrophysiologically defined subtypes of MVN neurons using the patch clamp method (see Table 2 on MVN neuron classification). They reported that the increase in discharge rates was restricted to the type B subtype of MVN neurons. In this subset, the action potential amplitudes and membrane potentials were higher. Further, the relative proportion of type B LTS neurons increased after compensation, however their spontaneous discharge rate was no higher than control. This was the first experimental evidence for a differential change in intrinsic properties between subtypes of MVN neurons.

**Johnston 2001 (*)** studied the effect of MVN neuron sensitivity to the inhibitory neurotransmitter GABA following UVD. Prior to drug delivery, they reported an increase in spontaneous discharge rate on the ipsilesional side following deafferentation. Immediately following UVD, sensitivity to GABA mediated by the fast GABA$_A$ and the slow GABA$_B$
receptors were downregulated. However, after 1 week, the responsiveness to GABA$_A$ returned but remained downregulated to GABA$_B$.

**Ris 2001** (*) studied the effect of neurotransmitter blockade on the recovery of MVN neuron activity 2 and 7 days following labyrinthectomy in a guinea pig model. This method was in contradiction to other studies which use a low calcium-high magnesium bath to attempt to prevent synaptic transmission. They reported that the number of spontaneously active neurons increased following labyrinthectomy at 7 days. Further, their spontaneous discharge rate also increased at both 2 and 7 days when compared to a normal control under the same conditions of synaptic blockade.

**Johnston 2002** investigated the role of the cerebellar flocculus in the process of vestibular compensation in a rodent model. They demonstrated that flocculectomy abolished the increase in spontaneous discharge rate observed in previous studies, suggesting this process of recovery may be dependent on the cerebellum. Results from this study were presented graphically and it was not possible to extract numerical data from the published plots with sufficient precision. Therefore, data from this study was not included in the meta-analysis.

**Ris 2002** examined the firing response to different profiles of injected currents using intracellular recordings in guinea pigs 7 days following UVD. After applying a hyperpolarising current to abolish spontaneous discharge, steps of square wave currents or ramps with increasing amplitudes of current followed by long plateaus were injected. In response to square wave currents, gain (discharge rate as a function of injected current amplitude) was unchanged following UVD. In contrast, gain was increased in response to ramp (or rapidly changing) current stimuli, most prominently in type B neurons.

**Patko 2003** investigated whether unilateral labyrinthectomy or facial nerve transection induced changes in sodium and calcium-activated potassium channel expression in the MVN.
They examined the mRNA expression of three subunits of voltage gated sodium channels and three subunits of small conductance calcium activated potassium (SK) channels 1, 3, 8 and 30 days after labyrinthectomy using in situ hybridisation in brainstem slices. They reported that there was no evidence to suggest changes in the abundance of these channels to explain the changes in excitability observed during compensation.

**Ris 2003** examined whether there was a change in the discharge profile of MVN neurons by performing intracellular recordings in guinea pigs 7 days following unilateral labyrinthectomy. They found that the proportion of type B neurons was increased following compensation. Further, they also report an increase in low threshold spiking type activity in both type A and B neurons. Interestingly, this was not associated with a significant change in the immunolabelling of protein subunits of T-type calcium channels.

**Eleore 2004** searched for changes in the expression of glycine receptors using in situ hybridisation at various time points up to 60 days following unilateral labyrinthectomy. They reported that there was no observable asymmetry, using both immunofluorescence and autoradiography, between the ipsi- and contralesional sides following labyrinthectomy.

**Guilding 2004** extended previous work (Cameron & Dutia, 1999; Johnston, Seckl & Dutia, 2002) to examine the mechanisms behind glucocorticoid dependence in the process of vestibular compensation. They used thin layer chromatography to determine the level of 11β-hydroxysteroid dehydrogenase type I, which potently actives inactive forms of glucocorticoids in the central nervous system. They reported no differences in the expression of this protein following labyrinthectomy.

**Guilding 2005** investigated the effects of synaptic blockade on the activity of MVN neurons up to a week following unilateral labyrinthectomy by applying selective glutamate, GABA
and glycine channel antagonists to acute brain slices and recording discharge rats for tonically active neurons. They reported that immediately following labyrinthectomy (4 hours) synaptic blockade had no effect on the increase in MVN neuron discharge rates. However, at later time periods (48 hours, 7 days) synaptic blockade reduced spontaneous firing rates. Results from this study were presented graphically and it was not possible to extract numerical data from the published plots with sufficient precision. Therefore, data from this study was not included in the meta-analysis.

Nelson 2017 examined the electrophysiological changes in MVN neurons of mice that had undergone UVD. The operative procedure in this study only used mechanical effects to disrupt the inner ear sensory epithelia. A sham-operated control was used as a comparator. In initial experiments, the optokinetic reflex was recorded using video oculography. Acute brainstem slices were then prepared for patch-clamp recordings up to 20 days following UVD. In contrast to other reports in this review, deafferentation did not increase the spontaneous firing of MVN neurons at any time point following the procedure. However, they reported that the gain (firing rate compared to injected depolarising current) of MVN neurons increased following deafferentation to both current steps and sinusoidal inputs. Deafferentation also abolished the phenomenon of firing rate potentiation (see Section 3.2.3 and Figure 8 for details) and pharmacological blockade of BK channels with iberiotoxin did not restore this firing characteristic. This latter data was collected from chronically deafferented animals. Unfortunately, numerical data was not reported in sufficient detail to allow inclusion in the meta-analysis. This study was particularly notable for being the only study in which intervention allocation (i.e. UVD) was blinded from the study investigators.
2.2 Excluded studies

Darlington 1989 explored whether the return of activity seen following UVD *in vivo* was also evident *in vitro*. They examined brainstem slices from guinea pigs that had undergone UVD 6 to 8 weeks prior. Due to the chronicity of the lesions, this study was excluded from the analysis. Of note, this study was the first to demonstrate the presence of spontaneous activity *in vitro* following labyrinthectomy. Further, this discharge was present despite a high magnesium bath used to uncouple synaptic activity, suggesting that intrinsic properties were capable of maintaining activity in this system despite deafferentation.

Smith 1992 investigated the role of NMDA receptors in vestibular compensation post UVD. They recorded spontaneous discharge rates from MVN neurons prior to, and 3 days to 2 months after, UVD in acute brain slices from guinea pigs. Following this they applied selective NMDA receptor antagonists to slices to examine changes in excitability. They reported that there was no difference between the spontaneous rates at all time points after UVD (data not reported individually) and pooled all time points into one group. Therefore, this study was excluded as it examined a composite of acute and chronic lesions. Interestingly, they reported a significant increase in the mean spontaneous discharge rate (11.3 to 15.1 spikes/sec) and this process was due to a mechanism independent of changes in NMDA receptor activity or expression.

Beraneck 2003 examined the specific firing dynamics of MVN neurons in the guinea pig following UVD. This study was excluded because it examined chronic lesions (1 month). This study was notable for demonstrating that neuronal responses to injected current steps, ramps and sinusoids was augmented. This was particularly apparent in type B neurons, where discharge properties tended to approach a type A profile, suggesting a homogenisation of intrinsic neuronal properties following UVD.
Beraneck 2004 used a very similar experimental paradigm to previous work (Beraneck et al., 2003), however in this circumstance examined contralesional MVN neurons. They confirmed the results of previous work and reported that properties of MVN neurons contralesionally appeared to approach a type B profile.

Beraneck 2009 examined whether gap junctions may play a role in vestibular compensation. After some debate, this was considered not to be an intrinsic property and therefore excluded. Of note, they reported no evidence to suggest a role for gap junctions in the phenomenon of vestibular compensation.

Shao 2009 examined the effect of UVD on tangential nucleus neurons of the chicken. This nucleus is an anatomical correlate of the MVN. It was excluded as it used juvenile chickens instead of an adult animal model. Due to the changes that may occur in this time period, it was not clear whether this study would reflect the process of vestibular compensation rather than that of development.
3. Quality assessment

To determine the quality of the evidence, each study was assessed on three methodological domains: criterion validity of the model (Table 4), precision of experimental technique (Table 5) and risk of bias (Table 6). The global assessments are summarised in Table 7 and Figure 10.

3.1 Model validity

A well conducted scientific experiment should aim to test a prespecified hypothesis or set of hypotheses. In biological fields, such hypotheses are usually tested in a model system that is closely related to, or mimics, the situation being investigated. For example, UVD is performed in various animals as a model for vestibular compensation. Whether such a model is valid depends on the way it is prepared for experimentation. In this case, this refers to the specific details of how each animal and tissues derived from it are used during experiments.

This tool assessed reporting of details of the animal model, its routine handling and the control used for experiments in each study. The following questions were asked of each study:

1. Was an ethical statement provided for animal handling and the use of biological tissue?\(^{16}\)
2. Were there clear descriptions of the model used to study vestibular compensation?
3. Was there a clear description of the routine maintenance of the model during experimentation?\(^{17}\)

\(^{16}\) This was not considered necessary, as experimentation is often not approved by institutions without ethical approval. However, whether such details are reported is an indication of the rigor of reporting.

\(^{17}\) Factors considered to be important included environmental stimuli and housing arrangements following deafferentation procedures, periods of incubation following preparation of brain slices, duration of recording per brain slice or neuron and checking of input resistance before and after recordings.
4. Were details provided of how the model was prepared for the experimentation?
5. Did the authors prove the success of deafferentation?
6. Was there an appropriate and comparable control?

If there was at least one negative answer (excluding the first domain), the study was classified as having a high risk of being invalid. If there was at least one unclear answer, it was not clear how the study should be assessed. Otherwise, the study classified as having a low risk of invalidity.

| Study             | 1 | 2 | 3 | 4 | 5 | 6 | Overall |
|-------------------|---|---|---|---|---|---|---------|
| de Waele 1994     | N | Y | N | Y | Y | Y | H       |
| Cameron 1997 (*)  | N | Y | U | Y | Y | Y | U       |
| Cameron 1999 (*)  | N | Y | U | Y | Y | Y | U       |
| Vibert 1999       | Y | Y | Y | Y | Y | Y | L       |
| Yamanaka 2000 (*) | N | Y | U | Y | Y | Y | U       |
| Him 2001 (*)      | N | Y | U | Y | Y | Y | U       |
| Johnston 2001 (*) | Y | Y | N | Y | Y | Y | L       |
| Ris 2001 (*)      | Y | Y | Y | Y | Y | Y | U       |
| Johnston 2002     | N | Y | Y | Y | Y | Y | L       |
| Ris 2002          | Y | Y | N | Y | U | Y | H       |
| Patko 2003        | Y | Y | Y | Y | Y | U | U       |
| Ris 2003          | Y | Y | N | Y | Y | U | H       |
| Eleore 2004       | Y | Y | U | Y | Y | Y | L       |
| Guilding 2004     | Y | Y | U | Y | U | Y | U       |
| Guilding 2005     | Y | Y | U | Y | U | Y | U       |
| Johnston 2005     | Y | Y | N | Y | U | Y | H       |
| Nelson 2017       | Y | Y | Y | Y | Y | Y | L       |

Table 4 – Ratings for domains assessing the validity of the model in studies included in the systematic review.
Asterisked studies were included in the meta-analysis. N = not satisfied, U = unclear or insufficient evidence to make an assessment, Y = criterion satisfied, L = low risk of invalidity, H = high risk of invalidity.
Based on these assessments, 5 studies (29%) were classified as having a low risk of model invalidity, 4 studies (24%) a high risk and 8 studies (47%) an unclear risk. All studies clearly reported the what animal model was used and the methods employed to prepare the model for experimentation. However, a number of early experiments did not provide an explicit statement of procedures or codes used to guide safe and ethical handling of animals used in experiments. Further, 5 studies did not adequately state the routine maintenance of the model during experiments. It was unclear in 4 reports whether deafferentation was successful or confirmed. In some cases, this was implicit through references to methods sections in previous papers reporting similar experiments by the same group of experimenters.

### 3.2 Precision

Scientific experiments should be conducted with a certain degree of procedural rigour to ensure that the results obtained are accurate and precise. A measure of precision is the repeatability of an experiment, which allows an estimation of how likely a particular result is due to simple chance. This tool assessed the reporting of technical details of experimental structure, statistical methods used to analyse the significance of data and sample sizes. Some of these particular assessments (for example, calculation of sample sizes to achieve an appropriately powered study) are not routine in such non-clinical experimental work, however do effect the precision of the conclusions made. The following questions were asked of each study:

1. Were repeats of experiments performed per animal? This is referred to as technical variability
2. Did the experiment give the same result when it was repeated in a different animal? This is referred to as observer variability
3. Is it clear whether repeatability is a combination of technical and observer variability? I.e. where these two repeats reported individually or as a pooled result?

4. Did the result include an appropriate measure of variability?

5. Did the authors pool data from previous experiments? If so, did they assess for heterogeneity between experiments?

6. Were sample sizes required for significance calculated prior to experiments being conducted?

7. Were indeterminate, missing or outlying results handled appropriately?

8. Was the study appropriately powered to reach statistical significance\textsuperscript{18}?

9. Was there a clear statement or description of the statistical method?

10. Was the chosen statistical method appropriate?

11. Was there any evidence of data dredging\textsuperscript{19}?

If there were three or more negative answers, the study was classified as having a high risk of imprecision. If there were three or more unclear answers, it was not clear how the study should be assessed. Otherwise, the study was classified as having a low risk of imprecision.

\textsuperscript{18} This could be determined by either an \textit{a priori} calculation of the required sample size to detect a specific effect size, or alternatively the minimum detectable effect size given a certain sample size.

\textsuperscript{19} This is the process of mining data to find patterns that may be statistically significant without devising a hypothesis to assess causality.
| Study               | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | Overall |
|---------------------|---|---|---|---|---|---|---|---|---|----|----|---------|
| de Waele 1994       | Y | Y | Y | Y | N | N | N | U | Y  | Y  | N  | L       |
| Cameron 1997 (*)    | Y | U | U | Y | N | N | N | U | Y  | Y  | N  | U       |
| Cameron 1999 (*)    | Y | U | U | Y | Y | N | N | U | Y  | Y  | N  | H       |
| Vibert 1999         | Y | U | U | Y | N | N | N | U | Y  | Y  | N  | U       |
| Yamanaka 2000 (*)   | Y | U | U | Y | N | N | U | U | Y  | Y  | N  | U       |
| Him 2001(*)         | Y | U | U | Y | N | N | U | U | Y  | Y  | N  | U       |
| Johnston 2001 (*)   | Y | U | U | Y | Y | N | N | U | Y  | Y  | N  | H       |
| Ris 2001 (*)        | Y | Y | Y | Y | N | N | U | U | Y  | Y  | N  | L       |
| Johnston 2002       | Y | U | U | Y | N | N | U | U | Y  | Y  | N  | U       |
| Ris 2002            | U | U | U | Y | N | N | U | U | Y  | Y  | N  | U       |
| Patko 2003          | U | U | U | Y | N | N | U | U | Y  | Y  | N  | U       |
| Ris 2003            | Y | U | U | Y | N | N | U | U | Y  | Y  | N  | U       |
| Elecore 2004        | U | U | U | Y | N | N | U | U | Y  | Y  | N  | U       |
| Guilding 2004       | Y | U | Y | Y | N | N | U | U | Y  | Y  | N  | L       |
| Guilding 2005       | U | U | U | Y | N | N | U | U | Y  | Y  | N  | U       |
| Johnston 2005       | Y | U | U | Y | N | N | U | U | Y  | Y  | N  | U       |
| Nelson 2017         | U | U | U | Y | N | N | U | U | Y  | Y  | N  | U       |

**Table 5**—Ratings for domains assessing imprecision in included studies. N = not satisfied, U = unclear or insufficient evidence to make an assessment, Y = criterion satisfied., L = low risk of imprecision, H = high risk of imprecision.

Based on these assessments, 3 studies (18%) were classed as having a low risk of imprecision, 2 studies (12%) a high risk and 12 studies (70%) an unclear risk. All studies clearly reported statistical methods used to assess significance of effects, utilised appropriate measures of variability\(^\text{20}\) and reported clear hypotheses to assess causality. However, there were consistent issues between studies in all domains assessed. No published study reported whether calculations of sample sizes or power required to reach significance were performed. No study

\(^{20}\) The most common being the standard error of the mean (SEM), except for two studies that reported standard deviations

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clearly accounted for missing data and 5 studies had discrepancies between numbers of cells and animals published within the report raising concerns about loss of data. Only one study attempted to justify exclusion of data based on pre-specified criteria, however the numbers of animals or cells excluded on this basis were not clearly reported. Only 2 studies reported the number of repeats of each experiment performed on a per animal and per cell basis, complicating the assessment of variability within studies.

