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Direktorin: Prof. Dr. Marianne Dieterich

Downbeat nystagmus:

Changes during daytime and its treatment

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Dr. Rainer Christian Spiegel

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Mitberichterstatter:	Prof. Dr. med. Oliver Ehrt
	Prof. Dr. Ines Golly
Mitbetreuung durch den promovierten Mitarbeiter:	Dr. med. Roger Kalla
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Aus meiner Doktorarbeit sind die folgenden Zeitschriftenartikel hervorgegangen. Aus diesem Grunde existieren Überlappungen zwischen Publikationen und den Kapiteln meiner Dissertation:

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Zusätzlich wurden folgende Konferenzarbeiten als “abstracts” in einer Fachzeitschrift publiziert, die ebenfalls Überlappungen mit den Kapiteln dieser Arbeit haben:

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Meine anderen Veröffentlichungen, die im Zeitraum dieser Doktorarbeit erschienen sind, jedoch nicht in direktem Zusammenhang damit stehen, sind an dieser Stelle nicht aufgeführt. Eine umfangreichere Liste findet sich im Lebenslauf am Ende der Doktorarbeit.

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Summary

In this thesis, three aspects of downbeat nystagmus (DBN) were examined. First, changes of its intensity during daytime; second, an analysis of the underlying mechanisms, in particular, the modulation of otolith input; and third, the effects of a pharmacotherapy with potassium channel blockers 4-aminopyridine in comparison with 3,4-diaminopyridine.

Downbeat nystagmus consists of ocular drifts upwards. These upward drifts cannot be deliberately controlled. As a correcting mechanism, the upward drifts are followed by downward saccades. Downbeat nystagmus is either due to lesions in the cerebellum, due to lesions to the brainstem or due to cryptogenic/idiopathic causes. In order to reduce symptoms effectively, it is of particular importance to increase our knowledge about DBN.

In chapter 1 of this thesis it is shown that the intensity of DBN decreases during daytime. In chapter 2, it is demonstrated that resting positions have an influence on the extent of DBN. During daytime, where people are generally in upright body position, DBN decreases effectively when people remain upright during their resting periods, i.e. when people sit instead of lying down to rest. There is a possible reason why DBN in upright position significantly decreases when people rest upright. This could have been due to otoliths exerting a stabilizing influence on the central vestibular neurons of the patients while remaining upright for a continuous period. Moreover, it does not make a difference whether patients with DBN rest with the light switched on or with the light switched off. Chapters 1 and 2 also have implications for symptomatic treatment. It can be suggested to patients to rest in an upright position during the day, and to engage in activities such as reading or screen-related work in the afternoon rather than in the morning. In chapter 3, another way of symptom reduction is presented, where the aminopyridines 4-AP and 3,4-DAP are compared against each other. The efficacy of reducing DBN had previously been demonstrated individually for both aminopyridines. In this thesis, the efficacy of both aminopyridines was

examined in a double-blind study with cross-over design. The major finding was that 4-AP is more effective than 3,4-DAP in terms of reducing the intensity of DBN. Moreover, 4-AP revealed a tentative trend towards a particular efficacy for cerebellar patients, which is in line with experimental evidence, where it had been reported to better cross the blood-brain barrier and to have at least the same (probably even a longer) half-life than 3,4-DAP. In conclusion, no causative treatment is in sight for DBN, but clinical studies can lead to a better understanding of DBN and may contribute to symptom alleviation.

Zusammenfassung

In dieser Doktorarbeit werden drei Apekte des Downbeatnystagmus (DBN) analysiert. Erstens werden Änderungen des DBN im Tagesverlauf untersucht. Zweitens werden die zugrunde liegenden Mechanismen, insbesondere die Modulation durch Otolithen, analysiert. Drittens wird die Pharmakotherapie mit Hilfe der Kaliumkanalblocker 4-aminopyridin und 3,4-diaminopyridin miteinander verglichen.

Downbeatnystagmus besteht aus einem wiederkehrenden, nach oben gerichteten Abdriften der Augen, das nicht willkürlich kontrolliert werden kann, sowie darauf folgenden, nach unten gerichteten, schnellen Sakkaden. Downbeatnystagmus entsteht entweder aufgrund von Kleinhirn- oder Hirnstammläsionen, oder aufgrund von kryptogenen/idiopathischen Ursachen. Um DBN-Symptome zu lindern, ist es in erster Linie notwendig, mehr über DBN zu wissen.

In Kapitel 1 dieser Arbeit wird gezeigt, dass die DBN-Intensität über den Tag hinweg abnimmt. In Kapitel 2 wird demonstriert, dass unterschiedliche Ruhepositionen einen Einfluss auf die Intensität des DBN haben. Während des Tages befinden sich Menschen meist in aufrechter Körperhaltung. In diesem Fall nimmt der DBN am effektivsten ab, wenn die Patienten auch Ruhepausen wählen, bei denen sie in aufrechter Körperhaltung bleiben, z.B. wenn sie sitzen anstelle sich auf den Bauch oder Rücken zu legen. Es gibt einen möglichen Grund, weshalb DBN in aufrechter Position signifikant abnimmt, nachdem Patienten sich in aufrechter Position ausgeruht haben (während es im Gegensatz dazu keine signifikante Abnahme gibt, wenn sich die Patienten zum Ausruhen hingelegt haben). Der Grund dafür ist, dass die Otolithen einen stabilisierenden Einfluss auf zentral-vestibuläre Neurone der Patienten hatten, wenn die aufrechte Position kontinuierlich aufrechterhalten wird. Ferner existiert hinsichtlich der Ausprägung des DBN kein Unterschied, ob Patienten sich bei Licht oder in Dunkelheit ausruhen. Kapitel 1 und 2, deren primäres Ziel das genauere Verständnis

des DBN war, haben jeweils auch Implikationen für die symptomatische Behandlung. Es kann den Patienten nahegelegt werden, sich im Tagesverlauf in aufrechter Körperposition auszuruhen, bzw. Aktivitäten wie z.B. Lesen oder Bildschirmarbeit am Nachmittag anstelle in den Morgenstunden zu planen. In Kapitel 3 werden die Aminopyridine 4-AP und 3,4-DAP miteinander verglichen. Die Effektivität beider Aminopyridine in der Reduktion des DBN wurde bereits in der Vergangenheit individuell sowohl für 4-AP, als auch für 3,4-DAP demonstriert. Basierend auf den vorherigen Studien stellt meine Arbeit einen Effektivitätsvergleich beider Aminopyridine in einer Doppelblindstudie mit cross-over Design dar. Das Hauptresultat von Kapitel 3 war, dass 4-AP die Intensität von DBN effektiver als 3,4-DAP reduziert. Ferner zeigte 4-AP einen Trend hinsichtlich einer vermehrten Wirksamkeit bei Patienten mit Kleinhirnläsionen, was mit experimentellen Daten vereinbar ist, die gezeigt haben, dass 4-AP die Bluthirnschranke besser überwindet bzw. eine zumindest ebenso lange (vermutlich jedoch längere) Halbwertszeit hat als 3,4-DAP. Zusammenfassend bleibt festzuhalten, dass zwar keine ursächliche Heilung für DBN in Sicht ist. Klinische Studien können jedoch zu einem besseren Verständnis von DBN führen und zu einer Symptomlinderung beitragen.

1. Introduction

Nystagmus can be understood as rhythmic eye movements that most often cannot be deliberately controlled (Kalla et al., 2008). It can be due to either peripheral or central vestibular or cerebellar dysfunction or due to a neurovascular compression of the eigth cranial nerve, i.e. the vestibular nerve (Brandt, 1990). Examples of peripheral vestibular dysfunction include the vestibular labyrinth, such as benign paroxysmal positioning vertigo, perilymphatic fistula, or Menière's disease or the vestibular nerve as in vestibular neuritis etc. (Brandt, 1990; Strupp & Brandt, 2006). Examples of central vestibular dysfunction include positional downbeat nystagmus, central positional nystagmus without major vertigo/dizziness, central positional vertigo/dizziness with nystagmus due to cerebellar and brainstem disorders (Brandt, 1990; Strupp & Brandt, 2006). An overview is presented in Brandt (1990). Based on prior work, e.g. Brandt (2000; 2003) or Brandt and Dieterich (1994; 1995), Heide and Kömpf (2005) describe central vestibular dysfunction in relation to the vestibulo-ocular reflex (VOR) in yaw, pitch and roll planes, often abbreviated as "yaw", "pitch", "roll". These planes were derived from the spatial configuration of vestibular receptors in the inner ear of humans and other vertebrates (Brandt & Dieterich, 1994; 1995; Heide & Kömpf, 2005). The VOR moves the eyes in the direction opposite to that of the head, compensating for high-frequency head perturbations including sudden movements, single or multiple positional changes of the head, vibrations or head unsteadiness (Heide & Kömpf, 2005), for example when recognising a face while walking, the harbour when navigating a boat, the handlebar when doing acrobatics or stunts on a BMX-bike, or a street sign when driving a bumpy road (e.g. Brandt, 2003). Following Brandt (2003), a tone difference of the VOR in horizontal plane (= yaw) is characterised by horizontal nystagmus, past pointing, rotational and lateral body falls, stumbling or just moving to the side, and a horizontal deviation of the perceived image straight ahead. A tone difference of the VOR in the sagittal plane (= pitch) is characterised by

DBN or upbeat nystagmus (UBN), forward/backward tilts and falls (forward/backward stumbling or just moving to the front/back), vertical deviation of the perceived image straight ahead, and finally, a tone difference of the VOR in the frontal plane (= roll) is characterised by torsional nystagmus, skew deviation, ocular torsion, tilts of head, body and perceived vertical, which may ultimately be associated with stumbling as well. The advantage of this classification is that, although tone differences in all three planes could be associated with stumbling, it allows for a topographic diagnosis of brainstem lesions with regard to their level and with regard to their side (Brandt, 2003). Based on Brandt and Dieterich (1994; 1995), a tone imbalance in yaw is associated with lesions of the lateral medulla including the vestibular nuclei and/or the entry zone of the root of Nervus vestibulocochlearis (the root of the eight's cranial nerve). A tone imbalance in pitch is topographically associated with bilateral paramedian lesions or topographically and functionally associated with a bilateral dysfunction of the flocculus / the floccular lobes (Brandt & Dieterich, 1994; 1995). According to the same authors, a tone imbalance in roll is topographically associated with unilateral lesions (these lesions would be ipsiversive at the pontomedullary level and contraversive at the pontomesencephalic level). A detailed overview is provided by Brandt (2003).

In nystagmus, the eye movements typically consist of an involuntary, slow (pathological) eye-drift and a fast compensatory saccade, leading to impaired acuity (Kalla et al., 2008; Spiegel et al, 2009a; 2009b; 2010; Strupp & Brandt, 2006). Nystagmus is frequently linked to a severe loss in terms of quality of life, e.g. people face difficulties when trying to read, work on a computer screen, watch TV or through postural state and gait instability (Kalla et al., 2008). This thesis is dedicated to DBN, which is the most frequent type of an acquired and persisting fixation nystagmus in central eye movement disorders (Baloh & Spooner, 1981; Kalla et al., 2007; Spiegel et al., 2009a; Wagner et al., 2008), though it has to be kept in mind that the absolute number of people suffering from DBN is rather low. DBN is named after its fast, correcting saccade, which beats downwards (Kalla et al., 2008). DBN is a

fixation nystagmus, which beats downwards in primary position and is enhanced in prone position or through downward gaze, as has been demonstrated by Marti et al. (2002). DBN often leads to impaired vision due to vertical oscillopsia[1] (Bronstein, 2004; Kalla et al., 2007; Leigh & Zee, 2006), blurred vision (Marti et al., 2008), and is associated with a postural state and gait instability in 80 percent of all patients (Kalla et al., 2008; Wagner et al., 2008). DBN is the consequence of an upward directed drift that typically increases in downward gaze and decreases or even reverses in upward gaze (Jeffcoat et al.; 2008, Marti et al., 2008; Robinson et al., 1984; Spiegel et al., 2009a). According to Alexander's law, slow-phase velocity (SPV) increases as gaze moves in the direction of the fast phase, which is downward in DBN, and decreases as gaze moves away from the direction of the fast phase, i.e. as gaze moves upwards (Jeffcoat et al.; 2008, Marti et al., 2008; Robinson et al., 1984; Spiegel et al., 2009a). When relating to eye movements during viewing, the correcting fast phases of DBN redirect gaze in the direction where patients attempt to fixate (Marti et al., 2008; Spiegel et al., 2009a). During gaze straight ahead, ocular drift is upward followed by fast phases beating downward (Leigh & Zee, 2006; Spiegel et al., 2009a). As was first reported in Straumann et al. (2000) and Glasauer et al. (2003) and later summarised in Spiegel et al. (2009a), ocular drift is composed of two components, (1) a vertical gaze-evoked drift, which is being caused by the leakiness of the mechanism for vertical gaze-holding, and (2) an upwards directed bias drift, for which a number of explanations have been proposed. The following pathomechanisms and their locations were made responsible for the bias drift (explained in Leigh and Zee, 2006; Kalla et al., 2004; Straumann et al., 2000; Glasauer et al., 2003; and summarised in Spiegel et al., 2009a): (1) pathomechanisms within the pathways associated with the vertical vestibulo-ocular reflex (Baloh & Spooner 1981; Böhmer & Straumann, 1998; Chambers et al., 1983; Gresty et al., 1986; Halmagyi et al., 1983; Pierrot-Deseilligny & Milea 2005), (2)

[1] According to Mosby's Medical Dictionary, 8th edition. (2009), Elsevier: "Oscillopsia consists of abnormal jerky eye movements … They create a subjective sensation that the environment is oscillating." Oscillopsia could thus be described as an illusionary movement of the visually perceived sensation.

pathomechanisms within the pathways associated with the vertical smooth pursuit (Zee et al. 1974), or (3) pathomechanisms within the internal coordinate systems dealing with vertical saccade generation and gaze holding, as proposed by Straumann et al. (2000) and Glasauer et al. (2003). As demonstrated by Marti et al. (2008) and later summarised in Spiegel et al. (2009a) and Kalla et al. (2011 in press), the bias drift of DBN may be due to a reduced function of inhibitory vertical gaze velocity sensitive Purkinje cells (PCs) located in the cerebellar flocculus. Following Marti et al. (2008), these PCs show a physiological asymmetry that is also present in non-clinical populations, causing a greater weight of cells with downward on-directions. Hence, a loss of vertical floccular PCs leads to a disinhibition of neurons in the superior vestibular nucleus and the adjacent Y group, which will result in a spontaneous upward drift (Marti et al., 2008, summarised in Spiegel et al., 2009a).

Thus so far, the pathophysiology of DBN is not completely understood. According to Kalla et al. (2007; 2008), the following three hypotheses are currently discussed: 1. a vestibulo-oculomotor cause with an imbalance of graviceptive vestibulo-ocular pathways, 2. an imbalance between a functionally disturbed neural-oculomotor integrator and the saccade burst generator, which is supported in animal experiments by an integrator deficit in DBN after a bilateral lesion to the cerebellar flocculus, 3. a central disorder of slow eye movements and smooth pursuit, which was first reported in Zee et al. (1981) and summarised by Kalla et al. (2007; 2008). According to the presently favoured hypothesis (Kalla et al., 2008), DBN is based on a bilateral damage to the flocculus and associated disorders of the vertical smooth pursuit (Glasauer et al., 2005a; Kalla et al., 2006; 2008). Following Kalla et al. (2008), these findings are further supported by functional magnetic resonance imaging studies (fMRI) in cerebellar DBN-patients, which showed a bilateral hypofunction of the flocculus (Kalla et al., 2006). Kalla et al. (2008) further report that fMRI studies with voxel-based morphometry indicated an atrophy of ocular-motor centres in the cerebellum, as was first discovered by Hüfner et al. (2007). In the following section, two recent approaches to explain the

pathomechanisms of DBN will be described. It will include the putative model on the pathomechanism of DBN by Hüfner et al. (2007) as well as a theory on the origin of DBN based on a theoretical model by Marti et al. (2008), which was implemented as a computational model by Stefan Glasauer (Sarah Marti, personal communication by email, 6th of July, 2009).

1.1. Two approaches to explain the origin of downbeat nystagmus

1.1.1. The putative model

Hüfner et al. (2007) proposed a putative model of the pathomechanism of DBN, which is depicted in Figure 1.1. According to the authors of this model, all patients with DBN share a pathway, which consists of a disinhibition of the Y-group brainstem neurons as well as a disinhibition of the superior vestibular nucleus (see Y/SVN in Figure 1.1). The ocular-motor circuitries have the Roman numbers I to III and consist of the smooth pursuit eye movement pathways (I/II) and the vertical gaze-holding pathway (III). For smooth pursuit eye movements, one pathway (grey line I) runs from the cortex via the dorsolateral pontine nuclei (DLPN) to the floccular/paraflocculare lobe (FL/PFL), and subsequently to the superior vestibular nucleus. This last projection is depicted as the red solid line. In particular, the authors assume this pathway to be important in smooth pursuit maintenance. The other pathway (grey line II) runs via the nucleus reticularis tegmenti pontis (NRTP) and ocular motor vermis (dorsal vermis, DV) to the fastigal nucleus (FN). This last projection is again depicted as a red solid line. The authors assume this pathway to be particularly important in smooth pursuit adaptation and initiation. The third pathway, i.e. the vertical gaze-holding pathway (grey dashed line III) runs from the interstitial nucleus of Cajal, which is not depicted in Figure 1.1., via the nucleus of the paramedian tract (PMT) or alternatively by

going directly via the paramedian tract (Hüfner et al., 2007). According to the authors, this pathway projects to the floccular lobe/parafloccular lobe. This last projection is depicted as the red dashed line. As the name of this pathway suggests, the authors assume it to be of particular importance for vertical gaze-holding. Hüfner and colleagues report a number of different diseases that can damage one or several of these three pathways. These diseases include inflammatory diseases, cerebellar degeneration or ischemia, craniocervical malformation, tumors, episodic ataxia type 2 (EA 2) or diseases responsible for demyelinisation such as multiple sclerosis (Hüfner et al., 2007). According to the authors, it can just as well happen that no pathway is damaged, but that the floccular/parafloccular lobes have lesions themselves, e.g. in cerebellar degeneration or craniocervical malformation. Another example provided by the authors is that an atrophy or a lesion of the ocular motor vermis, which plays a vital role in smooth pursuit, might lead to deficits in smooth pursuit initiation and impair the execution of smooth pursuit eye movements. Hüfner et al. point out that hypofunction of the floccular/parafloccular lobe (leading to DBN) may be the consequence of this process. They also mention that lesions of the ocular motor vermis may even lead to DBN without the involvement of the floccular/parafloccular lobe itself, because the ocular motor vermis contains Purkinje cells (PCs). Based on research of Shinmey et al. (2002), Hüfner et al. (2007) conclude that these Purkinje-cells fire more extensively with downward than they fire with upward smooth pursuit, which is also the case for the floccular/parafloccular Purkinje-cells. Finally, Hüfner and colleagues point out that lesions/damage to the vertical gaze-holding pathway or its related structures in the brainstem can have DBN as a consequence, e.g. if the paramedian tract (PMT) or its nucleus contains lesions. As an explanation how this could happen, they state that it might be due to interfering with the PMT by putting localised midline ponto-medullary lesions, which would then result in less floccular/parafloccular input (i.e. FL/PFL hypofunction). As the authors derive, this reduced input would in turn lead to less Purkinje cell output, so that DBN would be the

consequence. The different lesion sites leading to DBN are indicated by the red stars with Arabic numbers 1 to 3.

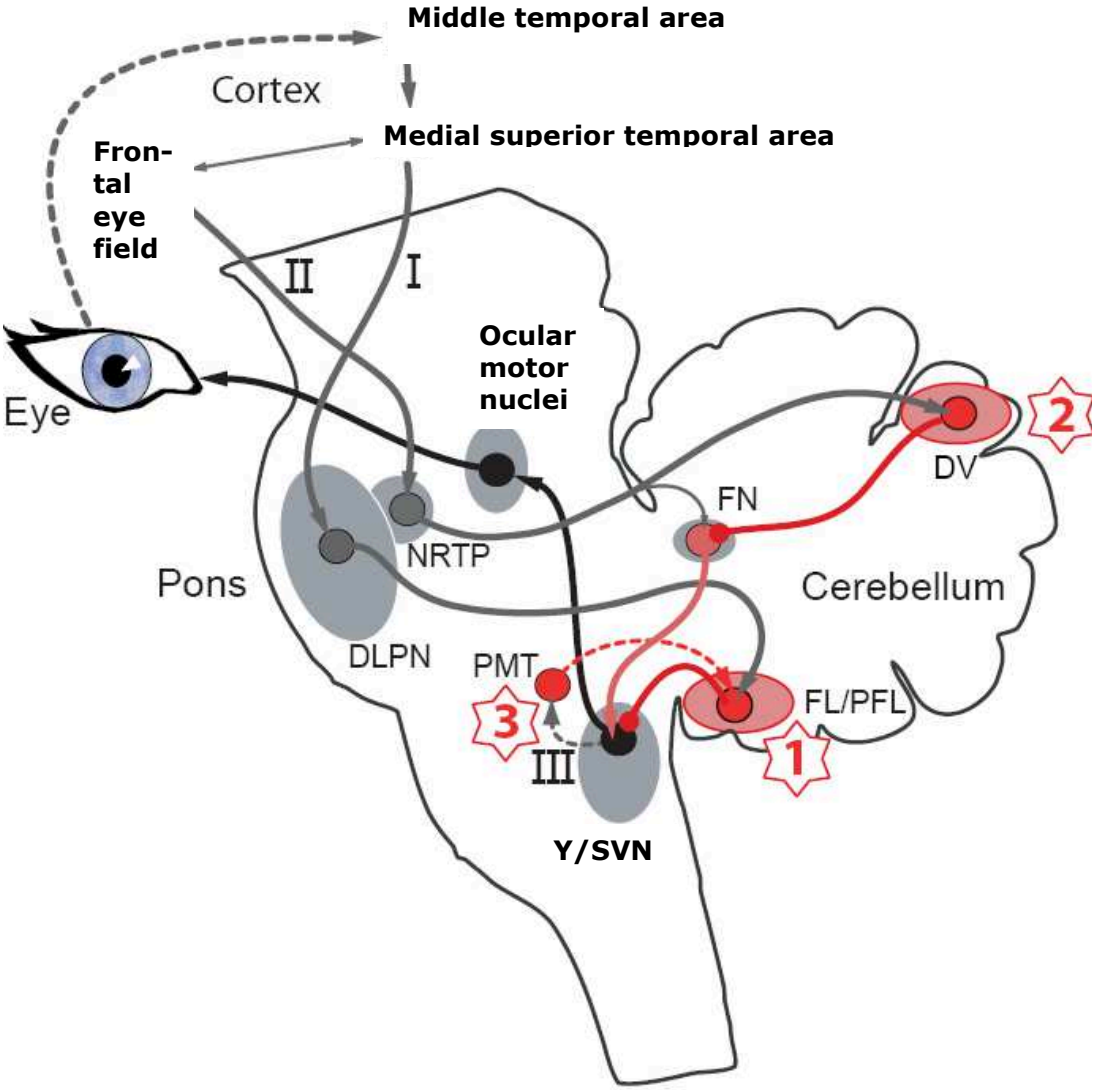


Figure 1.1 A putative model of the pathomechanism of DBN by Hüfner et al. (2007). The graph was slightly modified by the author of this thesis. Permission to display the figure in this thesis was obtained from the publisher. A detailed description of the pathomechanisms identified by Hüfner et al. (2007) can be found in the text of this introduction. Abbreviations: DLPN= dorsolateral pontine nuclei, DV= dorsal vermis (ocular motor vermis), FL/PFL= floccular/parafloccular lobe, FN= fastigal nucleus, NRTP= nucleus reticularis tegmenti pontis, PMT= paramedian tract, Y/SVN= neurons of the Y-group/superior vestibular nucleus.

The pathomechanisms described by Hüfner et al. (2007) are in line with the findings of other authors, e.g. it was reported by Kalla et al. (2008) that DBN is often caused by

cerebellar atrophy, different degenerative cerebellar diseases or ischemia, EA 2, Arnold-Chiari malformations or that it is caused by bilateral paramedian lesions in the medulla oblongata (referring to Wagner et al., 2008).

1.1.2. A model-based theory on the origin of downbeat nystagmus

Marti et al. (2008) developed a new theory (implemented in a computational model by Stefan Glasauer) that says that the ocular motor symptoms of DBN are due to a damage of the inhibitory gaze-velocity sensitive Purkinje cells (PCs) in the floccular lobe. Consequently, this computational model is not in opposition to the clinical model developed by Hüfner and colleagues, but rather based on common grounds. According to Marti et al. (2008), the PCs show spontaneous activity with a physiological asymmetry, where most of these PCs have downward on-directions. The authors conclude that a spontaneous upward drift results if vertical floccular PCs get damaged, because this would lead to disinhibition of the PCs' brainstem target neurons. The authors further conclude that the correcting saccade to this upward drift results in DBN. Similar as it had been described in the discussion of the clinical model by Hüfner et al. (2007), the floccular lobe in the model by Marti et al. (2008) is also associated with generating and controlling smooth pursuit and gaze holding. Therefore, a lesion to vertical floccular PCs could not only shed light on ocular-motor dysfunction in the model of Marti et al. (2008), but also in the model of Hüfner et al. (2007). To test the plausibility of the floccular involvement in the previously described ocular-motor functioning, Marti et al. (2008) created a computational model of vertical eye movements derived from experimental findings in neuroanatomy and neurophysiology. The aim of the model by Marti and colleagues was to show how the regions from cortex, cerebellum and brainstem interact to create the vertical eye movements typical for healthy participants, and to simulate the resulting ocular-motor effects after a large number of floccular PCs got damaged (Marti et al.,

2008). As a result of the simulation by Marti et al. (2008), ocular-motor symptoms evolved that are a characteristic of DBN: a spontaneous upward drift, which was the consequence of a lower spontaneous activity of PCs, a gaze-evoked DBN consistent with Alexander's law as previously described in this introduction for upward gaze and downward gaze (further details can be found in Jeffcoat et al.; 2008, Marti et al., 2008; Robinson et al., 1984; Spiegel et al., 2009a), a vertical smooth pursuit dysfunction due to asymmetries in the firing of PCs (Marti et al., 2008), and finally, a DBN-intensity dependent on gravity due to an interaction between a diminished function of the neural integrator and otolith-ocular pathways (Marti et al., 2008). The purpose to develop such an extensive model as this one was that none of the previous models to explain DBN covered all ocular-motor symptoms without the prior assumption of two or more alternative mechanisms, nor was any of the previous models (except Hüfner et al., 2007) able to explain the upwards-directed drift (Marti et al., 2008). Hence, the authors intend to (a) shed light on these issues and (b) aim at presenting a unifying theory to explain those mechanisms leading to DBN (Marti et al., 2008). The model (see Figure 1.2) is built around floccular Purkinje cells (PCs), which form the only output of the floccular lobe and appear right in the centre of the model (Marti et al., 2008). PCs are inhibitory. Hence, in the model of Marti et al. (2008), they have inhibitory connections to the vestibular nuclei, which are located in the brainstem (in the figure, the inhibitory connection goes to the superior vestibular nucleus). According to Marti et al. (2008), floccular PCs modulate their activity with the movements of the eyes, in particular with gaze velocity, and have different directional sensitivities, i.e. vertical or horizontal sensitivities. Whilst the overwhelming majority of vertical PCs in the model of Marti and colleagues are linked to downward on-directions by increasing their firing rate to eye movements caused by downward visual motion, almost no PCs with upward on-directions exist in their model (Marti et al., 2008). The distributional asymmetry relating to on-directions of vertical gaze-velocity PCs forms the heart of the model (Marti et al., 2008). According to the authors, the hypothesis is that the

spontaneous upward drift in DBN is due to a substantial loss of vertical PCs and the distributional asymmetry mentioned in the previous sentence. This process might be best understood when describing the entire model in detail (see Figure 1.2), and how the model simulates functioning in healthy people. Subsequently, it will be referred to the model's predictions when specific lesions are set to the model. In Figure 1.2, a number of boxes can be seen. According to the authors, these boxes indicate the responses of the model (and its individual elements) to VOR cancellation during head rotation (Marti et al., 2008). The process is displayed not only in the leftmost boxes, where the target rotates with the head, but also in the rightmost box, where the eye remains stable (Marti et al., 2008). While this process happens, i.e. target rotating with the head and eye remaining stable, the authors assume that a modulation to floccular PCs takes place in the central box of Figure 1.2, because the suppression of the VOR happens by pursuit commands. The next paragraph provides details to understand the model structure.

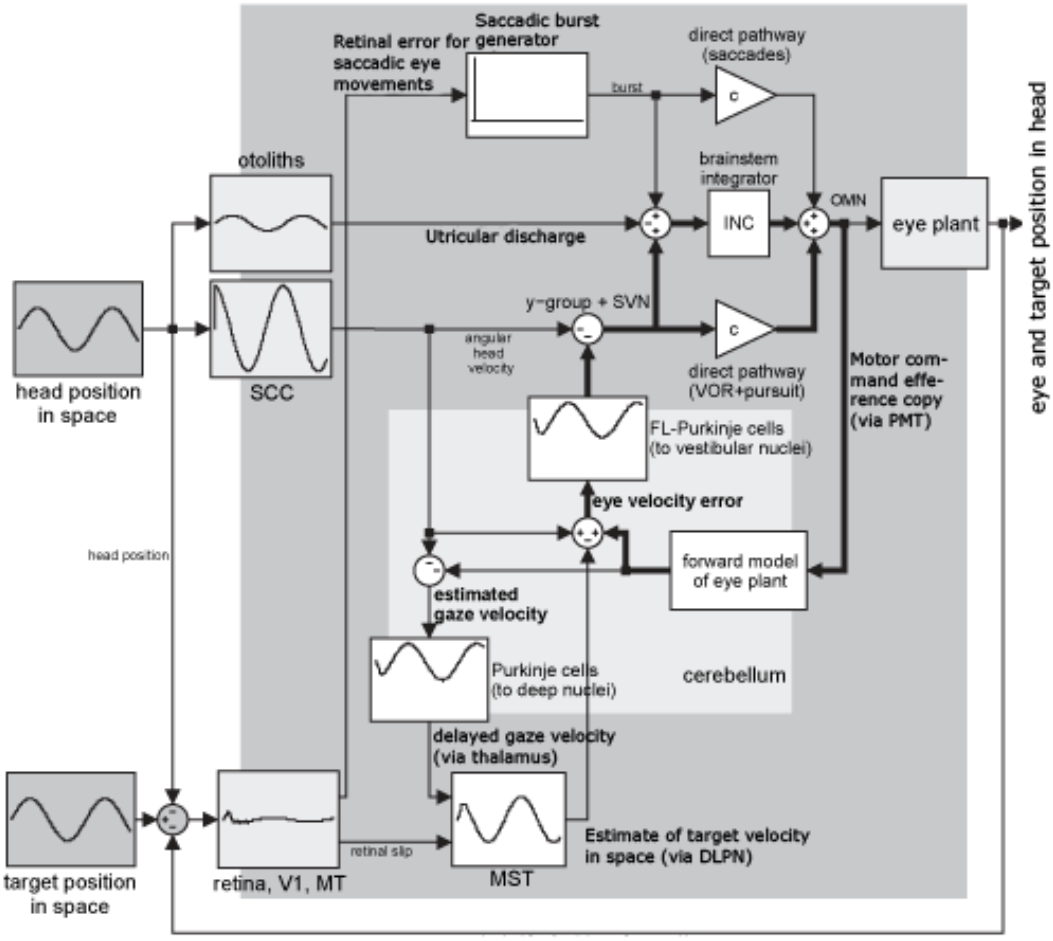
According to Marti et al. (2008), the bold connections/arrows indicate a negative feedback loop. Via this negative feedback loop, the authors assume that the flocculus inside the cerebellum augments the time constant (5 seconds) of the leaky brainstem integrator, the so-called interstitial nucleus of Cajal (INC). From the ocular-motor neurons, the outgoing motor command is copied back to the cerebellum by an efference copy via the paramedian tract neurons (PMT) or/and the neurons of the Y-group (as was initially hypothesised by Stefan Glasauer and subsequently implemented in the model of Marti et al., 2008, where Stefan Glasauer is a co-author). As assumed by the authors, the cerebellum also estimates the eye velocity on behalf of the eye plant's internal model. On the left side of the figure, the authors state that the head position in space (upper box) is processed not only by the otoliths leading to utricular discharge, but also by the semicircular canals (SCC) resulting in angular head velocity. The authors further assume that target position in space (lower box on the left side of the figure) is translated into retinal coordinates and further processed and analysed by

the visual system including the retina, area V1 and the middle temporal area (MT), eventually resulting in a retinal target position and retinal slip velocity. From the retinal slip, Marti et al. (2008) assume that a spatial estimate of target velocity is processed via the dorsolateral pontine nuclei (DLPN) and calculated in the middle superior temporal area (MST) making use of an efference copy feedback mechanism about estimated gaze velocity, which is processed back to the MST via floccular PCs to deep nuclei and from there via thalamic relay neurons. The authors further implemented a mechanism into their model where canal afferents from the semicircular canal (SCC) are also sent to the cerebellum as well as to the velocity-position integrator of the brainstem (INC: interstitial nucleus of Cajal) and from there to the ocular motor neurons (OMN) and the eye plant (Marti et al., 2008). As an alternative route, Marti et al. (2008) propose a direct pathway (i.e. not via the brainstem integrator), where the canal afferents project to the ocular motor neurons and from there to the eye plant. As was previously mentioned, the cerebellum in the model of Marti et al. (2008) has an internal model of the eye plant (see box titled "forward model of eye plant"). According to the authors, this internal model has the purpose to estimate the eye velocity coming from the motor command and to compare this estimate to the desired eye velocity in an error correcting way, for details on experimental data and error correction, refer to Spiegel and McLaren (2006). The desired eye velocity in Marti et al. (2008) consists of estimates of head velocity as well as target velocity. In their model, this comparison yields an error signal titled *eye velocity error*, which is returned back via the floccular PCs to the brainstem. In order to test the hypothesis that DBN is due to the previously mentioned asymmetric distribution in terms of vertical gaze-velocity sensitive PCs in the floccular lobe, Marti et al. (2008) lesioned a substantial part of the floccular PCs in their model. The authors' lesions set to the model had the consequence that the simulated vertical eye movements provided by the model showed all ocular-motor symptoms typical of DBN, i.e. diminished functioning of vertical smooth pursuit, problems with vertical gaze-holding as well as the upward directed drift suddenly

being influenced by gravity (Marti et al., 2008). Hence, the model's output was in line with clinical findings. Marti et al. (2008) come to the conclusion that fMRI studies by Stephan et al. (2005) and Kalla et al. (2006) found some evidence for the hypothesised

> "…inherently asymmetric distribution of on-directions of vertical gaze-velocity sensitive Purkinje cells (PC) in the cerebellar flocculus", (Marti et al., 2008, p. 622).

