Role of neural integrators in oculomotor systems: A systematic narrative literature review.

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Running title: Neural integration in eye movement control

Abstract

Purpose: To evaluate the role of neural integrators in the oculomotor system.

Methods: A literature search was carried out using several electronic databases during the months of June 2014 to March 2015. The following keywords were used to generate focused results: “neural integrators”, “gaze-holding”, “oculomotor integration”, “impaired gaze-holding”, “gaze evoked nystagmus” and “gaze dysfunction”. Further materials were found through searching relevant articles within reference lists. Seventy-one articles were sourced for this review which analysed animal and human subjects and network models; 45 were studies of humans, 16 studies of primates, 3 studies of felines and 1 study from rats and network models. The remaining articles were literature reviews.

Results: The horizontal and vertical, including torsional, neural integrators (NI) are located logically in the brainstem, nearby their appropriate target extraocular motoneuron nuclei for stable eye position in eccentric position. The nucleus prepositus hypoglossi (NPH) and medial vestibular nuclei (MVN) are closely linked at the caudal pons and dorsal rostral medulla, integrating horizontal conjugate eye movement. The interstitial nucleus of Cajal (INC) integrates vertical and torsional eye movement at the upper midbrain. The integrator time constant is averaged to 25 seconds in human horizontal and animal vertical NI to perform its function. Case reports revealed dysfunction of horizontal neural integrators also resulted in vertical ocular deviations, indicating some overlap of horizontal and vertical gaze control. Furthermore, pharmacological inactivation of neural integrators exposed a population of inhibitory neurotransmitters that permits its mechanism of action; allowing for smooth conjugate movement.

Conclusions: Neural integrators operate to integrate eye-velocity and eye-position information to provide signals to extraocular motoneurons in order to attain and maintain a new position. Therefore, neural integrators allow image stabilisation during horizontal and vertical eye movements at eccentric positions for comfortable single vision.

Keywords: Neural integrator, Oculomotor system, Interstitial nucleus of Cajal, Nucleus prepositus hypoglossi, Medial vestibular nucleus, Eye position, Calibration.

Introduction

Visual stimuli are processed by the brain to generate appropriate eye movements to focus stationary and/or mobile images of interest onto the clearest point of the eye, the fovea (Leigh & Zee 2015). This allows for steady, clear binocular single vision. The control of eye movements and the ability to maintain stable viewing of targets within our visual fields continue to inspire investigators.

Experimental research in humans, animals and network models have identified a mechanism that enables gaze-holding, termed oculomotor neural integrators. Studies revealed the midbrain and medulla oblongata within the brainstem contain nuclei involved in the integration of information from conjugate eye movement systems for stable gaze-holding, Figure 1. The nucleus prepositus hypoglossi and medial vestibular nuclei integrate horizontal gaze, while the interstitial nucleus of Cajal integrates vertical and torsional gaze (Büttner et al. 2002, Cannon & Robinson 1987, Crawford et al. 1991, Dalezios et al. 1998, Fukushima & Kaneko 1995, Glasauer 2003, Kaneko 1997, Kheradmand & Zee 2011, Lambert & Kaneko 1995, Leigh & Zee 2015, Mettens et al. 1994, Moschovakis 1997, Rowe 2003, Yokota et al. 1992). The cerebellum and cerebral cortical areas such as the parietal, occipital and temporal lobe have also been shown to contribute to ocular motor integration (Harris et al. 1993, Karatas 2009, Rowe et al. 2013, Shaikh & Ghasia 2014).

Whilst there is great knowledge and understanding of neural integrators, there is still a rise in case reports and studies that provide more supporting evidence and insight into other areas involved in neural integration (Kim et al. 2014a, Rowe et al. 2013, Shaikh & Ghasia 2014, Patel & Zee 2014). The structures involved in neural integration of conjugate horizontal, vertical and torsional eye movements whilst the

head is stationary, will be discussed. A review of reported cases of neural integrator failure, and clinical presentations will enhance existing concepts of neural integration.

Methods

Search strategy

A systematic search strategy was used to search the following key electronic databases: MEDLINE (1948 to March 2015), SCOPUS (1823 to March 2015), AMED (1985 to March 2015), CINAHL (1937 to March 2015) and PsycINFO (1887 to March 2015). Citation tracking was performed using Web of Science Cited Reference Search for all included studies, and reference lists of included articles were searched. Search terms included a variety of MESH terms and alternatives in relation to neural integration, the oculomotor system, Interstitial nucleus of Cajal, Nucleus prepositus hypoglossi, medial vestibular nucleus, eye position, gaze holding, gaze dysfunction and calibration.

Inclusion and exclusion criteria

Articles related to neural integration and eye position control were included along with literature that discussed the anatomy, physiology and pathophysiology of neural integrators from experimental research in animal and network models, and human studies. Studies in languages other than English were excluded.