### 3.3 Risk of bias

There are multiple potential sources of bias which introduce systematic error. In the domain of human clinical research, many of these sources are eliminated through effective study design. For example, practices such as randomisation of participants, allocation concealment and comprehensive reporting of prespecified outcomes are some of the attempts made to attenuate any potential bias. In laboratory experimentation, some particular concerns include confirmation bias, observer-expectancy effects and correlation bias. However, many laboratory-based studies are not explicitly required to match such standards, allowing for systematic errors to potentially creep into experimental analysis. This tool is adapted from the SYRCLE risk of bias tool, which is modelled along the criteria used to assess human trial data (Hooijmans et al., 2014). It should be noted that many of the criteria listed below are still not routine for animal studies (for example, random allocation or sequence generation) and this was taken into account when assessing risk of bias. The following questions were asked of each study:

1. Were participants allocated randomly to experimental and control groups? If so, was this sequence adequately generated and applied?
2. Were the groups similar at baseline, or were they adjusted for confounders in the analysis? The baseline characteristics considered to be important were the age of animal, sex of animal\textsuperscript{21} and housing arrangements.

3. Was the allocation adequately concealed?

4. Were the animals randomly housed during the experiment?

5. Were the caregivers and/or investigators blinded from knowledge of which intervention each animal received during the experiment? This is also known as allocation concealment

6. Were animals selected at random for outcome assessment? In other words, were control animals and experimental animals recorded in groups?

7. Was the outcome assessor blinded? This could be either during analysis or data collection

8. Were incomplete outcome data adequately addressed?

9. Are reports of the study free of selective outcome reporting?

10. Was the study apparently free of other problems that could result in high risk of bias?

If there were three or more negative answers (excluding the first criterion\textsuperscript{22}), the study was classified as having a high risk of bias. If there were three or more unclear answers, it was not clear how the study should be assessed. Otherwise, the study was classified as to having a low risk of bias.

\textsuperscript{21} This is important given differences in sensitivity to sex hormones in the vestibular nucleus. See Grassi, S, Frondaroli, A, Scarduzio, M, Dutia, MB, Dieni, C & Pettorossi, VE 2010, 'Effects of 17beta-estradiol on glutamate synaptic transmission and neuronal excitability in the rat medial vestibular nuclei', Neuroscience, vol. 165, no. 4, pp. 1100-14.

\textsuperscript{22} This practice is still not routine and was therefore not considered to be necessary
Table 6 – Ratings for domains assessing the risk of bias in studies included in the systematic review.

Asterisked studies were included in the meta-analysis. N = not satisfied, U = unclear or insufficient evidence to make an assessment, Y = criterion satisfied, L = low risk of bias, H = high risk bias.

Based on these assessments, only 1 study (6%) was classified as having a low risk of bias, 3 studies (18%) a high risk and 13 studies (76%) an unclear risk. All studies were free from obvious problems that could act as sources of bias. Only 2 studies provided enough information regarding the details of the experimental animals to ensure similar characteristics at baseline, however no study clearly reported between group differences. Only 1 study generated a random, concealed allocation sequence and blinded outcome assessors during data collection and analysis. Data was reported clearly for most measured outcomes studied in 6 studies, while 4 studies only reported data for certain outcomes in certain
experimental groups. An assessment could not be made for many of the criteria due to the lack of relevant information presented in most reports.

| Study               | Imprecision | Model validity | Risk of bias |
|---------------------|-------------|----------------|--------------|
| de Waele 1994       | L           | H              | U            |
| Cameron 1997 (*)    | U           | U              | U            |
| Cameron 1999 (*)    | H           | U              | U            |
| Vibert 1999         | U           | L              | U            |
| Yamanaka 2000 (*)   | U           | U              | U            |
| Him 2001 (*)        | U           | L              | U            |
| Johnston 2001 (*)   | H           | L              | H            |
| Ris 2001 (*)        | L           | U              | U            |
| Johnston 2002       | U           | L              | U            |
| Ris 2002            | U           | H              | U            |
| Patko 2003          | U           | U              | U            |
| Ris 2003            | U           | H              | U            |
| Eleore 2004         | U           | L              | H            |
| Guilding 2004       | L           | U              | U            |
| Guilding 2005       | U           | U              | U            |
| Johnston 2005       | U           | H              | H            |
| Nelson 2017         | U           | L              | L            |

Table 7 - Summary of ratings for each quality assessment domain. These ratings were pooled to generate an overall quality rating. L = low risk, H = high risk, U = unclear.

Across all studies, there was insufficient data to make appropriate assessments for a relatively large proportion of questions (Figure 10). Specifically, the risk of bias was unclear in 76% of studies, the risk of imprecision was unclear in 71% of studies and the risk of model invalidity was unclear in 41%. This precluded an accurate assessment of the quality of certain studies. Only 35% of studies were assessed as having a low risk of model invalidity, while even less a low risk of imprecision (18%) and bias (5%). This suggests that there is only a small amount
of evidence which had a relatively low risk of suffering from invalidity, bias and imprecision. There was also a slightly higher, but still small amount of evidence which had a high risk of imprecision (12%), model invalidity (24%) and bias (18%).

![Figure 10 - Graph of quality assessments for each domain pooled across all studies, presented as percentages of the whole.]

Together, these assessments suggest that there is often incomplete reporting of important methodological characteristics in reports on UVD and intrinsic properties. Therefore, it is difficult to assess the quality of the evidence testing the hypothesis, however it is generally weak based on methodological criteria alone.
4. Meta-analysis

Studies presenting electrophysiological studies used either mean spontaneous discharge rates or the gradients of input-output curve functions (i.e. gains) to describe changes in intrinsic excitability following UVD. 6 of the included studies (Cameron & Dutia, 1997; Cameron & Dutia, 1999; Him et al., 2001; Johnston, Him & Dutia, 2001; Ris et al., 2001a; Yamanaka et al., 2000) reported spontaneous spike discharge rates, while 2 (Nelson et al., 2017; Ris, Hachemaoui & Godaux, 2002) reported input-output gains. Unfortunately, there was not enough numerical data within the latter 2 reports to derive spontaneous spike discharge rate measures. Therefore, this data was not included in the final meta-analysis.

Each of the 6 studies presented spike discharge rates at various time points (between 4 hours and 7 days) following the lesion. 1 study (Him & Dutia, 2001) reported differences in firing between the two subtypes of MVN neuron, while another study (Yamanaka et al., 2000) distinguished neurons based on relative anatomical location. All data sets were treated as distinct experiments and analysed separately, creating 14 individual sets of data (See Discussion for validity of this pooling). The data sets reported spike discharge rates for a total of 1216 neurons (405 control, 811 experimental) across at least 2316 animals. Raw mean differences in discharge rates between experimental conditions and control were calculated and used as the effect size for the meta-analysis (Table 8). Data was plotted on a forest plot comparative purposes (Figure 11).

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23 There was incomplete reporting of the number of animals used in each study. See Discussion for an assessment of the effect of this.
| Study                        | # of cells | # of animals | RMD in spike rate | Lower CI | Upper CI | Cohen’s D | P-value |
|-----------------------------|------------|--------------|-------------------|----------|----------|-----------|---------|
| *Cameron 1997 - 4 hours*   | 32         | -            | 6.40              | 2.92     | 9.88     | 0.72      | 0.001   |
| *Cameron 1997 - 6 hours*   | 43         | -            | 3.82              | 0.47     | 7.17     | 0.40      | 0.05    |
| *Cameron 1997 - 24 hours*  | 36         | -            | 4.70              | 1.07     | 8.33     | 0.47      | 0.05    |
| *Cameron 1999 - 4 hours*   | 61         | 9            | 6.46              | 2.38     | 10.54    | 0.55      | 0.05    |
| *Yamanaka 2000 - rostral*  | 20         | 34           | 5.30              | 1.95     | 8.65     | 0.62      | 0.05    |
| *Yamanaka 2000 - caudal*   | 70         | 34           | 0.30              | -2.46    | 3.06     | 0.05      | 0.05    |
| *Him 2001 - 1-3 days, Type A* | 16         | 25           | -1.50             | -5.87    | 2.87     | -0.20     | -       |
| *Him 2001 - 1-3 days, Type B* | 68         | 25           | 3.30              | 0.43     | 6.17     | 0.36      | 0.01    |
| *Him 2001 - 7-10 days, Type A* | 42         | -            | 0.30              | -3.86    | 4.46     | 0.05      | 0.05    |
| *Him 2001 - 7-10 days, Type B* | 40         | -            | 5.90              | 3.05     | 8.75     | 0.69      | 0.05    |
| *Johnston 2001 - 2 days*   | 118        | 6            | 4.90              | 0.83     | 8.97     | 0.63      | 0.001   |
| *Johnston 2001 - 7 days*   | 159        | 6            | 6.00              | 2.89     | 9.11     | 0.99      | 0.001   |
| *Ris 2001 - 2 days*        | 63         | 42           | 4.40              | 2.27     | 6.53     | 0.68      | 0.05    |
| *Ris 2001 - 7 days*        | 43         | 42           | 4.80              | 2.66     | 6.94     | 0.72      | 0.05    |
| **Summary (<1 day)**       | 278        | -            | **4.24**          | **2.41** | **6.07** | **0.48** |         |
| **Summary (<1-10 days)**   | 533        | -            | **3.94**          | **2.44** | **5.43** | **0.47** |         |
| **Summary**                | **811**    | **116**      | **4.06**          | **2.90** | **5.21** | **0.49** |         |

Table 8 - Numerical data extracted from each study included in the meta-analysis. Confidence intervals (CI) are 95%. The p-value indicates the value published in each paper. RMD = raw mean difference.
The majority of data sets (11 of 14, 79%) reported an increase in the mean difference between spontaneous spike discharge rates at time points up to 1 week following labyrinthectomy compared to intact or sham-operated controls (Figure 11). The only studies reporting decreases found this was isolated to type A neurons (Him & Dutia, 2001) or those found in the caudal aspect of the MVN (Yamanaka et al., 2000), a region which is thought to contain a higher proportion of type A neurons (see Section 1.4.2 of introduction). Other studies did not explicitly distinguish between neuronal subtype or anatomical location and this difference could not be explored any further using the current data set.

![Forest plot of raw mean difference in discharge rates following labyrinthectomy observed in different studies. In the inset are calculated measures of heterogeneity. Error bars are 95% confidence intervals.](image)
Using a random effects model, the mean difference in spontaneous discharge following labyrinthectomy was estimated to be $4.06 \pm 1.14$ (n = 14, 95% CI) compared to the control rate (Figure 11). The Q statistic was not significant ($14.2, p = 0.36$, $\chi^2$ statistic with 13 degrees of freedom) and the H statistic was 1.1, both suggesting a moderate degree of heterogeneity. However, the $I^2$ value was 8% suggesting that a large proportion of the heterogeneity across studies is due to chance. The Cohen D statistic estimated the average effect size to be 0.48, consistent with a moderate size of effect. Together, this is strong evidence of a moderate increase in the intrinsic excitability of MVN neurons following UVD.

Subgroup analyses were performed based on the time post UVD. Data was divided into groups of less than or equal to 1 day from lesioning or between 1 and 10 days from lesioning.

**Figure 12** – Forest plot of raw mean difference in discharge rates following labyrinthectomy performed less than 1 day prior. In the inset are calculated measures of heterogeneity. Error bars are 95% confidence intervals.
Using a random effects model, for the less than or equal to 1 day subgroup, the mean difference in spontaneous discharge following labyrinthectomy was estimated to be $4.24 \pm 1.81$ (n = 6, 95% CI) compared to the control rate (Figure 12). The Q statistic was not significant ($5.69, p = 0.34$, $\chi^2$ statistic with 5 degrees of freedom) and the H statistic was 1.14, suggesting a moderate degree of heterogeneity. However, the $I^2$ value was 12% suggesting that a large proportion of the heterogeneity across studies is due to chance. The Cohen D statistic was 0.46, consistent with a moderate size of effect. This result is strong evidence of a moderate increase in the intrinsic excitability of MVN neurons in the acute period following UVD.

**Figure 13** – Forest plot of raw mean difference in discharge rates following labyrinthectomy performed between 1 to 10 days prior. In the inset are calculated measures of heterogeneity. Error bars are 95% confidence intervals.
Using a random effects model, for the 1 to 10 days subgroup, the mean difference in spontaneous discharge following labyrinthectomy was estimated to be $3.94 \pm 1.48$ (n = 8, 95% CI) compared to the control rate (Figure 13). The Q statistic was not significant (8.47, $p = 0.29$, $\chi^2$ statistic with 7 degrees of freedom) and the H statistic was 1.21, suggesting a moderate degree of heterogeneity. However, the $I^2$ value was 17% suggesting that a large proportion of the heterogeneity across studies is due to chance. The Cohen D statistic was 0.49, consistent with a moderate size of effect. This is evidence that the increase in the intrinsic excitability of MVN neurons persists outside of the acute and into the subacute period following UVD.
V - DISCUSSION

In this thesis, I present the results of the first comprehensive, systematic review of the published literature regarding the effect of UVD on the intrinsic properties of MVN neurons. I have reached the following conclusions:

- The intrinsic properties of MVN neurons change during UVD, as evidenced by an increase in their spontaneous discharge rates at rest. The magnitude of the effect is on average 4 spikes/second higher than pre-lesion rates.
- The change in intrinsic properties occurs in the acute phase following UVD and persists throughout a brief subacute phase of at least 2 weeks.
- There is insufficient evidence to determine whether intrinsic plasticity changes differ between anatomical location or animal model.
- There are a number of issues in the reporting of methodological details that make it difficult to assess the degrees of precision, model validity and risk of bias in this evidence base. This may influence the veracity of the evidence presented above and highlights the need for future experiments to address these issues.

I will discuss the strength of the evidence behind these conclusions, based on the quality assessments I have performed. Following this, I will make an assessment of what the current study adds to our understanding of the intrinsic plasticity of MVN neurons and which directions we need to take to improve this knowledge base.


1. The review process

The process of evaluation in a systematic review is dependent on details published in the report of each experiment. Generally, reporting of data in basic science is not held to the same standard of human clinical trial research (Muhlhausler, Bloomfield & Gillman, 2013). There are widely available, clear and precise guidelines for the conduct and reporting of the results of human trial data (Altman, 1996) and systematic reviews (Moher et al., 2009). These guidelines have been demonstrated to improve trial reporting in a way that enhances the quality of data and its utilisation by the broader scientific community (Kane, Wang & Garrard, 2007; Plint et al., 2006; Turner et al., 2012). Like in human trial research, there are now guidelines for the reporting of animal experimental data (Kilkenny et al., 2010) and some higher impact journals have made attempts to improve rigor using reporting checklists. However, unlike in human trials, these standards have not yet become widely accepted and therefore have little influence in the domain of animal experimental design.

There are a number of other factors that may prevent the presentation of sufficient details for comparisons across studies and repetition. Journals often place limitations on authors that restrict the word and page counts, limit the size of figures and stipulate potentially unnecessary details that must be included in reports. This reduces the level of detail that can be devoted to more pertinent features of the results or conclusions. This is of particular concern in abstracts, where restrictive word counts can reduce the presentation of experimental technique or numerical details in favour of narrative sweeping statements of significance which potentially have a higher impact (Hillier, Kelly & Klinger, 2016). This issue has been recognised in studies examining abstracts of clinical randomised controlled trials. A number of trials have consistently failed to report important methodological details,

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24 For example, see the submission guidelines for the journals Nature and Science, which are readily accessible online
side effects and harms in favour of positive effect sizes (Berwanger et al., 2009; Ghimire et al., 2014; Hays et al., 2016). Abstracts were the most readily available sections of the paper on which to base initial screening process for this study (Andrade, 2011). Therefore, there is a small chance that the range of studies that were included and excluded from the review may be biased to positive reports (Mueller et al., 2014; Schmucker et al., 2017), potentially increasing the risk of yielding a false positive result (Kicinski, 2014; Scherer, Dickersin & Langenberg, 1994; Scherer, Langenberg & von Elm, 2007).

One limitation of the search strategy used to find evidence is that initial searches revealed a very large number of studies. Using more restrictive search terms, searches revealed less reports which may have potentially excluded some relevant studies. For example, phrases ‘damage’ and ‘lesion’ revealed many more irrelevant studies than using the more specific terms ‘deafferentation’ and ‘labyrinthectomy’. However, some reports used the word ‘damage’ in their title and abstract to generalise their findings and were only found by a manual search of references from other papers. Further, certain phrases are not used consistently between studies to describe the changes they observed. A number of reports describe either increase in spontaneous discharge or firing rate and do not describe this consistently as a change in ‘intrinsic excitability’. These inconsistencies in vocabulary within the field could skew the range of evidence found by the search strategy, however all efforts were made to be as inclusive as possible (see Appendix 2 for a list of search terms used in each database).

1.1 Quality assessment

The strength of the conclusions of the systematic review are ultimately dependent on the quality of the evidence base. I have chosen to assess the quality of the evidence using three broad domains that aim to assess the internal validity of the research findings. This process was particularly difficult for some domains, an issue that has been noted in previous
systematic reviews of animal research due to incomplete reporting and lack of sufficient detail in reporting (Hooijmans & Ritskes-Hoitinga, 2013; van Luijk et al., 2014; van Luijk et al., 2013). However, it is paramount that such assessments are attempted.