Further evidence for the authors' model comes from the study of gravitational influences on patients with DBN and healthy individuals (Marti et al., 2002), which provided conclusive evidence for gravity dependence of the upward directed drift. These results will be summarised in a separate section (see section 1.4), because the influence of gravity plays a large role in the clinical studies of this thesis. The model of Marti and colleagues also explains why a continuous administration of aminopyridines is a successful treatment for DBN, as aminopyridines enhance the activity of the floccular PCs (Etzion & Grossman, 2001; Kalla et al., 2007; 2008; 2011; Strupp et al., 2003; Strupp & Brandt, 2006). Before referring to pharmacological approaches, mechanisms from daily life (daytime dependence of DBN, resting in different body positions) will be discussed that also have the potential to alleviate the symptoms of DBN (e.g. Marti et al., 2002; Spiegel et al., 2009a). Although these mechanisms are not part of the two summarised models, they do not stand in contrast to them.



Physical feedback loop of eye position

Figure 1.2 The theory on the origin of DBN by Marti et al. (2008). The graph was slightly modified and therefore slightly differs from the original figure. Permission to display the figure in this thesis was obtained from the publisher. A detailed description of the pathomechanisms identified by Marti et al. (2008) can be found in the text of this introduction. Abbreviations: DLPN= Dorsolateral pontine nuclei, FL= Floccular lobe, INC= Interstitial nucleus of Cajal, MT= Middle temporal area, MST= Middle superior temporal area, OMN= ocular-motor neurons, PMT= Paramedian tract, SCC= semicircular canal, SVN= superior vestibular nucleus, V1= Visual area 1, VOR= vestibulo-ocular reflex, Y-group= neurons of the Y-group, c=canal afferents.

The mechanisms will be described in chapters 2 and 3 of this thesis, where the intensity of DBN will be analysed throughout the day. The goal is to find out whether the intensity of DBN shows a circadian modulation and whether this modulation is directly related to time or rather the result of the patients' body-position relative to gravity (e.g. usually people lie in bed at night and are in upright position during the day). The consideration of circadian changes of DBN might even add further information to these models and include the dimension *time*, which could be considered for future model updates in the clinical model by Hüfner and colleagues and in the theoretical model by Marti and colleagues. The inspiration to analyse DBN throughout the day came from individual patients reporting to the clinical research group of Michael Strupp that their vertical oscillopsia typically becomes weaker in the course of the day. If this is the case, it still does not prove that it is a mere mechanism of time. It could, in turn, also result from adaptive changes of DBN, as DBN is strongly influenced by gravity, e.g. Brandt (1990), Marti et al. (2002), Spiegel et al. (2009a), Spiegel et al. (2010), Sprenger et al. (2006). In order to determine whether these circadian changes will also hold in situations that modify DBN, slow phase velocity was analysed in different body positions relative to gravity, with gaze in different directions, and with or without visual targets. As will be seen in the next chapter, the resting body position throughout the intervals between video-oculographic measurements (VOG-measurements) were held constant, i.e. the patients rested in upright position. In the chapter following the next chapter, the resting body position (i.e. in the intervals when patients took a break between the VOG-measurements) was varied so that patients were assessed under three different resting positions: in upright position, in supine position and in prone position. It was analysed whether these three different resting positions relative to gravity had an influence on DBN. A short summary of the VOG-technique is provided now. This is followed by a description of how to calculate slow phase velocity. Subsequently, it will be referred to the gravity dependence of DBN.

1.2. The technique for video-oculographic (VOG) measurements

Based on prior research with three-dimensional VOG (Schneider et al., 2002; 2003; Zingler et al., 2006), this technique was applied in the studies of the following chapters in order to assess the intensity of DBN. What follows is a description of this method as it was applied by Zingler et al. (2006) inspired by prior research of Schneider et al. (2002; 2003). The technique is summarised here because it was adapted for the studies described in this thesis. There are small differences between the technique applied by Zingler and colleagues and the one applied in the studies of the following chapters. These differences will be mentioned as well. Zingler et al. (2006) assessed the eye movements of the right eye with 3D-VOG, where patients had to fixate a small fluorescent spot in front of each particular eye. Apart from this spot, participants were exposed to complete darkness (Zingler et al., 2006). The difference in the clinical studies of this thesis is that the fluorescent spot was generated by a laser and that, depending on condition, the fixation spot only appeared when the light was switched on and did not appear in darkness. In Zingler et al. (2006) as well as in the studies for this thesis, a VOG-mask (Hortmann, Münster, Germany) was applied where the fixation points were located on the inner surface of this mask and appeared in a straight-ahead position. Prior to each recording in Zingler et al. (2006), local anaesthesia was applied to the right eye of each patient; following the anaesthesia, the sclera was marked with two black markers. In Zingler et al. (2006), they were made of a cosmetic pigment absorbing infrared (Chronos Vision, Berlin, Germany). The rotation of the two marks was applied to measure ocular torsion in the work of Zingler and colleagues. Because ocular torsion was not assessed for the purpose of measuring DBN in the following studies of my thesis, this step was skipped. In both Zingler et al. (2006) and the studies of my thesis, the recording of the images on videotape was conducted with a sampling rate of 50Hz. They were later analysed with X-Binocle (Erich

Schneider, Munich, Germany) and Matlab (The Mathworks, Natick, MA, USA) software. The calibrated data were low-pass filtered applying a digital Gaussian filter, i.e. a filter based on a Gaussian ("bell-shaped") distribution (e.g. Spiegel et al., 2009a; Spiegel et al., 2010). This filter had a bandwidth of 30 Hz (the same as in Spiegel et al., 2009a; Spiegel et al., 2010; Kalla et al., 2011 in press). Interactive software allowed to detect and remove saccades and fast phases using a combined velocity–acceleration criterion (this process is also described in Spiegel et al., 2010 and Kalla et al., 2011 in press). The mean slow phase velocity was computed from de-saccaded data and was averaged over a measurement period of 30 seconds in each condition. Following the description of assessing DBN via VOG, it will now be referred to the calculation of slow phase velocity, because this will be taken to indicate the extent of DBN.

1.3. The calculation of slow phase velocity

The following explanations on how to calculate slow phase velocity are all based on prior work by Barin (2004). Following this author, slow phase velocity is typically measured for a single nystagmus beat. In DBN, the slow phase describes the upward drift, because DBN is termed after its fast phase, which is downward. Because the recording consists of a potentially large number of updrifts and downbeats in the measurement period of 30 seconds per condition, it makes sense to measure the mean slow phase velocity. In order to assess slow phase velocity for a single downbeat, Barin points out that the distance that the eye travels during the slow phase will have to be determined and divided by the amount of time (slow phase velocity = Δdistance / Δtime). According to Barin (2004), an even easier way is to draw a line that represents the slow phase best and to subsequently measure the slope of this line. This permits to assess the eye movement for a predetermined time, which is one second in the explanation provided by Barin (2004). It also is one second in the analysis of this thesis. This

measurement will result in slow phase velocity = degrees/second. In order to complete this calculation, Barin (2004) points out that it is vital to know the scale of the time and eye movement axes. He explains that these values are chosen by the setting of the electronystagmographic equipment as well as during the calibration at the start of each measurement process. Having described details with regard to the measurement process, it will now be referred to the influence of gravity on DBN.

1.4. Gravity dependence of downbeat nystagmus

Brandt (1990) describes central positional nystagmus, which is nystagmus occurring or being altered by different head positions, to be linked to the brainstem or the vestibulo-cerebellum. It can be linked to DBN, but it can just as well beat diagonally or beat upwards such as in upbeat nystagmus (UBN), details appear in Brandt (1990) as well as Strupp and Brandt (2006). Marti et al. (2002) focused on the gravity dependence of eyeball drift particularly in patients with DBN due to cerebellar aetiology. The patients had lesions in their vestibulo-cerebellum. Marti et al. (2002) reveal that the rapid change of positions as well as static headhanging positions when the participant is placed on a turntable both increase the slow phase velocity of DBN, and rolling the head from ear to shoulder could have a similar effect. As the most likely cause for the influence of gravity on DBN, Marti and colleagues consider lesions in the pathways connecting the otoliths with the eyes. As an alternative explanation they regard DBN being due to an asymmetry of vertical vestibulo-ocular reflexes, possibly being modulated by signals coming from the otoliths. Their work was based on two mechanisms: a gaze-evoked drift which they consider to be due to an impaired vertical neural integrator (1), and a velocity-related bias (2), (Marti et al., 2002). With the help of a three-dimensional turntable, Marti and colleagues analysed what impact gravity had on these two mechanisms. In their work, the whole body of the patients was positioned in roll, pitch, and

yaw planes of the head and patients were recorded binocularly with dual search coils (Marti et al., 2002). According to the authors, it turned out that no gravity dependence of the vertical gaze-evoked drift was found, but the vertical velocity bias had the following two components: an upwards-directed component that was independent of gravity, the so-called gravity-independent (GI) component, and a component being gravity-dependent, hence named gravity-dependent component (GD). This GD-component was related to the vector of gravity in the pitch- (but not in the roll-) plane, being a result of sinusoidal modulation (Marti et al., 2008). In their work, combining the two components resulted in an overall drift being minimal in supine position, where the GD component's downward drift was maximal, which counteracted the DBN's upward drift (Marti et al., 2002). In the article of Marti and colleagues, it had also been shown that in prone position, the maximal vertical drift velocity was assessed, because both drift components were in upward direction. Added together, this resulted in stronger DBN. When patients were in upright position, the authors found that the GD component was near zero, which they interpreted as the vertical ocular drift almost being exclusively based on the GI component. In healthy participants, the authors were able to observe the same modulation of the GD component, but they also noticed that the amplitude of this component was much larger among their cerebellar patients. Marti et al. (2002) draw the following conclusions based on their results: an intact vestibulo-cerebellum is able to minimise an overacting otolith-reflex, which is being elicited by pitch tilt. They also point out that an intact vestibulo-cerebellum cancels an inherent upward ocular drift. According to Marti et al. (2002), this drift does not depend on otolith signals modulated by gravity. Marti et al. (2002) provide the following explanation:

> "The sinusoidal modulation of the GD component of vertical drift velocity in the pitch plane is most likely otolith driven and may represent an overacting otolith-ocular reflex. The normal function of the otolith-ocular reflex at low frequencies driven by pitch tilt is

> to keep the vertical gaze direction stable in space (Paige & Seidman, 1999). Thus, when the head is pitched downward, the eyes move upward and vice versa. The direction of the GD component is consistent with this pattern. The finding that healthy subjects showed the very same pattern of the GD component, but in a scaled-down version, supports the notion that the intact cerebellum minimizes the overacting otolith-ocular reflex driven by pitch tilt. In fact, previous clinical studies have demonstrated a substantial role of the cerebellum in controlling translational vestibuloocular reflex (Baloh et al., 1995; Crane et al., 2000; Zee et al., 2002). In electrophysiological studies, both the flocculus (Snyder & King, 1996) and the nodulus (Precht et al., 1976) modulated otolith-ocular reflexes“, (Marti et al., 2002, p. 720).

As a practical application of their results, Marti et al. (2002) recommend that patients with DBN due to cerebellar aetiologies should be advised that the best body position for reading is the supine position. This recommendation definitely makes sense on the basis of these results. The following chapters of this thesis will also relate to these three body positions (upright, supine and prone). It will be focused on DBN during measurement. In addition, it will also be focused on the question whether DBN during measurement is modulated by various resting positions (upright, supine and prone resting positions) in between the measurements or prior to the measurements. The hope is to give additional practical recommendations to patients, e.g. what resting position is optimal during the day, where people are usually in upright position (see chapter 3). Following chapter 3, a clinical study with aminopyridines will be described in chapter 4. The reason why aminopyridines are a promising treatment in DBN and what other pharmacological approaches exist will be discussed now.

1.5. Pharmacological approaches of downbeat nystagmus treatment

The following review of pharmacological approaches is mainly based on a literature review for my thesis, which also appeared in Kalla et al. (2008). As the second author of the publication, I contributed aspects of the text in this article that overlap with the following chapter of the thesis. Hence, there is an overlap between the publication and this chapter. The pathophysiology of DBN is probably based on a floccular dysfunction, which leads to a reduced release of gamma-amino-butter-acid (GABA) and a disinhibition of the vestibular nuclei (Kalla et al., 2008). Based on this assumption, a number of GABAergic substances were applied for treatment. In a dose of 1.5 to 3 mg per day, the $GABA_A$-agonist Clonazepam (which belongs to the group of benzodiazepines) is capable of alleviating DBN symptoms (Currie & Matsuo, 1986; Kalla et al., 2008; Young & Huang, 2001). Following Kalla and colleagues, it has to be considered, though, that the studies on Clonazepam were not placebo-controlled. Moreover, the use of benzodiazepines often leads to sleepiness and patients run the risk of benzodiazepine dependency if they take Clonazepam regularly (Kalla et al., 2008). Apart from Clonazepam, the $GABA_B$-agonist Baclofen can also alleviate the symptoms of DBN (Dieterich et al., 1991; Kalla et al., 2008). According to a double-blind cross-over trial, however, the symptoms of DBN only became less in one out of a total of six patients after administration of Baclofen (Averbuch-Heller et al., 1997; Kalla et al., 2008). On the basis of single observations, it was assumed that Gabapentine would also lead to a decrease in DBN symptoms, because Gabapentine acts as a ligand to the alpha-2-delta-subunit of voltage-gated N-type calcium ion channels (Davies et al., 2007; Kalla et al., 2008). Testing Gabapentine in a double-blind cross-over trial, however, only alleviated the symptoms of DBN in one out of six patients. Taken together, in no placebo-controlled study was it thus far possible to demonstrate a clinically relevant improvement of symptoms for either Clonazepam, Baclofen

or Gabapentine or any of the related substances (for a review see Kalla et al., 2008; Straube et al., 2004; Strupp & Brandt, 2006; Strupp et al., 2011a). Additional medications having been tested in a randomised, double-blind, crossover trial for the treatment of acquired nystagmus are the anticholinergic agents Trihexyphenidyl and Tridihexethyl chloride (Leigh et al., 1991, Kalla et al., 2008). Initially, ten patients were included in the clinical trial, but due to intolerance of medication or trial-intermitting illness, only five patients were able to complete the trial with both drugs. When considering the drugs separately, there were six patients having completed the tests in either drug. In Trihexyphenidyl, only one out of these six patients showed improvements. In Trihexethyl chloride, four out of these six showed improvement, but had experienced substantial side effects, which undermined the benefit of the treatment. Taken together, these results indicate that Trihexyphenidyl is not a suitable medication for acquired nystagmus, whereas Trihexethyl chloride seems suitable based on symptom alleviation, but at the cost of adverse side reactions, which makes it hard to justify the use of either medication should an individual patient experience serious adverse reactions. Moreover, it has to be kept in mind that these drugs were not tested for DBN in particular, but rather for acquired nystagmus in general. To conclude, none of the medications mentioned so far present a convincing treatment option for DBN.

1.5.1. Prior studies on the influence of the aminopyridines 3,4-Diaminopyridine and 4-Aminopyridine on the intensity of DBN

The review of the following subchapter has mainly appeared in the article of Kalla et al. (2011 in press), where my name is part of a shared first-authorship and where I contributed, among other aspects, substantial parts of the text. Hence, there is an overlap between the text in this chapter and the publication. Based on the pathomechanism of DBN, the potassium-channel

blockers 3,4-diaminopyridine (3,4-DAP) and 4-aminopyridine (4-AP) are an alternative way to achieve a clinically relevant improvement. One mechanism being made responsible for DBN is the loss of Purkinje-cells due to cerebellar damage. To understand this mechanism, it is important to consider that Purkinje-cells are the only cells leaving the cerebellum. Moreover, their signals are inhibitory, i.e. a loss of Purkinje-cells will result in less inhibitory signals leaving the cerebellum.

The two aminopyridines are non-selective blockers of the potassium channels (Hille, 2001), which also blocks potassium channels of the remaining Purkinje-cells, i.e. the ones not having been lost due to damage (Judge & Bever, 2006). In particular, they block the K_v-family of potassium channels, which consist of a heterogeneous group of integral membrane proteins (Judge & Bever, 2006). According to the authors, the ion channel can be either conducting, i.e. open, or non-conducting, i.e. closed. The authors conclude that the transmembrane electric field can result in a structural re-arrangement of the K_v-channels, so that their pore opens. According to Judge and Bever (2006), the aminopyridines can block the pore by inducing a structural rearrangement of the K_v-channels, so that their pore stays closed. As a consequence, there will be a higher resting activity and excitability of the Purkinje-cells (Etzion & Grossman, 2001). The higher resting activity as well as the increased excitability was confirmed in Purkinje-cells of guinea pigs by Etzion and Grossman (2001). As a consequence of being excited, Kalla et al. (2004; 2011) expect the remaining Purkinje-cells to restore the inhibitory influence on deep cerebellar and vestibular nuclei. The subsequent inhibitory effect on vertical eye movements is assumed to result in a reduced vertical ocular drift and therefore less DBN (Leigh, 2003; Kalla et al., 2004; 2011). The positive effects of aminopyridines on DBN (Strupp et al., 2003) and EA 2 (Strupp et al., 2004; 2011b) were first discovered clinically by Strupp and colleagues and later explained by this pathomechanism (Kalla et al., 2011). Additional clinical studies have shown that aminopyridines improve DBN (Helmchen et al., 2004; Kalla et al., 2004; Kalla et al., 2007; Sprenger et al., 2005). Relating

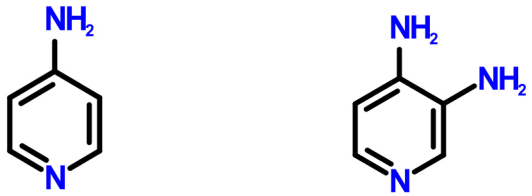
to Kalla et al. (2011), it turned out that not only DBN was reduced in patients with EA 2, but also the frequency of attacks (Strupp et al., 2004) as well as interictal cerebellar ataxia (Löhle et al., 2008). More recently, new evidence for the clinical discoveries of Michael Strupp was found. According to this new evidence, therapeutic concentrations of 4-aminopyridine restore the diminished precision of pacemaking in Purkinje cells of the ataxic P/Q channel mutant mouse (Kalla et al., 2011). This works by prolonging the action potential and by increasing the action potential after hyperpolarization (Alviña & Khodakhah, 2010; Kalla et al., 2011). This new evidence now acts as the currently assumed mechanism by which aminopyridines improve DBN (Kalla et al., 2011). Effects of 4-AP on the cerebellum were confirmed in a PET study demonstrating that 4-AP increased metabolic activity bilaterally in the floccular lobes of the cerebellum (Bense et al., 2006; Kalla et al., 2011).

Referring to the history of aminopyridine treatment in DBN, it is now worth having a closer look at the first double-blind, placebo-controlled cross-over trial with aminopyridines, conducted by Strupp et al. (2003) and comprising 17 patients with DBN due to cerebellar atrophy, Arnold-Chiari malformation, cerebellar infarction or due to idiopathic or cryptogenic causes. When measuring the mean peak slow phase velocity of DBN prior to and 30 minutes after ingestion of 20 mg 3,4-DAP or after ingestion of the placebo, DBN reduced from 7.2 deg/s to 3.1 deg/s ($p<0.001$) in the 3,4-DAP group, whilst placebo had no relevant effect (Strupp et al., 2003). In addition, the mean peak slow phase velocity in Strupp et al. (2003) decreased in 10 out of a total of 17 patients by over 50 percent and in 12 out of 17 patients by over 40 percent. These positive effects were not entirely independent of aetiology. According to the authors, the three patients with cerebellar infarctions only showed a minor reduction in mean peak slow phase velocity. Taken together, however, DBN-symptoms improved substantially after ingestion of 3,4-DAP (Strupp et al., 2003). Likewise, there was an improvement in postural stability and oscillopsia according to the authors. The advantages of 3,4-DAP clearly seemed to outweigh the side effects of three patients experiencing peri-oral

or digital paresthesias and one patient experiencing a headache and nausea. Another study by Kalla et al. (2004) analysed the effect of 4-AP by applying the magnetic search-coil technique. This case study showed that 4-AP not only improved DBN, but also VOR-gain and smooth pursuit. VOR-gain refers to the vestibulo-ocular reflex and should optimally equal one (Angelaki, 2004; Crawford & Vilis, 1991; Encyclopaedia Britannica, 1987). In this case, the ratio of the eye and head rotations is equal, i.e. if the head rotates in one direction, the eye should rotate in the other direction by an equal amount (Angelaki, 2004; Crawford & Vilis, 1991). In central neurological disorders, VOR-gain often differs from 1, i.e. shows a larger or smaller value (Angelaki, 2004; Crawford & Vilis, 1991; Kalla et al., 2004; Encyclopaedia Britannica, 1987). After the administration of 4-AP, however, it came closer to the optimal value. Likewise, smooth pursuit, which can be described as smooth, i.e. non-disruptive, eye movements when attempting to follow a target with the eyes smoothly (in contrast to saccaded pursuit as demonstrated by Grasse & Lisberger, 1992), also improved after the administration of 4-AP in the study of Kalla et al. (2004). An additional study by Kalla et al. (2007) including 15 patients with DBN of various aetiologies (cerebellar degeneration, cerebellar infarction, cerebellar meningioma, EA 2, multiple sclerosis, vascular causes or idiopathic aetiologies) led to reduced DBN during gaze straight ahead in 12 out of a total of 15 patients (before therapy: -4.99 +/- 1.07 deg/s (mean +/- SE). 45 minutes after administration of a 10 mg capsule of 4-AP the values were: -0.60 +/- 0.82 deg/s). A multiple regression analysis of slow-phase velocity (SPV) in different eye positions across all patients revealed that vertical and horizontal gaze-evoked drift was significantly lower irrespective of aetiology. On average, it led to perfect performance in terms of gaze holding, where a change of vertical eye position sensitivity towards zero was found in 13 out of a total of 15 patients. Because the results did not depend on target visibility, Kalla and colleagues concluded that 4-AP improved fixation by helping to restore the ability of gaze-holding. According to the authors, patients with cerebellar atrophy benefited the most out of the treatment. In EA 2,

which also belongs to central ocular-motor disorders, a case study by Strupp et al. (2004) could show that the daily dose of 5mg 4-AP resulted in a long-lasting effect, i.e. an absence of symptoms for a prolonged period. As reported in Strupp et al. (2004), the symptoms, however, recurred after treatment had been provisionally terminated. According to the authors, subsequent administration of 4-AP once more was associated with symptom alleviation. These effects were later confirmed in a placebo-controlled trial (Strupp et al., 2011b). Positive effects of aminopyridines also included research on the gravity dependence of DBN (Helmchen et al., 2004; Sprenger et al., 2006). An improvement in terms of postural instability was also confirmed by Sprenger et al. (2005). Thus far, aminopyridines have the most clinically relevant effects in the treatment of DBN, for a review see Kalla et al. (2008), Rucker (2005), Straube (2007), Strupp and Brandt (2006), or Strupp et al. (2011a). 4-AP seems to have several advantages over 3,4-DAP: it can cross the blood-brain barrier more easily and has a longer half life (Hayes, 1994; Hayes et al., 2003; Judge & Bever, 2006; Kalla et al., 2009; Kalla et al., 2011; Leigh, 2003), which is 3 to 4 hours according to Hayes et al. (2003) for 4-AP and 2 hours according to Witz et al. (2009) for 3,4-DAP. Its effects can be quickly measured in the plasma, where it reaches its maximal concentration approximately one hour after oral capsule intake (Judge & Bever, 2006; Kalla et al., 2011). Patients often realise a symptom reduction only half an hour after swallowing the capsule (Kalla et al., 2008). Following Kalla et al. (2008), the positive effects of 4-AP were also independently confirmed in an imaging study by Bense et al. (2006), who applied PET-scans (positron emission tomography) to show a 4-AP-dependent improvement of metabolic activity in the flocculus in a patient with DBN. Because of their positive effects on alleviating DBN symptoms, the aminopyridines 4-AP and 3,4-DAP will be subject to this thesis. After both aminopyridines showed positive effects in placebo-controlled trials, they will be compared to each other to see whether one reduces DBN better than the other. Following Judge and Bever (2006) and based on a review by Hayes (1994), 4-AP and 3,4-DAP have a long history for a

variety of diseases and phenomena, including multiple sclerosis treatment, botulinum poisoning, post-surgical antagonism of neuromuscular blockade, dementia such as Alzheimer's disease, myasthenia gravis, or Lambert-Eaton syndrome. According to Judge and Bever (2006), both 4-AP and 3,4-DAP have multi-compartment pharmacokinetics with serum half-lives ranging from one to three hours. They are rapidly absorbed after ingestion with peak serum levels from 20 to 60 minutes after administration (Judge & Bever, 2006; Hayes, 1994; Kalla et al., 2011). Based on Judge and Bever (2006) and Hayes (1994), 4-AP is lipid soluble to a high degree, i.e. it easily crosses the blood-brain-barrier. Hence, Judge and Bever (2006) conclude that it can be applied as a potassium channel blocker not only in the peripheral nervous system, but also in the central nervous system. On the contrary, 3,4-DAP is only soluble in aqueous solution and does not cross the blood-brain barrier so easily (Judge & Bever, 2006). Hence, its dominant application is the peripheral nervous system (Judge & Bever, 2006). As a result, it can be expected that 4-AP is better suited than 3,4-DAP due to its longer half-life and its ability to better cross the blood-brain barrier, but this still has to be shown in a clinical study. Therefore, chapter 4 of this thesis is dedicated to this comparison. Figure 1.3 shows the structure of both aminopyridines. The structure of 4-AP can be accessed in Yang et al. (2008), the structure of 3,4-DAP in Rubin-Preminger and Englert (2007).



4-AP **3,4-DAP**

Figure 1.3 The chemical structures of 4-AP (left) and 3,4-DAP (right). The chemical structures were created using ChemWriter (Metamolecular, La Jolla, CA, USA).

2. The intensity of downbeat nystagmus during daytime

In the following own study, the intensity of DBN during daytime, i.e. in the course of the day, was analysed. It has been published in Spiegel et al. (2009a). Because I had written the text of the publication and as I am the author of this thesis, part of the written text shows an overlap. The same holds true for the tables, figures, and their legends.

2.1. Methods

2.1.1. Patients

This study comprised 12 patients with DBN due to different aetiologies (for details see Table 2.1). In 5 patients, DBN was associated with cerebellar syndrome, whilst cerebellar atrophy was present in 4 out of these 5 patients. In 7 patients the aetiology of DBN was unknown. The mean duration since DBN was first diagnosed was 5.75 years (with a range of 0 to 17 years). The patients were 44 to 76 years old (with a mean of 65.75 years ± a standard deviation of 8.9 years). Neuro-ophthalmological findings (for details see Table 2.1) included disturbed visual fixation suppression of VOR, pathological head-thrust test, incomplete ocular tilt reaction, impaired horizontal and vertical opto-kinetic nystagmus, impaired horizontal and downward pursuit, provocation nystagmus, etc. In this study, the patients' eye movements were recorded four times on a single day: at 9am, 11am, 1pm and 3pm. During the intervals between VOG-measurements, patients were sitting upright (see Figure 2.1). All patients underwent a complete clinical examination that included neuro-otological, neuro-ophthalmological, and neurological tests, MRI (including high resolution MRI of the brainstem and the cerebellum), electronystagmography (including caloric irrigation), an electrocardiogram and laboratory tests (including vitamin B12 and Mg2+). At the time of the measurements, no patient was

taking medication affecting the vestibular or ocular motor systems. None of the patients in this study had DBN caused by metabolic disorders or drugs. Informed consent to participate in this study was given by all patients. The VOG-measurements were done in accordance with the Helsinki II Declaration and approved by the local ethics committee of the Ludwig-Maximilians-University Medical Faculty.

2.1.2. Recording of eye movements

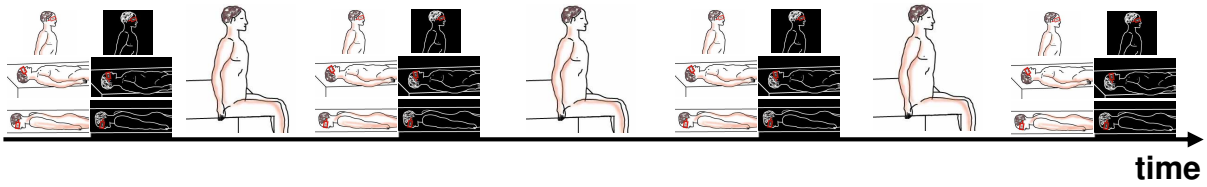
As mentioned before, people were tested four times on a single day. Each time, patients were monitored in the following sequence: (see Figure 2.1).