Selection of studies

The titles and abstracts identified from the search were screened using the pre-stated inclusion criteria. The full papers of any studies considered potentially relevant were then considered and the selection criteria applied. Further materials were found through searching relevant articles within reference lists. Seventy-one articles were sourced for this review which analysed animal and human subjects and network models; 45 were studies of humans, 16 studies of primates, 3 studies of felines and 1 study from rats and network models. The remaining articles were literature reviews.

Role of oculomotor neural integration

Targets in our field of view stimulate the brain, sending command signals via motoneurons which encode eye- and/or head-velocity signals. The appropriate conjugate eye movement system responds to generate accurate eye movements. Accordingly, the eyes move against the orbital forces that keep them in their habitual position following a pulse signal (velocity command), to ascertain a new position (Arnold & Robinson 1997, Fukushima & Kaneko 1995, Godaux & Cheron 1993, Kaneko 1997, Leigh & Zee 2015, Robinson 1981). This generates a step signal (positional command) to provide extraocular muscles enough neural activity to maintain the eye in an eccentric position. Moreover, the eye-velocity signal is converted into eye-position signals through mathematical integration by a neural network known as neural integrators, which will now be referred as NI throughout the text. However, due to the elastic restoring forces of the eye, the eyes begin to move back to their central position, occurring as the position signal decreases and when the NI is defective and/or 'leaky' (Leigh & Zee 2015, Robinson 1981). Therefore, the role of oculomotor NI is to establish and maintain the eyes in the desired eccentric

position for image stabilisation (Becker & Klein 1973, Cannon & Robinson 1987, Harris et al. 1993, Leigh & Zee 2015, Robinson 1981).

Neural integrator (NI) function

In order to assess NI function, a measurement of the time it takes for the eyes to drift by 63% of the distance made for horizontal and vertical eccentric gaze-holding is recorded (Cannon & Robinson 1987, Crawford et al. 1991, Harris et al. 1993, Leigh & Zee 2015). This is the time constant which has been defined as the time taken for slow-phase velocity to exponentially decline to 37% of its initial value after the onset of a velocity-step stimulus (Leigh & Zee 2015). Previous studies have assessed NI performance in animals and humans; with time constants of approximately 20-25 seconds (Becker & Klein 1973, Cannon & Robinson 1987, Harris et al. 1993). Assessments have been conducted in both light and dark conditions, where darkness is believed to reveal the true drift velocity of eye movements without the influence of visual input and feedback (Cannon & Robinson 1987, Harris et al. 1993). Experiments in dark conditions have also uncovered an inherent centripetal eye drift (Leigh & Zee 2015), as well as an upward eye drift (spontaneous downbeat nystagmus) in monkeys (Cannon & Robinson 1987, Kaneko 1997), also found in healthy humans (Marti et al. 2002). Downbeat nystagmus may occur due to the effect of gravity on the tension surrounding orbital tissues and extraocular muscles; causing the eye to drift up to counteract the force, subsequently, shifting down again.

Becker & Klein (1973) initially reported that a normal human horizontal NI has a time constant of 25 seconds in the dark. Recently, NI performance was reassessed in normal human subjects; average was 24.8 seconds for horizontal gaze-holding

(Khojasteh et al. 2012). Although the time constants are similar, the methodologies were dissimilar. Becker & Klein (1973) situated the target at a distance of 1.8 metres, almost treble the distance used by Khojasteh et al. (2012); longer distances immediately creates larger excursions of smaller saccades and muscular contractions needed for the eye to reach the target. Thus, the time taken to reach the target is increased, although marginally (Becker & Klein 1973).

One can speculate that the human horizontal NI time constants by Becker & Klein (1973) have been over-estimated due to the extreme position of targets (5°-70°), as Khojasteh et al. (2012) facilitated a uniform technique by presenting targets horizontally from ± 45° in steps of 5°. Viewing targets at 70° is both unrealistic and unfeasible as people naturally move their heads with such extremities. Despite the inconsistencies, both studies validate the time constant for horizontal NI in normal healthy human subjects at approximately 25 seconds. Although Khojasteh et al. (2012) assessed vertical gaze-holding, these results were not reported. The ocular drift in healthy subjects has been found to have a component of gravity dependence in complete darkness (Marti et al. 2002), where down-beat nystagmus is observed. This leads to the difficulty in accurately measuring the true time constant in vertical gaze-holding; thus there is limited evidence for the time constants of vertical NI in healthy subjects.

Furthermore, healthy subjects with no known pathologies exhibited end-point nystagmus (EPN) when viewing a target over 35° eccentricity (Bertolini et al. 2013, Khojasteh et al. 2012). This is a physiological phenomenon which usually disappears once gaze is held (Baier & Dieterich 2011, Bertolini et al. 2013, Leigh & Zee 2015). Subjects were able to visually follow a target, but unable to preserve the eyes in an eccentric position for prolonged target fixation. Eyes drifted back towards their

habitual central position, though the eye attempted to make a corrective saccade to look back at the target, thus creating repetitive rhythmic oscillations of the eye.