1.1.1 Model validity

The models chosen for the assessment of the study question were very similar across studies. Most experiments performed labyrinthectomies through mechanical disruption, with some groups using an additional protein denaturing step with 100% ethanol. All studies used appropriate animals (mouse, rat, guinea pig) that are known to experience a resolution in static symptoms following vestibular compensation within a week (see Section 3.1.1). Some studies utilised a sham-operated control to ensure observed effects were not simply a result of the stress related to undergoing a surgical procedure. This was not considered to be scientifically necessary for inclusion in the review, as results compared to normal unoperated controls were similar. Technically, a sham operation is the most appropriate control and should be considered the gold-standard control for future studies, however the ethics of this need to be considered (Niemansburg et al., 2015; Probst et al., 2016).

Three studies (Guilding & Dutia, 2005; Ris et al., 2003; Ris, Hachemaoui & Godaux, 2002) were assessed to have a high risk of model invalidity due to a lack of reporting of routine model maintenance. In particular, there were no details of housing or ages of animals (or a surrogate such as weight) that may influence experience-dependent changes. Reporting of whether the success of the procedure to achieve UVD was confirmed was not consistent across these three studies, however references to previous work was made suggesting that the chosen methods were likely appropriate. Interestingly, these three studies were all published
in a journal for shorter communications\textsuperscript{25}, which may have truncated the reporting of methodological details in favour of results and their discussion.

1.1.2 Precision

The precision of experiments was assessed using reported measures of variability. One major issue in this assessment was distinguishing between technical and observer variability. The former is a function of the number of repeats performed within each animal and the latter the number of animals used for all experiments. All studies made recordings from multiple individual neurons in each experiment, and most used the standard error of the mean (SEM) as a measurement of variability. SEM was relatively low across all studies, suggesting an acceptable level of technical variability. In addition, all studies used multiple animals for each experiment to reduce observer variability, however did not report whether these results were similar across different animals. Further, the number of slices created from each animal were not consistently reported\textsuperscript{26}. All reports were therefore assumed to have recorded results as a single pool of recorded neurons, such that measures of variability were probably a combination of technical and observer variability. This precluded an assessment of these domains independently and this distinction is important, as these domains reveal specific features of methodological rigour. Technical repeats attest to potentially modifiable issues with recording techniques, while observer repeats reveal more random uncontrollable differences between animals.

The repeats in experiments were probably a combination of between-neuron and between-animal repeats. Whether this is an appropriate way of pooling experimental data is unclear and raises the concern of pseudoreplication. The question posed in most studies was whether

\textsuperscript{25} Instructions for authors are that ‘papers should be concise and as short as possible”, with a character limit of 19500 including spaces. See http://edmgr.ovid.com/nr/accounts/ifauth.htm#14 for details.

\textsuperscript{26} Slices of differing thickness were created in each experiment, such that the MVN may have been included in more than a single slice in each animal.
UVD changed the intrinsic excitability of MVN neurons. This question can be answered by using the neuron as the experimental unit, as was done in each of the included studies. However, this does not address whether there are between-animal differences in the effect of UVD that have not been explicitly addressed. This is an important clinical question, as a number of patients suffering from acute unilateral vestibular disorders do not undergo significant compensation, suggesting inter-subject (or in the present study inter-animal) factors may be relevant in vestibular compensation. This domain can be accounted for using multi-level statistical models that take into account this animal factor during analysis. Alternatively, an experiment can be performed whereby the animal is the experimental unit and neurons from each animal are pooled into an average (Lazic & Essioux, 2013). This would have to be appropriately powered with a prior calculation of sample sizes to ensure sufficient animals to achieve a meaningful result.

Another observation was the possibility of missing data. A number of studies did not report how many animals were used in experiments, limiting an assessment of observer variability. Few studies reported whether all animals that underwent operations survived the procedures, which provides information regarding the care of animals, surgical techniques and dropout rates. Some studies presented all data graphically, however reported only numerical values for positive results in the body of the report. This precluded the negative results from being included in the meta-analysis. Statistical methods chosen in each study were appropriate for the data sets. However, no studies reported a calculation of sample sizes (of either neurons or animals) prior to experimentation required for statistical significance.

1.1.3 Risk of bias

As expected, bias was very difficult to assess in this study. Due to the lack of standardisation in the conduct of animal experimentation, less attention is focussed on reporting potential sources of bias which are often explicitly addressed in the human trial literature. There is
also a wider range of observed practices that have the potential to introduce systematic error into evaluations. For example, practices such as randomisation that are common in human trials aim to eliminate potential known and unknown factors between experimental groups that may influence the outcome (Sibbald & Roland, 1998). Given that a number of animals considered in this review underwent a surgical procedure, it would be important to eliminate any pre-surgical differences between operated animals and controls to ensure homogeneity between groups. Particular differences that may be important include the size and sex of the animal and housing arrangements between groups. Hypothetically, if experimental animals were at an earlier developmental stage than controls, this may have influenced the rate of recovery or the neuronal subtype changes observed (Straka et al., 2005). Similarly, if experimental animals were housed in separate locations, this may have influenced their rate or degree of compensation (Arndt et al., 2009). No reports made experimental or control group characteristics explicit, making it difficult to assess differences between groups. For experiments examining the hypothesis posed in this review, randomisation would be ethically sound and therefore appropriate in this form of experimental design. It would not be an onerous procedure to implement and therefore should be a benchmark for similar research in the future.

Another potential source of bias includes the lack of allocation concealment. Blinding experimenters\(^{27}\) to the experimental condition prevents the incursion of conscious or unconscious skews in the interpretation or collection of data. This was attempted by 1 included study (Nelson 2017), demonstrating the feasibility and potential benefits of this approach. Experimenters preparing slices for electrophysiology were blinded to the behavioural condition of the animal. Further, electrophysiology data collection was also performed blind to behavioural condition, with clearly documented criteria for determining acceptable recordings. This method prevents the exclusion of outlying data that does not

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\(^{27}\) This includes people along the spectrum from animal handlers, technicians performing experiments and to any investigators analysing data.
clearly fit into patterns that may be apparent from initial data analyses. However, these criteria may not have been prespecified, as the authors mention that this blinding was kept to the initial analysis.

### 1.2 Validity of meta-analysis

Meta-analysis is a powerful tool for averaging effects across multiple studies. The main benefit of this procedure over arithmetic averaging is the systematic evaluation of heterogeneity between studies and the weighting of studies based on the degree of observed variation. This process was valid for the purposes of the current review, as there was very little calculated heterogeneity between studies. The heterogeneity of studies as assessed by the $H$ statistic was relatively low, on average 1.1. On this scale, a $H$ value close to 1 suggests a high degree of homogeneity. The $H$ statistic is particularly effective for analyses of more than 8 studies and therefore is a good indication of low heterogeneity in this meta-analysis (Higgins & Thompson, 2002).

A question remains as to whether it is appropriate to consider MVN neurons as a whole pool for the purposes of this analysis. The spontaneous activity and firing characteristics in response to step currents are clearly different (see Chapter II, Section 2.2). However, there is evidence that, at least chronically, MVN neuronal subtypes ipsilaterally appear to become homogenised, approaching a more type A-like profile with linear characteristics (Beraneck et al., 2003). However, this work as not been conducted in the acute stage. Studies did not consistently differentiate between neuronal subtype and therefore it is not possible to make a conclusive determination of the validity of this pooling. Future studies should attempt to distinguish MVN neuronal subtypes as a characteristic to compare between groups.

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28 This prevents data mining, where conclusions that are strictly outside of the purview of experiments are made.
Some studies presented all data graphically, while reporting only numerical values for positive results. This precluded some of the results that demonstrated no change following UVD from being included in the meta-analysis. This potentially skews the results towards a false-positive assessment. Further, this prevented the analysis of data from 2 studies which were of high methodological quality, reducing the power of the meta-analysis. Incomplete reporting should therefore be avoided in the future to permit such analyses that integrate findings across studies and may potentially help reduce publication bias.

One minor issue encountered was that a number of studies were performed by the same group of experimenters. This is likely to have increased the homogeneity observed between studies due to similarities in experimental techniques. However, if there was a strong bias introduced by these experimental techniques, this would reduce the quality of the estimate of the effect. Given the lack of clarity in quality assessments, it remains unclear how to truly assess the nature or extent of this potential influence.
2. Implications for neuronal excitability

Based on the qualitative systematic review undertaken here, I will suggest the following conclusions about the nature of the acute stage of intrinsic plasticity in the MVN:

- There is a compensatory increase in spontaneous discharge rates following UVD. This appears to be most prominent in neurons populating the rostral MVN and may be restricted to the type B neuron subtype.
- The proportion of type A and B neurons may change following UVD. However, the expression of particular ion channels that endow different subtypes with their unique firing characteristics do not appear to change.
- MVN neurons are less responsive to GABA following UVD. This responsiveness improves to fast, but not slow, GABA-mediated inhibition within 1 week.
- The recovery of spontaneous discharge may be dependent on a perceptual experience of the syndrome (probably mediated by stress hormones), the presence of the intact cerebellar pathways and BK channels involved in AHP generation.
- The persistence of increases in excitability after the acute phase may be dependent on synaptic inputs.

2.1 Measures of excitability

This study clearly confirms that UVD increases neuronal excitability. One important question is whether the measure widely employed is appropriate. Most studies use spontaneous discharge rates, while a smaller proportion use input-output functions to determine neuronal gain. Both are valid measures of excitability and reflect intrinsic
properties under conditions of synaptic uncoupling and antagonism. However, the measure of spontaneous discharge rates poses a number of issues.

First, by measuring spontaneous activity to reflect the general excitability of MVN neurons, we are ignoring a potentially large proportion of MVN neurons that may no longer be active following UVD. Second, this makes assessment of the relative proportion of MVN neuronal subtypes following UVD very difficult. Third, spontaneous activity may be a relatively simple measure of the current state of excitation of a particular neuron. In other words, we may be detecting a temporary, hyper-excited neuronal state which does not accurately reflect the impact of UVD on neuronal function. Most importantly though, this measure gives us very little information on dynamic changes that may be induced by incoming inputs. Features such as potentiation and adaptation (see Chapter II, Section 2.2 for details) may change following UVD, however are not revealed by measuring spontaneous activity. Therefore, the assumption that the population of spontaneously active MVN neurons reflects the nature of all MVN neurons may not be accurate and introduce a positive measurement bias.

Using neuronal gain is arguably a more reliable, specific and complex measure of the changes in intrinsic excitability that could potentially occur following UVD. For example, work by Camp and colleagues reported that chronic reductions in inhibitory drive changed neuronal gains while leaving spontaneous discharge rates unchanged (Camp et al., 2010). My own work in the lateral geniculate nucleus in mice demonstrated that injected current noise can differentially alter the intrinsic excitability of neurons in a way that homogenises their outputs (Wijesinghe, Solomon & Camp, 2013). This measure was only revealed by calculating neuronal gains and not by measuring basic discharge rates in response to current steps. Indeed, in the studies by Ris and colleagues and Nelson and colleagues, intrinsic excitability changes were only evident when examining gain responses to current steps and ramps (Nelson et al., 2017; Ris et al., 2001a).
2.2 Mechanisms of intrinsic plasticity

The observed changes following UVD are a form of experience-dependent intrinsic plasticity. This phenomenon can be mediated by a number of mechanisms (See Chapter II, Section 2.3) and there is clear evidence for changes in ion channel conductances during the process of compensation. The defining feature of the B subtype can be considered to be the expression of channels that mediate the persistent sodium, low-threshold calcium and SK potassium conductances. As discussed above, firing rate increases can be mediated by modulation of potassium conductances that mediate the AHP. However, there were no clear differences in SK channel expression following UVD, suggesting an alternative mechanism for this change. There are clear acute changes in T-type channel expression, which is paralleled by an increase in the proportion of recordable type B neurons with LTS and plateau-like activity. More convincingly, BK channel inhibition appears to be less effective at increasing spontaneous discharge rates immediately following UVD, suggesting a downregulation of this current. This change also shows that dynamic properties such as FRP, which have also been directly correlated with changes in expression of BK channels in other neurons (Hull et al., 2013), can be occluded by UVD.

The ion conductances that have been observed to change are expressed on both subtypes of neurons. For example, BK channels are typically expressed primarily on type A neurons, while T-type channels are expressed solely on type B neurons. What this suggests is that UVD changes may affect both subtypes. However, there is a suggestion that UVD differentially alters type B neuron characteristics based on the following observations:

- Following UVD, there is a higher proportion of recordable type B than type A neurons
• Active type B neurons seem to display a larger increase in their spontaneous rate following UVD\(^{29}\), and they display more LTS activity, a characteristic of type B neurons

• Most of the observed changes following UVD appear to be concentrated to the rostral two thirds of the MVN (magnocellular part), which may contain a higher proportion of type B neurons

However, some of this evidence for a subtype-specific effect is circumstantial. Neuronal subtype was not explicitly delineated in a number of studies. Further, BK channels are typically expressed on type A neurons, yet the evidence implicating BK channel involvement was recorded from the rostral MVN where type B cells predominate. Could it be that, rather than converting MVN neurons between subtypes, UVD may reveal a continuum of excitability that is part of the homeostatic plasticity latent within the system? Such a mechanism has been suggested in the emergence of a third MVN neuron subtype in a model of chronic loss of inhibition within the MVN (Camp et al., 2010). Also, based on changes that are observed chronically following UVD, some have suggested that ipsilateral to the lesion, MVN neurons display more type A-like properties, while contralaterally they develop type B-like properties (Beraneck & Idoux, 2012).

Whether this form of intrinsic plasticity homogenises the division of neurons into subtypes by differentially modulating ion channels remains to be seen. What would assist in this distinction is elucidating the roles of different Na\(^+\) and SK channels following UVD. A dissection of detailed neuronal discharge dynamics in the presence of specific ion channel antagonists may help reveal the potential profiles of discharge that can emerge. The relative contribution of different potassium conductances appears to determine the diverse discharge rates in the transgenic mouse model that divides MVN neurons based on their

\(^{29}\) This subgroup could not be analysed through meta-analysis because this data is from a single study.
neurotransmitter output. The effect of labyrinthectomy acutely in this model may also help further our understanding of this process. Also, the sensitivity to GABA mediated inhibition appears to be attenuated following UVD. While GABA receptors are expressed on both type A and B neurons, glycine receptors are only expressed on type B neurons (see Table 2). Interestingly, there seems to be no differences in glycine receptor expression following UVD, however it is unclear whether their functional capacity changes. The changes in the responses to glycine following UVD may be instructive in delineating whether a change in subtype characteristics occurs.