1. they were sitting in upright position, 2. they were lying in supine position, 3. they were lying in prone position, all conditions either with the light switched on or off. In the resting intervals between the assessments (titled intermission in Figure 2.1), patients were in upright position with the light switched on. Based on previous research by Zingler et al. (2006) (a detailed description can be found in the introduction of this thesis), each position consisted of a 30 seconds eye movement recording with a three-dimensional video-oculography in the following order: a calibration in 8.5° position, 1. gaze straight ahead with fixation turned on, 2. gaze straight ahead with no possibility to fixate on a fixation point, i.e. in darkness, 3. 17° gaze to the right, 4. 17° gaze to the left, 5. 17° gaze upwards 6. 17° gaze downwards. The target was projected by a laser on a white cardboard at a distance of 60 cm in front of the participant. The leftward and rightward gazes were only recorded for completeness purposes, e.g. in order to generate hypotheses for possible future studies. In the Spiegel et al. (2009a) manuscript, no hypotheses with respect to leftward and rightward gazes existed. The only gazes of interest were gaze straight ahead, upward gaze and downward gaze.

Table 2.1. The clinical data of the patients where DBN was measured during daytime (see Spiegel et al., 2009a).

No./Sex/ Age	Neuro-ophthalmological findings	MRI findings	Aetiology	Disease duration
No 1M, 76	Disturbed visual fixation suppression of VOR, impaired horizontal and vertical opto-kinetic nystagmus with horizontal and vertical saccades, impaired horizontal and downward pursuit, pathological HTT bilaterally.	White matter lesions	Idiopathic cerebellar syndrome	2 years
No. 2F, 51	Disturbed visual fixation suppression of VOR, incomplete ocular tilt reaction, impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally, provocation nystagmus downwards and to the right, hypermetric saccades to the right.	Cerebellar atrophy	Cerebellar de-generation	7 years
No. 3F, 66	Disturbed visual fixation suppression of VOR, impaired horizontal and non-existing vertical opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally.	Cerebellar atrophy	Idiopathic cerebellar ataxia	4 years
No. 4F, 69	Disturbed visual fixation suppression of VOR, impaired horizontal and upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally, provocation DBN.	Cerebellar atrophy	Idiopathic cerebellar ataxia	17 years
No. 5M, 64	Disturbed visual fixation suppression of VOR, non-existing upright opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally.	Cerebellar atrophy	Cerebellar de-generation	3 years
No. 6M, 69	Disturbed visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT on the left.	Normal	Unknown	6 years
No. 7M, 65	Impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, hypometric upward saccades.	Normal	Unknown	10 years
No. 8F, 69	Disturbed vertical visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit.	Normal	Unknown	3 years
No. 9M, 44	Disturbed visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and vertical pursuit.	Normal	Unknown	10 years
No. 10F, 74	Horizontal and impaired downward opto-kinetic nystagmus with DBN when looking upwards, impaired horizontal and downward pursuit	Normal	Unknown	3 years
No. 11F, 70	Horizontally impaired and vertically nonexistent opto-kinetic nystagmus, impaired horizontal and downward pursuit.	Normal	Unknown	4 years
No. 12M, 72	DBN, incomplete ocular tilt reaction to the right, pathological HTT.	Normal	Unknown	0 years

VOR=vestibulo-ocular reflex; HTT=head-thrust test developed by Halmagyi and Curthoys (1988). The permission to display the table was received from the publisher of Spiegel et al. (2009a).



Test: 9am **Inter-mission** Test: 11am **Inter-mission** Test: 1pm **Inter-mission** Test: 3pm

Figure 2.1 An overview describing the testing conditions for all patients. The eye movements of the patients were monitored in the following order: 1. sitting in upright position in light/dark, 2. lying in supine position in light/dark, 3. lying in prone position in light/dark. All measurements took place at 9am, 11am, 1pm and 3pm. In between the measurements, patients rested in upright position with the room-light switched on (see Spiegel et al., 2009a). The permission to display the figure was received from the publisher of Spiegel et al. (2009a).

2.1.3. Data acquisition and calibration

In each body orientation, the eye position was measured with 3D video-oculography for 30 seconds. An off-line analysis of the data was carried out using Matlab (The Mathworks, Natick, MA, USA). Subsequently, the calibrated data were low-pass filtered applying a digital Gaussian filter with a bandwidth of 30 Hz. Usually, saccades and fast phases were automatically detected and removed from the data making use of a combined velocity–acceleration criterion in interactive software. Subsequently, saccades and fast phases that were not recognised automatically were removed manually. From the desaccaded data, mean slow phase velocity was computed. An explanation how slow phase velocity is computed can be found in the introduction.

2.1.4. Statistical data analysis

The statistical analysis consisted of repeated measurement ANOVAs (Statistica 6.1, Statsoft, Tulsa OK, USA) with post-hoc Scheffé tests for individual comparisons. The dependent variable was mean slow phase velocity (SPV). On all following figures in this thesis with SPV as the dependent variable, values have been transformed so that DBN indicated by SPV degrees/second occur as negative values on the scale, whereas no DBN would occur as a zero value on the scale. This also implies a specific terminology. Whenever in this thesis the terms *higher* or *more pronounced* are applied to SPV-values, it is meant *more negative* in spite of the fact that, in mathematical notation, -5 deg/s would be *lower* or *less pronounced* than for instance -4 deg/s. The same applies when it is said that SPV *decreased* from -5 deg/s to -4 deg/s. In mathematical notation, this would be an increase, because more negative values increase to less negative values. Nevertheless, the word *decreased* will be applied here, because of the scale transformation from positive to negative and because of the fact that a change from more negative to less negative SPV-values is associated with a decrease in DBN. The dependent variable SPV was measured in three gaze directions (straight ahead, upward, downward, more details are provided in 2.1.2. Recording of eye movements). The first analysis consisted of the within subjects factors *vertical versus horizontal measurement* and *daytime* (9am, 11am, 1pm, 3pm). The dependent variable was *mean slow phase velocity (SPV)*. All analyses following the first analysis had the dependent variable *vertical SPV*, i.e. not including horizontal measurements. The second analysis included the within subjects factors *light* (light on = fixation is possible versus light off = viewing in the dark with no possibility to fixate) and *daytime* (9am, 11am, 1pm, 3pm). The third analysis consisted of the within subject factors *gaze direction* (straight, upwards, downwards) and *daytime* (9am, 11am, 1pm, 3pm). The fourth analysis had the within subject factors *body orientation*

(upright, supine and prone) and *daytime* (9am, 11am, 1pm, 3pm). Finally, the same analyses were carried out with the inclusion of the between subjects factor *aetiology* (cerebellar aetiology versus unknown aetiology).

2.2. Results

2.2.1. Daytime dependency of downbeat nystagmus

It turned out that DBN during daylight significantly depends on *daytime* (Figure 2.2a, $F(3, 33)=6.89$, $p<0.001$) with vertical SPV decreasing from the first to all other measurements (Scheffé tests for individual comparisons $p<0.01$). Horizontal and vertical SPV were significantly different from each other, $F(1, 11)=13.775$, $p<0.01$. As revealed by Scheffé post-hoc tests, the 9am measurements ($p<0.00001$) as well as the 11am ($p<0.05$) and 1pm ($p<0.05$) measurements differed from each other. As can be seen in Figure 2.2a, horizontal SPV was much lower and close to zero. The daytime effect was less evident for horizontal SPV, but the interaction *daytime times vertical versus horizontal measurement* was still significant despite lower slow-phase velocities in this direction, $F(3, 33)=4.34$, $p<0.01$. From now on, it will be focused on vertical eye movements only, since the daytime effect was less evident for horizontal SPV. Another reason for analysing vertical eye movements stems from the fact that patients with DBN had reported a daytime-dependent decrease in vertical oscillopsia, which was already mentioned in the introduction of this thesis. All following figures within this chapter display the mean slow phase velocity along with the standard error bars of the mean.

2.2.2. The influence of fixation on daytime dependency of downbeat nystagmus

In the second analysis (Figure 2.2b), DBN assessed by vertical SPV was significantly smaller in the presence of a visible fixation point, $F(1, 11)=19.32$, $p<0.01$. However, the daytime dependence showed no significant difference between the two conditions (light on versus light off, i.e. no significant (though a marginally significant) interaction between daytime dependence and the possibility to fixate), $F(3, 33)=2.645$, $p=0.065$. This is a tentative sign that daytime dependence is not due to an increasing ability to suppress the nystagmus, but rather to a generic decrease in the slow phase velocity. Although there was only a marginally significant interaction, the probabilities of Scheffé post-hoc tests were revealed in order to provide a better comparison between Figure 2.2a and 2.2b).

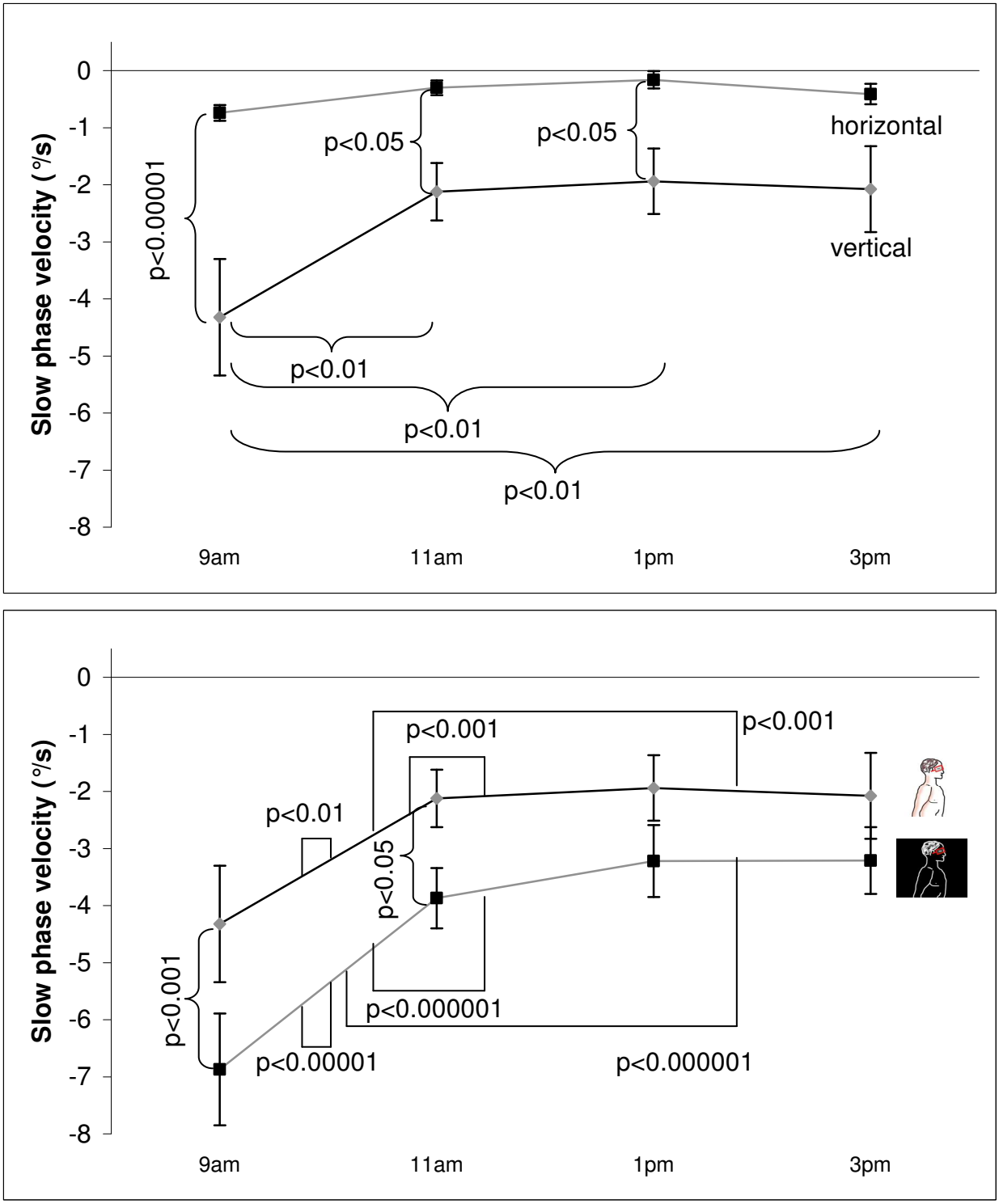


Figure 2.2 Comparing DBN intensity changes throughout the day. Display of mean slow phase velocities along with the standard error bars of the mean. In both cases, measurements took place in upright position with gaze straight ahead, see Spiegel et al. (2009a):
a Vertical and horizontal slow phase velocity with fixation (=light on) throughout the day.
b Vertical slow phase velocity: Fixation (= light on) and viewing in darkness (= light off) throughout the day. Permission to display the figure was received from the publisher.

When referring to the main effect of *daytime*, as was found in the first analysis, DBN once more decreased throughout the day (9am: -5.59 deg/s, 11am: -3 deg/s, 1pm: -2.58 deg/s, 3pm: -2.64 deg/s), $F(3, 33)=7.99$, $p<0.001$ (see Figure 2.3), which confirms the finding from the previous analysis.

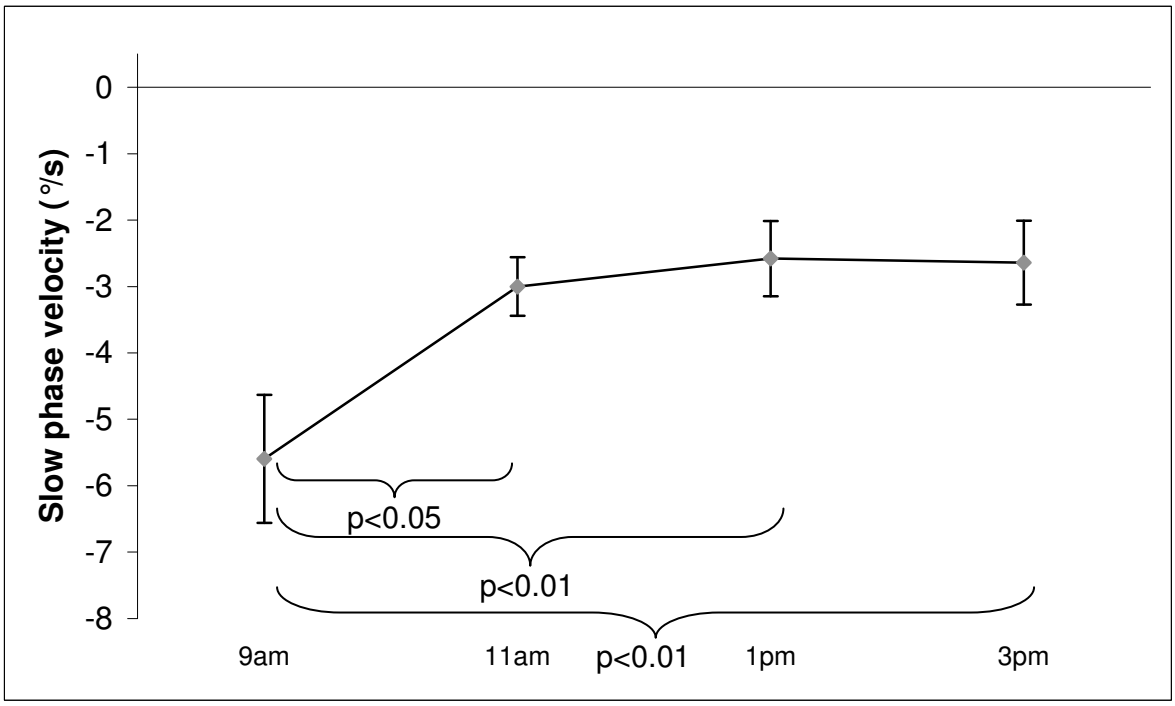


Figure 2.3 Comparing overall DBN intensity changes (across light on / light off condition) throughout the day (between 9am, 11am, 1pm, 3pm) in upright position with gaze straight ahead. Display of mean slow phase velocities along with the standard error bars of the mean. Permission to display the figure was received from the publisher.

2.2.3. The influence of gaze-direction on daytime dependency of downbeat nystagmus

The purpose of the third analysis was to find out whether gaze-direction had an influence on daytime dependence of DBN. Patients were sitting upright with the light switched on. The analysis showed a clear dependence of nystagmus SPV on *gaze direction*, $F(2, 22)=14.45$, $p<0.0001$ (Figure 2.4). Standing in line with Alexander's law, upward gaze showed the smallest SPV and was significantly different from gaze straight ahead and downward gaze (with Scheffé post-hoc tests revealing p-values <0.01). SPV in gaze straight ahead and in downward gaze, however, were not significantly different from each other.

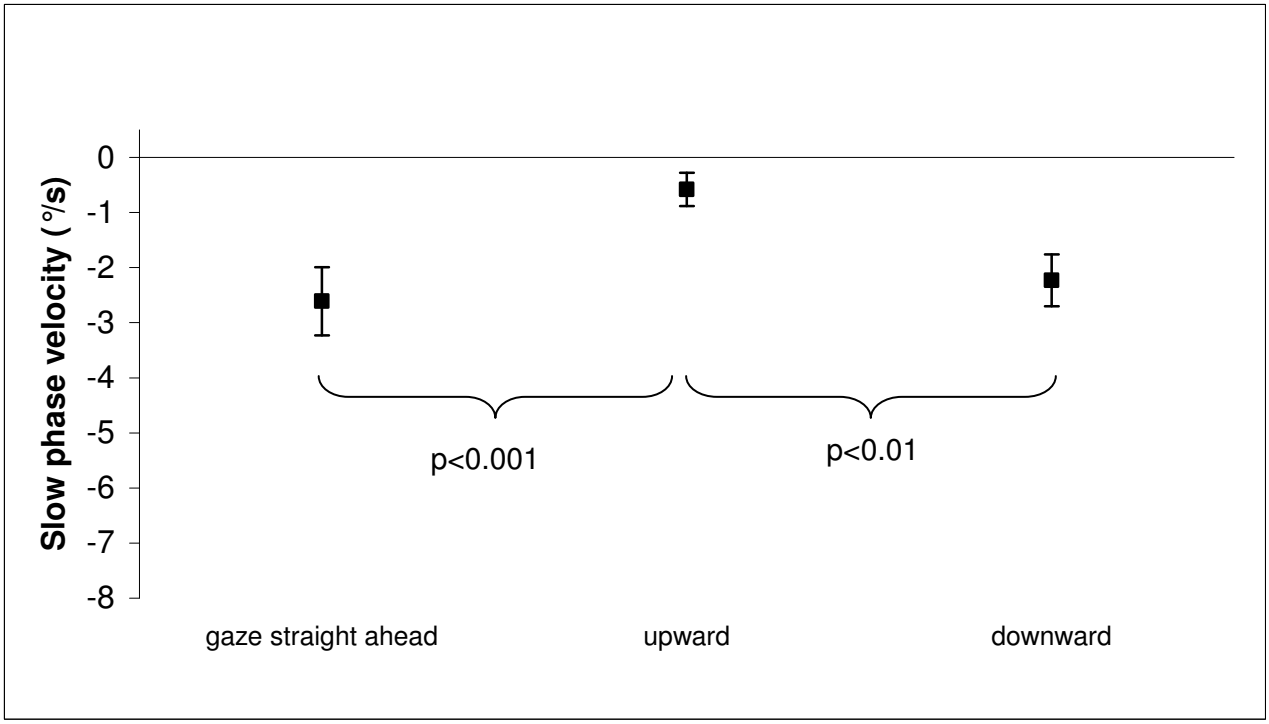


Figure 2.4 Comparing overall DBN intensity between gaze straight ahead, upward gaze and downward gaze, across daytime. All measurements took place in upright position. Display of mean slow phase velocities along with the standard error bars of the mean.

The figure 2.5a along with the significant *gaze times daytime* interaction, $F(6, 66)=2.39$, $p<0.05$, both indicate that daytime dependence reduces mean slow phase velocity towards zero, instead of shifting it towards positive values by a constant amount. As far as these data are concerned, gaze in the direction of the fast phase did not reverse the nystagmus from DBN to UBN (= upbeat nystagmus). At the 9am measurements, upward gaze is associated with significantly less DBN than downward gaze ($p<0.01$) and gaze straight ahead ($p<0.00001$). Only in gaze straight ahead, there is a significant reduction in DBN (from 9am to 11am, 1pm and 3pm each $p<0.01$).

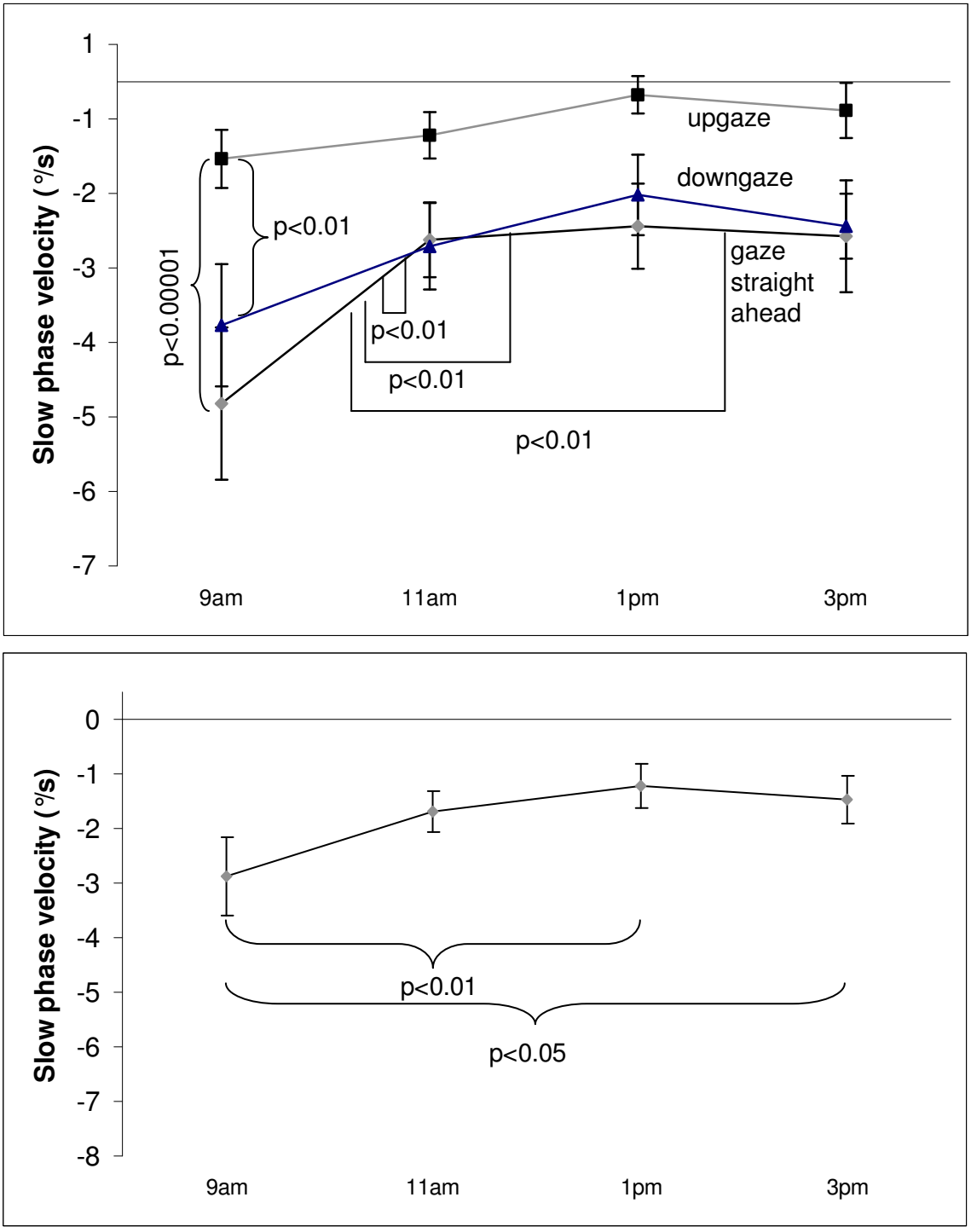
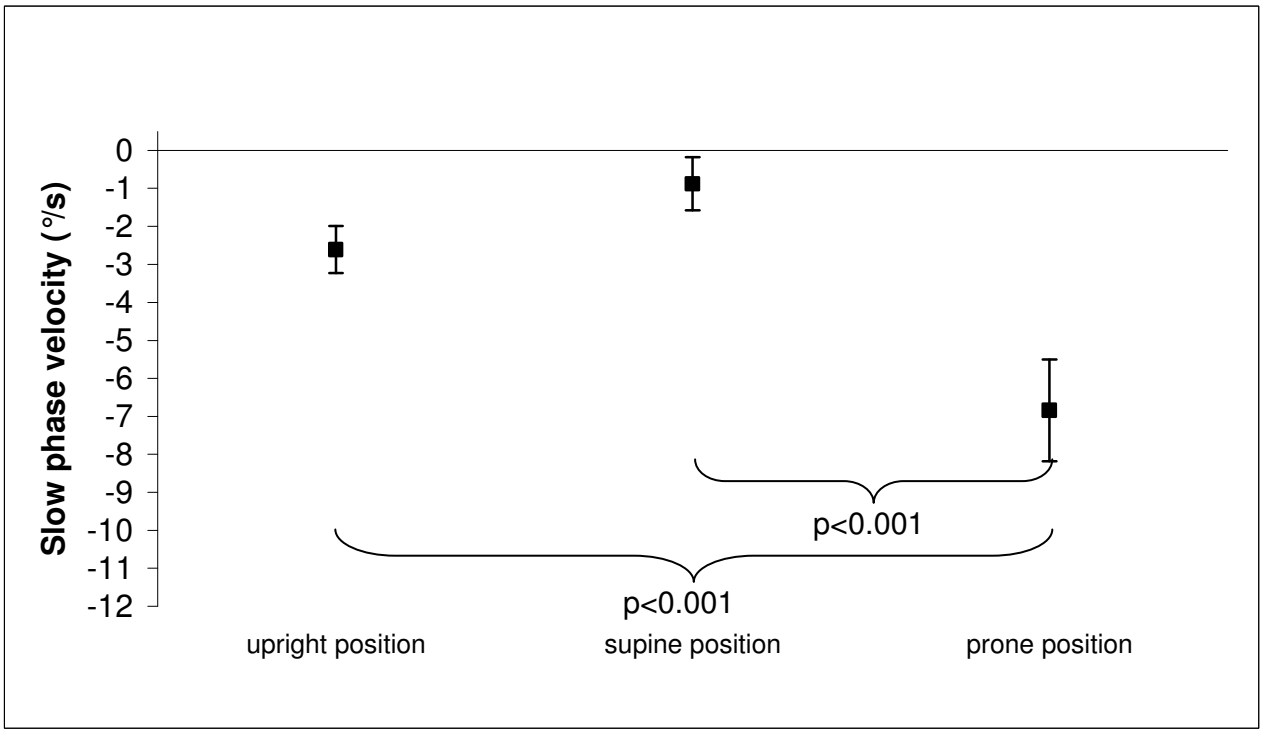


Figure 2.5a Dependence of SPV on gaze direction throughout the day whilst gaze was compared in three different positions: straight, upwards and downwards and fixation was possible (= light on). All measurements were performed in upright position with fixation on target (= light on),
b Comparing overall DBN intensity changes (across all gaze directions) throughout the day (between 9am, 11am, 1pm, 3pm). All measurements were performed in upright position with fixation on target (= light on). Display of mean slow phase velocities along with the standard error bars of the mean. Permission to display the figure was received from the publisher.

As was found in the previous two analyses, DBN once more decreased throughout the day, $F(3, 33)=5.56$, $p<0.01$, from -2.875 deg/s at 9am to -1.685 deg/s at 11am, -1.21 deg/s at 1pm and -1.47 deg/s at 3pm (Figure 2.5b). Scheffé post-hoc tests revealed that the differences between 9am and 1pm ($p<0.01$) and between 9am and 3pm ($p<0.05$) were statistically significant.

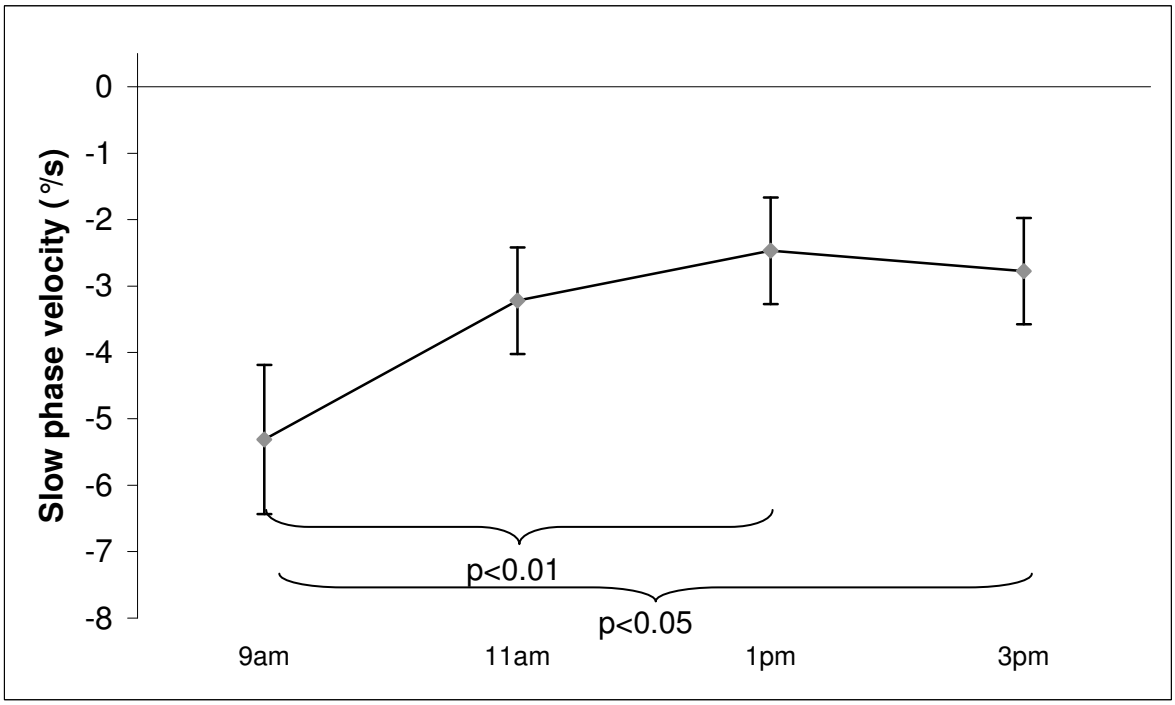
2.2.4. The influence of body-orientation on daytime dependence of downbeat nystagmus

The fourth analysis aimed at finding out whether body-orientation has an influence on daytime dependence of DBN. The light was switched on to enable patients the possibility to fixate. The analysis indicated a highly significant dependence of nystagmus SPV on *body orientation*, $F(2, 22)=21.03$, $p<0.00001$, Figure 2.6, with higher DBN in prone position (-6.84 deg/s) compared to upright (-2.61 deg/s) or supine positions (-0.88 deg/s, both Scheffé post-hoc tests $p<0.001$), but no significant difference between upright and supine position ($p>0.05$).



2.6 Comparing DBN intensity between upright position, supine position and prone position, across time. All measurements were performed with gaze straight ahead and fixation on target (= light on). Display of mean slow phase velocities along with the standard error bars of the mean.

As in the previous three analyses, DBN decreased throughout the day, $F(3, 33)=6.01$, $p<0.01$, but the daytime decrease did not depend on body orientation, $F(6, 66)=1.04$, $p=0.41$. The absence of a significant interaction shows that the time course of this decrease did not depend on the orientation of the body (upright vs. supine position vs. prone position). The overall daytime decrease can be found in Figure 2.7a, the decrease separated by positions in Figure 2.7b. When considering the overall daytime decrease, the difference from 9am (-5.31 deg/s) to 11am (-3.22 deg/s) was only marginally significant ($p=0.06$), whilst the decrease from 9am to 1pm (-2.47 deg/s, $p<0.01$) and from 9am to 3pm (-2.775 deg/s, $p<0.05$) were significant in the absence of any other significant Scheffé post-hoc tests.