Bertolini et al. (2013) found that at 40° eccentricity, the left eye of one subject showed EPN; however at angles below ± 20°, there was no evidence of this. When fixating > +20° rightward, the drift velocity began to decrease, contradicting the linear function that had been hypothesised (Khojasteh et al. 2012). This is possibly due to the rarity in looking at eccentric positions without moving our head.

Conversely, when gaze-holding mechanisms become dysfunctional, gaze-evoked nystagmus (GEN) occurs as a result. On attempt to look at or follow targets (± 40° horizontally or ± 20° vertically) whilst the head remains stationary, the eyes exhibit slow drifts towards primary position, with a fast movement back to the target (Büttner & Grundei 1995, Shaikh & Ghasia 2013). The direction of GEN depends on the position of the target, whether it is away or towards the affected side; fast phase increases when moving towards the side of the fast phase, in accordance to Alexander's Law (Kim et al. 2014a, Shaikh & Ghasia 2013, Bockisch & Hegemann 2008). Bockisch & Hegemann (2008) proposed the direction-changing GEN that follows Alexander's Law occurs to minimise drift in one gaze direction, allowing for optimal vision. GEN does consequently affect vision, reducing its clarity and perception, where objects may appear to be "wheeling" and subjects experience vertigo. Therefore, it is important to understand NI; the mechanism and interactions with other areas of the brainstem and brain, especially to determine aetiologies when abnormalities present (Baier & Dieterich 2011, Bockisch & Hegemann 2008, Büttner et al. 2002, Büttner & Grundei 1995, Cho et al. 2008, Dieterich et al. 2005, Helmchen et al. 2002, Karatas 2009, Kim et al. 2014a, Kheradmand & Zee 2011, Khojasteh et

al. 2012, Nakamagoe et al. 2012, Rowe et al. 2013, Seo et al. 2004, Shaikh & Ghasia 2013).

Location of oculomotor neural integrators

The anatomy and location of neural integrators have been identified in regions of the brainstem and cerebellum. Extensive studies in animals, network models and humans have enhanced current knowledge of the physiology and interaction of NI for maintenance of horizontal, vertical and torsional conjugate gaze.

Horizontal neural integrators

Studies for the control of horizontal conjugate eye movement have identified two key areas that facilitate neural integration for horizontal gaze-holding: the nucleus prepositus hypoglossi (NPH) and the medial vestibular nuclei (MVN) (Fukushima & Kaneko 1995, Leigh & Zee 2015, Moschovakis 1997, Rowe 2003). The NPH and MVN lie adjacent to each other at the floor of the fourth ventricle, dorsally situated in the caudal pons and rostral portion of medulla oblongata of the brainstem. The MVN is the longest of the four vestibular nuclei, situated lateral to the NPH. Above the NPH, lies the abducens nucleus that controls horizontal gaze. These structures communicate with each other, whilst sending and receiving information to areas involved in horizontal conjugate eye movements.

Vertical neural integrators (and torsional neural integrators)

The midbrain has long been recognised to contain structures responsible for vertical and torsional eye movements (Leigh & Zee 2015, Rowe 2003). The interstitial nucleus of Cajal (INC) is essential for the neural integration of vertical and torsional conjugate eye movement (Büttner et al. 2002; Crawford et al. 1991, Dalezios et al. 1998, Fukushima & Kaneko 1995, Helmchen et al. 1998, Moschovakis 1997, Rambold et al. 2000). The INC is a group of cells within the medial longitudinal fasciculus (MLF) of the upper midbrain of the brainstem. Anatomically, it is situated below the rostral interstitial nucleus of medial longitudinal fasciculus (riMLF) (Helmchen et al. 1998, Moschovakis 1997), the control centre for vertical eye movement (Büttner et al. 2002, Rowe 2003). This conveniently allows the riMLF to project signals to the INC for vertical gaze-holding (Büttner et al. 2002). Furthermore, the INC interacts with other structures for vertical gaze movements, including the dorsolateral oculomotor nucleus.

Horizontal and vertical neural integrators enhancer

It is hypothesised that humans have inherently leaky NI, thereby their performance needs modifying and enhancement (Bertolini et al. 2013, Kheradmand & Zee 2011). The time constant of 25 seconds (Becker & Klein 1973, Khojasteh et al. 2012) is thus achieved through further integration and fine-tuning by the cerebellum (Glasauer 2003), specifically the cerebellar flocculus and paraflocculus (Glasauer 2003, Kheradmand & Zee 2011, Leigh & Zee 2015, Moschovakis 1997). The cerebellum is located in the posterior cranial fossa, situated ventrally to the occipital and temporal lobes, and dorsal to the brainstem. The central portion of the cerebellum, termed the

vermis, connects the two cerebellar hemispheres which have three subdivisions: spinocerebellum, cerebrocerebellum and vestibulocerebellum (Kheradmand & Zee 2011, Leigh & Zee 2015). The vestibulocerebellum contains the nodule of vermis, flocculus and paraflocculus that are involved in gaze-holding of all conjugate eye movements (Glasauer 2003, Kheradmand & Zee 2011, Khojasteh et al. 2012, Nakamagoe et al. 2000). The floccular Purkinje cells, known for their inhibitory nature, discharge according to gaze-velocity signals (Glasauer et al. 2009, Marti et al. 2005, Patel & Zee 2014, Takagi et al. 1998). Connections are made to the midbrain, pons and medulla of the brainstem via the superior, inferior and middle cerebellar peduncles, respectively, allowing communication of cerebellar nuclei to areas within the brainstem.