### 2.3 Future directions

UVD has significant potential as a model of lesion-induced intrinsic plasticity because:

- There are easily observed behavioural and physiological consequences of the induced lesion
- There is no regeneration of the lesioned labyrinth or vestibular nerve, implying that observed changes are solely due to changes independent of sensory inputs
- The compensatory process occurs quickly, making experimentation pragmatic and feasible

However, there are a number of questions that remain unanswered by the current evidence base:

- Are there differences between the effect of UVD on neuronal subtypes in the acute phase of vestibular compensation? This question needs to be studied with a more comprehensive survey of both subtypes of neurons. In particular efforts should be
made to record responses to injected current stimuli in neurons that are made quiescent by UVD

- What are the ion channels that mediate the early increases in spontaneous activity? This question should be assessed by applying specific ion channel antagonists during the acute phase of UVD. Of particular interest would be the response to blockade of SK, BK, voltage-gated sodium and T-type calcium channels

- Do different types of current stimuli affect the nature of dynamic changes induced by UVD? The effect of current noise is of particular interest given recent developments in the use of vestibular prostheses employing stochastic noise galvanic stimulation (Goel et al., 2015; Wuehr, Decker & Schniepp, 2017)

- Will the methodological issues identified change the direction of effect observed in some of the studies performed to date? It would be instructive for some of the experiments to be re-examined with allocation concealment and stricter adherence to systematic methodological reporting
VI – CONCLUSIONS

In this thesis, I demonstrate that:

1. There are at least 17 reports of experiments that examine the effect of UVD on intrinsic properties of MVN neurons
2. The available data suggests that the intrinsic membrane properties of MVN neurons change following UVD. Using meta-analysis, the magnitude of this change is estimated to be an average increase in spontaneous discharge rates of 4 spikes/sec
3. There is no clear difference in intrinsic properties between the acute and subacute phase based on sub-group analysis that is revealed by using spontaneous discharge rates as a measure of neuronal excitability
4. The application of systematic review and meta-analysis techniques to basic experimental data is valid. However, this utility of these techniques is currently limited due to inconsistencies in the reporting of studies. There is room for improvement in the methodological reporting of studies in this field

Despite the presence of guidelines and reporting standards and for scientific reports, they are not often met or adhered to. Even systematic reviews and meta-analyses, which are held to be the highest standard of evidence, often do not consistently adhere to available guidelines (Cullis, Guðlaugsdóttir & Andrews, 2017; Page & Moher, 2017; Pussegoda et al., 2017), diluting the rigorous method that is applied. Imprecision is an ever important methodological concern (Collins, Ross & Lang, 2017; Moylan & Kowalczuk, 2016; Vogt et al., 2016) given the increasing translation of this basic data to drug development (Smith & Darlington, 1994) and prosthetic technologies (Lewis, 2016). This systematic review highlights that further rigour needs to be employed in the conduct and reporting of our animal experimental work.
## VII – APPENDICES

### Appendix 1 - Tables of Included studies

#### de Waele 1994

| Animal model | rat, unilateral labyrinthectomy via ischaemia (photocoagulation of the pterygopalatine artery) and mechanical disruption, compared to unoperated control |
|--------------|----------------------------------------------------------------------------------------------------------------------------------|
| Duration of compensation | 5 hours, 3 days, 3 weeks post labyrinthectomy |
| Recording type | visual identification cells labelled with antisense oligonucleotides against NMDA or metabotropic glutamate receptor |
| Sample size | control - 6 normal animals  
5 hours - 6 animals  
3 days - unclear, possibly 3 animals  
3 weeks - 6 animals |
| Outcome measure | number of silver grains per cell, silver grain density in cells |
| Notes | A total of 18 animals underwent labyrinthectomy, and those which did not display characteristic oculomotor or postural syndromes suggestive of a successful lesion were excluded from analysis. The number of excluded animals was not reported. There was inconsistent reporting of numbers of rats per experimental group in the methods and results. |

#### Cameron 1997 (*)

| Animal model | rat, unilateral labyrinthectomy via 100% ethanol injection, compared to sham-operated control |
|--------------|--------------------------------------------------------------------------------------------|
| Duration of compensation | 2, 4, 6, 24 and 48 hours post labyrinthectomy |
| Recording type | extracellular (presumed) recordings, ipsilesional |
| Sample size | control - 5 normal animals, 2 sham-operated, number undergoing UL unclear  
4 hours - 32 cells  
6 hours - 43 cells  
24 hours - 36 cells  
2 hours and 48 hours groups reported graphically, not numerically |
| --- | --- |
| Outcome measure | mean spontaneous discharge rate, spikes/second |
| Notes | Unclear from reporting how many animals underwent labyrinthectomy. Sprague-Dawley rats used for experimentation were at the lower end of maturity (60-120g) raising concerns about developmental stage. There was selective reporting of outcomes, with 2 and 48 hour rates reported graphically rather than numerically. |

*Cameron 1999 (*)*

| Animal model | rat, unilateral labyrinthectomy via 100% ethanol injection, compared to sham-operated control |
| --- | --- |
| Duration of compensation | 4 or 6 hours |
| Recording type | single unit extracellular recordings, ipsilesional |
| Sample size | control - 9 sham-operated animals, 41 neurons  
UL - 9 animals, 61 neurons |
| Outcome measure | mean spontaneous discharge rate, spikes/second |
| Notes | The type of animal and their baseline characteristics such as sex and age were not stated in the report/ Additional interventions studied - no withdrawal of anaesthesia following labyrinthectomy, and administration of dexamethasone or dexamethasone antagonist (RU38486) |

*Vibert 1999*

| Animal model | guinea pig, unilateral labyrinthectomy via mechanical disruption, compared to unoperated control |
| Duration of compensation | 1 day, 3-7 days (latter group pooled following analysis) |
|--------------------------|-------------------------------------------------------|
| Recording type           | single unit extracellular recordings and field potentials, ipsilesional and contralesional |
| Sample size              | Total of 65 animals                                  |
|                          | 1 day - 14 animals                                   |
|                          | 3 days - 26 animals                                  |
|                          | 5 days - 10 animals                                  |
|                          | 7 days - 15 animals                                  |
| Outcome measure          | mean spontaneous discharge rate, spikes/second       |
|                          | evoked field potentials following stimulation of the vestibular and abducens nerves |
| Notes                    | The method of confirmation of success of inducing Bechterew’s phenomenon (see text for details) using radiography was the most quantitative method amongst all included studies. An unclear number of animals were excluded the stated reason being the difficulty of the surgical procedure yielding ‘unusable data’ |

**Yamanaka 2000 (*)**

| Animal model               | rat, unilateral labyrinthectomy via ethanol injection, compared to unoperated control |
|----------------------------|-------------------------------------------------------------------------------------|
| Duration of compensation   | 4 hours                                                                             |
| Recording type             | extracellular whole cell, ipsilesional                                               |
| Sample size                | control - 28 animals, 77 cells                                                      |
|                            | 4 hours - 44 animals, 63 rostral cells, 43 caudal cells                             |
| Outcome measure            | mean spontaneous discharge rate, spikes/second                                      |
|                            | dose of GABA agonist required to inhibit tonic resting activity                     |
| Notes                      | Rostral and caudal MVN neurons were analysed separately in the study and therefore analysed separately in the meta-analysis |

**Him 2001 (*)**

| Animal model               | rat, unilateral labyrinthectomy via 100% ethanol injection, compared to normal     |
| Duration of compensation | 1-3 days, 7-10 days |
|--------------------------|---------------------|
| Recording type           | intracellular patch clamp, ipsilesional |
| Sample size              | control - 44 animals |
|                          | 1-3 day - 34 rats, 90 cells |
|                          | 7-10 day - 25 rats, 84 cells |
| Outcome measure          | mean spontaneous discharge rate, spikes/second |
|                          | action potential morphology |
| Notes                    | The inclusion criteria are mentioned in the body of the results, however there is no clear statement as to what these are. Some data is lost without clear accounting for this |

**Johnston 2001 (*)**

| Animal model                  | rat, unilateral labyrinthectomy via 100% ethanol injection, compared to normal |
|-------------------------------|--------------------------------------------------------------------------------|
| Duration of compensation      | 4 and 24 hours, 2 and 7-10 days                                                 |
| Recording type                | single unit extracellular recordings, ipsilesional                              |
| Sample size                   | control - 25 cells                                                              |
|                               | 2 days - 42 cells                                                              |
|                               | 7-10 days - 40 cells                                                           |
|                               | Unclear how many animals in control group or underwent UL                       |
| Outcome measure               | mean spontaneous discharge rate, spikes/second                                  |
| Notes                         | Control, 4 and 24 hour data was obtained from a previous study and therefore not included in the current set of data |

**Ris 2001 (*)**

| Animal model                  | guinea pig, unilateral labyrinthectomy via mechanical disruption, compared to normal |
|-------------------------------|-------------------------------------------------------------------------------------|
| Duration of compensation      | 2 and 7 days                                                                       |
| Recording type                | single unit extracellular recordings, ipsilesional                                  |
| Sample size                   | control - 10 animals, 57 cells                                                      |
| Animal model | rat, unilateral labyrinthectomy via 100% ethanol injection, compared to normal and animals that had undergone flocculectomy |
| Duration of compensation | 4 hours and 2 days |
| Recording type | single unit extracellular recordings, ipsilesional |
| Sample size | control - 5 animals, 189 cells  
4 hours - 5 animals, 187 cells  
2 days - 5 animals, 126 cells |
| Outcome measure | mean spontaneous discharge rate, spikes/second |
| Notes | Numerical data could not be extracted in sufficient detail from the study for inclusion in the meta-analysis as it was presented graphically |

*Ris 2002*

| Animal model | guinea pig, unilateral labyrinthectomy via mechanical disruption and ototoxic antibiotic injection, compared to normal |
| Duration of compensation | 7 days |
| Recording type | intracellular patch clamp recordings, ipsilesional |
| Sample size | control - 38 cells  
7 days - 38 cells |
| Outcome measure | steady state gain (spikes/s/nA)  
dynamic responsiveness (the ratio of maximal firing rate to steady state rate following ramp-plateau current inputs) |
### Patko 2003

| Animal model | Rats, unilateral labyrinthectomy by mechanical disruption, compared to unoperated controls |
|--------------|--------------------------------------------------------------------------------------|
| Duration of compensation | 1, 3, 8, and 30 days |
| Recording type | *In situ* hybridisation using mRNA probes to sodium and potassium channels |
| Sample size | total – 42 rats  
3 rats for each channel and time point |
| Outcome measure | Optical density of labelling |
| Notes | |

### Ris 2003

| Animal model | guinea pig, unilateral labyrinthectomy (UL) via mechanical disruption and ototoxic antibiotic injection, compared to normal |
|--------------|----------------------------------------------------------------------------------------------------------------------------------|
| Duration of compensation | 7 days |
| Recording type | Intracellular patch clamp recordings, ipsilesional  
Immunohistochemistry labelling calcium channel proteins |
| Sample size | Control – 28 animals, 41 cells  
7 days – 21 animals, 43 cells |
| Outcome measure | Spike discharge characteristics  
Changes in immunohistochemical staining patterns |
| Notes | |

### Eleore 2004

| Animal model | rat, unilateral labyrinthectomy (UL) via mechanical disruption, compared to unoperated control |
|--------------|-----------------------------------------------------------------------------------------------|
| Duration of compensation | 5 hours, 1, 3, 8, 30 and 60 days |
|--------------------------|----------------------------------|
| Recording type           | *In situ* hybridisation using mRNA probes to glycine receptor subunits and an anchor protein gephyrin, detected using autoradiography or immunofluorescence |
| Sample size              | Total – 60 rats                   |
|                          | Control – 12 animals, 6 used in final analysis |
|                          | Experimental - 48 animals, 36 used in final analysis, with 3 animals per experimental group |
| Outcome measure          | Optical density of labelling      |
|                          | Intensity of immunofluorescence   |
| Notes                    | The discrepancy between the original number of animals included in each group and the number used in the final analysis is presumed to be due to exclusion because of failure to compensate post labyrinthectomy, however this is not explicitly stated. |

**Guilding 2004**

| Animal model               | rat, unilateral labyrinthectomy via 100% ethanol injection, compared to sham operated control |
|----------------------------|--------------------------------------------------------------------------------------------|
| Duration of compensation   | 4 hours                                                                                     |
| Recording type             | Thin layer chromatography (TLC), quantified by optical densitometry                          |
| Sample size                | Sham control – 16 animals                                                                   |
|                            | 4 hours – 16 animals                                                                        |
| Outcome measure            | Change in density on TLC                                                                    |
| Notes                      |                                                                                             |

**Guilding 2005**

| Animal model               | rat, unilateral labyrinthectomy via ethanol injection, compared to unoperated control       |
|----------------------------|--------------------------------------------------------------------------------------------|
| Duration of compensation   | 4 and 48 hours, and 7 days                                                                  |
| Recording type | extracellular whole cell, ipsilesional, before and after application of a cocktail of neurotransmitter antagonists (for blockade of GABA$_A$, GABA$_B$, glycine, AMPA and NMDA receptors) |
|----------------|---------------------------------------------------------------------------------------------------------------------------------|
| Sample size    | Unclear how many animals were used in experiment control – 85 cells, 75 cells synaptic blockade 4 hours – 76 cells, 70 cells synaptic blockade 48 hours – 82 cells, 80 cells synaptic blockade 7 days - 90 cells, 90 cells synaptic blockade |
| Outcome measure| mean spontaneous discharge rate, spikes/second |
| Notes          | Rostral and caudal MVN neurons were analysed separately in the study. Numerical data could not be extracted in sufficient detail from the study for inclusion in the meta-analysis as it was presented graphically |

**Nelson 2017**

| Animal model | mouse, unilateral labyrinthectomy via mechanical disruption, compared to sham-operated control |
|--------------|-----------------------------------------------------------------------------------------------|
| Duration of compensation | 1, 3, 7, 21 days |
| Recording type | intracellular patch-clamp, ipsilesional ion channel protein expression ocular videography |
| Sample size | At least 6 animals 8 hours – 140 sham operated cells, 156 UL cells 1 day – 142 sham operated cells, 131 UL cells 3 days – 91 sham operated cells, 112 UL cells 7 days – 96 sham operated cells, 105 UL cells 21 days – 63 sham operated cells, 62 UL cells |
| Outcome measure | mean spontaneous discharge rate gain firing rate potentiation |
| Notes | Blinding of intervention allocation from investigators Additional interventions studied: iberiotoxin application It was unclear how many animals were used throughout the experiment and how many were in each experimental group. |
Appendix 2 - Search strategies

Medline search:
medial vestibular.mp or MVN.mp
labyrinthectomy.mp or labyrinthectomy*
deafferentation.mp or deafferent*
neurectomy.mp
lesion*
compensation.mp
intrinsic.mp
ion channels/
Action Potentials/
Membrane Potentials/
excitability.mp
(1 or 2) AND (3 or 4 or 5 or 6 or 7) AND (8 or 9 or 10 or 11 or 12)

Embase search:
medial vestibular.mp
MVN.mp
labyrinthectomy.mp or labyrinthectomy/
deafferentation.mp or deafferentation/
neurectomy.mp or neurectomy/
lesion*.mp
compensation.mp or compensation/
intrinsic.mp
ion channel.mp or ion channels/
action potential.mp or Action Potential/
membrane potential.mp or Membrane Potential/

excitability.mp or excitability/ or nerve cell excitability/
Appendix 3 – Work published during candidature

I have contributed to a number of published articles during my candidature:

Mathews, M. A., F. Mohammed Ali, R. Wijesinghe and A. J. Camp 2017, ‘Heading in the right direction: the importance of direction selectivity for cerebellar motor learning.’ *J Physiol.* In press

Mathews, M. A., A. Murray, R. Wijesinghe, K. Cullen, V. W. Tung and A. J. Camp 2015. ‘Efferent Vestibular Neurons Show Homogenous Discharge Output But Heterogeneous Synaptic Input Profile In Vitro.’ *PLoS One*, vol. 10, no. 9, e0139548.

Wijesinghe, R., D. A. Protti and A. J. Camp 2015. ‘Vestibular Interactions in the Thalamus.’ *Front Neural Circuits*, vol 9, no. 79.

Wijesinghe, R., V. W. Tung, A. J. Camp, D. A. Protti and M. A. Mathews 2015. ‘Exciting potential: the importance of the right environment.’ *J Physiol*, vol. 593, no. 10, pp. 2253-2255.
Aizenman, CD, Akerman, CJ, Jensen, KR & Cline, HT 2003, 'Visually driven regulation of intrinsic neuronal excitability improves stimulus detection in vivo', *Neuron*, vol. 39, no. 5, pp. 831-42.

Alice, C, Paul, AE, Sansom, AJ, Maclennan, K, Darlington, CL & Smith, PF 1998, 'The effects of steroids on vestibular compensation and vestibular nucleus neuronal activity in the guinea pig', *J Vestib Res*, vol. 8, no. 3, pp. 201-7.

Altman, DG 1996, 'Better reporting of randomised controlled trials: the CONSORT statement', *BMJ*, vol. 313, no. 7057, pp. 570-1.

Andrade, C 2011, 'How to write a good abstract for a scientific paper or conference presentation', *Indian J Psychiatry*, vol. 53, no. 2, pp. 172-5.

Angelaki, DE & Cullen, KE 2008, 'Vestibular system: the many facets of a multimodal sense', *Annu Rev Neurosci*, vol. 31, pp. 125-50.

Arndt, SS, Laarakker, MC, Van Lith, HA, Van Der Staay, FJ, Gieling, E, Salomons, AR, Van't Klooster, J & Ohl, F 2009, 'Individual housing of mice--impact on behaviour and stress responses', *Physiol Behav*, vol. 97, no. 3-4, pp. 385-93.

Baarsma, EA & Collewijn, H 1975, 'Changes in compensatory eye movements after unilateral labyrinthectomy in the rabbit', *Arch Otorhinolaryngol*, vol. 211, no. 4, pp. 219-30.

Babalian, A, Vibert, N, Assie, G, Serafin, M, Muhlethal, M & Vidal, PP 1997, 'Central vestibular networks in the guinea-pig: functional characterization in the isolated whole brain in vitro', *Neuroscience*, vol. 81, no. 2, pp. 405-26.

Babalian, AL & Vidal, PP 2000, 'Floccular modulation of vestibuloocular pathways and cerebellum-related plasticity: An in vitro whole brain study', *J Neurophysiol*, vol. 84, no. 5, pp. 2514-28.

Bagnall, MW, Stevens, RJ & Du Lac, S 2007, 'Transgenic mouse lines subdivide medial vestibular nucleus neurons into discrete, neurochemically distinct populations', *J Neurosci*, vol. 27, no. 9, pp. 2318-30.
Bailey, CH, Kandel, ER & Harris, KM 2015, 'Structural Components of Synaptic Plasticity and Memory Consolidation', Cold Spring Harb Perspect Biol, vol. 7, no. 7, pp. a021758.