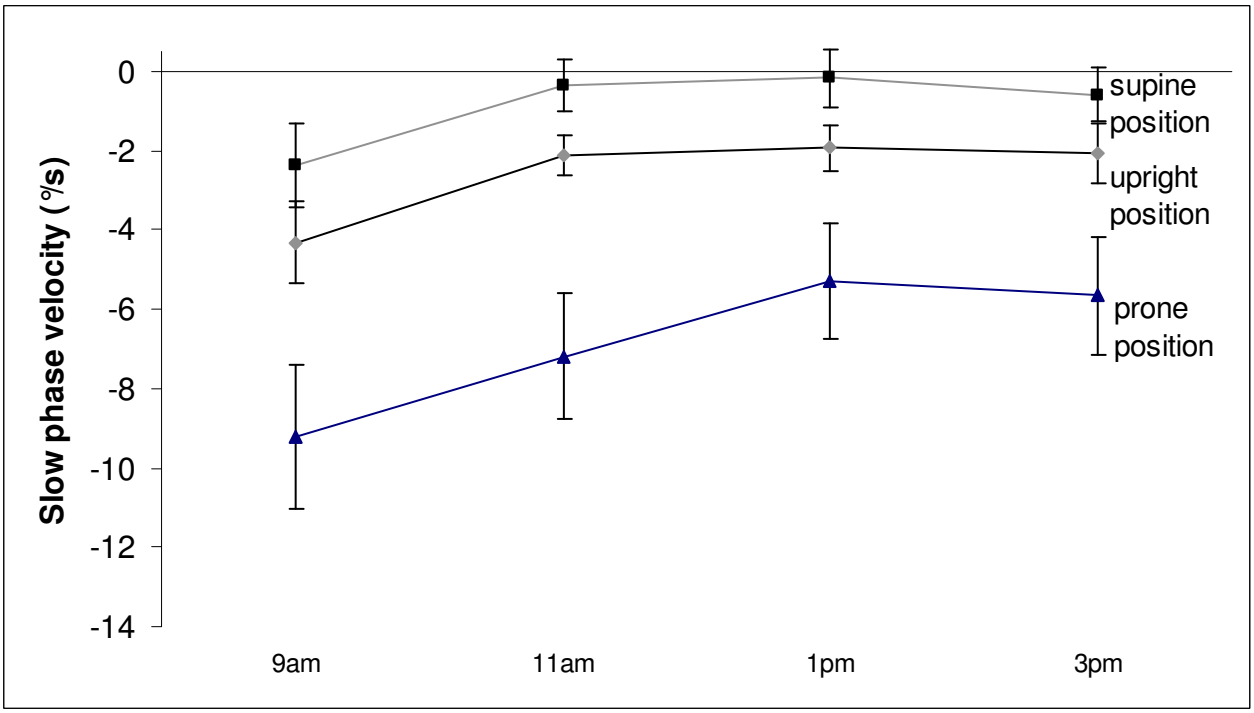


Figure 2.7a Daytime decrease of DBN between 9am, 11am, 1pm and 3pm, across body position. All measurements were performed in upright position with fixation on target (= light on),

b Dependence of SPV on body orientation throughout the day when comparing the three positions upright, supine and prone. All measurements were performed in upright position with fixation on target (= light on). Display of mean slow phase velocities along with the standard error bars of the mean. Permission to display the figure was received from the publisher.

2.2.5. Testing the influence of aetiology on the intensity of downbeat nystagmus during daytime

Because DBN in patients No. 1 to No. 5 was associated with cerebellar aetiologies, whereas DBN in patients No. 6 to No. 12 was associated with unknown causes, it was tested whether there was a significant difference in SPV-values based on the two different aetiologies. Neither in the first analysis, where horizontal and vertical SPV-values were included, nor in the second, third or fourth analysis of this study did the between subjects factor *aetiology* or any interaction including the between subjects factor *aetiology* turn out statistically significant. The first analysis neither resulted in a main effect for the between subjects factor *aetiology,* $F(1, 10)=1.825$, $p=0.21$, nor in an *aetiology times daytime* interaction, $F(3, 30)=0.79$, $p=0.51$, nor in an *aetiology times vertical versus horizontal measurement* interaction $F(1, 10)=0.78$, $p=0.4$, nor in an *aetiology times vertical versus horizontal measurement times daytime* interaction, $F(3, 30)=1.76$, $p=0.18$. Overall, however, the cerebellar patients had a descriptively higher average SPV-value (-2.015 deg/s) than the patients with unknown aetiology (-1.15 deg/s). Including the between subjects factor *aetiology* did not make any difference with respect to the overall interpretation of the results, as the same within subjects factors and their interaction became significant. This was also the case in the analysis where no between subjects factor had been included.

Turning to the second analysis, there was no significant main effect for the between subjects factor *aetiology*, $F(1, 10)=1.27$, $p=0.29$, nor an *aetiology times light* interaction, $F(1, 10)=0.41$, $p=0.54$, nor an *aetiology times daytime* interaction $F(3, 30)=1.22$, $p=0.32$, nor an *aetiology times light times daytime* interaction, $F(3, 30)=0.25$, $p=0.86$. Overall, however, the cerebellar patients had a descriptively higher average SPV-value (-4.13 deg/s) than the patients with unknown aetiology (-2.97 deg/s). Once more, the inclusion of the between subjects factor *aetiology* did not make any difference with respect to the overall interpretation

of the results, as the same within subjects factors and their absence of an interaction were present in the previous analysis with respect to light where no between subjects factor had been included.

In the third analysis, there was no significant main effect for the between subjects factor *aetiology*, F(1, 10)=1.66, p=0.23, nor an *aetiology times gaze direction* interaction, F(2, 20)=0.3, p=0.74, nor an *aetiology times daytime* interaction F(3, 30)=1.17, p=0.34, nor an *aetiology times gaze direction times daytime* interaction, F(6, 60)=1.53, p=0.18. Overall, however, the cerebellar patients had a descriptively higher average SPV-value (-2.43 deg/s) than the patients with unknown aetiology (-1.36 deg/s). Once more, the inclusion of the between subjects factor *aetiology* did not make any difference with respect to the overall interpretation of the results, because the same within subjects factors and their interaction became significant as in the previous analysis referring to gaze direction (where no between subjects factor had been included).

The fourth analysis did not reveal a significant main effect for the between subjects factor *aetiology*, F(1, 10)=1.53, p=0.24. Likewise, there was no *aetiology times body orientation* interaction, F(2, 20)=0.285, p=0.755, no *aetiology times daytime* interaction F(3, 30)=0.93, p=0.44, no *aetiology times body orientation times daytime* interaction, F(6, 60)=0.33, p=0.92. Overall, however, the cerebellar patients had a descriptively higher average SPV-value (-4.54 deg/s) than the patients with unknown aetiology (-2.66 deg/s). As in the previous analyses, the inclusion of the between subjects factor *aetiology* did not make any difference with respect to the overall interpretation of the results, because the same within subjects factors became significant (just like the previous analysis where no between subjects factor had been included). In the previous analysis referring to body orientation as well as in this analysis, none of the interactions had become significant.

2.3. Discussion

Based on patients with DBN who reported that their vertical oscillopsia symptoms are worst during the morning hours and become better in the course of the day, it was evaluated whether the intensity of DBN indeed changes throughout the day. To the best of my knowledge, no study thus far had reported on circadian changes of DBN. In the first analysis, it was therefore focused on changes in DBN intensity. It was demonstrated that DBN decreases throughout the day. This was investigated in greater detail in the second analysis, where it turned out that DBN decreases throughout the day irrespective of the possibility to fixate (= light switched on) or not (= light switched off). However, one has to be careful and should avoid over-interpreting this finding, as the interaction was very close to becoming statistically significant at the type one error level of five percent. It therefore does not mean that fixation has definitely no influence on daytime decrease of DBN. Future studies will be necessary to confirm that daytime dependence is indeed not dependent on a visible fixation point. According to the results of this chapter and Spiegel et al. (2009a), DBN was significantly higher (= worse) when people were not able to fixate, (i.e. with the light switched off), but the changes during daytime were not significantly affected by this difference. The finding that visual fixation can suppress DBN does not mean that it makes DBN completely vanish, though, as it needs to be acknowledged that DBN can also persist after fixation (e.g. Kalla et al., 2008). Given that, as far as the results of this study are concerned, fixation on target is associated with a lower DBN than no fixation, this finding is new when compared to current literature (e.g. Heide & Kömpf, 2005), where it is said that DBN is not suppressed by fixation. In summary, it is probably best to argue that DBN can at least be partly suppressed by fixation, although this effect does not necessarily have to occur. In the following chapters 3 and 4 it will also be seen that DBN during fixation is lower than DBN in the absence of

fixation. Given that the results of daytime-dependent decrease of DBN are also new, it might be worth to speculate about possible underlying mechanisms. Recall that in the first analysis, DBN at 9am was significantly worse than at all other measurements (11am, 1pm, 3pm), where DBN did not significantly differ between the measurements. Consequently, sleep inertia might be a possible explanation of this result. Sleep inertia is a transitional state of lowered arousal occuring after awakening from sleep (Ferrara & De Gennaro, 2000; Jewett et al. 1999; Tassi & Muzet, 2000). It is capable of producing a performance decrement spanning several cognitive functions that can last up to 4 hours (especially after an early wake-up when the person is sleep-deprived). To the best of my knowledge, the effect of sleep inertia on the cerebellum (especially the Purkinje cells) and central vestibular pathways has not yet been formally assessed, so at this time a possible effect of sleep inertia is nothing more than mere speculation. If it is assumed, however, that sleep inertia has a negative influence on the function of the Purkinje cells (which are inhibitory and therefore responsible for alleviating DBN), this would explain why DBN is relatively high at 9am and lower at the other times of the day. This corresponds to the previously mentioned successful pharmacological approaches to treat DBN with the potassium channel blockers 3,4-diaminopyridine (3,4-DAP) by Strupp et al. (2003) and Helmchen et al. (2004) or with 4-Aminopyridine (4-AP) by Kalla et al. (2004, 2007). As mentioned in the introduction, these drugs lead to an increase in the excitability of the Purkinje cells inside the cerebellum, and therefore they have an inhibitory effect on vertical eye movements. As an alternative explanation one could assume the possibility of a non-visual error signal such as extraocular proprioception (Büttner-Ennever & Horn, 2002) or efference copy (Glasauer et al. 2005b; Klier et al. 2008). According to these explanations, it might be the case that DBN becomes less because patients were able to adapt throughout the day. Since patients were allowed to keep their eyes open and the light switched on during the resting intervals between testing and because they were able to rest in upwards position, these conditions might have contributed to the adaptation process, which might itself

have alleviated the intensity of DBN. In order to investigate this issue in greater detail, more studies were carried out (see next chapter), where the conditions during the intervals between testing were varied (e.g. comparing patients who rested with the light switched on / off or patients in different body positions, e.g. upright, supine and prone).

In the third analysis, it turned out that, in line with Alexander's law, upward gaze exhibited the smallest DBN values expressed by vertical slow phase velocity, whilst gaze straight ahead or downward gaze did not differ significantly from each other. The last finding is not entirely consistent with Alexander's law, however, where it would be expected that slow phase velocity decreases as gaze moves away from the direction of the fast phase (Jeffcoat et al., 2008, Marti et al., 2002; Robinson et al., 1984), i.e. it should be lower in gaze straight ahead than in downward gaze. Albeit dependent on gaze direction, focusing on a potential *gaze times daytime* interaction showed that DBN also decreased in the course of the day, where the absence of a significant interaction revealed a constant improvement rather than a gaze dependent improvement.

The fourth analysis showed the dependence of DBN on body orientation, which complements earlier research on head position in relation to the gravitational vector by Brandt (1990), or experimental and theoretical work on gravity dependence of ocular drift in patients with DBN by Marti et al. (2002, 2008), or the treatment of gravity dependence of DBN with 3,4-DAP by Sprenger et al. (2006). Along with Marti et al. (2002), it was found that DBN was far more pronounced in prone position than in supine position. Furthermore, DBN was more pronounced in prone position than in upright position, whilst no significant difference was found between upright and supine position. The explanation of Marti et al. (2002) that the combination of a gravity-dependent and a gravity-independent component leads to an overall drift that is minimal in supine position, because the gravity-dependent component shows its maximal downward drift in supine position, counteracting the upward drift of the gravity-independent component in DBN, is entirely consistent with the finding in this study.

Likewise, the maximal vertical drift velocity is observed in prone position according to Marti et al. (2002), because both drift components are directed upward, hence resulting in stronger DBN. This finding is also consistent with the results in the study presented in this chapter. When patients are in upright position, the gravity-dependent component should be near zero, so that the vertical ocular drift is almost exclusively based on the gravity-independent component, i.e. according to Marti et al. (2002), the intensity of DBN in upright position should lie between the intensities in supine and prone position. Once more, this result was confirmed in this study. In all three positions, DBN decreases throughout the day. To evaluate whether this change in body orientation also has a positive effect after patients return to their original position, this was further analysed in another study (see the following chapter 3). Another study was necessary because the previously demonstrated study had the same resting interval in all four analyses, where patients were sitting upright with the light switched on. It is vital to know, however, whether the resting interval *per se* has an influence on DBN. As a result, chapter 3 will investigate three different resting positions (upright, supine and prone) as well as a condition where the light is switched off.

To conclude, this study shows that DBN decreases throughout the day (irrespective of the presence of a visual fixation point), that it is less pronounced when looking upward and less in supine / upright position than in prone position. It also suggests a more detailed study (see chapter 3) to test the clinical efficacy of different prolonged day time positions in order to further modulate the intensity of DBN throughout the day. The results in this chapter are not dependent on the aetiology of DBN, as the inclusion of a between subjects factor *aetiology* did not make any difference to the overall results. None of the analyses revealed a significant effect with respect to the between subjects factor *aetiology*, nor was there any significant interaction with respect to *aetiology*. It needs to be acknowledged, though, that according to the descriptive trend, the SPV-values were more pronounced in the group of cerebellar patients than in the group of patients with unknown aetiology. The absence of a significant

value in the comparison between both groups could also be due to the fact that the sample size was rather small, and therefore lacked power to reveal a significant result. On the other hand, DBN is a very rare condition and it is difficult to find a large number of patients for clinical studies. In spite of the small sample size, the results of the first two analyses have the practical consequence that they permit to make immediate suggestions to patients. Given that DBN decreases throughout the day, patients might benefit from the following advice: they should rather engage in activities such as reading, working on a computer or watching TV at a later time of the day, and spend the morning hours with activities that depend less on the ocular-motor system.

3. An analysis of positional effects on the changes of intensity of downbeat nystagmus during daytime

A large part of the results of the following chapter has been published in Spiegel et al. (2010). For that reason, part of the text shows an overlap. The same holds true for the tables, figures, and their legends, for which I also received permission from the publisher, *Neurology*®. As mentioned in the previous chapter, the intensity of DBN may also depend on prolonged positions (e.g. resting positions during the day). Another interesting aspect is whether it is better to rest in darkness or with the light switched on. For this reason, it will be first focused on an upright resting position with the light switched on versus an upright resting position with the light switched off (part 1) under conditions that come closest to the daily routine of the patients (i.e. being measured in upright position with the light switched on and comparing the two resting intervals upright light on versus upright light off). Subsequently, part 2 will focus on the same measurement in upright position with the light switched on, but will compare the three resting intervals upright, supine position and prone position, each with the light switched off. The major results of parts 1 and 2 were published in Spiegel et al. (2010). Parts 3 to 6 will then focus on the same analyses as the ones in the previous chapter, but with different resting positions (upright light on versus upright light off as well as upright, supine and prone, each with the light switched off). These analyses will be carried out to see whether the results including different resting positions are congruent with the results from the previous chapter, where resting position was not varied. Based on the results of this chapter it might be possible to derive insights with clinical relevance. These insights could be suggested to patients with DBN, e.g. they could be informed how to rest in order to alleviate their intensity of DBN.

3.1. Measurement in upright position with gaze straight ahead and the light switched on intermitted by the resting intervals upright with the light switched on and upright with the light switched off (part 1)

In order to find out whether resting upright with fixation on target (= light on) or not (= light off) makes a difference to the measurement in upright position with fixation on target (which can be regarded as the typical position during the day), the following analysis was carried out.

3.1.1. Methods

3.1.1.1. Patients

In the present part of this study, the eye movements of eight patients with a history of DBN due to different aetiologies were recorded three times on a single day: at 9am, 11am and 1pm. To vary the resting positions from upright with fixation on target to upright in complete darkness, there was an interval of one week between the two days where patients were either measured in light or in darkness. The aetiologies were idiopathic cerebellar syndrome (n = 1), idiopathic cerebellar ataxia (n = 1), cerebellar degeneration (n = 1), or unknown (n = 5), see Table 3.1. The mean duration of DBN was 6.81 years (range 2-17 years, see Table 3.1). The patients (6 males, 2 females) were 44 to 82 years old, with a mean of 67.25 years and a standard deviation of ± 10.365 years. The purpose of this part of the study was to analyse the intensity of DBN to find out whether it differs between the two resting intervals (upright with the light on versus upright with the light off). The intensity of DBN was assessed by vertical mean slow phase velocity. Patients' eye movements were recorded with 3D videooculography (VOG). All patients underwent a complete clinical examination. The clinical examination, the laboratory tests, the approval by the ethics committee and the study being in line with the Helsinki II Declaration were identical to the previous study (for details see chapter 2).

Table 3.1 Clinical data of the patients with DBN where upright positions in light and darkness were compared with each other

No./Sex/ Age	Neuro-ophthalmological findings	MRI findings	Aetiology	Disease duration
No. 1M, 76	Disturbed visual fixation suppression of VOR, impaired horizontal and vertical opto-kinetic nystagmus with horizontal and vertical saccades, impaired horizontal and downward pursuit, pathological HTT bilaterally.	White matter lesions	Idiopathic cerebellar syndrome	2 years
No. 2M, 64	Disturbed visual fixation suppression of VOR, non-existing upright opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally.	Cerebellar atrophy	Cerebellar de-generation	3 years
No. 3F, 69	Disturbed visual fixation suppression of VOR, impaired horizontal and upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally, provocation DBN.	Cerebellar atrophy	Idiopathic cerebellar ataxia	17 years
No. 4M, 82	Deviant SVV, non-existing upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, provocation downward nystagmus.	Normal	Unknown	3.5 years
No. 5M, 69	Disturbed visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT on the left.	Normal	Unknown	6 years
No. 6M, 44	Disturbed visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and vertical pursuit.	Normal	Unknown	10 years
No. 7M, 65	Impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, hypometric upward saccades.	Normal	Unknown	10 years
No. 8F, 69	Disturbed vertical visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit.	Normal	Unknown	3 years

VOR = vestibulo-ocular reflex; SVV = subjective visual vertical axis, HTT = head-thrust test developed by Halmagyi and Curthoys (1988).

3.1.1.2. Recording of eye movements

Patients were tested three times on a single day in upright position with the light switched on (see Figure 3.1). After a calibration in 8.5° position, people where measured in gaze straight

ahead with the light switched on (i.e. with the possibility to fixate). The target was projected by a laser on a white cardboard at a distance of 60 cm in front of the participant. The recordings with regard to the different resting intervals took place with the same patients (in each patient, the recordings in the different resting intervals were separated by approximately one week).

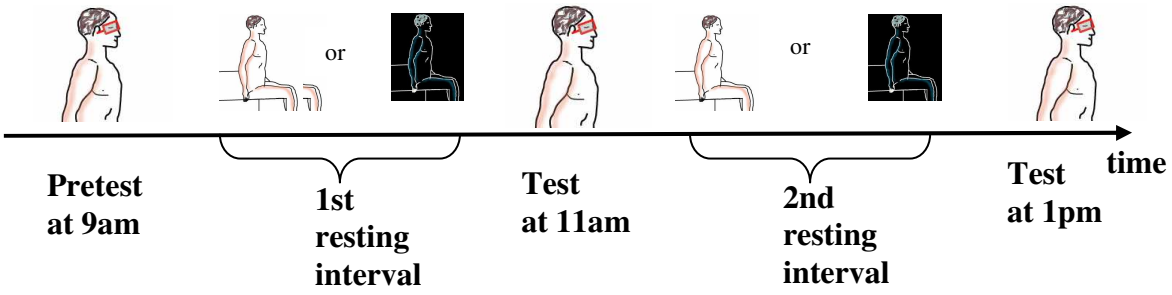


Figure 3.1. An overview describing the testing conditions for all patients. All measurements took place at 9am, 11am, and 1pm. In between the measurements, patients were sitting in upright position with the light switched on or off.

3.1.1.3. Data acquisition and calibration

The eye position was measured with 3D video-oculography for 30 seconds. An off-line analysis of the data was carried out using Matlab (The Mathworks, Natick, MA, USA). Subsequently, the calibrated data were low-pass filtered applying a digital Gaussian filter with a bandwidth of 30 Hz. Saccades and fast phases, as had already been described in the methods section of the previous chapter, were automatically detected and removed from the data using a combined velocity–acceleration criterion in interactive software. This was followed by a manual task, where saccades and fast phases not having been recognised automatically were removed manually. From the desaccaded data, mean slow phase velocity was computed in the same way as described in the introduction and the previous chapter.

3.1.1.4. Statistical data analysis

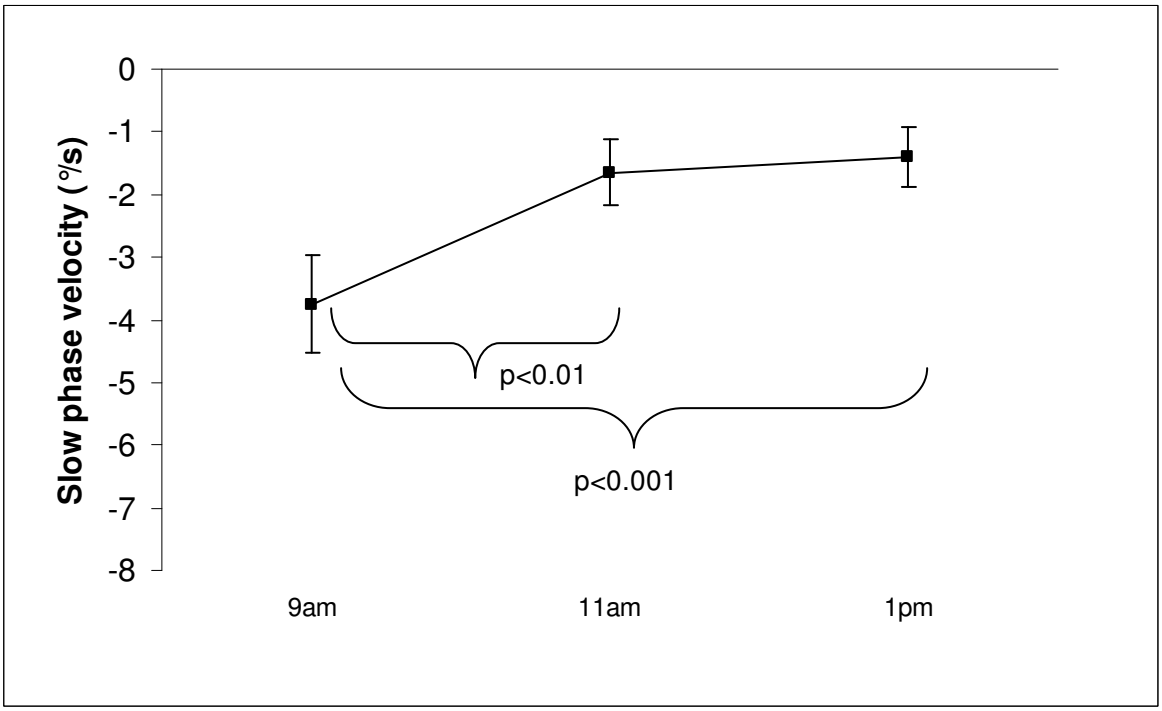
The statistical analysis consisted of an ANOVA (Statistica 6.1, Statsoft, Tulsa OK, USA) with post-hoc Scheffé tests for individual comparisons. The dependent variable was mean slow phase velocity (SPV). The first analysis had the within subject factors *resting interval* (upright with the light on versus upright with the light off) and *daytime following the resting intervals* (11am, 1pm). The second analysis was identical, but also included the 9am measurement. Due to the low number of patients with cerebellar symptoms, the nonparametric Kolmogorov-Smirnov test was taken to compare the two independent samples. The two independent groups were the two different aetiologies (cerebellar patients versus patients with unknown aetiology). The two groups were compared with respect to their overall SPV-values. The test was developed by Andrej Nikolaevič Kolmogorov and Nikolaj Vasilevič Smirnov and aims to find out whether the differences between two empirical distributions are significant. Details can be found in Toutenburg et al. (2008).

3.1.2. Results

The analysis showed no significant main effect of *resting interval*, $F(1, 7)=1.81$, $p=0.22$, no main effect of *daytime* ($F(1, 7)=0.85$, $p=0.39$) and no *interval times daytime* interaction, $F(1, 7)=1.58$, $p=0.25$. Having previously rested with the light switched off was associated with a descriptively lower intensity of DBN (average SPV=-1.16 deg/s) than having rested with the light switched on (average SPV=-1.89 deg/s). When including the 9am measurements (i.e. prior to the first resting interval), there was no significant main effect for resting interval, $F(1, 7)=1.15$, $p=0.32$ and no *interval times daytime* interaction, $F(2, 14)=1.14$, $p=0.35$. Consistent with chapter 2, there was a significant overall daytime improvement of DBN ($F(2, 14)=15.24$,

p<0.001), which was obviously not present in the first analysis, as the first analysis did not include the 9am measurements. Hence, DBN decreased from 9am (where SPV was -3.75 deg/s) to 11am (SPV=-1.65 deg/s) and to 1pm (SPV=-1.39 deg/s). Scheffé post-hoc tests indicated that the decrease from 9am to 11am (p<0.01) and the one from 9am to 1pm (p<0.001) turned out statistically different, whilst no significant difference turned out between 11am and 1pm (p=0.86), Figure 3.2a. Although the *interval times daytime interaction* was not significant, the overall results will be displayed in Figure 3.2b, as this gives the reader an idea of the results in both resting intervals. Because the *interval times daytime interaction* was not significant, no post-hoc Scheffé tests had been carried out. Consequently, it is not indicated within Figure 3.2 whether there were significant post-hoc results.

With regard to the comparison between cerebellar patients and patients with unknown aetiology, cerebellar patients had an average SPV-value of -3.77 deg/s, whilst patients with unknown aetiology had an average SPV-value of -1.36 deg/s. According to the Kolmogorov-Smirnov test (p>0.1), this is not a significant difference. When excluding the 9am measurements, because they had taken place before the first intermission, cerebellar patients had an average SPV-value of -2.78 deg/s, whilst patients with unknown aetiology had an average SPV-value of -0.77 deg/s. According to the Kolmogorov-Smirnov test (p>0.1), this descriptive difference is not significant.



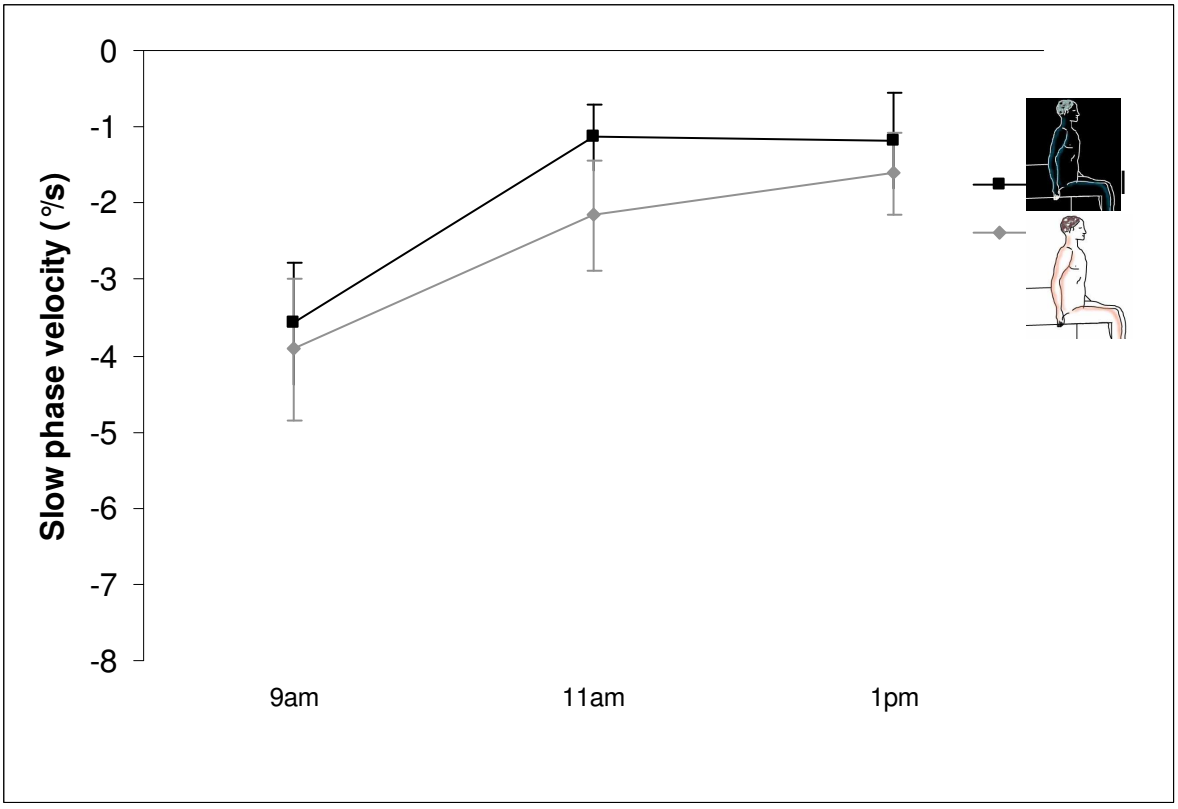


Figure 3.2a Comparing SPV in upright position and gaze straight ahead with the light switched on between 9am, 11am and 1pm across both resting intervals (resting upright in light vs. darkness). Display of mean slow phase velocities along with the standard error bars of the mean, **b** The same comparison as in 3.2a, but between the two resting intervals (upright with the light switched on versus upright with the light switched off).

3.1.3. Discussion

As far as upright measurements with the light switched on are concerned, it does not make a statistically significant difference whether people previously rest upright with the light switched on or whether they previously rest with the light switched off. It is noteworthy that the data cannot be explained by visual input, as there was no significant difference when patients were able to fixate a target during their resting period (where the light was switched on) and when they were in complete darkness and hence, fixation was impossible (= light off). From a descriptive point of view, however, a slightly lower DBN is associated with the resting condition where the light was switched off. Hence, the following comparisons between the different resting positions were all in the light off condition. Moreover, the daytime decrease in the intensity of DBN from the previous chapter was confirmed. There is a significant decrease from 9am to 11am and from 9am to 1pm, but the decrease is not differentially affected by the resting positions, as the interaction did not turn out significant. Although the between-subjects factor aetiology does not have a significant effect on the results, it is obvious that patients with cerebellar aetiology have a more pronounced intensity of DBN. In a larger sample size with more statistical power, the descriptive difference between the two groups could have become statistically significant.

3.2. Measurement in upright position with gaze straight ahead and the light switched on intermitted by the resting intervals upright, supine and prone (part 2)

According to the results from the previous chapter (chapter 2), different body positions seem to have an influence on the intensity of DBN. This might be due to gravitational influences

(e.g. Brandt, 1990; Marti et al., 2002). In the previous chapter, however, patients rested in upright position between the measurements. It will now be analysed whether the resting positions *per se* have an influence on the daytime decrease of DBN. Because there was a descriptive trend towards lower intensity of DBN in the darkness upright resting position as compared to the upright resting position with fixation on target (= light on), patients in this study rested with the light switched off in all three positions (upright, supine and prone).