Neural integrator failure

Damage to the gaze-holding mechanisms disrupts the ability of the eyes to attain and maintain an eccentric position. Consequently, its strong network with eye movement systems, such as saccades and smooth pursuit, are also affected, giving rise to ocular motility abnormalities (Büttner & Grundei 1995, Rowe et al. 2013, Shaikh & Ghasia 2013). This leads to visual disturbances and vestibular imbalances that are symptom producing.

As NIs have an immense network of connections with a vast array of structures, there may be presenting signs other than GEN. Additional neuro-ophthalmological findings have varied from impaired gaze-holding, different types of nystagmus, ocular misalignment and vestibular imbalance (Table 1) (Büttner & Grundei 1995, Dieterich et al. 2005, Kim et al. 2014a, Rowe et al. 2013, Shaikh & Ghasia 2013,

Shaikh & Ghasia 2014). Cases reported have aetiologies such as infarctions and haemorrhages (Büttner et al. 2002, Dieterich et al. 2005, Halmagyi et al. 1994, Helmchen et al. 2002, Hommel & Bogousslavsky 1991, Kim et al. 2014a, Rowe et al. 2013), space-occupying lesions (Karatas 2009, Rett 2007, Lloyd et al. 2009), syringobulbia (Nogués et al. 2010, Weissman et al. 1990), Arnold-Chiari malformation (Ghasia et al. 2014, Wagner et al. 2008, Weissman et al. 1990), demyelination (Averbuch-Heller et al. 1995, Kim et al. 2006, Kim & Lee 2014, Kim et al 2014b), infection (Livorsi et al. 2010), drug intoxications (Corbett et al. 1989, Fischera et al. 2009) and trauma (Kulkarni et al. 2005, Odebode et al. 2005, Sabates et al. 1991, Van Stavern et al. 2001). Additional investigations using imaging techniques such as CT or MRI scans have localised lesions within the brainstem and cerebellum, indicative of involvement of NIs, including their abundant connecting structures which complete the gaze-holding system (Büttner et al. 2002, Cho et al. 2008, Dieterich et al. 2005, Helmchen et al. 2002, Kim et al. 2014a, Nakamagoe et al. 2012, Rowe et al. 2013, Seo et al. 2004, Tarnutzer et al. 2015). Thus, it is important to be aware of the vicinity of NIs and characterise gaze-holding ability in order to differentially diagnose a NI defect.

Clinical findings

Several cases have been reported that occur as a result of damage to areas within the posterior fossa and cerebral cortex with associated neuro-ophthalmological defects.

Midbrain

Insults to the midbrain result in depletion of vertical gaze movements and vestibular imbalance (Büttner et al. 2002, Halmagyi et al. 1994, Helmchen et al. 2002, Hommel & Bogousslavsky 1991). It is well known that the midbrain contains important structures for vertical gaze. Torsional nystagmus has been reported in patients with midbrain infarctions and haemorrhages (Büttner et al. 2002, Helmchen et al. 2002). Lesions affecting the right INC predominantly caused clockwise torsional nystagmus with GEN in up-gaze, respective to the patients view. Time constants of patients with INC lesions were shortened to 100-300 milliseconds (Helmchen et al. 2002), corresponding with earlier monkey findings (Crawford et al. 1991, Helmchen et al 1998). Additionally, patients without INC involvement had measured time constants of more than 500 milliseconds (Helmchen et al. 2002). Greater time constants in patients with INC-sparing lesions suggested a mechanism is in place to prolong stable fixation.

Seesaw nystagmus (SSN) is the simultaneous incyclorotation and elevation of one eye, where the other excyclorotates and depresses (Halmagyi et al. 1994), whereas hemi-seesaw nystagmus (HSSN) specifies the jerky wave form. Other clinical characteristics are ocular misalignment and the ocular tilt reaction, which suggests the otolith-ocular pathway, including the INC, plays a part (Wong 2010, Khan & Lueck 2013). Determining the aetiology of SSN and HSSN has been a topic of controversy since authors have reported both SSN and HSSN in patients with midbrain and medullary infarctions (Hommel & Bogousslavsky 1991, Khan & Lueck 2013, Rett 2007). SSN after bilateral INC lesions in one monkey (Helmchen et al. 1998) has been observed. Conversely, previous studies of the INC did not elicit this nystagmic condition (Büttner et al. 2002, Crawford et al. 1991, Rambold et al. 2000). Moreover, Das et al. (2010) were able to identify the aetiology of this nystagmus

using primates. Muscimol was injected to an area 2 millimetres beneath the INC which produced HSSN. Vertical gaze-holding was not compromised, indicating that although the lesions were close to the INC with risk of Muscimol spread, the vertical NI could not be responsible. The association of INC was excluded in this experiment.