Baird, RA, Desmadryl, G, Fernandez, C & Goldberg, JM 1988, 'The vestibular nerve of the chinchilla. II. Relation between afferent response properties and peripheral innervation patterns in the semicircular canals', J Neurophysiol, vol. 60, no. 1, pp. 182-203.

Balaban, CD, Hoffer, ME & Gottshall, KR 2012, 'Top-down approach to vestibular compensation: translational lessons from vestibular rehabilitation', Brain Res, vol. 1482, pp. 101-11.

Baloh, RW, Honrubia, V, Yee, RD & Hess, K 1984, 'Changes in the human vestibulo-ocular reflex after loss of peripheral sensitivity', Ann Neurol, vol. 16, no. 2, pp. 222-8.

Barker, BS, Nigam, A, Ottolini, M, Gaykema, RP, Hargus, NJ & Patel, MK 2017, 'Pro-excitatory alterations in sodium channel activity facilitate subiculum neuron hyperexcitability in temporal lobe epilepsy', Neurobiol Dis, vol. 108, pp. 183-194.

Bean, BP 2007, 'The action potential in mammalian central neurons', Nat Rev Neurosci, vol. 8, no. 6, pp. 451-65.

Beck, H & Yaari, Y 2008, 'Plasticity of intrinsic neuronal properties in CNS disorders', Nat Rev Neurosci, vol. 9, no. 5, pp. 357-69.

Benecke, H, Agus, S, Kuessner, D, Goodall, G & Strupp, M 2013, 'The Burden and Impact of Vertigo: Findings from the REVERT Patient Registry', Front Neurol, vol. 4, pp. 136.

Beraneck, M, Hachemaoui, M, Idoux, E, Ris, L, Uno, A, Godaux, E, Vidal, PP, Moore, LE & Vibert, N 2003, 'Long-term plasticity of ipsilesional medial vestibular nucleus neurons after unilateral labyrinthectomy', Journal of Neurophysiology, vol. 90, no. 1, pp. 184-203.

Beraneck, M & Idoux, E 2012, 'Reconsidering the role of neuronal intrinsic properties and neuromodulation in vestibular homeostasis', Front Neurol, vol. 3, pp. 25.
Beraneck, M, Idoux, E, Uno, A, Vidal, PP, Moore, LE & Vibert, N 2004, 'Unilateral labyrinthectomy modifies the membrane properties of contralesional vestibular neurons', Journal of Neurophysiology, vol. 92, no. 3, pp. 1668-84.

Beraneck, M, Uno, A, Vassias, I, Idoux, E, De Waele, C, Vidal, PP & Vibert, N 2009, 'Evidence against a role of gap junctions in vestibular compensation', Neuroscience Letters, vol. 450, no. 2, pp. 97-101.

Berger, T, Larkum, ME & Luscher, HR 2001, 'High I(h) channel density in the distal apical dendrite of layer V pyramidal cells increases bidirectional attenuation of EPSPs', J Neurophysiol, vol. 85, no. 2, pp. 855-68.

Bernard, C, Anderson, A, Becker, A, Poolos, NP, Beck, H & Johnston, D 2004, 'Acquired dendritic channelopathy in temporal lobe epilepsy', Science, vol. 305, no. 5683, pp. 532-5.

Berwanger, O, Ribeiro, RA, Finkelsztejn, A, Watanabe, M, Suzumura, EA, Duncan, BB, Devereaux, PJ & Cook, D 2009, 'The quality of reporting of trial abstracts is suboptimal: survey of major general medical journals', J Clin Epidemiol, vol. 62, no. 4, pp. 387-92.

Beutner, D, Voets, T, Neher, E & Moser, T 2001, 'Calcium dependence of exocytosis and endocytosis at the cochlear inner hair cell afferent synapse', Neuron, vol. 29, no. 3, pp. 681-90.

Black, FO & Nashner, LM 1984, 'Vestibulo-spinal control differs in patients with reduced versus distorted vestibular function', Acta Otolaryngol Suppl, vol. 406, pp. 110-4.

Black, FO, Shupert, CL, Peterka, RJ & Nashner, LM 1989, 'Effects of unilateral loss of vestibular function on the vestibulo-ocular reflex and postural control', Ann Otol Rhinol Laryngol, vol. 98, no. 11, pp. 884-9.

Blumenfeld, H, Lampert, A, Klein, JP, Mission, J, Chen, MC, Rivera, M, Dib-Hajj, S, Brennan, AR, Hains, BC & Waxman, SG 2009, 'Role of hippocampal sodium channel Nav1.6 in kindling epileptogenesis', Epilepsia, vol. 50, no. 1, pp. 44-55.
Bolger, C, Sansom, AJ, Smith, PF & Darlington, CL 1999, 'An antisense oligonucleotide to brain-derived neurotrophic factor delays postural compensation following unilateral labyrinthectomy in guinea pig', *Neuroreport*, vol. 10, no. 7, pp. 1485-8.

Bonsacquet, J, Brugaud, A, Compan, V, Desmadryl, G & Chabbert, C 2006, 'AMPA type glutamate receptor mediates neurotransmission at turtle vestibular calyx synapse', *J Physiol*, vol. 576, no. Pt 1, pp. 63-71.

Borel, L, Lopez, C, Peruch, P & Lacour, M 2008, 'Vestibular syndrome: a change in internal spatial representation', *Neurophysiol Clin*, vol. 38, no. 6, pp. 375-89.

Borel, L, Redon-Zouiteni, C, Cauvin, P, Dumitrescu, M, Deveze, A, Magnan, J & Peruch, P 2014, 'Unilateral vestibular loss impairs external space representation', *PLoS One*, vol. 9, no. 2, pp. e88576.

Brandt, T, Schautzer, F, Hamilton, DA, Bruning, R, Markowitsch, HJ, Kalla, R, Darlington, C, Smith, P & Strupp, M 2005, 'Vestibular loss causes hippocampal atrophy and impaired spatial memory in humans', *Brain*, vol. 128, no. Pt 11, pp. 2732-41.

Bronstein, AM, Patel, M & Arshad, Q 2015, 'A brief review of the clinical anatomy of the vestibular-ocular connections-how much do we know?', *Eye (Lond)*, vol. 29, no. 2, pp. 163-70.

Buttner-Ennever, JA 1992, 'Patterns of connectivity in the vestibular nuclei', *Ann N Y Acad Sci*, vol. 656, pp. 363-78.

Cameron, SA & Dutia, MB 1997, 'Cellular basis of vestibular compensation: changes in intrinsic excitability of MVN neurones', *Neuroreport*, vol. 8, no. 11, pp. 2595-9.

Cameron, SA & Dutia, MB 1999, 'Lesion-induced plasticity in rat vestibular nucleus neurones dependent on glucocorticoid receptor activation', *Journal of Physiology*, vol. 518, no. 1, pp. 151-158.

Camp, AJ 2012, 'Intrinsic neuronal excitability: a role in homeostasis and disease', *Front Neurol*, vol. 3, pp. 1-2.
Camp, AJ, Callister, RJ & Brichta, AM 2006, 'Inhibitory synaptic transmission differs in mouse type A and B medial vestibular nucleus neurons in vitro', J Neurophysiol, vol. 95, no. 5, pp. 3208-18.

Camp, AJ, Lim, R, Anderson, WB, Schofield, PR, Callister, RJ & Brichta, AM 2010, 'Attenuated glycine receptor function reduces excitability of mouse medial vestibular nucleus neurons', Neuroscience, vol. 170, no. 1, pp. 348-360.

Camp, AJ & Wijesinghe, R 2009, 'Calretinin: modulator of neuronal excitability', Int J Biochem Cell Biol, vol. 41, no. 11, pp. 2118-21.

Cass, SP & Goshgarian, HG 1991, 'Vestibular compensation after labyrinthectomy and vestibular neurectomy in cats', Otolaryngol Head Neck Surg, vol. 104, no. 1, pp. 14-9.

Cass, SP, Kartush, JM & Graham, MD 1992, 'Patterns of vestibular function following vestibular nerve section', Laryngoscope, vol. 102, no. 4, pp. 388-94.

Castellucci, V, Pinsker, H, Kupfermann, I & Kandel, ER 1970, 'Neuronal mechanisms of habituation and dishabituation of the gill-withdrawal reflex in Aplysia', Science, vol. 167, no. 3926, pp. 1745-8.

Ceballos, CC, Roque, AC & Leao, RM 2017, 'A Negative Slope Conductance of the Persistent Sodium Current Prolongs Subthreshold Depolarizations', Biophys J, vol. 113, no. 10, pp. 2207-2217.

Champney, T 2016, Essential Clinical Neuroanatomy, 1st ed. edn, Wiley, Oxford.

Chapuis, N, Krimm, M, De Waele, C, Vibert, N & Berthoz, A 1992, 'Effect of post-training unilateral labyrinthectomy in a spatial orientation task by guinea pigs', Behav Brain Res, vol. 51, no. 2, pp. 115-26.

Chen, F, Moran, JT, Zhang, Y, Ates, KM, Yu, D, Schrader, LA, Das, PM, Jones, FE & Hall, BJ 2016, 'The transcription factor NeuroD2 coordinates synaptic innervation and cell intrinsic properties to control excitability of cortical pyramidal neurons', J Physiol, vol. 594, no. 13, pp. 3729-44.

Cheung, MW, Ho, RC, Lim, Y & Mak, A 2012, 'Conducting a meta-analysis: basics and good practices', Int J Rheum Dis, vol. 15, no. 2, pp. 129-35.
Child, ND & Benarroch, EE 2014, 'Differential distribution of voltage-gated ion channels in cortical neurons: implications for epilepsy', Neurology, vol. 82, no. 11, pp. 989-99.

Cohen, J 1992, 'A power primer', Psychol Bull, vol. 112, no. 1, pp. 155-9.

Collins, A, Ross, J & Lang, SH 2017, 'A systematic review of the asymmetric inheritance of cellular organelles in eukaryotes: A critique of basic science validity and imprecision', PLoS One, vol. 12, no. 5, pp. e0178645.

Cook, DJ, Mulrow, CD & Haynes, RB 1997, 'Systematic reviews: synthesis of best evidence for clinical decisions', Ann Intern Med, vol. 126, no. 5, pp. 376-80.

Crill, WE 1996, 'Persistent sodium current in mammalian central neurons', Annu Rev Physiol, vol. 58, pp. 349-62.

Cullen, KE 2016, 'Physiology of central pathways', Handb Clin Neurol, vol. 137, pp. 17-40.

Cullen, KE & Mccrea, RA 1993, 'Firing behavior of brain stem neurons during voluntary cancellation of the horizontal vestibuloocular reflex. I. Secondary vestibular neurons', J Neurophysiol, vol. 70, no. 2, pp. 828-43.

Cullen, KE, Minor, LB, Beranec, M & Sadeghi, SG 2009, 'Neural substrates underlying vestibular compensation: contribution of peripheral versus central processing', J Vestib Res, vol. 19, no. 5-6, pp. 171-82.

Cullis, PS, Gudlaugsdottir, K & Andrews, J 2017, 'A systematic review of the quality of conduct and reporting of systematic reviews and meta-analyses in paediatric surgery', PLoS One, vol. 12, no. 4, pp. e0175213.

Curthoys, IS 1982, 'The response of primary horizontal semicircular canal neurons in the rat and guinea pig to angular acceleration', Exp Brain Res, vol. 47, no. 2, pp. 286-94.

Curthoys, IS 2000, 'Vestibular compensation and substitution', Curr Opin Neurol, vol. 13, no. 1, pp. 27-30.

Curthoys, IS & Halmagyi, GM 1992, 'Behavioural and neural correlates of vestibular compensation', Baillieres Clin Neurol, vol. 1, no. 2, pp. 345-72.
Curthoys, IS & Halmagyi, GM 1995, 'Vestibular compensation: a review of the oculomotor, neural, and clinical consequences of unilateral vestibular loss', J Vestib Res, vol. 5, no. 2, pp. 67-107.

Curthoys, IS & Halmagyi, GM 1999, 'Vestibular compensation', Adv Otorhinolaryngol, vol. 55, pp. 82-110.

Curthoys, IS, Smith, PF & Darlington, CL 1988, 'Postural compensation in the guinea pig following unilateral labyrinthectomy', Prog Brain Res, vol. 76, pp. 375-84.

Darlington, CL, Dutia, MB & Smith, PF 2002, 'The contribution of the intrinsic excitability of vestibular nucleus neurons to recovery from vestibular damage', Eur J Neurosci, vol. 15, no. 11, pp. 1719-27.

Darlington, CL, Gallagher, JP & Smith, PF 1995, 'In vitro electrophysiological studies of the vestibular nucleus complex', Prog Neurobiol, vol. 45, no. 4, pp. 335-46.

Darlington, CL & Smith, PF 1996, 'The recovery of static vestibular function following peripheral vestibular lesions in mammals: the intrinsic mechanism hypothesis', J Vestib Res, vol. 6, no. 3, pp. 185-201.

Darlington, CL & Smith, PF 2000, 'Molecular mechanisms of recovery from vestibular damage in mammals: recent advances', Prog Neurobiol, vol. 62, no. 3, pp. 313-25.

Darlington, CL, Smith, PF & Hubbard, JI 1989, 'Neuronal activity in the guinea pig medial vestibular nucleus in vitro following chronic unilateral labyrinthectomy', Neuroscience Letters, vol. 105, no. 1-2, pp. 143-148.

De Vries, RB, Wever, KE, Avey, MT, Stephens, ML, Sena, ES & Leenaars, M 2014, 'The usefulness of systematic reviews of animal experiments for the design of preclinical and clinical studies', ILAR J, vol. 55, no. 3, pp. 427-37.

De Waele, C, Abitbol, M, Chat, M, Menini, C, Mallet, J & Vidal, PP 1994, 'Distribution of glutamatergic receptors and GAD mRNA-containing neurons in the vestibular nuclei of normal and hemilabyrinthectomized rats', European Journal of Neuroscience, vol. 6, no. 4, pp. 565-576.
De Waele, C, Serafin, M, Khateb, A, Yabe, T, Vidal, PP & Muhlethaler, M 1993, 'Medial vestibular nucleus in the guinea-pig: apamin-induced rhythmic burst firing--an in vitro and in vivo study', Exp Brain Res, vol. 95, no. 2, pp. 213-22.

Deroualle, D & Lopez, C 2014, 'Toward a vestibular contribution to social cognition', Front Integr Neurosci, vol. 8, pp. 16.

Dersimonian, R & Laird, N 1986, 'Meta-analysis in clinical trials', Control Clin Trials, vol. 7, no. 3, pp. 177-88.

Desai, NS 2003, 'Homeostatic plasticity in the CNS: synaptic and intrinsic forms', J Physiol Paris, vol. 97, no. 4-6, pp. 391-402.

Deveze, A, Bernard-Demanze, L, Xavier, F, Lavieille, JP & Elziere, M 2014, 'Vestibular compensation and vestibular rehabilitation. Current concepts and new trends', Neurophysiol Clin, vol. 44, no. 1, pp. 49-57.

Dickman, JD & Angelaki, DE 2004, 'Dynamics of vestibular neurons during rotational motion in alert rhesus monkeys', Exp Brain Res, vol. 155, no. 1, pp. 91-101.

Driscoll, HE, Muraro, NI, He, M & Baines, RA 2013, 'Pumilio-2 regulates translation of Nav1.6 to mediate homeostasis of membrane excitability', J Neurosci, vol. 33, no. 23, pp. 9644-54.

Duensing, F & Schaefer, KP 1958, 'The activity of single neurons in the region of vestibular nuclei in horizontal acceleration, with special reference to vestibular nystagmus', Arch Psychiatr Nervenkr Z Gesamte Neurol Psychiatr, vol. 198, no. 2, pp. 225-52.

Dumenieu, M, Oule, M, Kreutz, MR & Lopez-Rojas, J 2017, 'The Segregated Expression of Voltage-Gated Potassium and Sodium Channels in Neuronal Membranes: Functional Implications and Regulatory Mechanisms', Front Cell Neurosci, vol. 11, pp. 115.

Dutia, MB 2010, 'Mechanisms of vestibular compensation: recent advances', Curr Opin Otolaryngol Head Neck Surg, vol. 18, no. 5, pp. 420-4.

Epema, AH, Gerrits, NM & Voogd, J 1988, 'Commissural and intrinsic connections of the vestibular nuclei in the rabbit: a retrograde labeling study', Exp Brain Res, vol. 71, no. 1, pp. 129-46.
Eugene, D, Deforges, S, Guimont, F, Idoux, E, Vidal, PP, Moore, LE & Vibert, N 2007, 'Developmental regulation of the membrane properties of central vestibular neurons by sensory vestibular information in the mouse', *J Physiol*, vol. 583, no. Pt 3, pp. 923-43.

Faber, ES 2009, 'Functions and modulation of neuronal SK channels', *Cell Biochem Biophys*, vol. 55, no. 3, pp. 127-39.