3.2.1. Methods

3.2.1.1. Patients

Nine patients (4 males, 5 females, aged 44 to 72 years, mean 63.67 years, SD ± 7.92 years, mean duration of DBN 6.81 years, range 3 to 17 years, see Table 3.2.) were included. They were tested at 9am, 11am and 1pm. In the intermissions between testing, they either rested in upright, supine or prone position. In all cases, the light was switched off, i.e. they rested in darkness. The intensity of DBN was assessed by vertical mean slow phase velocity. Patients' eye movements were recorded with 3D-videooculography (VOG). All patients underwent a complete clinical examination. The clinical examination, the laboratory tests, the approval by the ethics committee and the study being in line with the Helsinki II Declaration were identical to the previous study (for details see chapter 2).

Table 3.2 Clinical data of the patients with DBN

No./Sex/ Age	Neuro-ophthalmological findings	MRI findings	Aetiology	Disease duration
No. 1M, 64	Disturbed visual fixation suppression of VOR, non-existing upright opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally.	Cerebellar atrophy	Cerebellar de-generation	3 years
No. 2F, 69	Disturbed visual fixation suppression of VOR, impaired horizontal and upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally, provocation DBN.	Cerebellar atrophy	Idiopathic cerebellar ataxia	17 years
No. 3M, 69	Deviant SVV, impaired horizontal and downward pursuit, saccades with rebound after gaze to the right, provocation DBN.	Normal	Unknown	4.5 years
No. 4F, 60	Disturbed visual fixation suppression of VOR, DBN overran horizontal opto-kinetic nystagmus, non-existing upward opto-kinetic nystagmus, deviant SVV, impaired horizontal and downward pursuit.	Normal	Unknown	12 years
No. 5F, 61	Disturbed visual fixation suppression of VOR, deviant SVV, provocation DBN, vertical saccades and saccades to the left.	Normal	Unknown	5 years
No. 6M, 44	Disturbed visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and vertical pursuit.	Normal	Unknown	10 years
No. 7M, 65	Impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, hypometric upward saccades.	Normal	Unknown	10 years
No. 8F, 69	Disturbed vertical visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit.	Normal	Unknown	3 years
No. 9F, 72	Disturbed visual fixation suppression of VOR, impaired horizontal and non-existing upward opto-kinetic nystagmus, impaired horizontal and downward pursuit.	Normal	Unknown	6 years

VOR = vestibulo-ocular reflex; SVV = subjective visual vertical axis, HTT = head-thrust test developed by Halmagyi and Curthoys (1988). See Spiegel et al. (2010).

3.2.1.2. Recording of eye movements

Patients were tested three times on a single day in upright position with the light switched on (see Figure 3.3). After a calibration in 8.5° position, people where measured in gaze straight ahead with the light switched on (i.e. with the possibility to fixate). The target was projected

by a laser on a white cardboard at a distance of 60 cm in front of the participant. The recordings with regard to the different resting intervals took place with the same patients (in each patient, the recordings in the different resting intervals were separated by approximately one week).

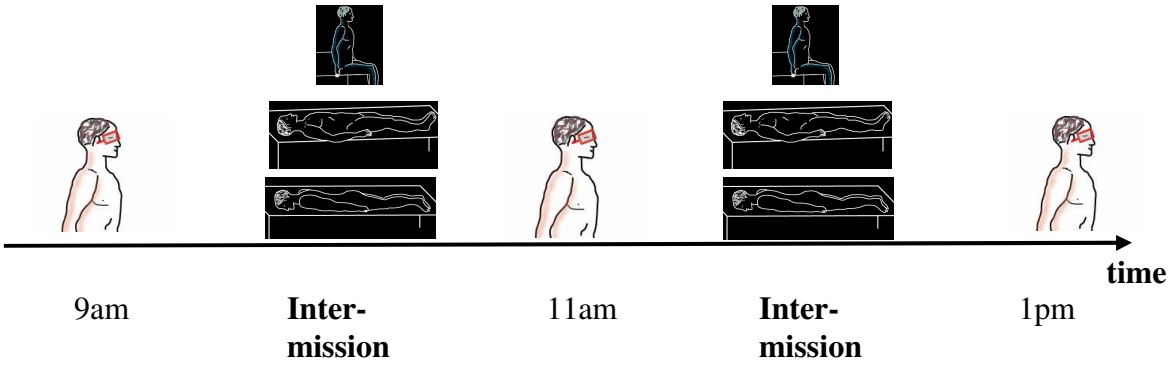


Figure 3.3. An overview describing the testing conditions for all patients. All measurements took place at 9am, 11am, and 1pm, in upright position, with gaze straight ahead and the light switched on. In the resting intervals between the measurements, patients were sitting in upright position, lying in supine position or lying in prone position, in all cases with the light switched off.

3.2.1.3. Data acquisition and calibration

The eye position was measured with 3D video-oculography for 30 seconds. An off-line analysis of the data was carried out using Matlab (The Mathworks, Natick, MA, USA). Subsequently, the calibrated data were low-pass filtered applying a digital Gaussian filter with a bandwidth of 30 Hz. As in the previous chapter, saccades and fast phases were automatically detected and removed from the data using a combined velocity–acceleration criterion in interactive software. Those saccades and fast phases that were not recognised automatically were subsequently removed manually. From the de-saccaded data, mean slow phase velocity was computed from a 30 seconds long measurement period.

3.2.1.4. Statistical data analysis

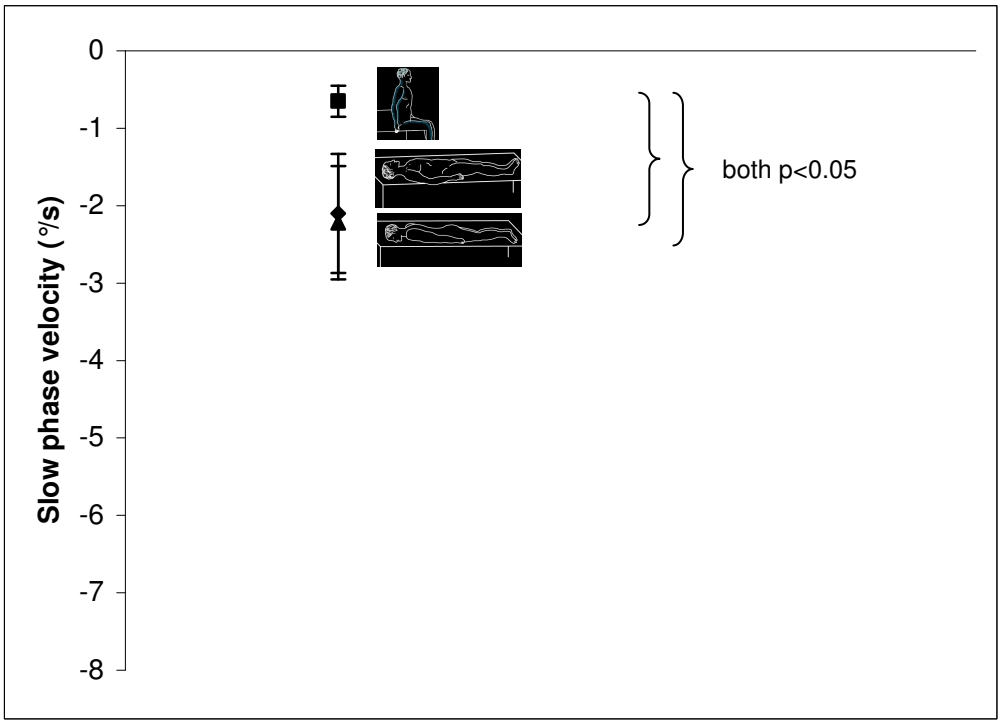
The statistical analysis consisted of an ANOVA with post-hoc Scheffé tests for individual comparisons. The dependent variable was mean slow phase velocity (SPV). The first analysis had the within subject factors *resting interval* (upright, supine and prone) and *daytime following the resting intervals* (11am, 1pm). The second analysis was identical, but also included the 9am measurement. As in part 1, an analysis with the nonparametric Kolmogorov-Smirnov test was applied to compare patients with different aetiologies (i.e. two independent samples) in terms of their overall SPV-values (the two cerebellar patients versus the seven patients with unknown aetiology).

3.2.2. Results

The first analysis (excluding the 9am measurements) showed a significant main effect for resting interval, $F(2, 16)=5.54$, $p=0.01$, no main effect for *daytime,* $F(1, 8)=0.06$, $p=0.805$, and no *interval times daytime* interaction, $F(2, 16)=1.5$, $p=0.25$. When being measured in the typical daytime position (= upright), having previously rested in upright position was associated with a significantly lower average SPV-value (-0.65 deg/s) than having previously rested in prone position (-2.22 deg/s, Scheffé post-hoc test: $p<0.05$) or supine position (-2.1 deg/s; Scheffé post-hoc test: $p<0.05$). The overall results are displayed in Figure 3.4a and the results separated by the time of the measurement in Figure 3.4b. In Figure 3.4b, the results of the post-hoc tests are not indicated separately, because the *interval times daytime* interaction did not become significant.

The 9am measurements, i.e. prior to the first resting interval, were comparable ($p>0.98$) in all three conditions (prior to the upright resting interval: -3.05 deg/s, SE=0.65, the

supine resting interval: -3.12 deg/s, SE=0.98, the prone resting interval: -3.6 deg/s, SE=1.2). Integrating the 9am measurement (i.e. prior to the first resting interval) showed identical overall results with respect to resting interval, $F(2, 16)=3.97$, $p<0.05$, but also included a significant effect with respect to daytime decrease of DBN, $F(2, 16)=4.33$, $p<0.05$, in the absence of a significant *interval times daytime* interaction, which was marginally significant, $F(4, 32)=2.6$, $p=0.054$, where only upright resting position was associated with a significant decrease of DBN from 9am to 11am ($p<0.01$) and from 9am to 1pm ($p<0.001$), though it needs to be kept in mind that, strictly speaking, post-hoc significance tests are not permitted due to the marginal nature of the interaction. Post-hoc tests following the significant main effects in the second analysis (*interval, daytime*) did not turn out significant, though. Because this information is redundant to previous information, i.e. the daytime decrease known from the previous chapter as well as the main effect for interval displayed in Figure 3a, no separate figure will be displayed for the second analysis.



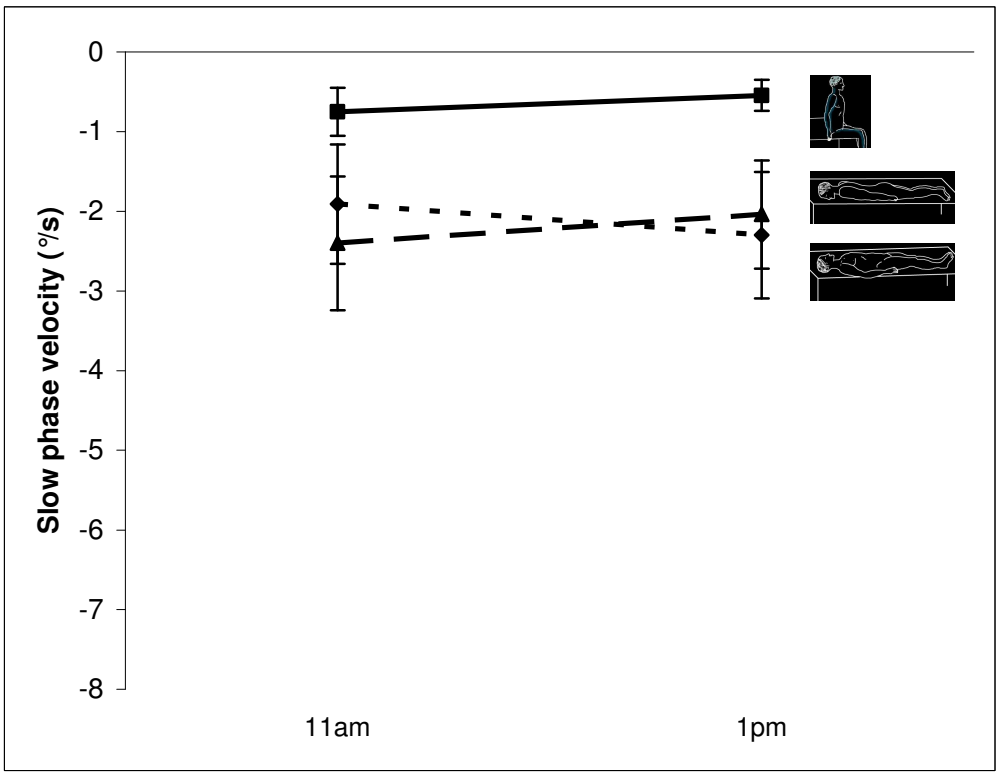


Figure 3.4a Comparing SPV differences in upright measurement during straight ahead gaze between the three different resting intervals across time, **b** Comparing SPV differences in upright measurement during straight ahead gaze between the three different resting intervals and between time (11am, 1pm). Display of mean slow phase velocities along with the standard error bars of the mean.

When turning to the comparison between cerebellar patients and patients with unknown aetiology in the first analysis (excluding the 9am measurements), cerebellar patients had an average SPV-value of -3.01 deg/s, whilst patients with unknown aetiology had an average SPV-value of -1.27 deg/s. According to the analysis with the Kolmogorov-Smirnov test for the two independent samples ($p>0.1$), this is not a significant difference (despite the obvious descriptive trend). When the 9am measurements were considered, cerebellar patients turned out to have an average SPV-value of -4.48 deg/s, whereas patients with unknown aetiology reached an average SPV-value of -1.54 deg/s. According to the Kolmogorov-Smirnov test for two independent samples ($p>0.05$), this descriptive difference, however large it seems, is not significant either.

3.2.3. Discussion

This analysis has shown that resting position influences the known spontaneous decrease of DBN during daytime. When measured in upright position, the intensity of DBN is lower after resting in an upright position than after resting in a supine or prone position. Although the overall extent of DBN did not differ between patients with cerebellar and idiopathic aetiologies, it needs to be acknowledged that there was a clear descriptive trend towards DBN being larger in cerebellar patients. This trend could have turned out significant had the sample size been larger.

The results complement earlier studies reporting that DBN was modulated by head position relative to gravity (Marti et al., 2002) and it is in line with experimental results in primates showing the activity of otolith-related central vestibular neurons (Eron et al., 2008) and the incorporation of otolith-related neurons in the model of Marti et al. (2008). Hence, it could be the case that the otoliths have exerted a stabilizing influence on the central vestibular neurons (and therefore on vertical eye movements) during prolonged upright resting. The

clinical relevance of these results is to advise patients with DBN to rest in an upright position during the day. This is likely to alleviate distressing oscillopsia due to the involuntary retinal slip being caused by the fixation nystagmus. This is a particularly interesting finding, as it complements earlier research on head position relative to the gravitational vector, where it was postulated that a change in head position relative to the gravitational vector could be responsible for DBN (Brandt, 1990; Marti et al., 2002; 2008). According to this explanation (Brandt, 1990), the positional response is a vestibular tone imbalance caused by a disinhibition of the vestibular reflexes on perception, head, eye and the position of the body. Although the patients in this study already had DBN prior to the positional changes, this explanation could also account for an increased intensity of DBN following positional changes. Future research will be necessary, though, to find out what resting position suits patients best prior to transitioning into a body orientation in supine or prone position, e.g. prior to a massage. Another explanation would be an adaptation of the one by Marti et al. (2002), where DBN in upright position is only due to the gravity-independent component, whereas DBN resulting from supine or prone position are modulated by the gravity-dependent component. Although one would assume DBN to be lower in supine position than in prone or upright position, this assumption only refers to being measured in supine or prone position. If people are resting in supine/prone position and switching to upright position for the measurement, the rotation relative to the gravitational vector could have an impact on otolith-related vestibular neurons. This impact might be able to explain why DBN during daytime improves significantly when resting in upright position, but is significantly worse when resting in supine or prone position. The rotation relative to the gravitational vector might exert an absolute influence (i.e. a modulus in mathematical terms) on otolithic function, which could explain why resting in supine and prone position is associated with a similar intensity of DBN when being measured in upright position. It is of particular interest that the data in this sub-chapter (part 2 of chapter 3) cannot be explained by visual input, as the previous sub-

chapter (part 1 of chapter 3) had already demonstrated that there was no significant difference when patients were able to fixate a target during resting and when they were in complete darkness and fixation was therefore made impossible.

3.3. Replicating the study on daytime dependence of downbeat nystagmus mediated by upright resting positions with the light switched on / off (part 3)

The study in chapter 2 analysed daytime dependence of DBN by including comparisons where patients fixated on a target (= light switched on) or not (= light switched off), as well as other comparisons with respect to gaze direction or body position. It did not include different resting positions, though. Hence, the following analyses will be identical to the ones in chapter 2 with the additional inclusion of different resting positions in order to find out whether the intensity of DBN is mediated by different resting positions. The first analysis compares upright resting positions in light and darkness.

3.3.1. Methods (part 3)

3.3.1.1. Patients

In the present part of this study, the eye movements of eight patients with a history of DBN due to different aetiologies were recorded three times on a single day: at 9am, 11am and 1pm.

The aetiologies were idiopathic cerebellar syndrome (n = 1), idiopathic cerebellar ataxia (n = 1), cerebellar degeneration (n = 1), or unknown (n = 5), see Table 3.3. With the exception of patient No. 4, all of these patients had already participated in the study of the previous chapter. The study in the previous chapter had several additional patients, however.

The mean duration of DBN was 6.81 years (range 2-17 years, see Table 3.3, which is identical to Table 3.1, because the patients were the same). The patients were 44 to 82 years old, with a mean of 67.25 years and a standard deviation of ± 10.365 years. The purpose of this part of the study was to analyse the intensity of DBN at the three times of measurement and to find out whether it differs between the two resting intervals (upright with the light on versus upright with the light off). All other procedures (clinical examination, laboratory tests and the approval from the ethics committee) were identical to the previous study and parts 1 and 2 of this study.

Table 3.3 Clinical data of the patients with DBN where upright positions in light and darkness were compared with each other

No./Sex/ Age	Neuro-ophthalmological findings	MRI findings	Aetiology	Disease duration
No. 1M, 76	Disturbed visual fixation suppression of VOR, impaired horizontal and vertical opto-kinetic nystagmus with horizontal and vertical saccades, impaired horizontal and downward pursuit, pathological HTT bilaterally.	White matter lesions	Idiopathic cerebellar syndrome	2 years
No. 2M, 64	Disturbed visual fixation suppression of VOR, non-existing upright opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally.	Cerebellar atrophy	Cerebellar de-generation	3 years
No. 3F, 69	Disturbed visual fixation suppression of VOR, impaired horizontal and upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally, provocation DBN.	Cerebellar atrophy	Idiopathic cerebellar ataxia	17 years
No. 4M, 82	Deviant SVV, non-existing upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, provocation downward nystagmus.	Normal	Unknown	3.5 years
No. 5M, 69	Disturbed visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT on the left.	Normal	Unknown	6 years
No. 6M, 44	Disturbed visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and vertical pursuit.	Normal	Unknown	10 years
No. 7M, 65	Impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, hypometric upward saccades.	Normal	Unknown	10 years
No. 8F, 69	Disturbed vertical visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit.	Normal	Unknown	3 years

VOR = vestibulo-ocular reflex; SVV = subjective visual vertical axis, HTT = head-thrust test developed by Halmagyi and Curthoys (1988).

3.3.1.2. Recording of eye movements

Patients were tested three times on a single day. Each time, patients were monitored in the following sequence: (see Figure 3.5).

1. they were sitting in upright position, 2. they were lying in supine position, 3. they were lying in prone position. In the intervals between testing, people rested in upright position, either with the light switched on or with the light switched off. The same patients were measured with the light switched on / off, i.e. they came to the hospital twice with a delay of approximately one week between these two measurements. As in the previous chapter and prior publications (e.g. Spiegel et al., 2009a; Zingler et al., 2006), a 30 seconds eye movement recording with 3-D VOG took place in the following order: Calibration in 8.5° position, 1. gaze straight ahead with fixation turned on, 2. gaze straight ahead in darkness (with no possibility to fixate on a fixation point), 3. 17° rightward gaze, 4. 17° leftward gaze, 5. 17° upward gaze 6. 17° downward gaze. The projection of the target occurred with a laser onto a white cardboard placed 60 cm in front of the patient. The horizontal gaze directions were only recorded for completeness purposes, e.g. to have a collection of these data should they be of interest for future studies, e.g. to generate possible hypotheses on gaze direction and medication.

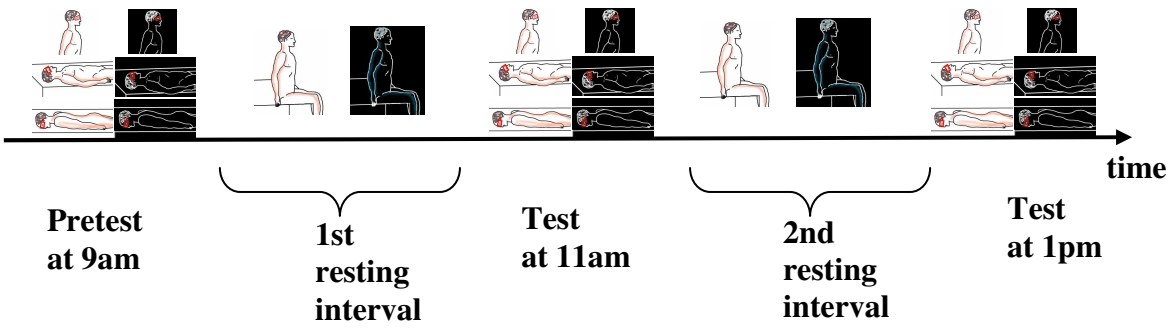


Figure 3.5. An overview describing the testing conditions for all patients. The eye movements of the patients were monitored in the following order: 1. sitting in upright position in light/dark, 2. lying in supine position in light/dark, 3. lying in prone position in light/dark. All measurements took place at 9am, 11am, and1pm. In between the measurements, patients rested in upright position with the room-light either switched on or switched off.

3.3.1.3. Data acquisition and calibration

Data acquisition and calibration was done in exactly the same way as described in the previous chapter, i.e. eye position was measured with 3D-VOG for 30 seconds as in Zingler et al. (2006). The data were analysed off-line using Matlab (The Mathworks, Natick, MA, USA). The calibrated data were low-pass filtered applying a digital Gaussian filter with a bandwidth of 30 Hz. Interactive software allowed to detect and remove saccades and fast phases using a combined velocity–acceleration criterion. Consequently, it was possible to exclude detection errors manually. The mean slow phase velocity was computed from de-saccaded data.

3.3.1.4. Statistical data analysis

The statistical analysis consisted of repeated measurement ANOVAs (Statistica 6.1, Statsoft, Tulsa OK, USA) with post-hoc Scheffé tests for individual comparisons. The dependent variable was *mean slow phase velocity* (SPV). The dependent variable SPV was measured in three gaze directions (straight ahead, upward, downward, more details are provided in 3.3.1.2. Recording of eye movements). The first analysis consisted of the within subjects factors *light* (light on = fixation on target versus light off = no fixation), *interval* (resting upright with the light switched on versus resting upright with the light switched off) and *daytime* (9am, 11am, 1pm). The second analysis consisted of the within subject factors *gaze direction* (straight, upward, downward), *interval* (resting upright with the light switched on versus resting upright with the light switched off), and *daytime* (9am, 11am, 1pm). The third analysis had the within subject factors *body orientation* (upright, supine and prone), *interval* (resting upright with the light switched on versus resting upright with the light switched off), and *daytime* (9am, 11am,

1pm). Due to the low number of three patients with cerebellar symptoms, a nonparametric test for two independent samples was applied, i.e. the Kolmogorov-Smirnov test.

3.3.2. Results

3.3.2.1. First section including the within subjects factor fixation versus viewing in the dark

During the measurement, patients were sitting in upright position with gaze straight ahead. During the resting intervals, patients were in upright position either with the light switched on or with the light switched off. As in the previous chapter, the analysis revealed a significant main effect for the within-subjects factor *light*, $F(1, 7)=14.81$, $p<0.01$ (Figure 3.6), where fixation on target (= light turned on) resulted in lower average SPV-values than viewing in the dark (-2.26 deg/s vs. -4.0 deg/s).

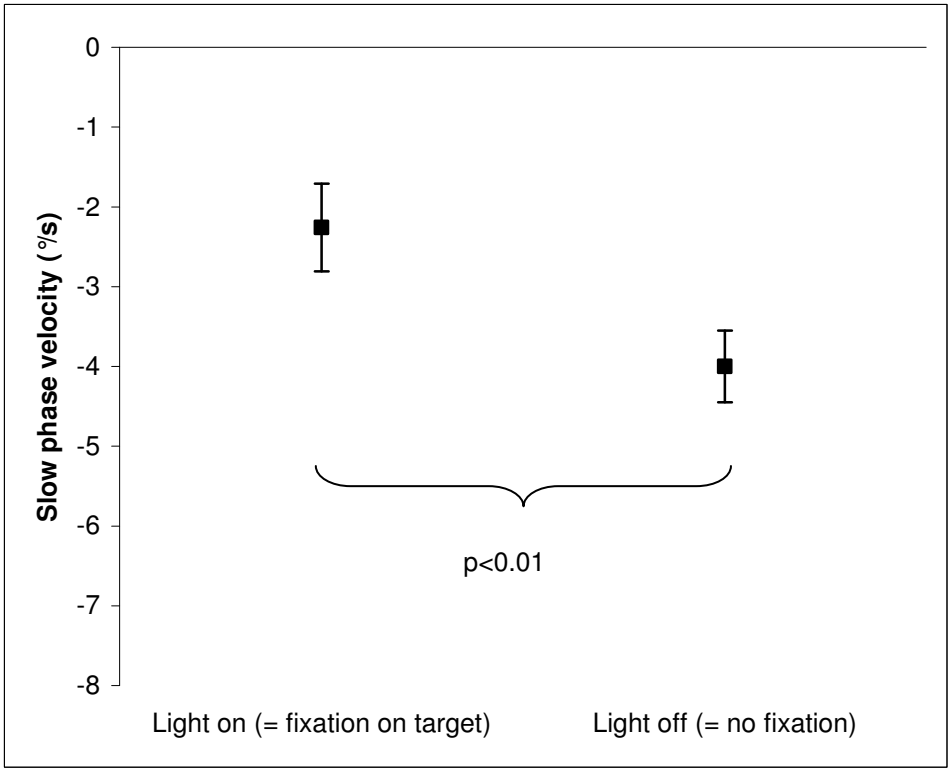


Figure 3.6 Comparing SPV across both intervals (resting upright in light vs. darkness) and daytime (9am, 11am, 1pm) between light (= fixation on target) and darkness conditions (= patients cannot fixate) in upright position with gaze straight ahead. Display of mean slow phase velocities along with the standard error bars of the mean.

In addition, the analysis replicated the daytime decrease reported in Spiegel et al. (2009a) and in the previous chapter, because there was a significant main effect for the within subjects factor *daytime* (9am vs. 11am vs. 1pm), $F(2, 14)=17.19$, $p<0.001$ (Figure 3.7), where average SPV decreased from 9am (-5.03 deg/s) to 11am (-2.41 deg/s) and 1pm (-1.96 deg/s). As revealed by post-hoc Scheffé tests, the decrease from 9am to 11am ($p<0.01$) and from 9am to 1pm ($p<0.001$) was statistically significant, whereas there was no significant difference between 11am and 1pm ($p=0.73$).

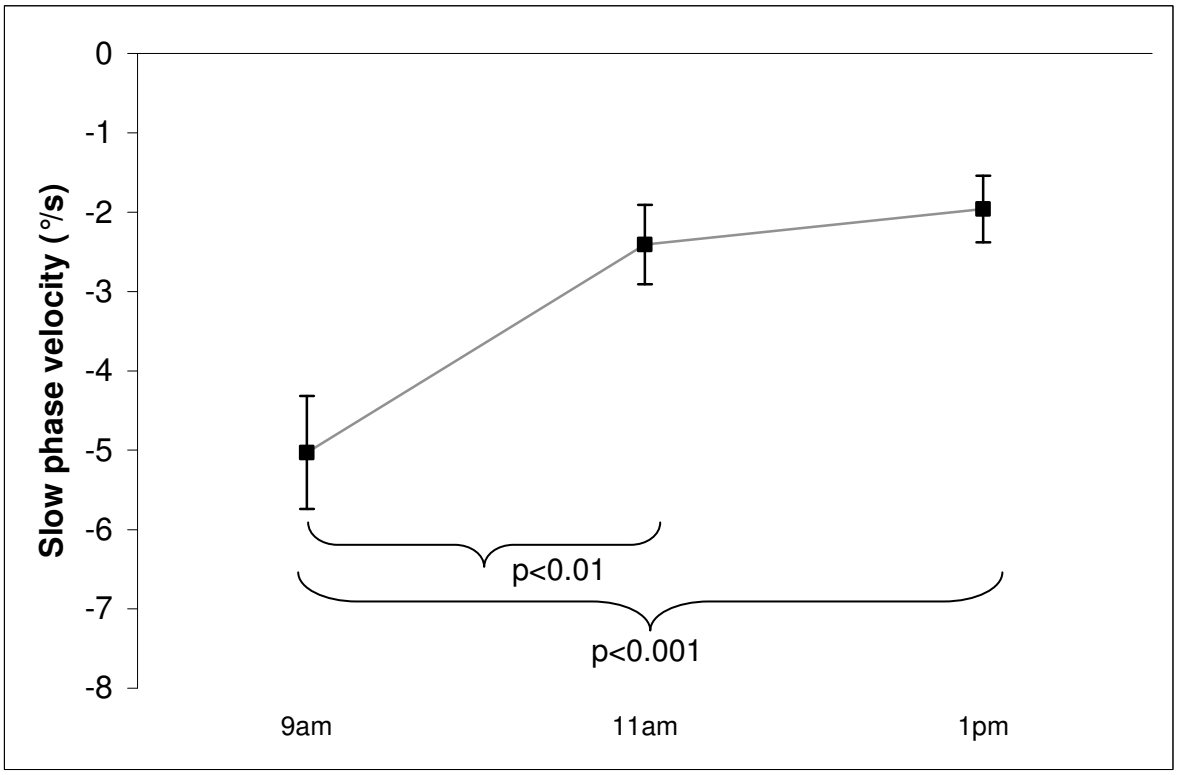


Figure 3.7 SPV between daytime (9am versus 11am versus 1pm) and across both light conditions (light during testing switched on or off) and intervals (resting upright in light vs. darkness) in upright position with gaze straight ahead. Display of mean slow phase velocities along with the standard error bars of the mean.

Referring to the two different intervals between testing, i.e. whether patients rested in upright position with the light switched on or whether they rested in upright position with the light switched off, resulted in a significant main effect for the within subjects factor *interval*, $F(1, 7)=5.715$, $p<0.05$ (Figure 3.8a), where resting in darkness (-2.67 deg/s) was associated with significantly lower average SPV values than resting with the light switched on (-3.6 deg/s). To have an additional comparison on how the measurements were influenced by the intervals, the measurements at 9am (prior to the first resting interval) were skipped and the results were analysed across 11am and 1pm. This step was carried out even though the 9am measurements prior to the *upright-light on interval* (-5.39 deg/s) and the *upright-light off interval* (-4.675 deg/s) were not significantly different from each other ($p=0.85$). The subsequent analysis (across 11am and 1pm) confirmed the earlier finding, where the within subjects factor *interval* again resulted in a significant main effect, $F(1, 7)=16.9$, $p<0.01$ (Figure 3.8b).