Despite this, authors still postulated NI dysfunction in HSSN, due to the manifestation of GEN on lateral gaze, and connections of integrators with vestibular neurons (Karatas 2009, Khan & Lueck 2013, Shaikh & Ghasia 2013). Recently, a report of a patient with torsional-upbeat nystagmus due to a left rostral medial medullary infarct was outlined, which subsequently developed into HSSN after 3 days of presentation (Lee et al. 2014). Examination of this patient provided insight into the role of the anterior and posterior semi-circular canals of the vestibular system. Regardless that these structures comprise the vestibular complex connecting to the descending INC pathway (Kokkoroyannis et al. 1996), it takes sole focus away from the INC, concurring with Das et al. (2010).

Progressive supranuclear palsy (PSP) is a neurodegenerative disease whereby vertical eye movement impairment is a common clinical sign, particularly with reduced vertical saccades as the chief initial loss of ocular motility (Chen et al. 2010). Defective down-gaze is problematic for patients, and usually the most obvious sign. Reports have shown patients performing slower and shorter downward and upward saccades with INC involvement (Büttner et al. 2002) - also seen in primates (Helmchen et al. 1998). A clinical study contradicted this, whereby the vertical saccadic velocity was not affected in patients with lesions mainly affecting the INC (sparing riMLF) (Helmchen et al. 2002). The aetiology of these ocular deficits is not yet fully understood. Although GEN and/or impaired gaze-holding are not common features of PSP, the influence of INC in PSP is considered (Chen et al. 2010).

Human INC has been measured as 4 millimetres in width (Büttner et al. 2002), so its involvement in PSP may be possible due its close proximity to the riMLF from the midline (Büttner et al. 2002, Kokkoroyannis et al. 1996). It is therefore susceptible to simultaneous damage, consequently disrupting vertical saccades, as seen in PSP.

Pons and Medulla

Damage to the medulla is usually associated with vestibular pathologies. Patients may complain of suddenly being nauseous and experience an unsettling sensation of the world moving around them (Bockisch & Hegemann 2008, Cho et al. 2008, Dieterich et al. 2005, Kim et al. 2014a, Seo et al. 2004). Often, this is a consequence of the dysfunction of the ocular stabilisation and vestibular system. Patients are also seen to exhibit a swaying movement or falls towards one side, classically to the affected side in MVN lesions (Cho et al. 2008, Dieterich et al. 2005, Seo et al. 2004) - also seen in monkeys (Straube et al. 1991). Vestibular disorders ultimately interrupt ocular and vestibular connections i.e. the utriculo-ocular pathways, provoking vestibular imbalance, double vision and perception of a “wheeling” visual scene (Dieterich et al. 2005, Wong 2010). Compromise of the NI status is also apparent, with horizontal, vertical and torsional GEN (Bockisch & Hegemann 2008). Imaging techniques such as MRI scans have identified areas of the NPH and MVN affected due to infarctions of the nuclei or nearby blood vessels (Cho et al. 2008, Dieterich et al. 2005, Kim et al. 2014a, Seo et al. 2004).

Seo et al. (2004) and Cho et al. (2008) examined patients with small infarctions in the dorsomedial region of the medulla. MRI scans indicated lesions mainly in the NPH, where patients expectedly showed horizontal GEN and signs of vestibular

dysfunction. Understandably, these findings led both authors to presume NPH has a vestibular function as there was no suggestion of MVN lesions from MRI scans. The authors did not acknowledge the close proximity of the NPH and MVN thus excluding the possibility that the vestibular signs and symptoms are likely because of MVN involvement. These structures communicate to integrate velocity and positional signals for horizontal gaze at eccentric positions, and are in fact close neighbours, approximately 0.9-1.1 millimetres apart in felines (Mettens et al. 1994) and 0.5-1.2 millimetres apart in primates (Arnold et al. 1999). However, authors have previously recommended treating the NPH and MVN as a single complex as electrical activities of neurons are similar (Mettens et al. 1994, McFarland & Fuchs 1992). Unilateral injections of Muscimol to inactivate the NPH alone was shown to cause vestibular dysfunction and gaze-holding failure; justifying the assumption of a vestibular function for NPH. Yet, the authors did not take into account the possibility that the inhibitory agent leaked. Rat studies have shown that injection of Muscimol (1 microlitre of 2%) into the cerebellum can spread up to 4 millimetres within 2.5 hours (Arikan et al. 2002). Although the compatibility of results is weak due to the differing species, it implies Muscimol does spread to inactivate nearby activity. Therefore, depending on the extent of damage to the NPH, it may have a knock-on effect to its neighbouring MVN, consequently giving rise to vestibular symptoms. Nonetheless, these studies give scope to the impact NPH lesions have on vestibular syndromes.