Fernandez, C & Goldberg, JM 1971, 'Physiology of peripheral neurons innervating semicircular canals of the squirrel monkey. II. Response to sinusoidal stimulation and dynamics of peripheral vestibular system', *J Neurophysiol*, vol. 34, no. 4, pp. 661-75.

Fernandez, C & Goldberg, JM 1976, 'Physiology of peripheral neurons innervating otolith organs of the squirrel monkey. II. Directional selectivity and force-response relations', *J Neurophysiol*, vol. 39, no. 5, pp. 985-95.

Fetter, M 2016, 'Acute unilateral loss of vestibular function', *Handb Clin Neurol*, vol. 137, pp. 219-29.

Fetter, M & Zee, DS 1988, 'Recovery from unilateral labyrinthectomy in rhesus monkey', *J Neurophysiol*, vol. 59, no. 2, pp. 370-93.

Fetter, M, Zee, DS & Proctor, LR 1988, 'Effect of lack of vision and of occipital lobectomy upon recovery from unilateral labyrinthectomy in rhesus monkey', *J Neurophysiol*, vol. 59, no. 2, pp. 394-407.

Fisch, U 1973, 'The vestibular response following unilateral vestibular neurectomy', *Acta Otolaryngol*, vol. 76, no. 4, pp. 229-38.

Frazzini, V, Guarnieri, S, Bomba, M, Navarra, R, Morabito, C, Mariggio, MA & Sensi, SL 2016, 'Altered Kv2.1 functioning promotes increased excitability in hippocampal neurons of an Alzheimer's disease mouse model', *Cell Death Dis*, vol. 7, pp. e2100.

Gallagher, JP, Lewis, MR & Gallagher, PS 1985, 'An electrophysiological investigation of the rat medial vestibular nucleus in vitro', *Prog Clin Biol Res*, vol. 176, pp. 293-304.
Ghimire, S, Kyung, E, Lee, H & Kim, E 2014, 'Oncology trial abstracts showed suboptimal improvement in reporting: a comparative before-and-after evaluation using CONSORT for Abstract guidelines', J Clin Epidemiol, vol. 67, no. 6, pp. 658-66.

Gilchrist, DP, Curthoys, IS, Cartwright, AD, Burgess, AM, Topple, AN & Halmagyi, M 1998, 'High acceleration impulsive rotations reveal severe long-term deficits of the horizontal vestibulo-ocular reflex in the guinea pig', Exp Brain Res, vol. 123, no. 3, pp. 242-54.

Gillespie, PG & Muller, U 2009, 'Mechanotransduction by hair cells: models, molecules, and mechanisms', Cell, vol. 139, no. 1, pp. 33-44.

Gittis, AH & Du Lac, S 2007, 'Firing properties of GABAergic versus non-GABAergic vestibular nucleus neurons conferred by a differential balance of potassium currents', J Neurophysiol, vol. 97, no. 6, pp. 3986-96.

Gittis, AH & Du Lac, S 2008, 'Similar properties of transient, persistent, and resurgent Na currents in GABAergic and non-GABAergic vestibular nucleus neurons', J Neurophysiol, vol. 99, no. 5, pp. 2060-5.

Gittis, AH, Moghadam, SH & Du Lac, S 2010, 'Mechanisms of sustained high firing rates in two classes of vestibular nucleus neurons: differential contributions of resurgent Na, Kv3, and BK currents', J Neurophysiol, vol. 104, no. 3, pp. 1625-34.

Gliddon, CM, Darlington, CL & Smith, PF 2005, 'GABAergic systems in the vestibular nucleus and their contribution to vestibular compensation', Prog Neurobiol, vol. 75, no. 1, pp. 53-81.

Goel, R, Kofman, I, Jeevarajan, J, De Dios, Y, Cohen, HS, Bloomberg, JJ & Mulavara, AP 2015, 'Using Low Levels of Stochastic Vestibular Stimulation to Improve Balance Function', PLoS One, vol. 10, no. 8, pp. e0136335.

Goldberg, JM & Brichta, AM 2002, 'Functional analysis of whole cell currents from hair cells of the turtle posterior crista', J Neurophysiol, vol. 88, no. 6, pp. 3279-92.
Goldberg, JM, Wilson, VJ, Cullen, KE, Angelaki, DE, Broussard, DM, Buttner-Ennever, JA, Fukushima, M & Minor, LB 2012, The Vestibular System: A Sixth Sense, Oxford University Press, London.

Goto, F, Straka, H & Dieringer, N 2000, 'Expansion of afferent vestibular signals after the section of one of the vestibular nerve branches', J Neurophysiol, vol. 84, no. 1, pp. 581-4.

Goto, F, Straka, H & Dieringer, N 2001, 'Postlesional vestibular reorganization in frogs: evidence for a basic reaction pattern after nerve injury', J Neurophysiol, vol. 85, no. 6, pp. 2643-6.

Gough, D, Oliver, S & Thomas, J 2017, An introduction to systematic reviews, Second edn, SAGE, Los Angeles.

Grassi, S, Frondaroli, A, Scarduzio, M, Dutia, MB, Dieni, C & Pettorossi, VE 2010, 'Effects of 17beta-estradiol on glutamate synaptic transmission and neuronal excitability in the rat medial vestibular nuclei', Neuroscience, vol. 165, no. 4, pp. 1100-14.

Guilding, C & Dutia, MB 2005, 'Early and late changes in vestibular neuronal excitability after deafferentation', NeuroReport, vol. 16, no. 13, pp. 1415-1418.

Guilding, C, Seckl, JR & Dutia, MB 2004, '11Beta-hydroxysteroid dehydrogenase type 1 activity in medial vestibular nucleus and cerebellum after unilateral vestibular deafferentation in the rat', Stress, vol. 7, no. 2, pp. 127-30.

Haddad, GM, Friendlich, AR & Robinson, DA 1977, 'Compensation of nystagmus after VIIIth nerve lesions in vestibulo-cerebellectomized cats', Brain Res, vol. 135, no. 1, pp. 192-6.

Halmagyi, GM, Curthoys, IS, Brandt, T & Dieterich, M 1991, 'Ocular tilt reaction: clinical sign of vestibular lesion', Acta Otolaryngol Suppl, vol. 481, pp. 47-50.

Halmagyi, GM, Curthoys, IS, Cremer, PD, Henderson, CJ, Todd, MJ, Staples, MJ & D’cruz, DM 1990, The human horizontal vestibulo-ocular reflex in response to high-acceleration stimulation before and after unilateral vestibular neurectomy', Exp Brain Res, vol. 81, no. 3, pp. 479-90.
Halmagyi, GM, Weber, KP & Curthoys, IS 2010, 'Vestibular function after acute vestibular neuritis', Restor Neurol Neurosci, vol. 28, no. 1, pp. 37-46.

Hamann, KF & Lannou, J 1987, 'Dynamic characteristics of vestibular nuclear neurons responses to vestibular and optokinetic stimulation during vestibular compensation in the rat', Acta Otolaryngol Suppl, vol. 445, pp. 1-19.

Hanse, E 2008, 'Associating synaptic and intrinsic plasticity', J Physiol, vol. 586, no. 3, pp. 691-2.

Hargus, NJ, Nigam, A, Bertram, EH, 3rd & Patel, MK 2013, 'Evidence for a role of Nav1.6 in facilitating increases in neuronal hyperexcitability during epileptogenesis', J Neurophysiol, vol. 110, no. 5, pp. 1144-57.

Hays, M, Andrews, M, Wilson, R, Callender, D, O'malley, PG & Douglas, K 2016, 'Reporting quality of randomised controlled trial abstracts among high-impact general medical journals: a review and analysis', BMJ Open, vol. 6, no. 7, pp. e011082.

He, C, Chen, F, Li, B & Hu, Z 2014, 'Neurophysiology of HCN channels: from cellular functions to multiple regulations', Prog Neurobiol, vol. 112, pp. 1-23.

Higgins, JP & Green, S 2011, 'Cochrane Handbook for Systematic Reviews of Interventions', The Cochrane Collaboration.

Higgins, JP & Thompson, SG 2002, 'Quantifying heterogeneity in a meta-analysis', Stat Med, vol. 21, no. 11, pp. 1539-58.

Higgins, JP, Thompson, SG, Deeks, JJ & Altman, DG 2003, 'Measuring inconsistency in meta-analyses', BMJ, vol. 327, no. 7414, pp. 557-60.

Highstein, SM & Holstein, GR 2006, 'The anatomy of the vestibular nuclei', Prog Brain Res, vol. 151, pp. 157-203.

Hille, B 2001, Ion Channels of Excitable Membranes, 3rd ed. edn, Sinauer, Sunderland, Mass.

Hillier, A, Kelly, RP & Klinger, T 2016, 'Narrative Style Influences Citation Frequency in Climate Change Science', PLoS One, vol. 11, no. 12, pp. e0167983.

Him, A & Dutia, MB 2001, 'Intrinsic excitability changes in vestibular nucleus neurons after unilateral deafferentation', Brain Research, vol. 908, no. 1, pp. 58-66.
Him, A, Johnston, AR, Yau, J LW, Seckl, J & Dutia, MB 2001, 'Tonic activity and GABA responsiveness of medial vestibular nucleus neurons in aged rats', *NeuroReport*, vol. 12, no. 18, pp. 3965-3968.

Hoffman, DA & Johnston, D 1998, 'Downregulation of transient K+ channels in dendrites of hippocampal CA1 pyramidal neurons by activation of PKA and PKC', *J Neurosci*, vol. 18, no. 10, pp. 3521-8.

Hoffman, DA, Magee, JC, Colbert, CM & Johnston, D 1997, 'K+ channel regulation of signal propagation in dendrites of hippocampal pyramidal neurons', *Nature*, vol. 387, no. 6636, pp. 869-75.

Holstege, G 1988, 'Brainstem-spinal cord projections in the cat, related to control of head and axial movements', *Rev Oculomot Res*, vol. 2, pp. 431-70.

Holt, JC, Xue, JT, Brichta, AM & Goldberg, JM 2006, 'Transmission between type II hair cells and bouton afferents in the turtle posterior crista', *J Neurophysiol*, vol. 95, no. 1, pp. 428-52.

Hooijmans, CR & Ritskes-Hoitinga, M 2013, 'Progress in using systematic reviews of animal studies to improve translational research', *PLoS Med*, vol. 10, no. 7, pp. e1001482.

Hooijmans, CR, Rovers, MM, De Vries, RB, Leenaars, M, Ritskes-Hoitinga, M & Langendam, MW 2014, 'SYRCLE's risk of bias tool for animal studies', *BMC Med Res Methodol*, vol. 14, pp. 43.

Horii, A, Kitahara, T, Smith, PF, Darlington, CL, Masumura, C & Kubo, T 2003, 'Effects of unilateral labyrinthectomy on GAD, GAT1 and GABA receptor gene expression in the rat vestibular nucleus', *Neuroreport*, vol. 14, no. 18, pp. 2359-63.

Hughes, GM & Tauc, L 1963, 'An Electrophysiological Study of the Anatomical Relations of Two Giant Nerve Cells in Aplysia Depilans', *J Exp Biol*, vol. 40, pp. 469-86.

Hull, CA, Chu, Y, Thanawala, M & Regehr, WG 2013, 'Hyperpolarization induces a long-term increase in the spontaneous firing rate of cerebellar Golgi cells', *J Neurosci*, vol. 33, no. 14, pp. 5895-902.
Idoux, E, Eugene, D, Chambaz, A, Magnani, C, White, JA & Moore, LE 2008, 'Control of neuronal persistent activity by voltage-dependent dendritic properties', J Neurophysiol, vol. 100, no. 3, pp. 1278-86.

Igarashi, M, Alford, BR, Watanabe, T & Maxian, PM 1970, 'Direction of ataxic gait after unilateral partial destruction of the vestibular system in squirrel monkeys', Laryngoscope, vol. 80, no. 6, pp. 896-914.

Igarashi, M, Levy, JK, Reschke, MF, Kubo, T & Watson, T 1978, 'Locomotor dysfunction after surgical lesions in the unilateral vestibular nuclei region in squirrel monkeys', Arch Otorhinolaryngol, vol. 221, no. 2, pp. 89-95.

Igarashi, M, Levy, JK, Takahashi, M, Alford, BR & Homick, JL 1979, 'Effect of exercise upon locomotor balance modification after peripheral vestibular lesions (unilateral utricular neurotomy) in squirrel monkeys', Adv Otorhinolaryngol, vol. 25, pp. 82-7.

Jensen, DW 1979a, 'Reflex control of acute postural asymmetry and compensatory symmetry after a unilateral vestibular lesion', Neuroscience, vol. 4, no. 8, pp. 1059-73.

Jensen, DW 1979b, 'Vestibular compensation: tonic spinal influence upon spontaneous descending vestibular nuclear activity', Neuroscience, vol. 4, no. 8, pp. 1075-84.

John Leigh, R & Zee, DS 2015, The Neurology of Eye Movements, 5th ed. edn, Oxford University Press.

Johnston, AR, Him, A & Dutia, MB 2001, 'Differential regulation of GABA(A) and GABA(B) receptors during vestibular compensation', Neuroreport, vol. 12, no. 3, pp. 597-600.

Johnston, AR, Macleod, NK & Dutia, MB 1994, 'Ionic conductances contributing to spike repolarization and after-potentials in rat medial vestibular nucleus neurones', J Physiol, vol. 481 (Pt 1), pp. 61-77.

Johnston, AR, Seckl, JR & Dutia, MB 2002, 'Role of the flocculus in mediating vestibular nucleus neuron plasticity during vestibular compensation in the rat', Journal of Physiology, vol. 545, no. 3, pp. 903-911.
Johnston, D, Hoffman, DA, Magee, JC, Poolos, NP, Watanabe, S, Colbert, CM & Migliore, M 2000, 'Dendritic potassium channels in hippocampal pyramidal neurons', J Physiol, vol. 525 Pt 1, pp. 75-81.

Jung, SC, Kim, J & Hoffman, DA 2008, 'Rapid, bidirectional remodeling of synaptic NMDA receptor subunit composition by A-type K+ channel activity in hippocampal CA1 pyramidal neurons', Neuron, vol. 60, no. 4, pp. 657-71.

Kalachikov, S, Evgrafov, O, Ross, B, Winawer, M, Barker-Cummings, C, Martinelli Boneschi, F, Choi, C, Morozov, P, Das, K, Teplitskaya, E, Yu, A, Cayanis, E, Penchasazadeh, G, Kottmann, AH, Pedley, TA, Hauser, WA, Ottman, R & Gilliam, TC 2002, 'Mutations in LGII cause autosomal-dominant partial epilepsy with auditory features', Nat Genet, vol. 30, no. 3, pp. 335-41.

Kamii, H, Kurosawa, R, Taoka, N, Shinohara, F, Minami, M & Kaneda, K 2015, 'Intrinsic membrane plasticity via increased persistent sodium conductance of cholinergic neurons in the rat laterodorsal tegmental nucleus contributes to cocaine-induced addictive behavior', Eur J Neurosci, vol. 41, no. 9, pp. 1126-38.

Kandel, ER 2001, 'The molecular biology of memory storage: a dialogue between genes and synapses', Science, vol. 294, no. 5544, pp. 1030-8.

Kane, RL, Wang, J & Garrard, J 2007, 'Reporting in randomized clinical trials improved after adoption of the CONSORT statement', J Clin Epidemiol, vol. 60, no. 3, pp. 241-9.

Keen, EC & Hudspeth, AJ 2006, 'Transfer characteristics of the hair cell's afferent synapse', Proc Natl Acad Sci U S A, vol. 103, no. 14, pp. 5537-42.

Kerber, KA & Baloh, RW 2015, 'Neuro-otology: Diagnosis and management of neuro-otological disorders', in Darroff, RB (ed.), Bradley's Neurology in Clinical Practice, 7th edn, Elsevier, Philadelphia.

Kerr, DR, Sansom, AJ, Smith, PF & Darlington, CL 2000, 'Comparison of protein kinase activity and protein phosphorylation in the medial vestibular nucleus and prepositus hypoglossi in labyrinthine-intact and labyrinthectomized guinea pigs', J Vestib Res, vol. 10, no. 2, pp. 107-17.
Kicinski, M 2014, 'How does under-reporting of negative and inconclusive results affect the false-positive rate in meta-analysis? A simulation study', BMJ Open, vol. 4, no. 8, pp. e004831.

Kilkenny, C, Browne, WJ, Cuthill, IC, Emerson, M & Altman, DG 2010, 'Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research', PLoS Biol, vol. 8, no. 6, pp. e1000412.

Kim, J, Jung, SC, Clemens, AM, Petralia, RS & Hoffman, DA 2007, 'Regulation of dendritic excitability by activity-dependent trafficking of the A-type K+ channel subunit Kv4.2 in hippocampal neurons', Neuron, vol. 54, no. 6, pp. 933-47.