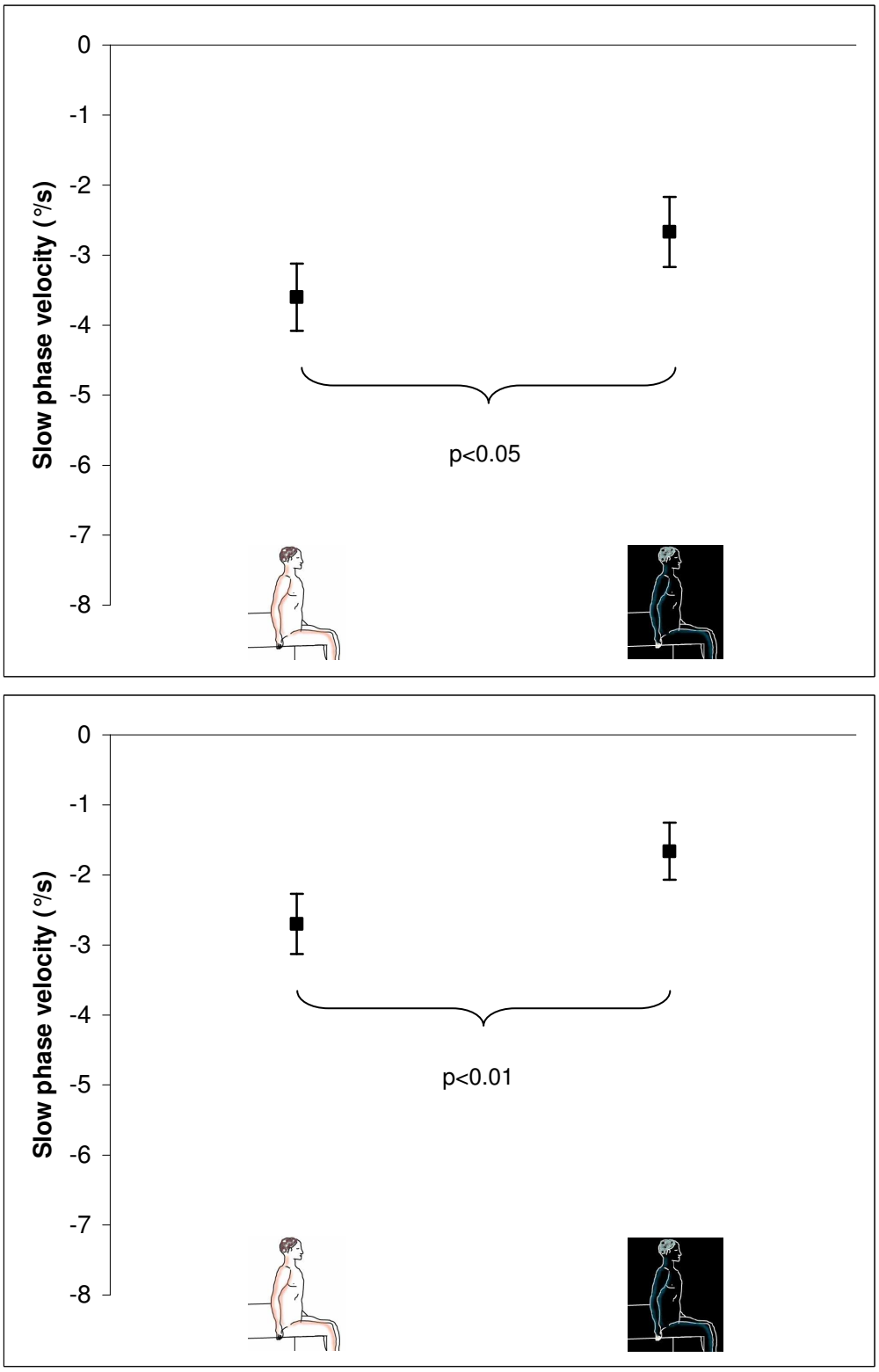


Figure 3.8a SPV between both intervals (resting upright with the light switched on vs. resting upright with the light switched off) and across light (light during testing switched on or off) and daytime (9am, 11am, 1pm) in upright position with gaze straight ahead, **b** SPV across light (light during testing switched on or off) and daytime (11am, 1pm) between both intervals (resting upright with the light switched on vs. resting upright with the light switched off) in upright position with gaze straight ahead. Display of mean slow phase velocities along with the standard error bars of the mean.

Resting in darkness (-1.66 deg/s) was associated with significantly lower average SPV values than resting with the light switched on (-2.7 deg/s).

Going back to the original analysis (including the 9am measurements), none of the other statistical tests revealed a significant finding. Only the *light times daytime* interaction came close to approaching statistical significance, $F(2, 14)=3.21$, $p=0.07$. Neither the *light times interval* interaction, $F(1, 7)=1.44$, $p=0.27$, nor the *interval times daytime* interaction, $F(2, 14)=1.06$, $p=0.37$, nor the *light times interval times daytime* interaction, $F(2, 14)=0.34$, $p=0.72$ approached statistical significance. With regard to the comparison between cerebellar patients and patients with unknown aetiology, cerebellar patients had an average SPV-value of -4.51 deg/s, whilst patients with unknown aetiology had an average SPV-value of -2.31 deg/s. This is a significant difference according to the Kolmogorov-Smirnov test ($p<0.05$).

3.3.2.2. Second section including the within subjects factor gaze direction

As in the previous chapter, it turned out that there was a main effect with respect to the within subjects factor *gaze direction*, $F(2, 14)=13.43$, $p<0.001$ (Figure 3.9), where Scheffé post-hoc tests revealed that gaze upwards (-0.065 deg/s) was associated with significantly lower average SPV values than gaze straight ahead (-2.265 deg/s) and gaze downwards (-2.32 deg/s), (both Scheffé post-hoc tests: $p<0.01$), whereas gaze straight ahead and downwards did not significantly differ from each other ($p=0.99$).

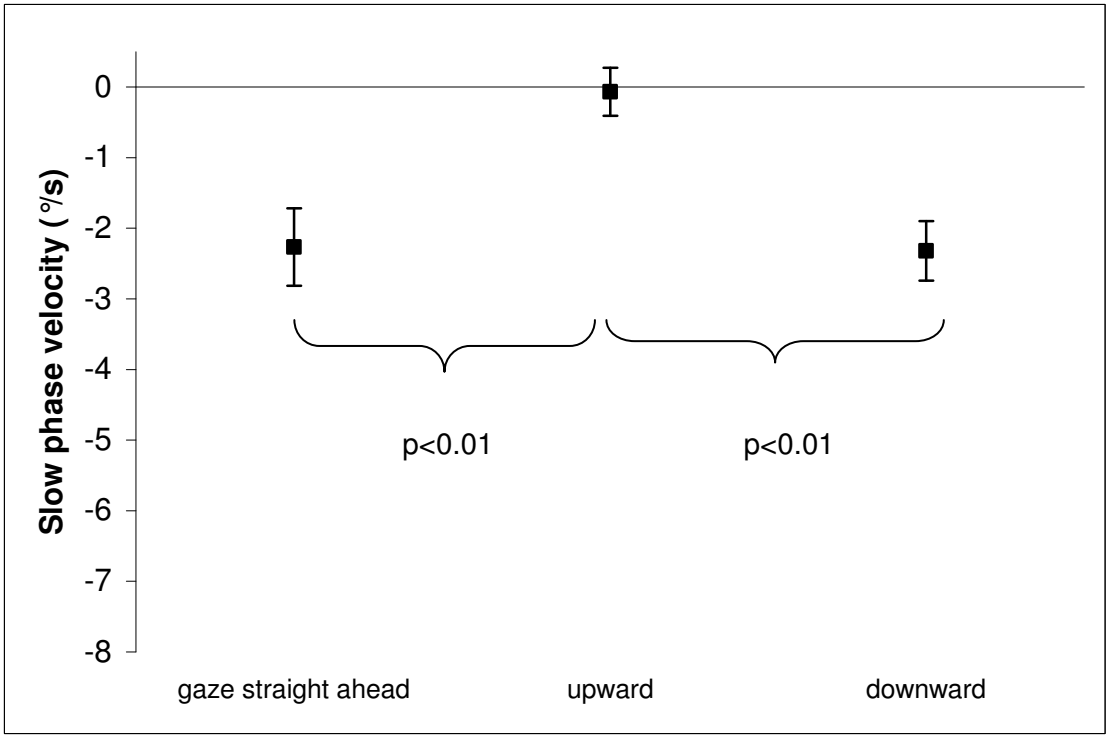


Figure 3.9 Comparing SPV between gaze straight ahead, upward and downward and across both intervals and time, in upright position and with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

Consistent with the previous chapter, the analysis revealed a significant daytime decrease in SPV-values, $F(2, 14)=14.82$, $p<0.001$ (Figure 3.10), where average SPV decreased from -2.545 deg/s at 9am to -1.28 deg/s at 11am to -0.82 deg/s at 1pm. Scheffé post-hoc tests revealed that the decrease from 9am to 11am had a p-value of $p<0.01$, whereas the decrease from 9am to 1pm had a p-value of $p<0.001$. There was no significant difference between 11am and 1pm ($p=0.4$).

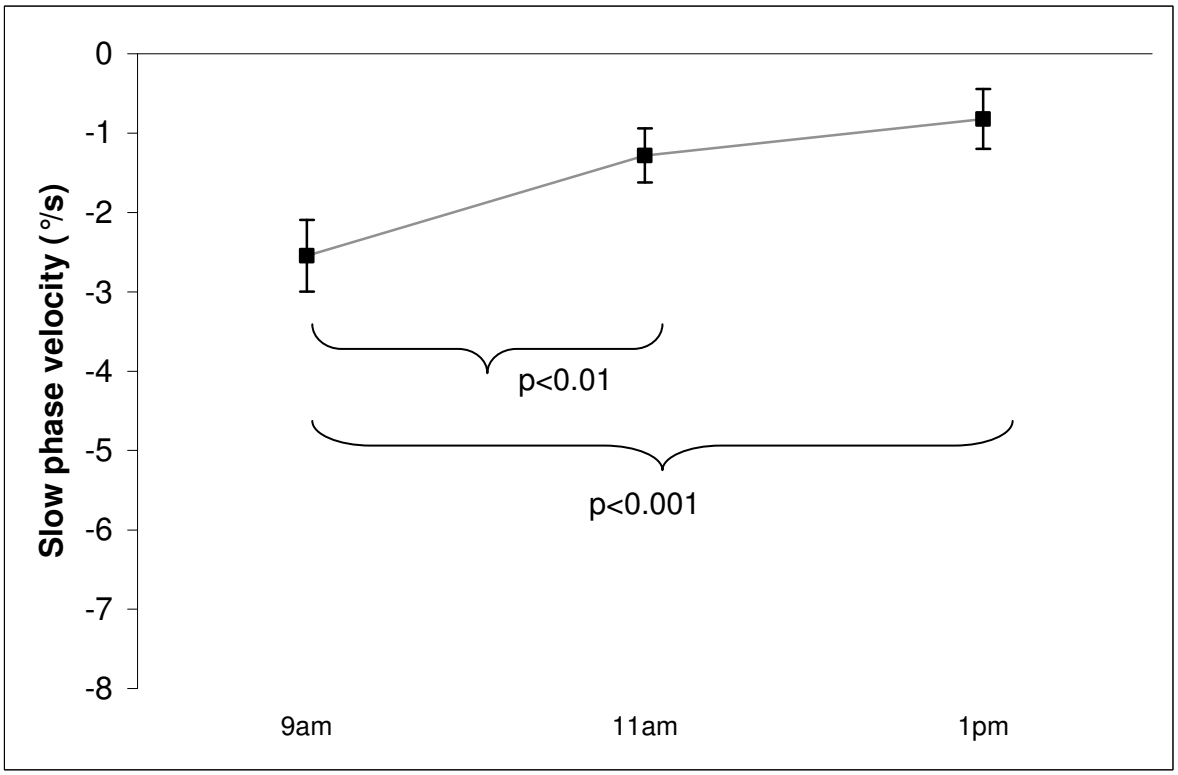


Figure 3.10 Daytime decrease in SPV across all three gaze conditions and both intervals, in upright position and with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

In addition, there was a significant *gaze times daytime* interaction, $F(4, 28)=3.475$, $p<0.05$ (Figure 3.11), where upward gaze and downward gaze showed an almost parallel SPV-decrease throughout time (with upward gaze even shifting towards UBN), whilst gaze straight ahead showed a steep decrease from 9am to 11am. As revealed by Scheffé post-hoc tests, only gaze straight ahead showed a significant decrease from 9am to 11am ($p<0.001$) and from from 9am to 1pm ($p<0.0001$), whilst downward gaze also showed a significant effect from 9am to 1pm ($p<0.01$).

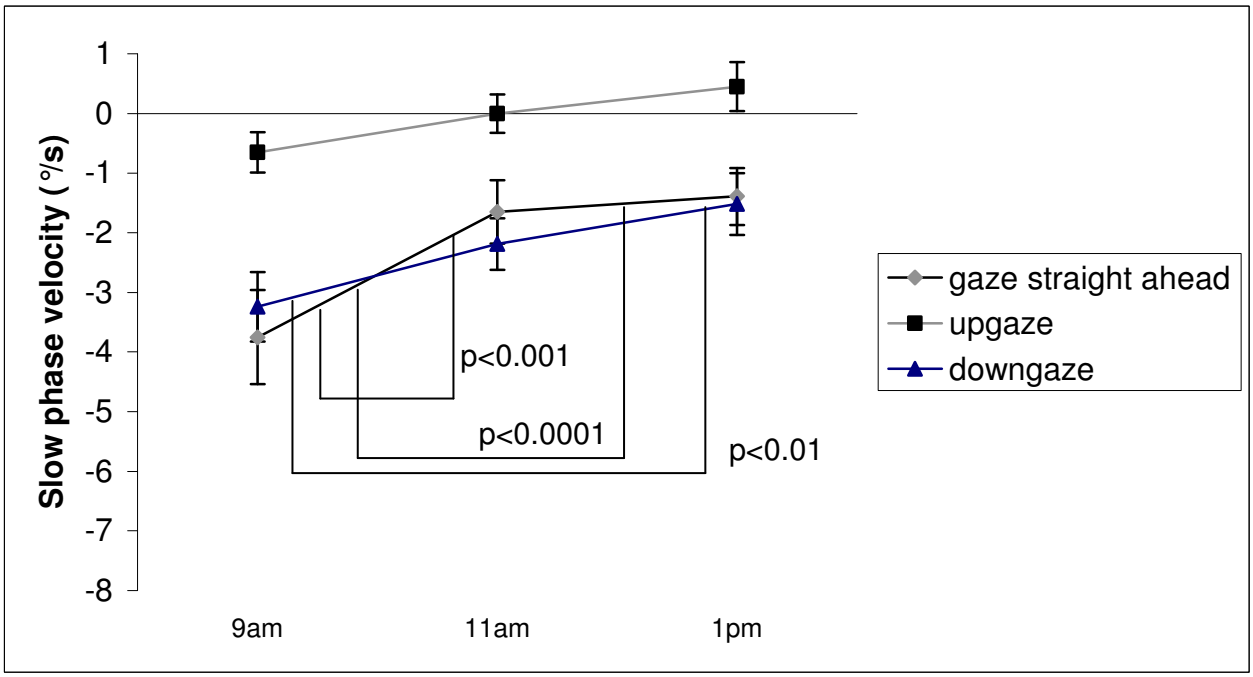


Figure 3.11 Daytime decrease in SPV between all three gaze conditions and across both intervals, in upright position and with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

Turning to the remaining findings of this analysis, there was a marginally significant *interval times daytime* interaction, F(2, 14)=3.61, p=0.054, where resting upright with the light switched off appeared to have a steeper SPV-decrease than resting upright with the light switched on. Nevertheless, it needs to be considered that this was only a marginally significant interaction. Even when excluding the 9am measurement (where no resting interval had taken place yet), there was no significant main effect with respect to *interval*, F(1, 7)=4.165, p=0.08 and no significant *interval times daytime* interaction, F(1, 7)=5.49, p=0.052. Going back to the original analysis in this chapter (i.e. including the 9am measurements), there was no significant main effect for the within subjects factor *interval* either, F(1, 7)=1.92, p=0.21 (the descriptive trend when resting in upright position with the light switched off was associated with a lower average SPV (-1.24 deg/s) than resting in upright position with the light switched on (-1.86 deg/s)). In addition, there was no significant *gaze times interval* interaction, F(2, 14)=0.17, p=0.84, and no significant *gaze times interval times daytime*

interaction, F(4, 28)=1.26, p=0.31. With regard to the comparison between cerebellar patients and patients with unknown aetiology, cerebellar patients had an average SPV-value of -2.64 deg/s, whilst patients with unknown aetiology had an average SPV-value of -0.89 deg/s, which is a significant difference according to the Kolmogorov-Smirnov test ($p<0.05$).

3.3.2.3. Third section including the within subjects factor body orientation

Consistent with the findings from the previous chapter, the analysis with respect to *body orientation* resulted in a significant main effect, $F(2, 14)=20.1$, $p<0.0001$ (Figure 3.12). The Scheffé post-hoc comparisons between upright (-2.26 deg/s), supine (-0.62 deg/s) and prone (-6.44 deg/s) led to a significant difference between upright and prone position ($p<0.01$) and to a significant difference between supine and prone position ($p<0.001$), but no significant difference between upright and supine position ($p=0.255$).

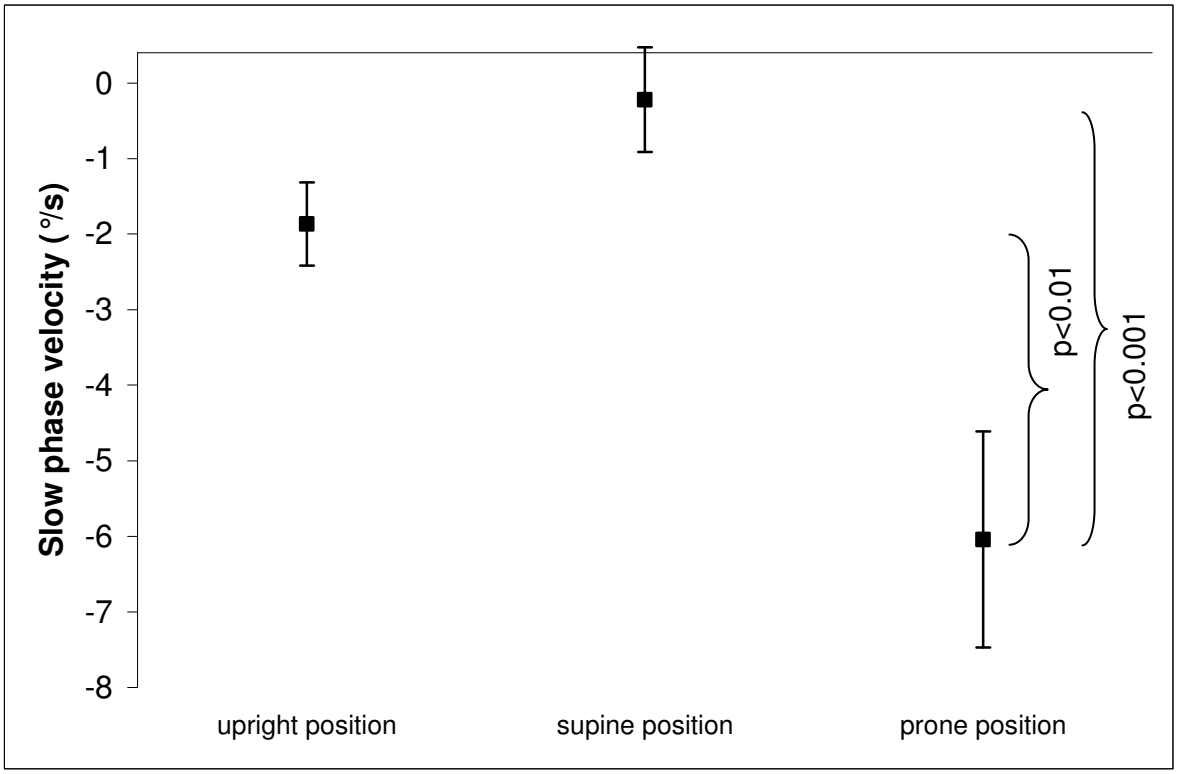


Figure 3.12 Comparing SPV between upright, supine and prone positions and across both intervals and daytime, in gaze straight ahead and with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

Once more, there was a significant main effect for the within-subjects factor *daytime*, F(2, 14)=6.34, p<0.05 (Figure 3.13), where average SPV decreased from -4.54 deg/s at 9am to -2.64 deg/s at 11am and -2.15 deg/s at 1pm. Scheffé post-hoc tests revealed that only the difference between 9am and 1pm was statistically significant (p<0.05), whereas the difference between 9am and 11am was marginally significant (p=0.055) and the difference between 11am and 1pm did not reach significance (p=0.79).

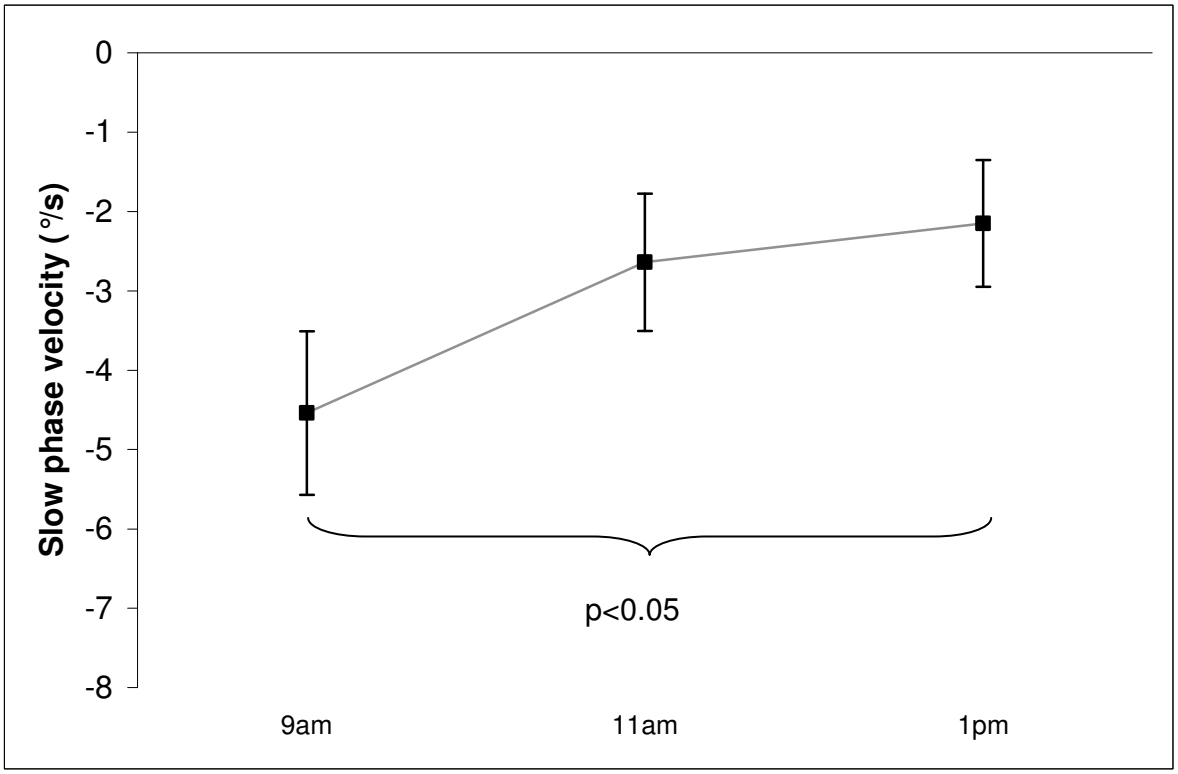


Figure 3.13 Daytime decrease in SPV across all three body positions and both intervals, in gaze straight ahead and with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

Among the interactions, only the *body orientation times interval* interaction became statistically significant, F(2, 14)=3.95, p<0.05 (Figure 3.14), where post-hoc Scheffé tests revealed that there was a significant difference between resting upright with the light switched on and resting upright with the light switched off only in prone position (p<0.05).

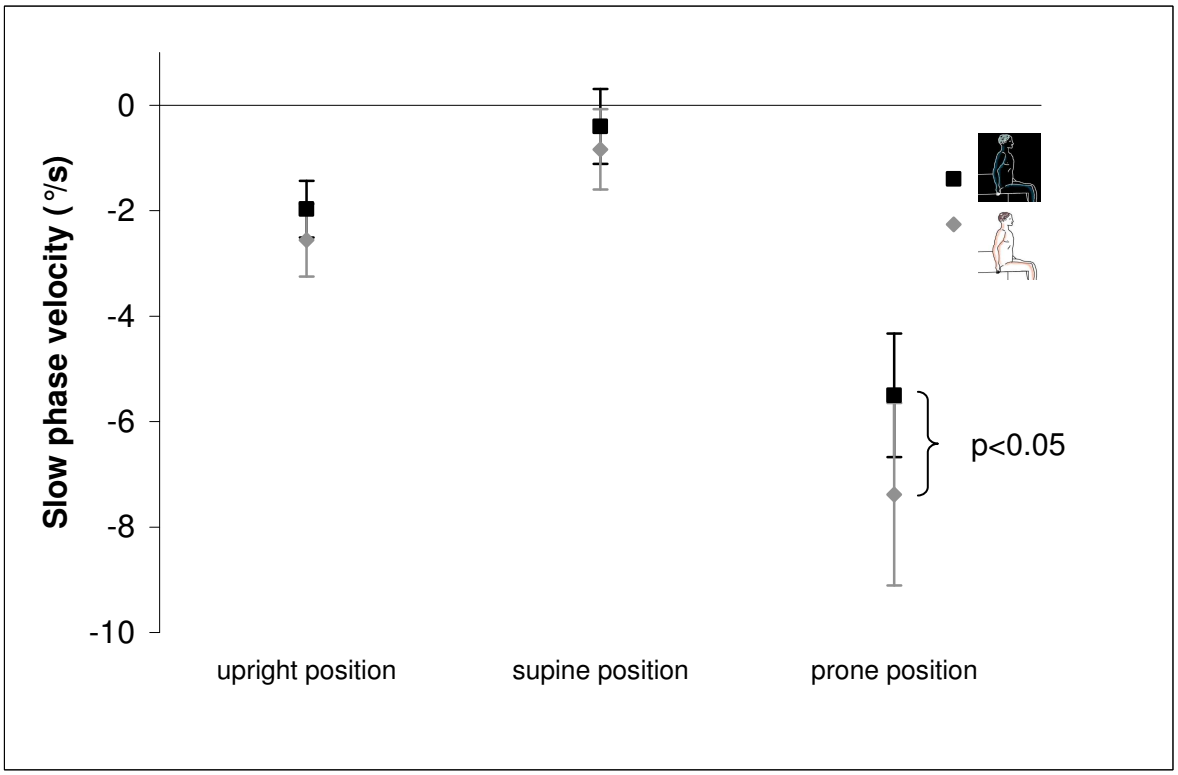


Figure 3.14 Comparing SPV differences across daytime between the within subjects factors interval (light on/off) and position (upright, supine and prone), in gaze straight ahead and with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

Among the remaining tests, only the within subjects factor *interval* became marginally significant, $F(1, 7)=3.74$, $p=0.09$, where resting in upright position with the light switched off was associated with a descriptively lower average SPV (-2.625 deg/s) than resting in upright position with the light switched on (-3.59 deg/s). Neither the *body orientation times daytime* interaction became significant, $F(4, 28)=0.13$, $p=0.97$, nor the *interval times daytime* interaction, $F(2, 14)=1.34$, $p=0.29$, nor the *body orientation times interval times daytime* interaction, $F(4, 28)=0.53$, $p=0.715$. With regard to the comparison between cerebellar patients and patients with unknown aetiology, cerebellar patients had an average SPV-value of -5.305 deg/s, whilst patients with unknown aetiology had an average SPV-value of -1.79 deg/s. This descriptive difference is not significant according to the Kolmogorov-Smirnov test ($p>0.1$).

3.3.3. Discussion

This part of the study confirmed a couple of findings that were reported in the previous chapter as well as in Spiegel et al. (2009a):

The first section of the analysis included the within subjects factor *light* (fixation versus viewing in the dark). It showed that DBN (as measured by SPV) decreases in the course of the day. In addition, the ability to fixate (when the light is switched on) is associated with a lower intensity of DBN. As a result, this outcome is consistent with the earlier findings and the finding that visual fixation can suppress DBN. A new finding in this section of the analysis is related to the resting position during the intervals between the tests. Resting upright with the light switched off was associated with significantly less DBN (as expressed by SPV) than resting upright with the light switched on. Given that the 9am measurements were prior to the first resting interval, an additional test was carried out where only those two measurements (11am and 1pm) were included that immediately followed a resting interval. This test confirmed that resting with the light switched off led to a lower intensity of DBN. It has to be kept in mind that this effect is across the *light* conditions during the measurement, i.e. it includes the measurements with the light switched on as well as the measurements with the light switched off. In part 1 of this study, where only light-on data were included, there was only a descriptive trend towards light-off being associated with lower DBN. When considering practical applications of this finding, one could say that it does not make a difference whether people rest upright with the light switched on or off as long as they engage in usual daytime activities under light conditions. If they, for example, work in an environment where they are intermittently exposed to both light and darkness, it would be better to rest upright with the light switched off, i.e. in darkness.

The second section of this analysis included the within subjects factor *gaze direction*. Consistent with the study of the previous chapter, there was a significant main effect of *gaze*

direction, where upward gaze was associated with significantly lower average SPV-values than downward gaze or gaze straight ahead. Although this finding is consistent with Alexander's law, it is interesting that downward gaze and gaze straight ahead did not significantly differ from each other. According to the descriptive findings, downward gaze had more pronounced DBN than gaze straight ahead, i.e. at least the descriptive trend is consistent with Alexander's law, where slow phase velocity decreases when gaze moves away from the direction of the fast phase (Jeffcoat et al., 2008, Robinson et al., 1984). As in the previous analyses, the intensity of DBN decreased throughout daytime. In addition, there was a significant *gaze times daytime* interaction, where upward gaze and downward gaze showed an almost parallel SPV-decrease throughout time, whilst gaze straight ahead showed a steeper decrease from 9am to 11am and the only decrease that was statistically significant between 9am and 11am. It is difficult to interpret this kind of interaction, though, as there was no hypothesis with regard to such an interaction prior to carrying out this study. It is entirely unclear why there should be a steeper decrease from 9am to 11am only in gaze straight ahead and not in the other gaze directions.

The third section of this analysis included the within subjects factor *body orientation*. In line with Marti et al. (2002), the study in the previous chapter and Spiegel et al. (2009a), there was a significant main effect with respect to *body orientation*. The intensities of DBN between upright and supine position were not significantly different from each other, but prone position had a significantly higher intensity of DBN than upright and supine positions. Hence, the finding was in line with the earlier reported gravitational influence through different body positions. As in the previous analyses of this and the previous chapter, the intensity of DBN also decreased throughout daytime. Among the interactions, only the *body orientation times interval* interaction became statistically significant, where a significant difference could only be found in prone position between resting upright with the light switched on and resting upright with the light switched off. One possible interpretation is that

prone position was generally associated with more pronounced SPV-values. As a result, small variations of the values in prone position (e.g. due to chance) could result in more pronounced differences than in the other two body positions.

Only a nonparametric comparison between patients with cerebellar and unknown aetiologies was carried out, because the number of three cerebellar patients was considered too low to carry out a parametric comparison. As it turned out, aetiology had a significant influence in the first two sections of part 3, but not in the third section. In all three sections, however, it appears that patients with cerebellar aetiology have stronger symptoms of DBN than patients with unknown aetiology.

Having looked at the influence of light and darkness during the resting intervals in upright position, it will now be interesting to look at the positional effects. Because part 1 and part 3 of this study had shown that resting in darkness is at least descriptively associated with a lower intensity of DBN, all resting positions (upright, supine and prone) will be compared with each other in darkness.

3.4. Replicating the study on daytime dependence of downbeat nystagmus mediated by upright and prone resting positions with the light switched off (part 4)

Having compared upright resting positions with the light switched on / off, the following comparisons will refer to the light off condition only. The first comparison will be upright versus prone resting position.

3.4.1. Methods

The method of part 4 overlaps one to one with the method of part 3. The only differences are with respect to the participants and the intervals between testing.