Medullary infarctions have been analysed to show lesions extending to areas of the right and left MVN (Dieterich et al. 2005, Kim et al. 2014a). Patients presented with neurological signs and ocular deficits including left and upward GEN in primary position, which changed depending on direction of gaze. Direction-changing GEN

coincides with NI failure (Bockisch & Hegemann 2008) which is anticipated with lesions to the MVN.

When the lateral medulla is injured, the condition is known as Wallenberg's syndrome, associated with skew deviation. The majority of patients with infarcts to the right MVN demonstrated left-beating GEN, supporting earlier findings in felines of the fast phase component beating towards the contralesional side (Mettens et al. 1994). In addition, the patients' signs implied MVN contained neurons for the facilitation of both horizontal and vertical gaze movement. In Wallenberg's syndrome, patients had vertical ocular misalignment where the ipsilesional eye was usually hypotropic and excyclorotated, which constitute skew deviation, and an ipsilateral head tilt (Dieterich et al. 2005, Wong 2010). Furthermore, it appears that Wallenberg's syndrome has ocular torsion mainly in the ipsilesional eye (Odebode et al. 2005). Extensive lesions of the MVN resulted in larger amounts of ocular torsion, albeit greater when combined with lesions to the inferior vestibular nuclei (Dieterich et al. 2005).

Arnold-Chiari malformations are usually associated with downbeat nystagmus (DBN) due to cerebellar changes (Kheradmand & Zee 2011, Wagner et al. 2008). A patient with Arnold Chiari malformation type 1 only exhibited horizontal left-beating nystagmus evident in primary position (Ghasia et al. 2014). Left-beating nystagmus dampened, stabilising gaze-holding to the right, whereas on left-gaze, nystagmus increased with ensuing GEN and increasing slow drift velocity when looking to the affected side (Bockisch & Hegemann 2008, Kim et al. 2014a, Shaikh & Ghasia 2014). Though the cerebellum is chiefly affected in this condition, it appears that the nystagmic pattern corresponds to damage of the horizontal NI. Localisation of specific structures involved were not disclosed. However it was presumed from the

eye movements produced by the patient and the MRI images, that the source of the ocular abnormality was compression to the left dorsal medulla, containing horizontal NI. Conversely, structural deformation of the cerebellum may have disturbed projections involved in horizontal neural integration.

Cerebellum

Cerebellar lesions and defects in patients have been reported to show horizontal GEN and DBN (Baier & Dieterich 2011, Büttner & Grundei 1995, Dieterich et al. 2005, Karatas 2009, Kheradmand & Zee 2011, Lloyd et al. 2009, Patel & Zee 2014, Tarnutzer et al. 2015, Wagner et al. 2008). In addition to the ocular signs, patients commonly are unable to coordinate movement and posture.

DBN typically shows an upward slow drift of the eyes, subsequently followed by a corrective saccade to quickly move the eyes downwards (Wagner et al. 2008). A patient with DBN has been reported (Nakamagoe et al. 2012) where MRI scans exposed an infarct to the PMT in the medullary region. The presence of DBN may well be a presenting sign of disrupted communication to the flocculus, as seen previously in animal studies (Das et al. 2010, Kokkoroyannis et al. 1996).

In spite of the flocculus being known to participate in vertical and horizontal gaze-holding, there was no involvement of the flocculus in patients who have suffered strokes (Baier & Dieterich 2011) and neurodegenerative disorders that involved cerebellar atrophy (Tarnutzer et al. 2015) whom exhibited horizontal GEN. MRI scans of patients with GEN revealed cerebellar vermis, uvula, pyramid and tonsils affected. However, lesions to these structures are known to cause abnormal

saccadic movement only (Glasauer 2003). It appears the flocculus/paraflocculus is more specific for vertical gaze-holding, where floccular Purkinje cells have more downward on-directions detected on functional MRI (Glasauer et al. 2009). This is in keeping with 20% of patients identified with DBN (Wagner et al. 2008) caused by deterioration of cerebellar function, particularly at the flocculus/paraflocculus region and purkinje cells of the cerebellum (Marti et al. 2002, Nakamagoe et al. 2012, Tarnutzer 2015).

Space-occupying tumors such as vestibular Schwannomas and astrocytomas compress structures in the cerebello-pontine region (Lloyd et al. 2009, Rett 2007). As a result, communication of fibres between the cerebellum and pons are disturbed. Horizontal GEN has been reported and the condition of Bruns' Nystagmus (Karatas 2009, Rett 2007). Bruns' nystagmus is characterised by a direction- and quality-changing GEN: fast and fine nystagmus towards the unaffected side, with slow, jerky nystagmus to the affected side (Karatas 2009, Lloyd et al. 2009). This was more likely to arise if the tumour had a diameter that measured more than 3.5 centimetres (Lloyd et al. 2009).

Interestingly, long-term use of Lithium for treatment of bipolar disorders, as well as accidental intoxication has been reported to affect cerebellar structures and regions of the brainstem (Corbett et al. 1989, Fischera et al. 2009). Signs of primary position DBN and down-beating GEN nystagmus on depression are typical, causing symptoms such as loss of balance, nausea and visual disturbances.