Kitahara, T, Horii, A, Kizawa, K, Maekawa, C & Kubo, T 2007, 'Changes in mitochondrial uncoupling protein expression in the rat vestibular nerve after labyrinthection', Neurosci Res, vol. 59, no. 3, pp. 237-42.

Kitahara, T, Horii, A, Uno, A, Imai, T, Okazaki, S, Kamakura, T, Takimoto, Y & Inohara, H 2012, 'Changes in beta-2 adrenergic receptor and AMP-activated protein kinase alpha-2 subunit in the rat vestibular nerve after labyrinthection', Neurosci Res, vol. 72, no. 3, pp. 221-6.

Kitahara, T, Nakagawa, A, Fukushima, M, Horii, A, Takeda, N & Kubo, T 2002, 'Changes in fosl expression in the rat brainstem after bilateral labyrinthection', Acta Otolaryngol, vol. 122, no. 6, pp. 620-6.

Kitahara, T, Takeda, N, Saika, T, Kubo, T & Kiyama, H 1995, 'Effects of MK801 on Fos expression in the rat brainstem after unilateral labyrinthection', Brain Res, vol. 700, no. 1-2, pp. 182-90.

Lacour, M, Dutheil, S, Tighilet, B, Lopez, C & Borel, L 2009, 'Tell me your vestibular deficit, and i'll tell you how you'll compensate', Ann NY Acad Sci, vol. 1164, pp. 268-78.

Lacour, M, Helmchen, C & Vidal, PP 2016, 'Vestibular compensation: the neuro-otologist's best friend', J Neurol, vol. 263 Suppl 1, pp. S54-64.
Lacour, M & Tighilet, B 2010, 'Plastic events in the vestibular nuclei during vestibular compensation: the brain orchestration of a "deafferentation" code', Restor Neurol Neurosci, vol. 28, no. 1, pp. 19-35.

Lai, M, Huijbers, MG, Lancaster, E, Graus, F, Bataller, L, Balice-Gordon, R, Cowell, JK & Dalmau, J 2010, 'Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series', Lancet Neurol, vol. 9, no. 8, pp. 776-85.

Langer, T, Kaneko, CR, Scudder, CA & Fuchs, AF 1986, 'Afferents to the abducens nucleus in the monkey and cat', J Comp Neurol, vol. 245, no. 3, pp. 379-400.

Lazic, SE & Essioux, L 2013, 'Improving basic and translational science by accounting for litter-to-litter variation in animal models', BMC Neurosci, vol. 14, pp. 37.

Lewis, RF 2016, 'Vestibular implants studied in animal models: clinical and scientific implications', J Neurophysiol, vol. 116, no. 6, pp. 2777-2788.

Lin, L, Sun, W, Kung, F, Dell'acqua, ML & Hoffman, DA 2011, 'AKAP79/150 impacts intrinsic excitability of hippocampal neurons through phospho-regulation of A-type K+ channel trafficking', J Neurosci, vol. 31, no. 4, pp. 1323-32.

Lin, Y & Carpenter, DO 1993, 'Medial vestibular neurons are endogenous pacemakers whose discharge is modulated by neurotransmitters', Cell Mol Neurobiol, vol. 13, no. 6, pp. 601-13.

Lindeman, HH 1969, 'Studies on the morphology of the sensory regions of the vestibular apparatus with 45 figures', Ergeb Anat Entwicklungsgesch, vol. 42, no. 1, pp. 1-113.

Llinas, RR 1988, 'The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function', Science, vol. 242, no. 4886, pp. 1654-64.

Llinas, RR 2014, 'Intrinsic electrical properties of mammalian neurons and CNS function: a historical perspective', Front Cell Neurosci, vol. 8, pp. 320.

Lopez, C & Elziere, M 2017, 'Out-of-body experience in vestibular disorders - A prospective study of 210 patients with dizziness', Cortex.
Lopez-Santiago, LF, Yuan, Y, Wagnon, JL, Hull, JM, Frasier, CR, O’malley, HA, Meisler, MH & Isom, LL 2017, 'Neuronal hyperexcitability in a mouse model of SCN8A epileptic encephalopathy', *Proc Natl Acad Sci U S A*, vol. 114, no. 9, pp. 2383-2388.

Lowenstein, O & Sand, A 1936, 'The activity of the horizontal semicircular canal of the dogfish, *Scyllium canalicula*', *J Exp Biol*, vol. 13, pp. 416-428.

Lowenstein, O & Wersäll, J 1954, 'A functional interpretation of the electron microscopic structure of the sensory hairs in the cristae of the elasmobranch, Raja clavata', *Nature*, vol. 184, pp. 1807-1810.

Ludman, H 2014, 'Vertigo and imbalance', *BMJ*, vol. 348, pp. g283.

Lysakowski, A 1996, 'Synaptic organization of the crista ampullaris in vertebrates', *Ann N Y Acad Sci*, vol. 781, pp. 164-82.

Lysakowski, A, Minor, LB, Fernandez, C & Goldberg, JM 1995, 'Physiological identification of morphologically distinct afferent classes innervating the cristae ampullares of the squirrel monkey', *J Neurophysiol*, vol. 73, no. 3, pp. 1270-81.

Macdougall, HG & Curthoys, IS 2012, 'Plasticity during Vestibular Compensation: The Role of Saccades', *Front Neurol*, vol. 3, pp. 21.

Maioli, C & Precht, W 1985, 'On the role of vestibulo-ocular reflex plasticity in recovery after unilateral peripheral vestibular lesions', *Exp Brain Res*, vol. 59, no. 2, pp. 267-72.

Maioli, C, Precht, W & Ried, S 1983, 'Short- and long-term modifications of vestibulo-ocular response dynamics following unilateral vestibular nerve lesions in the cat', *Exp Brain Res*, vol. 50, no. 2-3, pp. 259-74.

Mantegazza, M, Curia, G, Biagini, G, Ragsdale, DS & Avoli, M 2010, 'Voltage-gated sodium channels as therapeutic targets in epilepsy and other neurological disorders', *Lancet Neurol*, vol. 9, no. 4, pp. 413-24.

Marini, C & Mantegazza, M 2010, 'Na+ channelopathies and epilepsy: recent advances and new perspectives', *Expert Rev Clin Pharmacol*, vol. 3, no. 3, pp. 371-84.

Markham, CH 1968, 'Midbrain and contralateral labyrinth influences on brain stem vestibular neurons in the cat', *Brain Res*, vol. 9, no. 2, pp. 312-33.
Markham, CH, Yagi, T & Curthoys, IS 1977, 'The contribution of the contralateral labyrinth to second order vestibular neuronal activity in the cat', Brain Res, vol. 138, no. 1, pp. 99-109.

Marlinski, V, Plotnik, M & Goldberg, JM 2004, 'Efferent actions in the chinchilla vestibular labyrinth', J Assoc Res Otolaryngol, vol. 5, no. 2, pp. 126-43.

Massot, C, Chacron, MJ & Cullen, KE 2011, 'Information transmission and detection thresholds in the vestibular nuclei: single neurons vs. population encoding', J Neurophysiol, vol. 105, no. 4, pp. 1798-814.

Mathews, MA, Camp, AJ & Murray, AJ 2017, 'Reviewing the role of the efferent vestibular system in motor and vestibular circuits', Frontiers in Physiology, vol. 8 (AUG) (no pagination), no. 552.

Matsubara, A, Takumi, Y, Nakagawa, T, Usami, S, Shinkawa, H & Ottersen, OP 1999, 'Immunoelectron microscopy of AMPA receptor subunits reveals three types of putative glutamatergic synapse in the rat vestibular end organs', Brain Res, vol. 819, no. 1-2, pp. 58-64.

Mayford, M, Siegelbaum, SA & Kandel, ER 2012, 'Synapses and memory storage', Cold Spring Harb Perspect Biol, vol. 4, no. 6.

Mccall, AA & Yates, BJ 2011, 'Compensation following bilateral vestibular damage', Front Neurol, vol. 2, pp. 88.

Mccrea, RA, Strassman, A, May, E & Highstein, SM 1987, 'Anatomical and physiological characteristics of vestibular neurons mediating the horizontal vestibulo-ocular reflex of the squirrel monkey', J Comp Neurol, vol. 264, no. 4, pp. 547-70.

Mccue, MP & Guinan, JJ, Jr. 1994, 'Influence of efferent stimulation on acoustically responsive vestibular afferents in the cat', J Neurosci, vol. 14, no. 10, pp. 6071-83.

Mcelvain, LE, Faulstich, M, Jeanne, JM, Moore, JD & Du Lac, S 2015, 'Implementation of linear sensory signaling via multiple coordinated mechanisms at central vestibular nerve synapses', Neuron, vol. 85, no. 5, pp. 1132-44.
Meadows, JP, Guzman-Karlsson, MC, Phillips, S, Brown, JA, Strange, SK, Sweatt, JD & Hablitz, JJ 2016, 'Dynamic DNA methylation regulates neuronal intrinsic membrane excitability', Sci Signal, vol. 9, no. 442, pp. ra83.

Misonou, H, Mohapatra, DP, Menegola, M & Trimmer, JS 2005, 'Calcium- and metabolic state-dependent modulation of the voltage-dependent Kv2.1 channel regulates neuronal excitability in response to ischemia', J Neurosci, vol. 25, no. 48, pp. 11184-93.

Moher, D, Liberati, A, Tetzlaff, J, Altman, DG & Group, P 2009, 'Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement', BMJ, vol. 339, pp. b2535.

Moylan, EC & Kowalczuk, MK 2016, 'Why articles are retracted: a retrospective cross-sectional study of retraction notices at BioMed Central', BMJ Open, vol. 6, no. 11, pp. e012047.

Mozzachiodi, R & Byrne, JH 2010, 'More than synaptic plasticity: role of nonsynaptic plasticity in learning and memory', Trends Neurosci, vol. 33, no. 1, pp. 17-26.

Mueller, KF, Briel, M, Strech, D, Meerpohl, JJ, Lang, B, Motschall, E, Gloy, V, Lamontagne, F & Bassler, D 2014, 'Dissemination bias in systematic reviews of animal research: a systematic review', PLoS One, vol. 9, no. 12, pp. e116016.

Muhlhausler, BS, Bloomfield, FH & Gillman, MW 2013, 'Whole animal experiments should be more like human randomized controlled trials', PLoS Biol, vol. 11, no. 2, pp. e1001481.

Nelson, AB, Faulstich, M, Moghadam, S, Onori, K, Meredith, A & Du Lac, S 2017, 'BK Channels Are Required for Multisensory Plasticity in the Oculomotor System', Neuron, vol. 93, no. 1, pp. 211-220.

Nelson, AB, Gittis, AH & Du Lac, S 2005, 'Decreases in CaMKII activity trigger persistent potentiation of intrinsic excitability in spontaneously firing vestibular nucleus neurons', Neuron, vol. 46, no. 4, pp. 623-31.

Neuhauser, HK 2016, 'The epidemiology of dizziness and vertigo', Handb Clin Neurol, vol. 137, pp. 67-82.
Newlands, SD & Perachio, AA 1990a, 'Compensation of horizontal canal related activity in the medial vestibular nucleus following unilateral labyrinth ablation in the decerebrate gerbil. I. Type I neurons', *Exp Brain Res*, vol. 82, no. 2, pp. 359-72.

Newlands, SD & Perachio, AA 1990b, 'Compensation of horizontal canal related activity in the medial vestibular nucleus following unilateral labyrinth ablation in the decerebrate gerbil. II. Type II neurons', *Exp Brain Res*, vol. 82, no. 2, pp. 373-83.

Niemansburg, SL, Van Delden, JJ, Dhert, WJ & Bredenoord, AL 2015, 'Reconsidering the ethics of sham interventions in an era of emerging technologies', *Surgery*, vol. 157, no. 4, pp. 801-10.

Ohtsuki, G, Piochon, C, Adelman, JP & Hansel, C 2012, 'SK2 channel modulation contributes to compartment-specific dendritic plasticity in cerebellar Purkinje cells', *Neuron*, vol. 75, no. 1, pp. 108-20.

Olson, JE & Wolfe, JW 1984, 'Responses to rotational stimulation of the horizontal canals from patients with acoustic neuromas', *Acta Otolaryngol Suppl*, vol. 406, pp. 203-8.

Ottolini, M, Barker, BS, Gaykema, RP, Meisler, MH & Patel, MK 2017, 'Aberrant Sodium Channel Currents and Hyperexcitability of Medial Entorhinal Cortex Neurons in a Mouse Model of SCN8A Encephalopathy', *J Neurosci*, vol. 37, no. 32, pp. 7643-7655.

Page, MJ & Moher, D 2017, 'Evaluations of the uptake and impact of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement and extensions: a scoping review', *Syst Rev*, vol. 6, no. 1, pp. 263.

Paige, GD 1989, 'Nonlinearity and asymmetry in the human vestibulo-ocular reflex', *Acta Otolaryngol*, vol. 108, no. 1-2, pp. 1-8.

Panichi, R, Faralli, M, Bruni, R, Kiriakarely, A, Occhigrossi, C, Ferraresi, A, Bronstein, AM & Pettorossi, VE 2017, 'Asymmetric vestibular stimulation reveals persistent disruption of motion perception in unilateral vestibular lesions', *J Neurophysiol*, vol. 118, no. 5, pp. 2819-2832.

Patko, T, Vassias, I, Vidal, PP & De Waele, C 2003, 'Modulation of the voltage-gated sodium- and calcium-dependent potassium channels in rat vestibular and facial nuclei after
unilateral labyrinthectomy and facial nerve transsection: An in situ hybridization study', *Neuroscience*, vol. 117, no. 2, pp. 265-280.

Petticrew, M 2001, 'Systematic reviews from astronomy to zoology: myths and misconceptions', *BMJ*, vol. 322, no. 7278, pp. 98-101.

Peusner, K, Vidal, PP, Minor, L, Cullen, K, Yates, B, Shao, M & Dutia, M 2009, 'Vestibular compensation: new clinical and basic science perspectives', *J Vestib Res*, vol. 19, no. 5-6, pp. 143-6.

Plint, AC, Moher, D, Morrison, A, Schulz, K, Altman, DG, Hill, C & Gaboury, I 2006, 'Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review', *Med J Aust*, vol. 185, no. 5, pp. 263-7.

Probst, P, Grummich, K, Harnoss, JC, Huttner, FJ, Jensen, K, Braun, S, Kieser, M, Ulrich, A, Buchler, MW & Diener, MK 2016, 'Placebo-Controlled Trials in Surgery: A Systematic Review and Meta-Analysis', *Medicine (Baltimore)*, vol. 95, no. 17, pp. e3516.

Pulec, JL 1974, 'Labyrinthectomy: indications, technique and results', *Laryngoscope*, vol. 84, no. 9, pp. 1552-73.

Purcell, IM & Perachio, AA 2001, 'Peripheral patterns of terminal innervation of vestibular primary afferent neurons projecting to the vestibulocerebellum in the gerbil', *J Comp Neurol*, vol. 433, no. 1, pp. 48-61.

Pussegoda, K, Turner, L, Garrity, C, Mayhew, A, Skidmore, B, Stevens, A, Boutron, I, Sarkis-Onofre, R, Bjerre, LM, Hrobjartsson, A, Altman, DG & Moher, D 2017, 'Systematic review adherence to methodological or reporting quality', *Syst Rev*, vol. 6, no. 1, pp. 131.

Ramachandran, R & Lisberger, SG 2006, 'Transformation of vestibular signals into motor commands in the vestibuloocular reflex pathways of monkeys', *J Neurophysiol*, vol. 96, no. 3, pp. 1061-74.

Ramakers, GM & Storm, JF 2002, 'A postsynaptic transient K(+) current modulated by arachidonic acid regulates synaptic integration and threshold for LTP induction in hippocampal pyramidal cells', *Proc Natl Acad Sci U S A*, vol. 99, no. 15, pp. 10144-9.
Rennie, KJ & Streeter, MA 2006, 'Voltage-dependent currents in isolated vestibular afferent calyx terminals', *J Neurophysiol*, vol. 95, no. 1, pp. 26-32.

Ried, S, Maioli, C & Precht, W 1984, 'Vestibular nuclear neuron activity in chronically hemilabyrinthectomized cats', *Acta Otolaryngol*, vol. 98, no. 1-2, pp. 1-13.

Ris, L, Capron, B, Nonclercq, D, Alexandre, H, Sindic, C, Toubeau, G & Godaux, E 2003, 'Labyrinthectomy changes T-type calcium channels in vestibular neurones of the guinea pig', *Neuroreport*, vol. 14, no. 12, pp. 1585-9.

Ris, L, Capron, B, Vibert, N, Vidal, PP & Godaux, E 2001a, 'Modification of the pacemaker activity of vestibular neurons in brainstem slices during vestibular compensation in the guinea pig', *European Journal of Neuroscience*, vol. 13, no. 12, pp. 2234-40.

Ris, L, De Waele, C, Serafin, M, Vidal, PP & Godaux, E 1995, 'Neuronal activity in the ipsilateral vestibular nucleus following unilateral labyrinthectomy in the alert guinea pig', *J Neurophysiol*, vol. 74, no. 5, pp. 2087-99.