3.4.1.1. Patients

In part 4, a total number of 9 participants were tested at 9am, 11am and 1pm. In the intermissions between testing, they rested in either upright or prone position. In both cases, the light was switched off, i.e. they rested in darkness. All patients were identical to part 2 of this study. Five of the patients were the same as in parts 1 and 3, four patients had not been tested in parts 1 and 3. In addition, patients No. 7 and No. 8 had already participated in the study of the previous chapter. The mean duration of DBN was 6.81 years (range 3-17 years, see Table 3.4). The patients were 44 to 72 years old, with a mean of 63.67 years and a standard deviation of ± 7.92 years. All other factors and clinical examinations to the previous parts of this study and the study of the previous chapter.

3.4.1.2. Recording of eye movements

Patients were tested three times on a single day. Each time, patients were monitored in the following sequence: (see Figure 3.15).

1. they were sitting in upright position, 2. they were lying in supine position, 3. they were lying in prone position. In the intermissions between testing, people rested in prone position and upright position, in both cases with the light switched off. The same patients were measured in prone position and upright position, i.e. they came to the hospital twice with a

delay of approximately one week between these two measurements. The VOG-measurements were identical to those in the study of the previous chapter and the previous parts of this study.

Table 3.4 Clinical data of the patients with DBN where upright and prone positions in darkness were compared with each other

No./Sex/ Age	Neuro-ophthalmological findings	MRI findings	Aetiology	Disease duration
No. 1M, 64	Disturbed visual fixation suppression of VOR, non-existing upright opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally.	Cerebellar atrophy	Cerebellar de-generation	3 years
No. 2F, 69	Disturbed visual fixation suppression of VOR, impaired horizontal and upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally, provocation DBN.	Cerebellar atrophy	Idiopathic cerebellar ataxia	17 years
No. 3M, 69	Deviant SVV, impaired horizontal and downward pursuit, saccades with rebound after gaze to the right, provocation DBN.	Normal	Unknown	4.5 years
No. 4F, 60	Disturbed visual fixation suppression of VOR, DBN overran horizontal opto-kinetic nystagmus, non-existing upward opto-kinetic nystagmus, deviant SVV, impaired horizontal and downward pursuit.	Normal	Unknown	12 years
No. 5F, 61	Disturbed visual fixation suppression of VOR, deviant SVV, provocation DBN, vertical saccades and saccades to the left.	Normal	Unknown	5 years
No. 6M, 44	Disturbed visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and vertical pursuit.	Normal	Unknown	10 years
No. 7M, 65	Impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, hypometric upward saccades.	Normal	Unknown	10 years
No. 8F, 69	Disturbed vertical visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit.	Normal	Unknown	3 years
No. 9F, 72	Disturbed visual fixation suppression of VOR, impaired horizontal and non-existing upward opto-kinetic nystagmus, impaired horizontal and downward pursuit.	Normal	Unknown	6 years

VOR = vestibulo-ocular reflex; SVV = subjective visual vertical axis, HTT = head-thrust test developed by Halmagyi and Curthoys (1988).

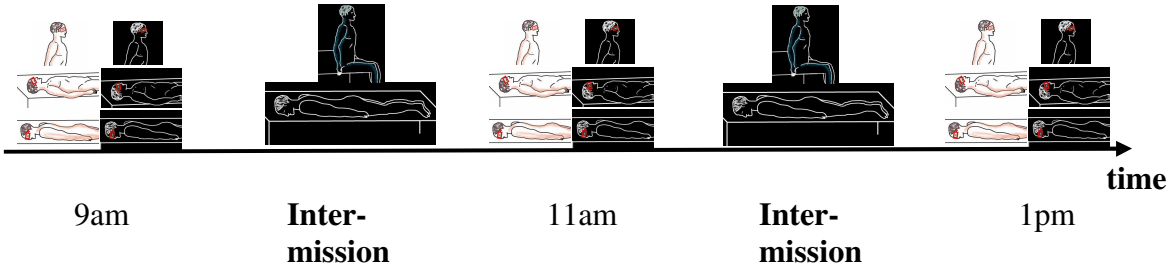


Figure 3.15. An overview describing the testing conditions for all patients. The eye movements of the patients were monitored in the following order: 1. sitting in upright position in light/dark, 2. lying in supine position in light/dark, 3. lying in prone position in light/dark. All measurements took place at 9am, 11am, and1pm. In between the measurements, patients were lying in prone position or sitting in upright position, in both cases with the light switched off.

3.4.1.3. Data acquisition and calibration

Data acquisition and calibration was identical to the study of the previous chapter and the previous parts of this study.

3.4.1.4. Statistical data analysis

The statistical analysis consisted of repeated measurement ANOVAs (Statistica 6.1, Statsoft, Tulsa OK, USA) with post-hoc Scheffé tests for individual comparisons. The dependent variable was slow phase velocity (SPV). The first analysis consisted of the within subjects factors *light* (= light on, where fixation is possible vs. light off, where no fixation is possible), *interval* (resting in prone position with the light switched off versus resting in upright position with the light switched off) and *daytime* (9am, 11am, 1pm). The second analysis consisted of the within subject factors *gaze condition* (straight, upwards, downwards), *interval* (resting in prone position with the light switched off versus resting in upright position with the light switched off) and *daytime* (9am, 11am, 1pm). The third analysis had the within subject factors *body orientation* (upright, supine and prone), *interval* (resting in prone position with the light

switched off versus resting in upright position with the light switched off) and *daytime* (9am, 11am, 1pm). Due to the low number of patients with cerebellar symptoms, the previously mentioned nonparametric Kolmogorov-Smirnov test was applied for two independent samples. The two independent groups were the two different aetiologies (cerebellar patients versus patients with unknown aetiology). The two groups were compared with respect to their overall SPV-values.

3.4.2 Results

3.4.2.1. First section including the within subjects factor fixation versus viewing in the dark

In the first section of part 4, patient No. 4 was missing, because in prone position, she was not assessed in the dark. As a result, no comparison for the within subjects factor *light* (fixation versus viewing in the dark) would have been possible for this patient. Hence, this patient is not included in this part of the analysis. As in the previous chapter, the analysis revealed a significant main effect for the within-subjects factor *light*, $F(1, 7)=6.475$, $p<0.05$ (Figure 3.16), where the possibility of fixation (= light turned on) resulted in lower average SPV-values than viewing in the dark (-2.06 deg/s vs. -3.19 deg/s).

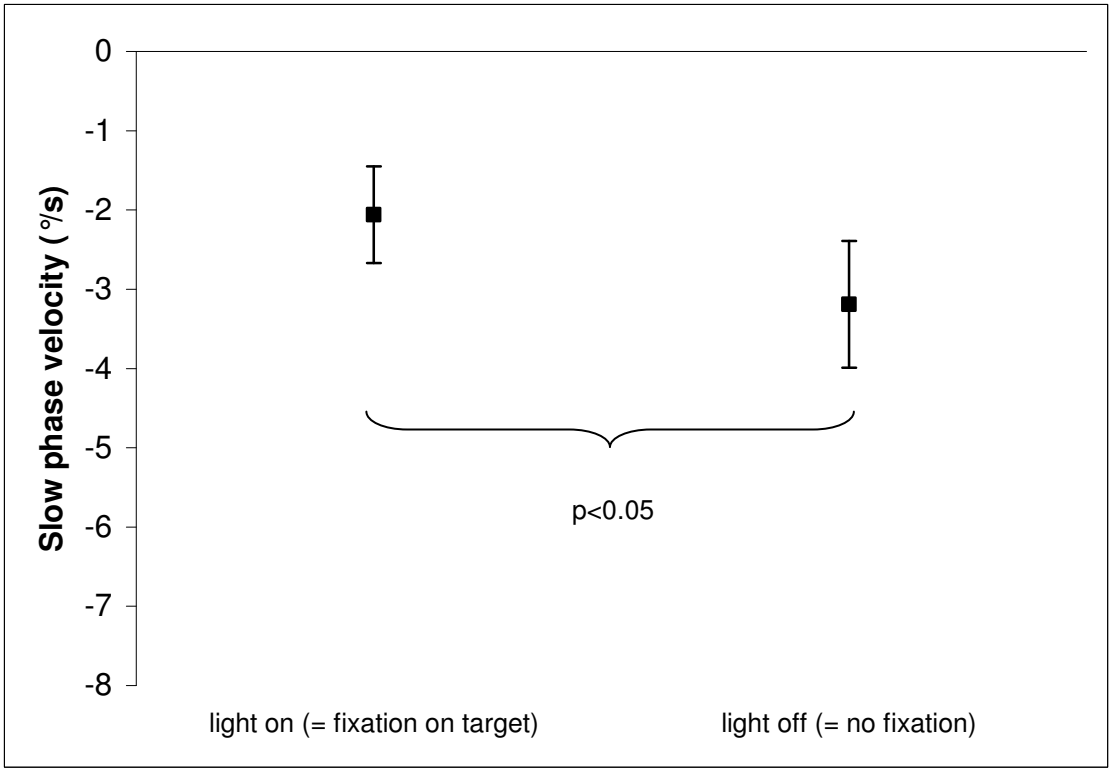


Figure 3.16 Comparing SPV between light (= fixation on target) and darkness conditions (= patients cannot fixate), across both intervals (resting upright or prone) and daytime (9am, 11am, 1pm), measured in upright position and during gaze straight ahead. Display of mean slow phase velocities along with the standard error bars of the mean.

Consistent with the previous chapter and the first part of this study, the analysis revealed a significant daytime decrease in SPV-values, $F(2, 14)=12.58$, $p<0.001$ (Figure 3.17), where average SPV decreased from -4.44 deg/s at 9am to -1.94 deg/s at 11am to -1.5 deg/s at 1pm. Scheffé post-hoc tests revealed that the decrease from 9am to 11am and from 9am to 1pm each had a p-value of $p<0.01$. There was no significant difference between 11am and 1pm ($p=0.79$).

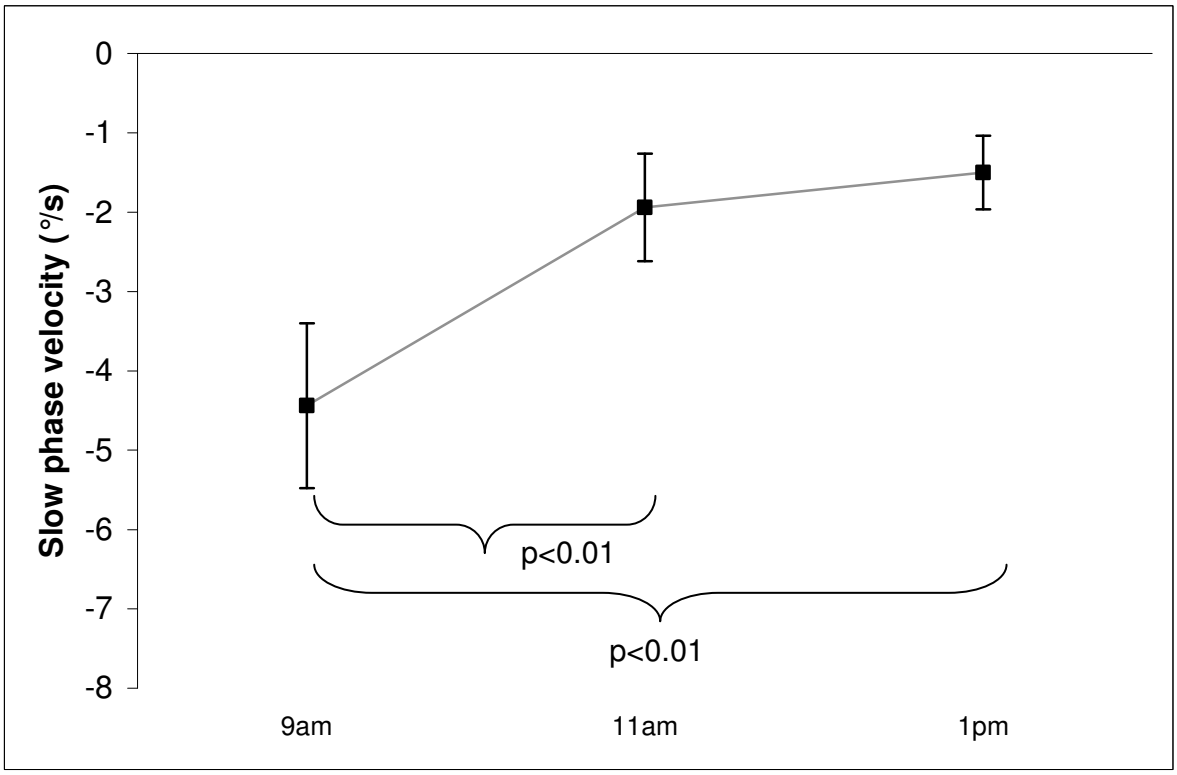


Figure 3.17 Daytime decrease in SPV across both light conditions (light on / light off) and both intervals (upright/prone), measured in upright position and during gaze straight ahead. Display of mean slow phase velocities along with the standard error bars of the mean.

None of the other comparisons revealed a significant result. The within subjects factor *interval* (resting in prone position versus resting in upright position, both in darkness) did not reveal a significant result, $F(1, 7)=1.69$, $p=0.23$. According to the descriptive trend, resting in upright position (-2.29 deg/s) was associated with slightly lower average SPV-values than resting in prone position (-2.97 deg/s). Among the interactions, the *light times interval* interaction, $F(1, 7)=5.21$, $p=0.056$, the *light times daytime* interaction, $F(2, 14)=3.53$, $p=0.0575$, the *interval times daytime* interaction, $F(2, 14)=2.91$, $p=0.087$, all became marginally significant only. The *light times interval times daytime* interaction did not become significant either, $F(2, 14)=0.69$, $p=0.52$. With regard to the comparison between cerebellar patients and patients with unknown aetiology, cerebellar patients had an average SPV-value of -4.98 deg/s, whilst patients with unknown aetiology had an average SPV-value of -1.84

deg/s. This descriptive difference is not significant according to the Kolmogorov-Smirnov test ($p>0.05$).

3.4.2.2. Second section including the within subjects factor gaze direction

As in the previous chapter and in part 1 of this study, it turned out that there was a main effect with respect to the within subjects factor *gaze direction*, $F(2, 16)=16.17$, $p<0.001$ (Figure 3.18), where Scheffé post-hoc tests revealed that gaze upwards (+0.32 deg/s, i.e. a slight UBN) was associated with significantly lower average SPV values than gaze straight ahead (-2.07 deg/s) and gaze downwards (-1.91 deg/s), (both Scheffé post-hoc tests: $p<0.001$), whereas gaze straight ahead and downwards did not significantly differ from each other ($p=0.95$).

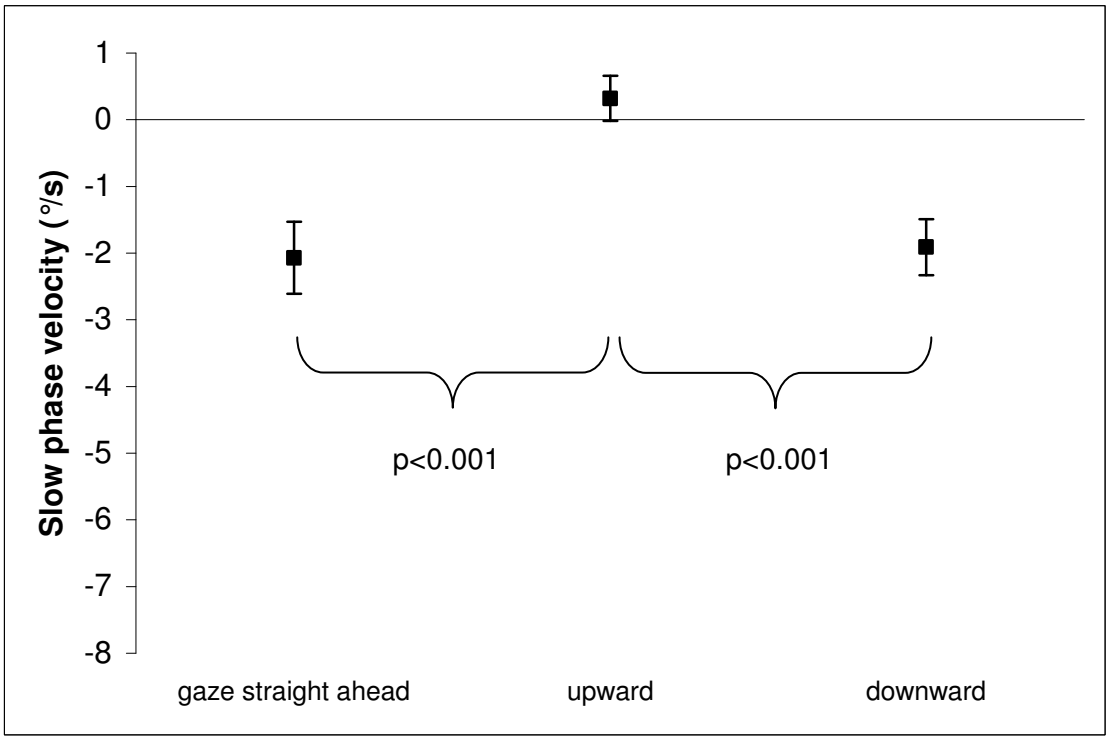


Figure 3.18 Comparing SPV between gaze straight ahead, upward and downward, across both intervals and daytime, measured in upright position with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

Consistent with the previous chapter, the analysis revealed a significant daytime decrease in SPV-values, $F(2, 16)=7.18$, $p<0.01$ (Figure 3.19), where average SPV decreased from -2.19 deg/s at 9am to -0.85 deg/s at 11am to -0.615 deg/s at 1pm. Scheffé post-hoc tests revealed that the decrease from 9am to 11am and from 9am to 1pm each had a p-value of $p<0.05$. There was no significant difference between 11am and 1pm ($p=0.87$).

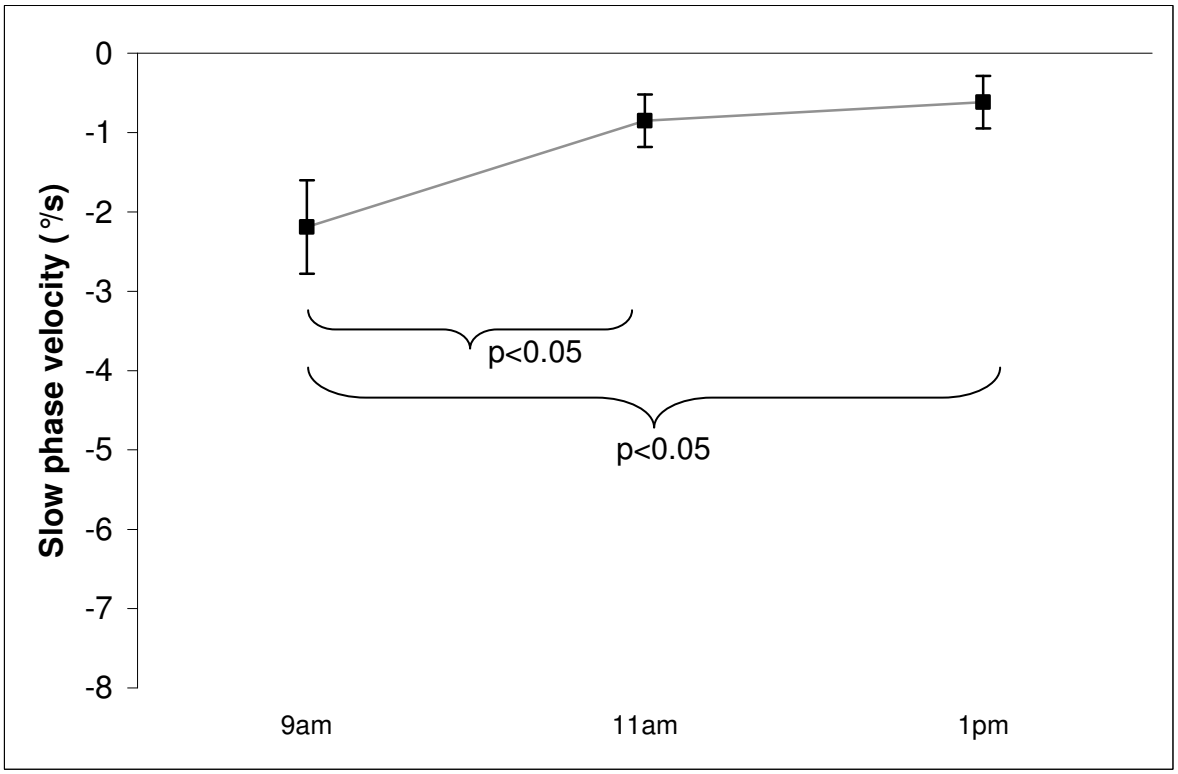


Figure 3.19 Daytime decrease in SPV across all three gaze conditions and both intervals, measured in upright position with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

None of the other comparisons revealed a significant result. The within subjects factor *interval* (resting in prone position versus resting in upright position) revealed a marginally significant finding, $F(1, 8)=4.27$, $p=0.07$. According to the descriptive trend, resting in upright position (-0.83 deg/s) was associated with lower average SPV-values than resting in prone position (-1,61 deg/s). None of the interactions approached statistical significance, neither the *gaze times interval* interaction, $F(2, 16)=2.39$, $p=0.12$, nor the *gaze times daytime* interaction,

F(4, 32)=0.89, p=0.48, nor the *interval times daytime* interaction, F(2, 16)=1.7, p=0.21, nor the *gaze times interval times daytime* interaction, F(4, 32)=1.09, p=0.38. With regard to the comparison between cerebellar patients and patients with unknown aetiology, cerebellar patients had an average SPV-value of -2.69 deg/s, whilst patients with unknown aetiology had an average SPV-value of -0.8 deg/s. This descriptive difference is not significant according to the Kolmogorov-Smirnov test (p>0.05).

3.4.2.3. Third section including the within subjects factor body orientation

Consistent with the findings from the study in the previous chapter and from part 1 of this study, the analysis with respect to *body orientation* resulted in a significant main effect, F(2, 16)=6.31, p<0.01 (Figure 3.20). The Scheffé post-hoc comparisons between upright (-2.07 deg/s), supine (-0.43 deg/s) and prone (-3.22 deg/s) revealed that only the difference between supine and prone position was statistically significant (p<0.01). Comparing upright and supine position (p=0.15) and upright and prone position (p=0.36) did not yield a significant finding.

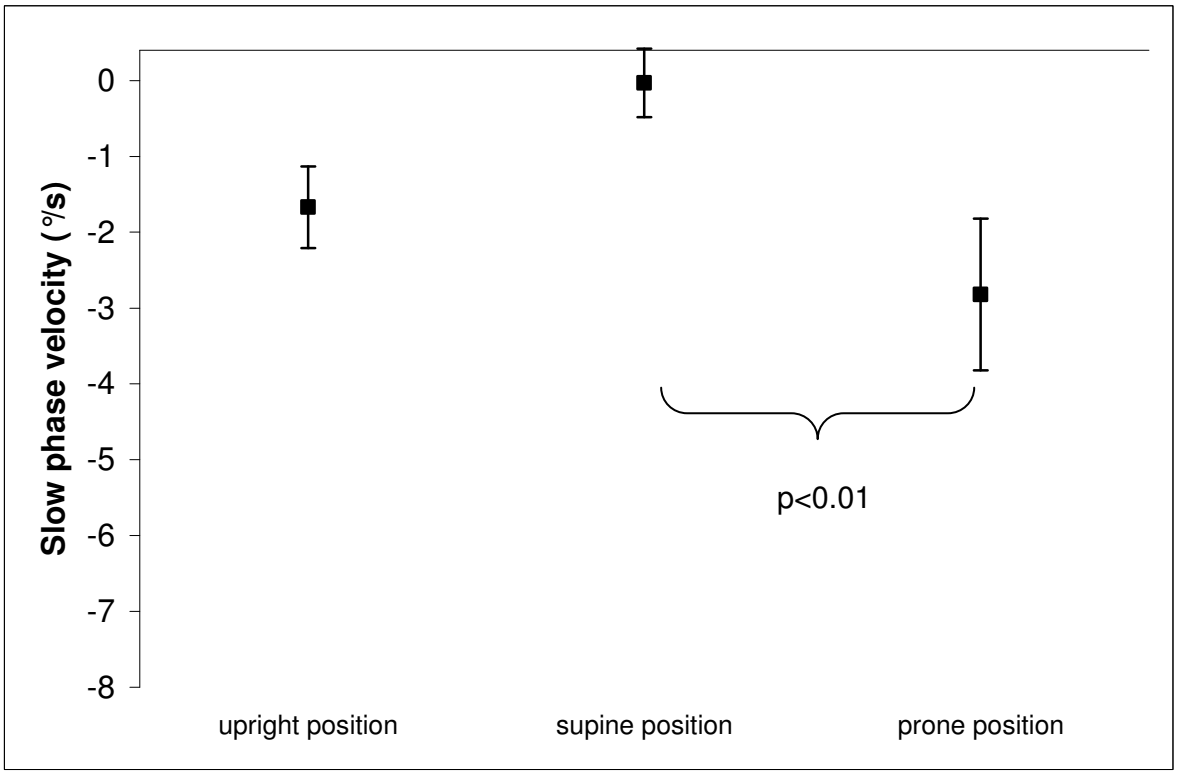


Figure 3.20 Comparing SPV between upright, supine and prone position, across intervals and daytime, measured in gaze straight ahead with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

As in previous analyses, there was a significant main effect for the within-subjects factor *daytime*, $F(2, 16)=16.04$, $p<0.001$ (Figure 3.21), where average SPV decreased from -3.44 deg/s at 9am to -1.26 deg/s at 11am and -1.02 deg/s at 1pm. Scheffé post-hoc tests revealed that the difference between 9am and 11am ($p<0.01$) and between 9am and 1pm ($p<0.001$) was statistically significant, whereas the difference between 11am and 1pm was not significant ($p=0.87$).

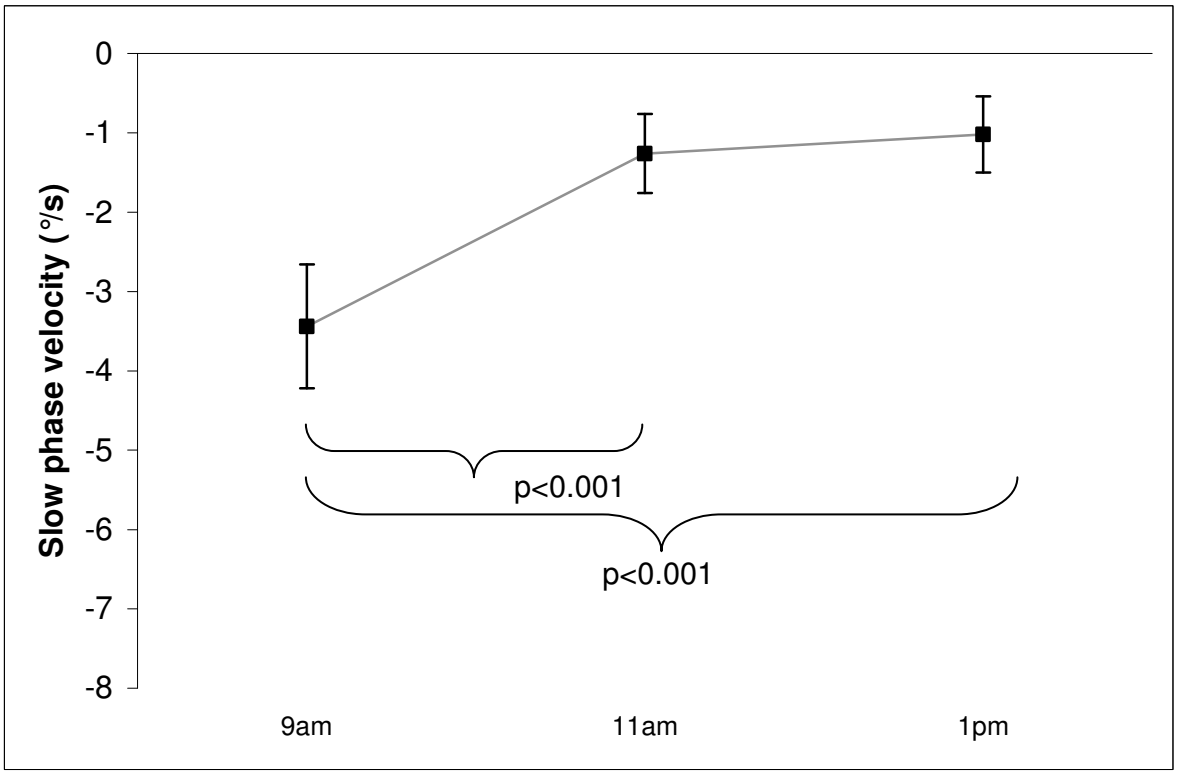
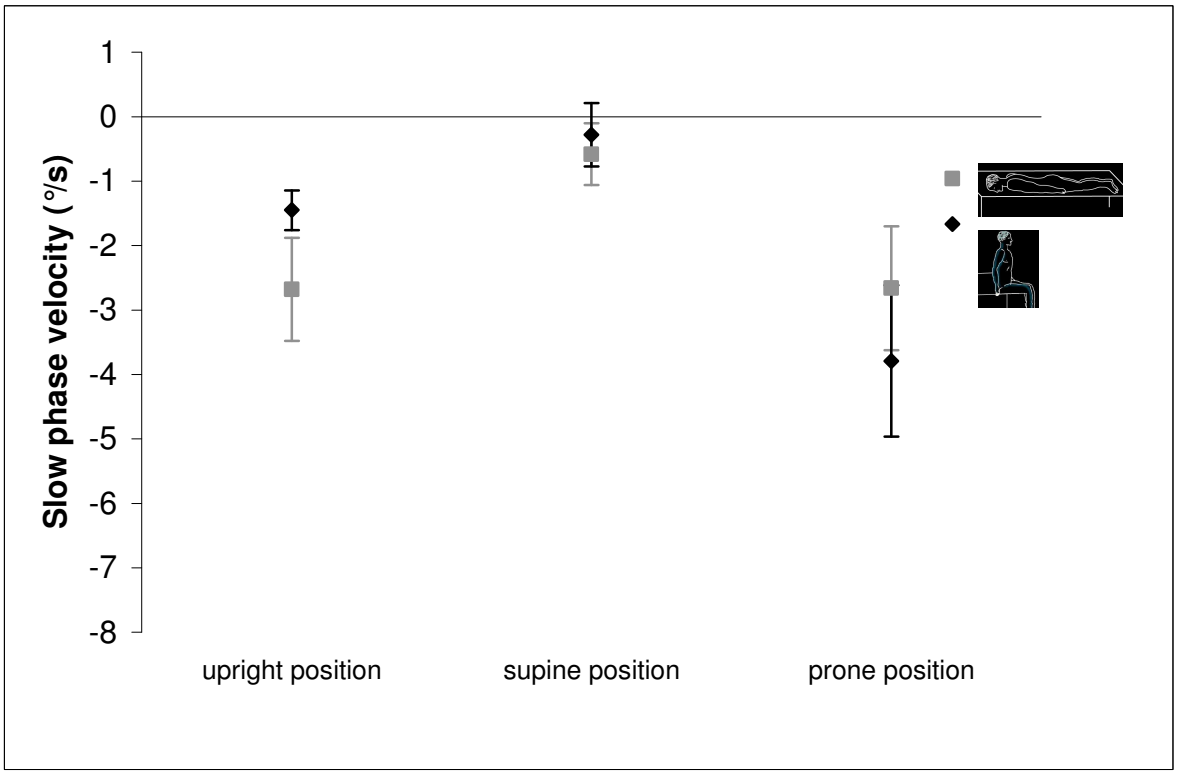


Figure 3.21 Daytime decrease in SPV across all three body positions and both intervals, measured in gaze straight ahead with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

Among the interactions, the *body orientation times interval* interaction became statistically significant, $F(2, 16)=10.46$, $p<0.01$ (Figure 3.22a). Although post-hoc Scheffé tests were not significant, the descriptive trend reveals that having rested in upright position is, during the test, associated with a lower average SPV-value in upright position (-1.45 deg/s) than in prone position (-2.68 deg/s, Scheffé: $p=0.1$), whereas having rested in prone position is, during the test, associated with a lower average SPV-value in prone position (-2.66) than in upright position (-3.79, Scheffé: $p=0.15$).