Büttner & Grundei (1995) assessed a large group of patients (n=52) with horizontal gaze impairment. Thirty-eight percent of patients with smooth pursuit and horizontal gaze-holding defects were diagnosed with disorders affecting the cerebellum alone.

Rowe et al. (2013) also diagnosed 4% of patients with impaired gaze-holding (n=46) to have reduced smooth pursuit, where lesions were generally at the parietal lobe and cerebellum. Combination of smooth pursuit and gaze-holding deficiencies suggest these systems are intertwined, as proposed by Lambert & Kaneko (1995).

Generalised damage to the brainstem and cerebellum

Prospective studies have identified 83.5% (Kulkarni et al. 2005) and 25.3% (Odebode et al. 2005) of patients with closed head and traumatic brain injuries to suffer from ocular complications. Abnormal ocular motility is uncommon, however retrospective studies revealed severe head injuries that affected the posterior fossa and occipital lobe produced SSN and DBN in 1% (Sabates et al. 1991) and central vestibular nystagmus in 2% (Van Stavern et al. 2001) of patients.

Cases of patients with syringobulbia commonly report nystagmus with ocular and visual symptoms such as blurred vision and oscillopsia (Nogués et al. 2010, Weissman et al. 1990). This condition is compressive affecting the brainstem, including the hypoglossal nucleus with fluid-filled cavities. Thus, as the hypoglossal nucleus is surrounded by the NPH, signs of NI failure may arise as a result of medullary compression. Vestibular damage is likely to produce torsional nystagmus. Weissman et al. (1990) identified subtle combinations of horizontal, vertical and torsional nystagmus, that resembled HSSN and “bow-tie” nystagmus in a patient found to have syringomyelia, syringobulbia and Arnold-Chiari malformation.

Ocular manifestations of upbeat nystagmus (UBN), horizontal and vertical GEN in patients with multiple sclerosis (MS) have been observed (Averbuch-Heller et al.

1995, Büttner & Grundei 1995, Kim et al. 2006, Kim & Lee 2014, Kim et al. 2014b). Common demyelinated areas found from MRI scans are the cerebellum, pontine tegmentum, dorso-rostral and dorso-caudal medulla. Where patients had associated signs of horizontal and vertical GEN, lesions were found in caudal pontine/dorsal rostral medulla indicative of NPH and MVN damage to relate with the nystagmic movement. An MS patient (Kim & Lee 2014) was reported with rare signs of vertical GEN and bilateral internuclear ophthalmoplegia due to demyelination at the PMT region. While the presence of vertical GEN lends weight to support PMT neurons contribution in neural integration (Nakamagoe et al. 2012), it is an unusual incident.

Conclusion

The aim of this study was to discuss the contribution of NI in the oculomotor system during eye movements whilst the head is stationary. Several animal studies in primates and felines infer functions of the NPH, MVN, INC and cerebellum for gaze-holding. Interestingly, NI are topographically located in a logical manner in the brainstem, near their appropriate target extraocular motoneuron nuclei. NI integrates eye-velocity and eye-position information in order to provide positional signals to motoneurons to move towards the visual target. The NPH and MVN are highly involved in the integration of horizontal eye movement, caudal to the abducens nuclei. The INC predominantly integrates vertical and torsional movement, situated rostral to the oculomotor and trochlear nuclei. Damage to the MVN resulted in vertical ocular misalignments. It is likely that all neural integration structures inter-relate in the maintenance of eccentric gaze positions. Hence, damage to one structure could result in one specific gaze deficit. Moreover, the cerebellum

optimises the inherent leaky brainstem NI, by refining the signals, to achieve the normal time constant of 25 seconds. Additionally, experimental studies revealed the inhibitory nature of NI which permits smooth horizontal and vertical conjugate eye movement.

Further studies should address re-calculating the time constant for vertical NI in healthy humans, as this has not been documented. Focus on other ocular stabilisation systems: visual fixation, optokinetic system and vestibular ocular reflexes may be beneficial to supplement knowledge on the integration of head and eye velocity and position signals. The circuitry and relations to vestibular complexes can also be explored.

In conclusion, NI play an important role for image stabilisation in the oculomotor system. As discussed in this review, general dysfunction results in patients experiencing blurred vision, vestibular imbalance, vertigo and oscillopsia. Therefore, NI allows the eyes to attain and sustain a new position at an eccentric point. Thus, allowing for comfortable single vision to view an object of interest.

Declaration/Conflict of Interest. The authors have no declarations to disclose.