Ris, L & Godaux, E 1998, 'Neuronal activity in the vestibular nuclei after contralateral or bilateral labyrinthectomy in the alert guinea pig', *J Neurophysiol*, vol. 80, no. 5, pp. 2352-67.

Ris, L & Godaux, E 2001, 'Voltage-gated calcium channels contribute to the pattern of the resting discharge in guinea pig medial vestibular nucleus neurons', *Neurosci Lett*, vol. 297, no. 2, pp. 142-4.

Ris, L, Hachemaoui, M & Godaux, E 2002, 'Effect of labyrinthectomy on the spike generator of vestibular neurons in the guinea pig', *NeuroReport*, vol. 13, no. 15, pp. 1875-1879.

Ris, L, Hachemaoui, M, Vibert, N, Godaux, E, Vidal, PP & Moore, LE 2001b, 'Resonance of spike discharge modulation in neurons of the guinea pig medial vestibular nucleus', *J Neurophysiol*, vol. 86, no. 2, pp. 703-16.

Royeck, M, Horstmann, MT, Remy, S, Reitze, M, Yaari, Y & Beck, H 2008, 'Role of axonal NaV1.6 sodium channels in action potential initiation of CA1 pyramidal neurons', *J Neurophysiol*, vol. 100, no. 4, pp. 2361-80.
Sadeghi, SG, Chacron, MJ, Taylor, MC & Cullen, KE 2007, 'Neural variability, detection thresholds, and information transmission in the vestibular system', *J Neurosci*, vol. 27, no. 4, pp. 771-81.

Saito, Y, Takazawa, T & Ozawa, S 2008, 'Relationship between afterhyperpolarization profiles and the regularity of spontaneous firings in rat medial vestibular nucleus neurons', *Eur J Neurosci*, vol. 28, no. 2, pp. 288-98.

Sansom, AJ, Brent, VA, Jarvie, PE, Darlington, CL, Smith, PF, Laverty, R & Rostas, JA 1997, 'In vitro phosphorylation of medial vestibular nucleus and prepositus hypoglossi proteins during behavioural recovery from unilateral vestibular deafferentation in the guinea pig', *Brain Res*, vol. 778, no. 1, pp. 166-77.

Sansom, AJ, Smith, PF & Darlington, CL 1993, 'Evidence that L-type calcium channels do not contribute to static vestibular function in the guinea pig vestibular nucleus', *Brain Res*, vol. 630, no. 1-2, pp. 349-52.

Scherer, RW, Dickersin, K & Langenberg, P 1994, 'Full publication of results initially presented in abstracts. A meta-analysis', *JAMA*, vol. 272, no. 2, pp. 158-62.

Scherer, RW, Langenberg, P & Von Elm, E 2007, 'Full publication of results initially presented in abstracts', *Cochrane Database Syst Rev*, no. 2, pp. MR000005.

Schmucker, CM, Blumle, A, Schell, LK, Schwarzer, G, Oeller, P, Cabrera, L, Von Elm, E, Briel, M, Meerpohl, JJ & Consortium, O 2017, 'Systematic review finds that study data not published in full text articles have unclear impact on meta-analyses results in medical research', *PLoS One*, vol. 12, no. 4, pp. e0176210.

Scudder, CA & Fuchs, AF 1992, 'Physiological and behavioral identification of vestibular nucleus neurons mediating the horizontal vestibuloocular reflex in trained rhesus monkeys', *J Neurophysiol*, vol. 68, no. 1, pp. 244-64.

Sekirnjak, C & Du Lac, S 2002, 'Intrinsic firing dynamics of vestibular nucleus neurons', *J Neurosci*, vol. 22, no. 6, pp. 2083-95.
Sekirnjak, C & Du Lac, S 2006, 'Physiological and anatomical properties of mouse medial vestibular nucleus neurons projecting to the oculomotor nucleus', J Neurophysiol, vol. 95, no. 5, pp. 3012-23.

Sekirnjak, C, Vissel, B, Bollinger, J, Faulstich, M & Du Lac, S 2003, 'Purkinje cell synapses target physiologically unique brainstem neurons', J Neurosci, vol. 23, no. 15, pp. 6392-8.

Serafin, M, De Waele, C, Khateb, A, Vidal, PP & Muhlethaler, M 1991a, 'Medial vestibular nucleus in the guinea-pig. I. Intrinsic membrane properties in brainstem slices', Exp Brain Res, vol. 84, no. 2, pp. 417-25.

Serafin, M, De Waele, C, Khateb, A, Vidal, PP & Muhlethaler, M 1991b, 'Medial vestibular nucleus in the guinea-pig. II. Ionic basis of the intrinsic membrane properties in brainstem slices', Exp Brain Res, vol. 84, no. 2, pp. 426-33.

Shao, M, Popratiloff, A, Yi, J, Lerner, A, Hirsch, JC & Peusner, KD 2009, 'Adaptation of chicken vestibular nucleus neurons to unilateral vestibular ganglionectomy', Neuroscience, vol. 161, no. 4, pp. 988-1007.

Shen, L, Lin, Y, Sun, Z, Yuan, X, Chen, L & Shen, B 2016, 'Knowledge-Guided Bioinformatics Model for Identifying Autism Spectrum Disorder Diagnostic MicroRNA Biomarkers', Sci Rep, vol. 6, pp. 39663.

Shimazu, H & Precht, W 1965, 'Tonic and kinetic responses of cat's vestibular neurons to horizontal angular acceleration', J Neurophysiol, vol. 28, no. 6, pp. 991-1013.

Shinoda, Y, Sugiuchi, Y, Izawa, Y & Hata, Y 2006, 'Long descending motor tract axons and their control of neck and axial muscles', Prog Brain Res, vol. 151, pp. 527-63.

Shotwell, SL, Jacobs, R & Hudspeth, AJ 1981, 'Directional sensitivity of individual vertebrate hair cells to controlled deflection of their hair bundles', Ann N Y Acad Sci, vol. 374, pp. 1-10.

Sibbald, B & Roland, M 1998, 'Understanding controlled trials. Why are randomised controlled trials important?', BMJ, vol. 316, no. 7126, pp. 201.
Smith, CE & Goldberg, JM 1986, 'A stochastic afterhyperpolarization model of repetitive activity in vestibular afferents', *Biol Cybern*, vol. 54, no. 1, pp. 41-51.

Smith, MR, Nelson, AB & Du Lac, S 2002, 'Regulation of firing response gain by calcium-dependent mechanisms in vestibular nucleus neurons', *J Neurophysiol*, vol. 87, no. 4, pp. 2031-42.

Smith, PF 1997, 'Vestibular-hippocampal interactions', *Hippocampus*, vol. 7, no. 5, pp. 465-71.

Smith, PF 2017, 'The vestibular system and cognition', *Curr Opin Neurol*, vol. 30, no. 1, pp. 84-89.

Smith, PF & Curthoys, IS 1988a, 'Neuronal activity in the contralateral medial vestibular nucleus of the guinea pig following unilateral labyrinthectomy', *Brain Res*, vol. 444, no. 2, pp. 295-307.

Smith, PF & Curthoys, IS 1988b, 'Neuronal activity in the ipsilateral medial vestibular nucleus of the guinea pig following unilateral labyrinthectomy', *Brain Res*, vol. 444, no. 2, pp. 308-19.

Smith, PF & Darlington, CL 1992, 'Comparison of the effects of NMDA antagonists on medial vestibular nucleus neurons in brainstem slices from labyrinthine-intact and chronically labyrinthectomized guinea pigs', *Brain Res*, vol. 590, no. 1-2, pp. 345-9.

Smith, PF & Darlington, CL 1994, 'Can vestibular compensation be enhanced by drug treatment? A review of recent evidence', *J Vestib Res*, vol. 4, no. 3, pp. 169-79.

Smith, PF, Darlington, CL & Curthoys, IS 1986, 'The effect of visual deprivation on vestibular compensation in the guinea pig', *Brain Res*, vol. 364, no. 1, pp. 195-8.

Smith, PF, Darlington, CL, Yan, Q & Dragunow, M 1998, 'Unilateral vestibular deafferentation induces brain-derived neurotrophic factor (BDNF) protein expression in the guinea pig lateral but not medial vestibular nuclei', *J Vestib Res*, vol. 8, no. 6, pp. 443-7.

Smith, SE, Xu, L, Kasten, MR & Anderson, MP 2012, 'Mutant LGI1 inhibits seizure-induced trafficking of Kv4.2 potassium channels', *J Neurochem*, vol. 120, no. 4, pp. 611-21.
Spruston, N 2008, 'Pyramidal neurons: dendritic structure and synaptic integration', Nat Rev Neurosci, vol. 9, no. 3, pp. 206-21.

Stegen, M, Kirchheim, F, Hanuschkin, A, Staszewski, O, Veh, RW & Wolfart, J 2012, 'Adaptive intrinsic plasticity in human dentate gyrus granule cells during temporal lobe epilepsy', Cereb Cortex, vol. 22, no. 9, pp. 2087-101.

Straka, H, Lambert, FM, Pfanzelt, S & Beraneck, M 2009, 'Vestibulo-ocular signal transformation in frequency-tuned channels', Ann N Y Acad Sci, vol. 1164, pp. 37-44.

Straka, H, Vibert, N, Vidal, PP, Moore, LE & Dutia, MB 2005, 'Intrinsic membrane properties of vertebrate vestibular neurons: Function, development and plasticity', Progress in Neurobiology, vol. 76, no. 6, pp. 349-392.

Straka, H, Zwergal, A & Cullen, KE 2016, 'Vestibular animal models: contributions to understanding physiology and disease', J Neurol, vol. 263 Suppl 1, pp. S10-23.

Strupp, M & Magnusson, M 2015, 'Acute Unilateral Vestibulopathy', Neurol Clin, vol. 33, no. 3, pp. 669-85, x.

Sun, Y, Waller, HJ, Godfrey, DA & Rubin, AM 2002, 'Spontaneous activity in rat vestibular nuclei in brain slices and effects of acetylcholine agonists and antagonists', Brain Res, vol. 934, no. 1, pp. 58-68.

Sweatt, JD 2016, 'Neural plasticity and behavior - sixty years of conceptual advances', J Neurochem, vol. 139 Suppl 2, pp. 179-199.

Takahashi, M, Uemura, T & Fujishiro, T 1984, 'Recovery of vestibulo-ocular reflex and gaze disturbance in patients with unilateral loss of labyrinthine function', Ann Otol Rhinol Laryngol, vol. 93, no. 2 Pt 1, pp. 170-5.

Takazawa, T, Saito, Y, Tsuzuki, K & Ozawa, S 2004, 'Membrane and firing properties of glutamatergic and GABAergic neurons in the rat medial vestibular nucleus', J Neurophysiol, vol. 92, no. 5, pp. 3106-20.

Titley, HK, Brunel, N & Hansel, C 2017, 'Toward a Neurocentric View of Learning', Neuron, vol. 95, no. 1, pp. 19-32.
Tomko, DL, Peterka, RJ, Schor, RH & O'leary, DP 1981, 'Response dynamics of horizontal canal afferents in barbiturate-anesthetized cats', *J Neurophysiol*, vol. 45, no. 3, pp. 376-96.

Tomlinson, RD & Robinson, DA 1984, 'Signals in vestibular nucleus mediating vertical eye movements in the monkey', *J Neurophysiol*, vol. 51, no. 6, pp. 1121-36.

Turner, L, Shamseer, L, Altman, DG, Weeks, L, Peters, J, Kober, T, Dias, S, Schulz, KF, Plint, AC & Moher, D 2012, 'Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals', *Cochrane Database Syst Rev*, vol. 11, pp. MR000030.

Turrigiano, G, Abbott, LF & Marder, E 1994, 'Activity-dependent changes in the intrinsic properties of cultured neurons', *Science*, vol. 264, no. 5161, pp. 974-7.

Van Luijk, J, Bakker, B, Rovers, MM, Ritskes-Hoitinga, M, De Vries, RB & Leenaars, M 2014, 'Systematic reviews of animal studies; missing link in translational research?', *PLoS One*, vol. 9, no. 3, pp. e89981.

Van Luijk, J, Leenaars, M, Hooijmans, C, Wever, K, De Vries, R & Ritskes-Hoitinga, M 2013, 'Towards evidence-based translational research: the pros and cons of conducting systematic reviews of animal studies', *ALTEX*, vol. 30, no. 2, pp. 256-7.

Vibert, N, Babalian, A, Serafin, M, Gasc, JP, Muhlethaler, M & Vidal, PP 1999, 'Plastic changes underlying vestibular compensation in the guinea-pig persist in isolated, in vitro whole brain preparations', *Neuroscience*, vol. 93, no. 2, pp. 413-32.

Vitureira, N, Letellier, M & Goda, Y 2012, 'Homeostatic synaptic plasticity: from single synapses to neural circuits', *Curr Opin Neurobiol*, vol. 22, no. 3, pp. 516-21.

Vogt, L, Reichlin, TS, Nathues, C & Wurbel, H 2016, 'Authorization of Animal Experiments Is Based on Confidence Rather than Evidence of Scientific Rigor', *PLoS Biol*, vol. 14, no. 12, pp. e2000598.

Vollrath, MA, Kwan, KY & Corey, DP 2007, 'The micromachinery of mechanotransduction in hair cells', *Annu Rev Neurosci*, vol. 30, pp. 339-65.
Whitaker, LR, Warren, BL, Venniro, M, Harte, TC, Mcpherson, KB, Beidel, J, Bossert, JM, Shaham, Y, Bonci, A & Hope, BT 2017, 'Bidirectional Modulation of Intrinsic Excitability in Rat Prelimbic Cortex Neuronal Ensembles and Non-Ensembles after Operant Learning', *J Neurosci*, vol. 37, no. 36, pp. 8845-8856.

Wijesinghe, R & Camp, AJ 2011, 'Intrinsic neuronal excitability: implications for health and disease', *Biomol Concepts*, vol. 2, no. 4, pp. 247-59.

Wijesinghe, R, Protti, DA & Camp, AJ 2015, 'Vestibular Interactions in the Thalamus', *Front Neural Circuits*, vol. 9, pp. 79.

Wijesinghe, R, Solomon, SG & Camp, AJ 2013, 'Noise normalizes firing output of mouse lateral geniculate nucleus neurons', *PLoS One*, vol. 8, no. 2, pp. e57961.

Wijesinghe, R, Tung, VW, Camp, AJ, Protti, DA & Mathews, MA 2015, 'Exciting potential: the importance of the right environment', *J Physiol*, vol. 593, no. 10, pp. 2253-5.

Williams, SR & Stuart, GJ 2000, 'Site independence of EPSP time course is mediated by dendritic I(h) in neocortical pyramidal neurons', *J Neurophysiol*, vol. 83, no. 5, pp. 3177-82.

Wuehr, M, Decker, J & Schniepp, R 2017, 'Noisy galvanic vestibular stimulation: an emerging treatment option for bilateral vestibulopathy', *J Neurol*, vol. 264, no. Suppl 1, pp. 81-86.

Xu, J, Kang, N, Jiang, L, Nedergaard, M & Kang, J 2005, 'Activity-dependent long-term potentiation of intrinsic excitability in hippocampal CA1 pyramidal neurons', *J Neurosci*, vol. 25, no. 7, pp. 1750-60.

Yagi, T & Markham, CH 1984, 'Neural correlates of compensation after hemilabyrinthectomy', *Exp Neurol*, vol. 84, no. 1, pp. 98-108.

Yamanaka, T, Him, A, Cameron, SA & Dutia, MB 2000, 'Rapid compensatory changes in GABA receptor efficacy in rat vestibular neurones after unilateral labyrinthectomy', *Journal of Physiology*, vol. 523, no. 2, pp. 413-424.
Yates, BJ & Miller, DM 2009, 'Integration of nonlabyrinthine inputs by the vestibular system: role in compensation following bilateral damage to the inner ear', *J Vestib Res*, vol. 19, no. 5-6, pp. 183-9.

Yin, J & Yuan, Q 2014, 'Structural homeostasis in the nervous system: a balancing act for wiring plasticity and stability', *Front Cell Neurosci*, vol. 8, pp. 439.

Zanazzi, G & Matthews, G 2009, 'The molecular architecture of ribbon presynaptic terminals', *Mol Neurobiol*, vol. 39, no. 2, pp. 130-48.

Zenisek, D, Davila, V, Wan, L & Almers, W 2003, 'Imaging calcium entry sites and ribbon structures in two presynaptic cells', *J Neurosci*, vol. 23, no. 7, pp. 2538-48.

Zhu, H, Zhao, Y, Wu, H, Jiang, N, Wang, Z, Lin, W, Jin, J & Ji, Y 2016, 'Remarkable alterations of Nav1.6 in reactive astrogliosis during epileptogenesis', *Sci Rep*, vol. 6, pp. 38108.