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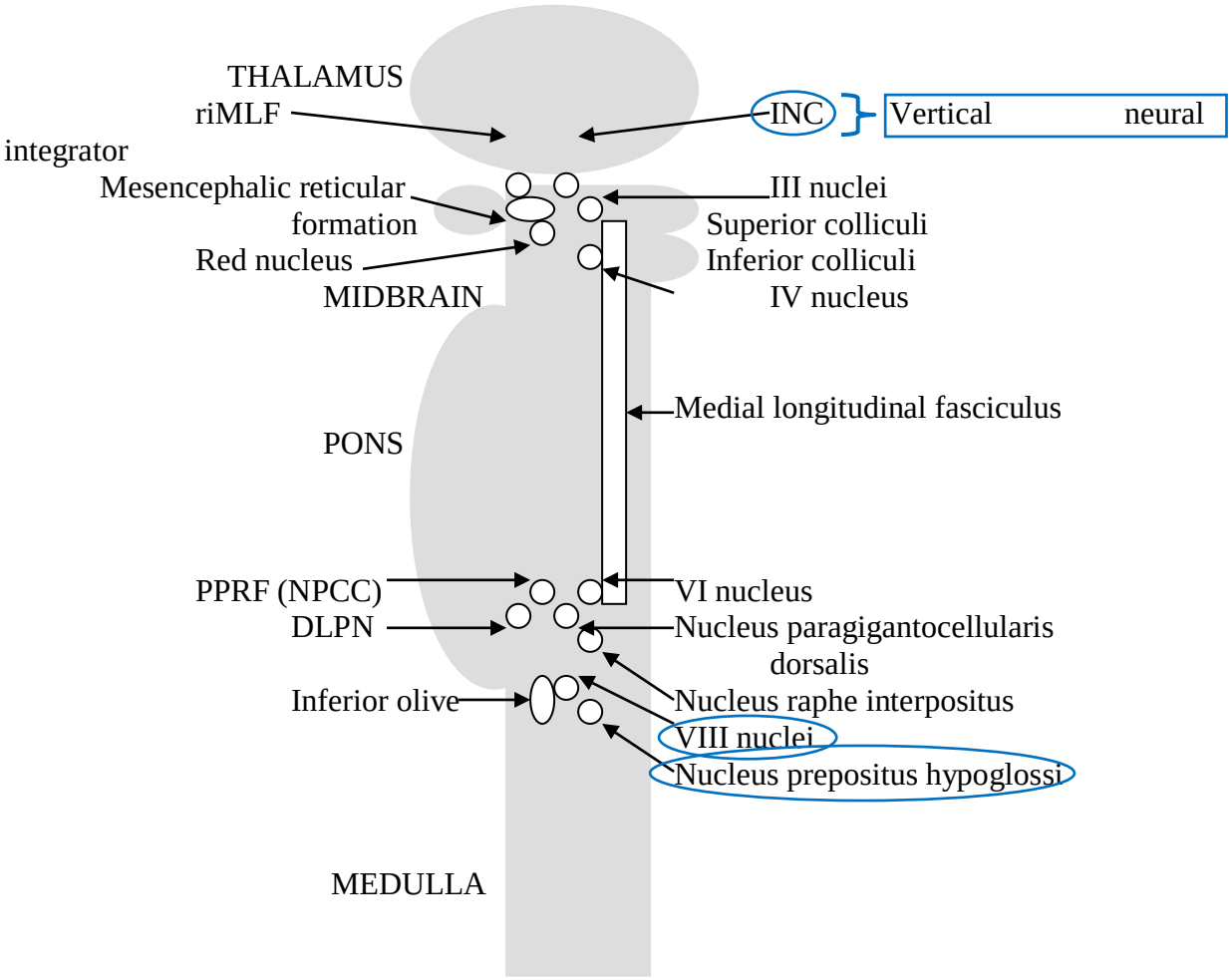

Figure 1: A schematic representation of a sagittal cross-section view of the brainstem. The horizontal and vertical neural integrators are encircled in blue. VIII nuclei consist of the vestibular nuclei involved in horizontal neural integration. (Image adapted and taken from Rowe 2003).

Table 1: Clinical disorders associated with neural integrator failure.

Affected areas	Clinical diagnosis	Neuro-ophthalmological findings
Posterior Fossa		
Brainstem:	Haemorrhage	Central vestibular nystagmus
	HSV Encephalitis	DBN
	Infarction	GEN
	Lithium intoxication	HSSN
	Multiple Sclerosis	SD
	Progressive supranuclear palsy	SSN
	Syringobulbia	UBN
	Trauma	Vertical-torsional nystagmus
	Wallenberg's Syndrome	
Cerebellum:	Arnold-Chiari malformation	Brun's Nystagmus
	Astrocytoma	DBN
	Infarction	GEN
	Lithium intoxication	Impaired gaze-holding
	Trauma	SD
	Vascular tumour	UBN
	Vestibular schwannoma	
Cerebral cortex		
Parietal lobe:	Haemorrhagic Stroke	Impaired gaze-holding
Occipital lobe:	Ischaemic Stroke	
	Trauma	

Abbreviations: HSV: Herpes simplex virus. *Ocular motor deficits:* DBN: Downbeat nystagmus; GEN: Gaze-evoked nystagmus; HSSN: Hemi-seesaw nystagmus; SD: Skew deviation; SSN: Seesaw nystagmus; UBN: Upbeat nystagmus.