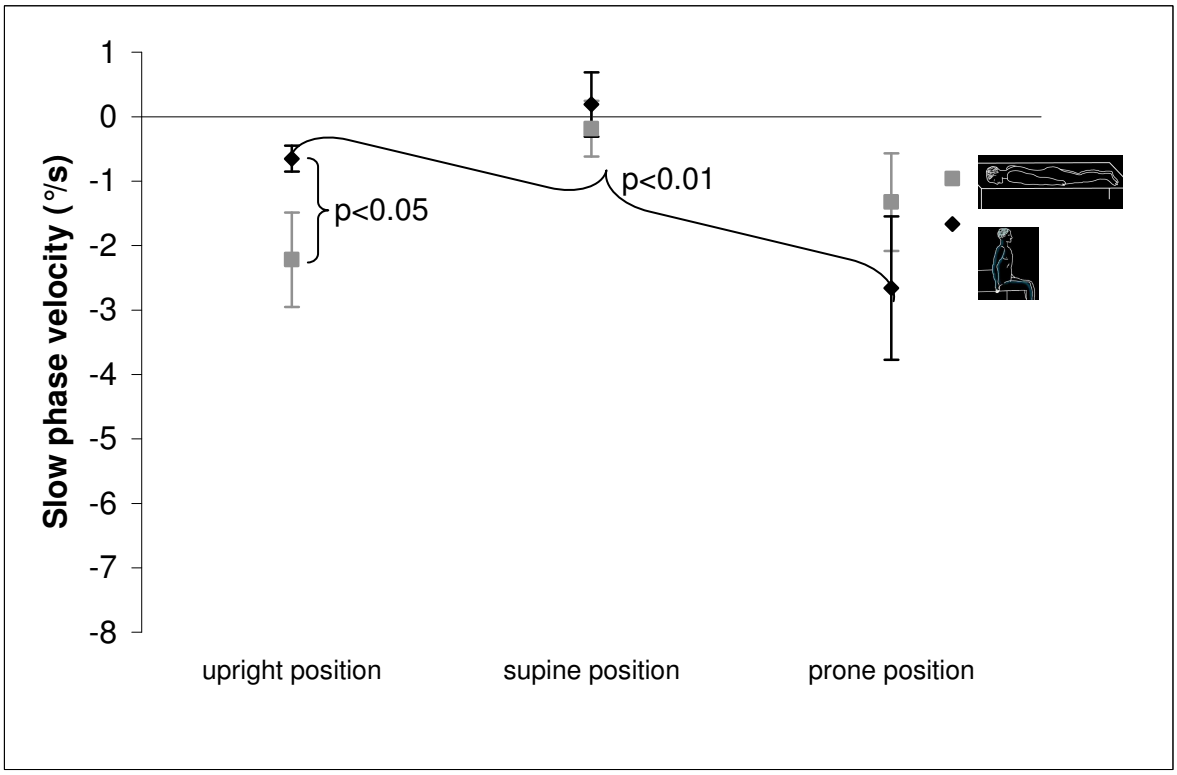


Figure 3.22a Comparing SPV differences across daytime (9am, 11am, 1pm) between the within subjects factors interval and position, measured in gaze straight ahead with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean, **b** The same comparison as 3.22a, but without the 9am measurements.

To have an additional comparison on how the measurements were influenced by the intervals, the measurement at 9am (prior to the first resting interval) was skipped and the results were analysed across 11am and 1pm. This step was carried out even though the 9am measurements prior to the prone position interval (-3.43 deg/s) and the upright position interval (-3.44 deg/s) were not significantly different from each other (p=1). The subsequent analysis (across 11am and 1pm) confirmed the earlier finding with a significant *body orientation times interval interaction*, $F(2, 16)=10.46$, $p<0.01$ (Figure 3.22b). Having rested in upright position is, during the test, associated with a lower average SPV-value in upright position (-0.65 deg/s) than in prone position (-2.66 deg/s, Scheffé: $p<0.01$), whereas having rested in prone position is, during the test, associated with a descriptively lower average SPV-value in prone position (-1.325) than in upright position (-2.22 deg/s, Scheffé: p=0.39). Likewise, when being measured in upright position, having previously rested in upright position is associated with a significantly lower average SPV-value (-0.65 deg/s) than having previously rested in prone position (-2.22 deg/s, Scheffé: $p<0.05$). When being measured in prone position, having previously rested in prone position (-1.325 deg/s) is associated with a marginally significant lower SPV-value than having rested in upright position (-2.66 deg/s, p=0.076).

Going back to the analysis where the 9am measurements were included, the remaining comparisons revealed that only the *body orientation times daytime* interaction became statistically significant, $F(4, 32)=7.02$, $p<0.001$ (Figure 3.23). At the 9am measurements, i.e. prior to the first resting interval, the average SPV-values in all three body positions (upright: -3.33 deg/s, supine: -1.3 deg/s, prone: -5.68 deg/s) are significantly different from each other, as Scheffé post-hoc comparisons revealed a difference of $p<0.01$ between upright and supine, $p<0.001$ between upright and prone and $p<0.000001$ between supine and prone. After the first resting interval, the decrease of SPV in prone position is relatively pronounced, so that the lines between the three body orientations appear almost parallel after the first resting interval (i.e. from 11am onwards, see Figure 3.23). When excluding the 9am measurements, the

significant *body orientation times daytime* interaction vanishes, F(2, 16)=0.38, p=0.69, though there is still a main effect of *body orientation*, F(2, 16)=4.15, p=0.035.

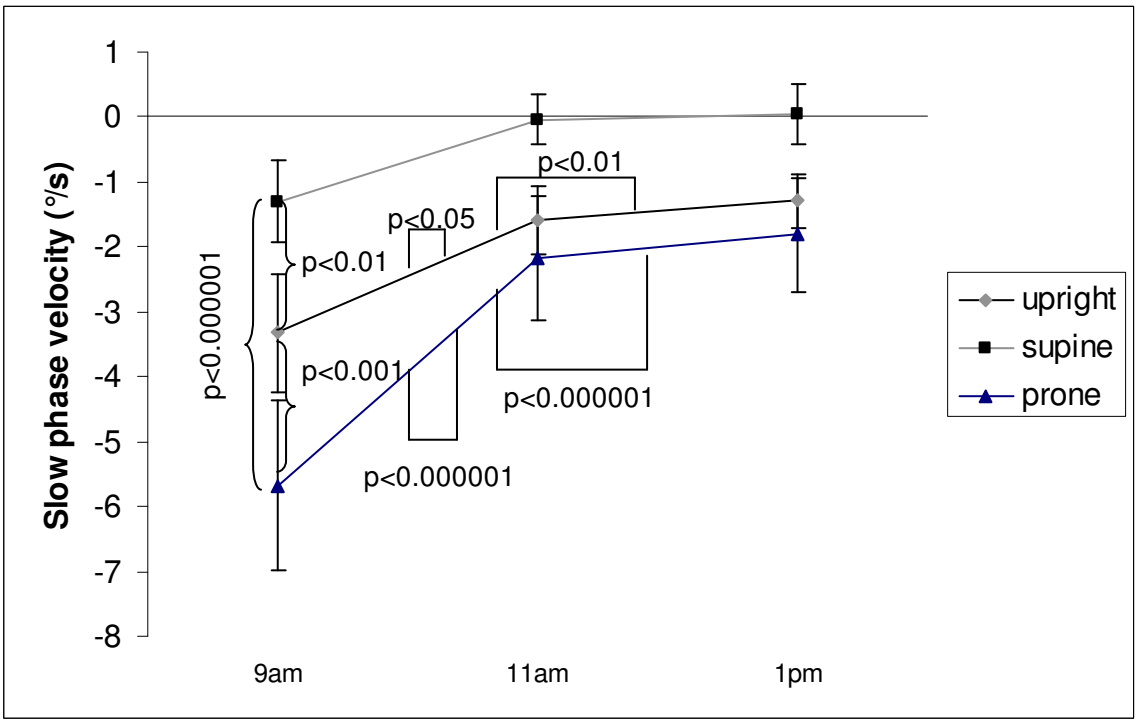


Figure 3.23 Comparing SPV differences across intervals between the within subjects factors body position and daytime, measured in gaze straight ahead and with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

Going back to the original analysis (i.e. the one that includes the 9am measurements), there were no further significant results. Neither the tests for *interval*, F(1, 8)=0.07, p=0.8, nor for the *interval times daytime* interaction, F(2, 16)=0.17, p=0.84, nor for the *body orientation times interval times daytime* interaction, F(4, 32)=0.95, p=0.45, approached statistical significance. With regard to the comparison between cerebellar patients and patients with unknown aetiology, cerebellar patients had an average SPV-value of -4.48 deg/s, whilst patients with unknown aetiology had an average SPV-value of -1.17 deg/s. This descriptive difference is not significant according to the Kolmogorov-Smirnov test (p>0.05).

3.4.3. Discussion

The majority of findings from part 3 of this study as well as the previous chapter were confirmed in part 4 of this study.

The first section of the analysis included the within subjects factor *light* (fixation versus viewing in the dark). Once more it was confirmed that the possibility to fixate (= the light is switched on) is associated with a lower DBN than no possibility to fixate (= the light is switched off). The same holds true for the confirmation of a daytime decrease in the intensity of DBN.

The second section of this analysis included the within subjects factor *gaze direction*. It confirmed earlier findings of a significant main effect for *gaze direction*, where upward gaze was associated with significantly lower SPV-values than downward gaze or gaze straight ahead. Although this finding is consistent with Alexander's law, it is interesting that downward gaze and gaze straight ahead did not significantly differ from each other. According to the descriptive findings, gaze straight ahead had even lower SPV-values than downward gaze, which is not entirely consistent with Alexander's law, where slow phase velocity decreases when gaze moves away from downward gaze (i.e. the direction of the fast phase, Jeffcoat et al., 2008; Robinson et al., 1984). As in the previous analyses, the intensity of DBN decreased throughout daytime.

The third section of this analysis included the within subjects factor *body orientation*. In line with previous findings, there was a significant main effect with regard to body orientation, with supine position being associated with the lowest intensity of DBN. However, only the difference between supine and prone position was statistically significant, whereas upright and supine position and upright and prone position were not significantly different from each other. As already known from the previous analyses, the intensity of DBN decreased in the course of the day. The vital comparison in part 2 of this study, however,

deals with the significant *body orientation times interval* interaction. Usually (e.g. part 1 of this study), being measured in upright position is associated with lower DBN intensity than being measured in prone position. Although this difference was not significant in the analysis of part 2, the descriptive trend again points into that direction. After the resting positions of the patients were varied between prone position and upright position, it turned out that having rested in upright position (compared to prone position) is associated with significantly lower SPV-values when being measured in upright position, but being measured in prone position can also lead to marginally significant lower SPV-values when having rested in prone position rather than in upright position. This is also reflected in the descriptive trend. The measurements in upright position are not necessarily linked to lower SPV-values than the measurements in prone position, as having rested in prone position can lead to descriptively lower SPV-values in the prone-position measurements than in the upright position measurements. When linking this result to part 2 of this chapter, where it was argued that rotation relative to the gravitational vector would be associated with higher DBN than no rotation, it becomes clear why a change from prone resting to upwards measurement can result in descriptively higher DBN than being measured in prone after having rested in prone, although prone position is usually associated with the highest intensity of DBN according to Marti et al. (2002). When being assessed in upright, supine and prone, the results are fully in line with Marti et al. (2002), and the results where different resting positions are tested (which was not subject to the Marti et al. (2002) paper), requires an adjustment in terms of otolithic influence that would be new, but could be subsumed under the explanation of gravity-dependent and gravity-independent components by Marti et al. (2002). The interesting finding of this study is that the resting position seems to have an influence on the intensity of DBN during the measurements. When considering practical applications of this finding, one could, for example, recommend patients to rest in upright position with the light switched off when they intend to do office work after the resting period. Alternatively, one could recommend

patients to rest in prone position when they intend to work in prone position, swim in prone position, get a massage or do gymnastics in prone position after the resting period. The third section of this analysis also revealed a significant *body orientation times daytime* interaction, but this interaction is mainly due to differences between the three body positions at the 9am measurements. When excluding the 9am measurements and focusing on the measurements that were preceded by the different resting intervals, the significant interaction vanishes.

Only a nonparametric comparison between patients with cerebellar and unknown aetiologies was carried out, because the number of two cerebellar patients was considered too low to carry out a parametric comparison. Although not significant according to the nonparametric Kolmogorov-Smirnov test, it has to be acknowledged, though, that the descriptive trend indicates that patients with cerebellar aetiology appear to have stronger symptoms of DBN as expressed by a larger average SPV.

Having looked at the influence of prone position versus upright position during the resting intervals, it will now be interesting to look at other positional effects. In part 3 of this study, supine position and upright position are compared with each other.

3.5. Replicating the study on daytime dependence of downbeat nystagmus mediated by upward versus supine resting position (part 5)

Having compared upright versus prone resting positions in the previous part, the following comparison will deal with upright versus supine resting positions.

3.5.1. Methods

The method of part 5 overlaps one to one with the method of parts 3 and 4. The only differences are with respect to the participants and the intermission between testing.

3.5.1.1. Patients

In part 5, a total number of 10 participants were tested. In the intermissions between testing, they rested in either supine position or upright position. In both cases, the light was switched off, i.e. they rested in darkness. All patients were identical to parts 2 and 4, with the addition of another patient (patient No. 10) who had already participated in parts 1 and 3, so that nine out of ten patients were already present in parts 2 and 4 and six patients in parts 1 and 3. There is a reason why there was one more patient in this part. Actually, it was planned to measure this patient in all three positions: upright, supine and prone. After measuring him in upright and supine position, however, he indicated that he was feeling unwell. Therefore, the measurement in prone position was not carried out anymore. Consequently, none of the comparisons between prone position and another position included this patient. Due to the progress of the patient's disease, it was considered unethical to ask him to return to the hospital for another test in prone position. The mean duration of DBN was 6.81 years (range 3-17 years, see Table 3.5). The patients were 44 to 82 years old, with a mean of 65.5 years and a standard deviation of ± 9.31 years. Patients No. 7 and No. 8 had already participated in the study of the previous chapter. All other factors and clinical examinations were identical to the study in the previous chapter and parts 1 to 4 of this study.

Table 3.5 Clinical data of the patients with DBN where upright and supine positions in darkness were compared with each other

No./Sex/ Age	Neuro-ophthalmological findings	MRI findings	Aetiology	Disease duration
No. 1M, 64	Disturbed visual fixation suppression of VOR, non-existing upright opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally.	Cerebellar atrophy	Cerebellar de-generation	3 years
No. 2F, 69	Disturbed visual fixation suppression of VOR, impaired horizontal and upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally, provocation DBN.	Cerebellar atrophy	Idiopathic cerebellar ataxia	17 years
No. 3M, 69	Deviant SVV, impaired horizontal and downward pursuit, saccades with rebound after gaze to the right, provocation DBN.	Normal	Unknown	4.5 years
No. 4F, 60	Disturbed visual fixation suppression of VOR, DBN overran horizontal opto-kinetic nystagmus, non-existing upward opto-kinetic nystagmus, deviant SVV, impaired horizontal and downward pursuit.	Normal	Unknown	12 years
No. 5F, 61	Disturbed visual fixation suppression of VOR, deviant SVV, provocation DBN, vertical saccades and saccades to the left.	Normal	Unknown	5 years
No. 6M, 44	Disturbed visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and vertical pursuit.	Normal	Unknown	10 years
No. 7M, 65	Impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, hypometric upward saccades.	Normal	Unknown	10 years
No. 8F, 69	Disturbed vertical visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit.	Normal	Unknown	3 years
No. 9F, 72	Disturbed visual fixation suppression of VOR, impaired horizontal and non-existing upward opto-kinetic nystagmus, impaired horizontal and downward pursuit.	Normal	Unknown	6 years
No. 10M, 82	Deviant SVV, non-existing upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, provocation downward nystagmus.	Normal	Unknown	3.5 years

VOR = vestibulo-ocular reflex; SVV = subjective visual vertical axis, HTT = head-thrust test developed by Halmagyi and Curthoys (1988).

3.5.1.2. Recording of eye movements

Patients were tested three times on a single day. Each time, patients were monitored in the following sequence: (see Figure 3.24).

1. they were sitting in upright position, 2. they were lying in supine position, 3. they were lying in prone position. In the intermissions between testing, people rested in supine position and upright position, in both cases with the light switched off. The same patients were measured in supine position and upright position, i.e. they came to the hospital twice with a delay of approximately one week between these two measurements. The VOG-measurements were identical to those in the previous chapter and in parts 1 to 4 of this chapter.

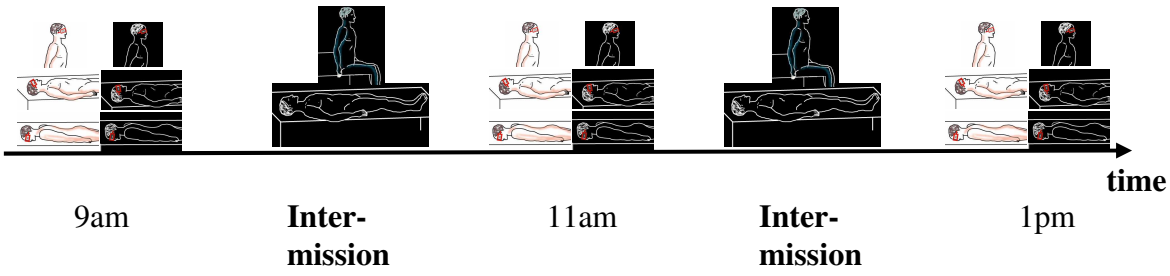


Figure 3.24. An overview describing the testing conditions for all patients. The eye movements of the patients were monitored in the following order: 1. sitting in upright position in light/dark, 2. lying in supine position in light/dark, 3. lying in prone position in light/dark. All measurements took place at 9am, 11am, and1pm. In between the measurements, patients were lying in supine position or sitting in upright position, in both cases with the light switched off.

3.5.1.3. Data acquisition and calibration

Data acquisition and calibration was identical to the previous chapter and parts 1 to 4 of this chapter.

3.5.1.4. Statistical data analysis

The statistical analysis consisted of repeated measurement ANOVAs (Statistica 6.1, Statsoft, Tulsa OK, USA) with post-hoc Scheffé tests for individual comparisons. The dependent variable was slow phase velocity (SPV). The first analysis consisted of the within subjects factors *light* (light on = fixation is possible versus light off = viewing in the dark with no possibility to fixate), *interval* (resting in supine position with the light switched off versus resting in upright position with the light switched off) and *daytime* (9am, 11am, 1pm). The second analysis consisted of the within subject factors *gaze condition* (straight, upwards, downwards), *interval* (resting in supine position with the light switched off versus resting in upright position with the light switched off) and daytime (9am, 11am, 1pm). The third analysis had the within subject factors *body orientation* (upright, supine and prone), *interval* (resting in supine position with the light switched off versus resting in upright position with the light switched off) and *daytime* (9am, 11am, 1pm). Due to the low number of patients with cerebellar symptoms, the previously explained nonparametric Kolmogorov-Smirnov test for two independent samples was applied. The two independent groups were the two different aetiologies (cerebellar patients versus patients with unknown aetiology). The two groups were compared with respect to their overall SPV-values.

3.5.2. Results

3.5.2.1. First section including the within subjects factor fixation versus viewing in the dark

As in the previous chapter, the analysis revealed a significant main effect for the within-subjects factor *light*, $F(1, 9)=16.04$, $p<0.01$ (Figure 3.25), where fixation on target (= light

switched on) resulted in lower average SPV-values than viewing in the dark (-1.84 deg/s vs. -3.09 deg/s).

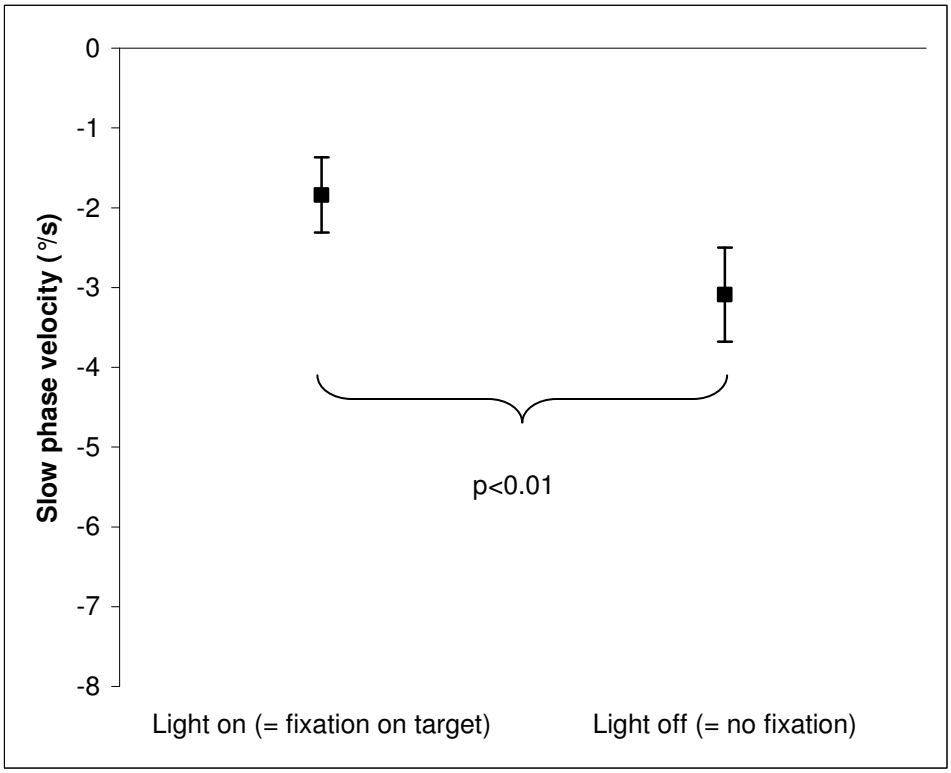


Figure 3.25 Comparing SPV between light (= patients have the ability to fixate) and darkness conditions (= patients cannot fixate) across both intervals (resting upright versus supine) and time (9am, 11am, 1pm), measured in upright position with gaze straight ahead. Display of mean slow phase velocities along with the standard error bars of the mean.

Consistent with the previous study and the previous parts of this study, there was a significant daytime decrease in SPV-values, $F(2, 18)=10.33$, $p<0.01$ (Figure 3.26), where average SPV decreased from -3.92 deg/s at 9am to -1.69 deg/s at 11am and -1.79 deg/s at 1pm. Scheffé post-hoc tests revealed that the decrease from 9am to 11am and from 9am to 1pm each had a p-value of $p<0.01$. There was no significant difference between 11am and 1pm ($p=0.98$). Note that the descriptive trend shows lower SPV-values at 11am than at 1pm.

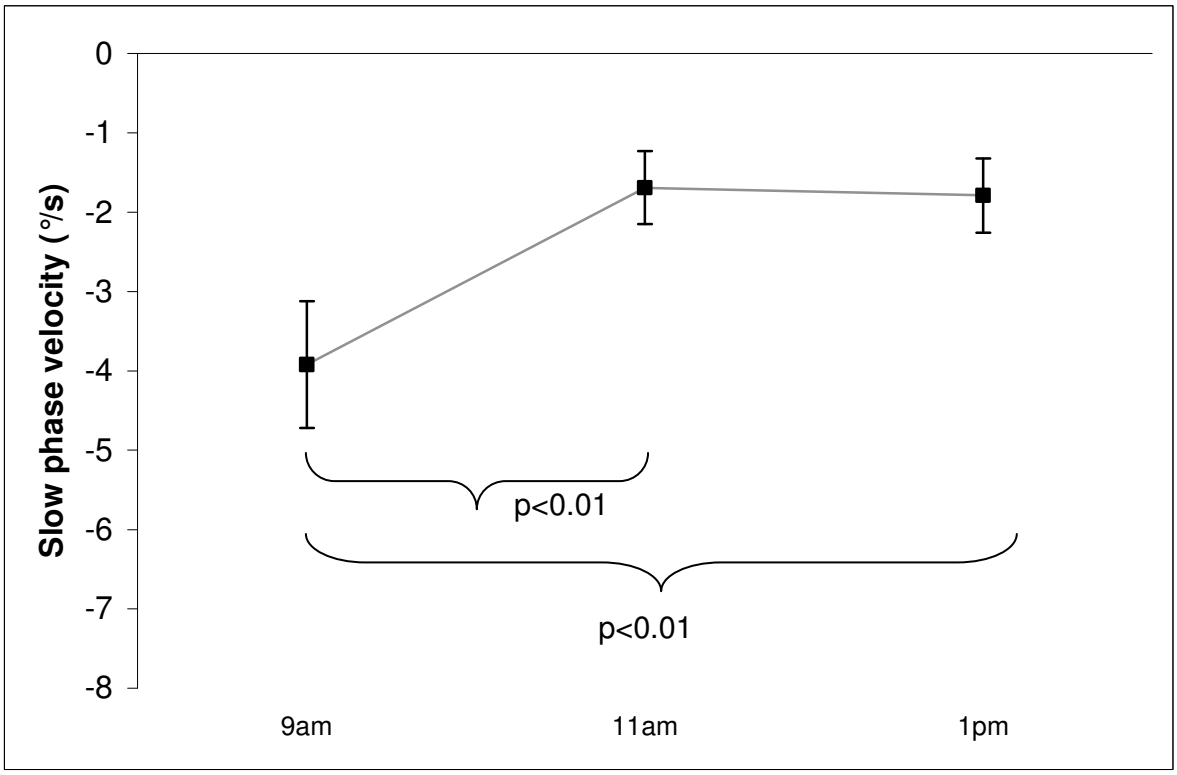


Figure 3.26 Daytime decrease in SPV across both light conditions and both intervals, measured in upright position with gaze straight ahead. Display of mean slow phase velocities along with the standard error bars of the mean.

Additional significant findings included a *light times daytime* interaction, where the SPV-decrease from 9am to 11am was steeper when the measurement took place in darkness (= with no possibility to fixate) than with the light switched on (= with the possibility to fixate), $F(2, 18)=9.63$, $p<0.01$ (Figure 3.27). As revealed by Scheffé post-hoc comparisons, the decrease from 9am to 11am and from 9am to 1pm with the light switched on (each $p<0.001$) as well as the decrease from 9am to 11am and from 9am to 1pm with the light switched off (each $p<0.000001$) were statistically significant. Whilst there was a significant difference between both 9am measurements (-2.88 deg/s with the light switched on versus -4.96 deg/s with the light switched off, Scheffé: $p<0.00001$), the 11am and 1pm measurements did not differ from each other (Scheffé: $p>0.05$).

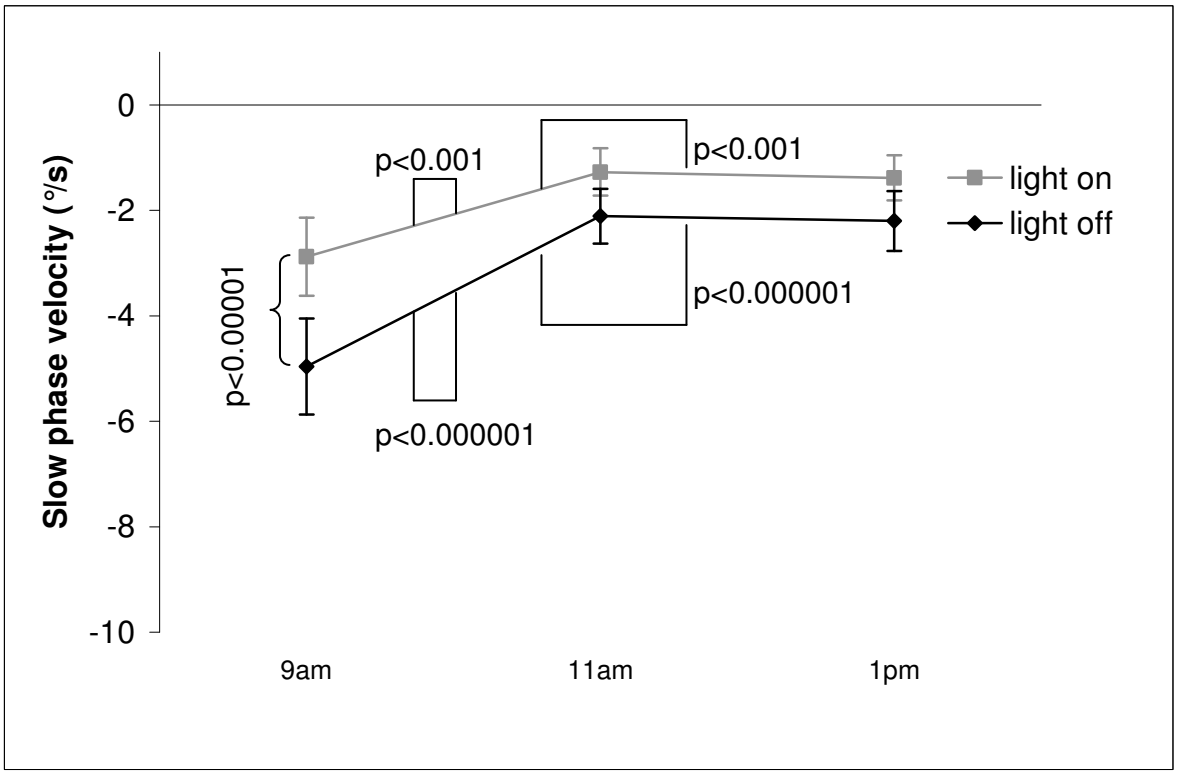


Figure 3.27 Daytime decrease in SPV between the within subjects factors light and daytime and across both intervals, measured in upright position with gaze straight ahead. Display of mean slow phase velocities along with the standard error bars of the mean.

If the 9am measurements were excluded, the lines looked almost parallel (see Figure 3.27). This apparent absence of a *light times daytime* interaction was confirmed in the analysis where the 9am measurements were excluded, $F(1, 9)=0{,}0025$, $p=0.96$, so that only a main effect for *light* was present, $F(1, 9)=8.53$, $p<0.05$. Going back to the original analysis (including the 9am measurements), there was a significant *interval times daytime* interaction, $F(2, 18)=4.76$, $p<0.05$ (Figure 3.28). The 9am measurements prior to both intervals were almost identical (-3.91 deg/s prior to the supine interval and -3.93 deg/s prior to the upright interval, Scheffé: $p=1$), but the decrease in SPV appeared steeper following the resting interval in upright position than in supine position (Figure 3.28). When the resting interval was in upright position, the decrease from 9am to 11am ($p<0.0001$) and from 9am to 1pm ($p<0.00001$) was statistically significant, whilst there was no significant difference between 11am and 1pm ($p=0.999$). When the resting interval was in supine position, the decrease from

9am to 11am ($p<0.01$) and from 9am to 1pm ($p<0.05$) was statistically significant, whilst there was no significant difference between 11am and 1pm ($p=0.94$). Comparing the 11am measurements after the upright interval (-1.27 deg/s) and the supine interval (-2.11 deg/s) did not yield a significant result (Scheffé: $p=0.26$), whereas the 1pm measurements after the upright interval (-1.12 deg/s) and the supine interval (-2.46) were significantly different from each other (Scheffé: $p<0.05$). Excluding the 9am measurements made this *interval times daytime* interaction vanish, $F(1, 9)=1.26$, $p=0.29$ and resulted in a marginally significant main effect for *interval*, $F(1, 9)=4.63$, $p=0.06$ and no significant main effect for *daytime*, $F(1, 9)=0.11$, $p=0.75$.

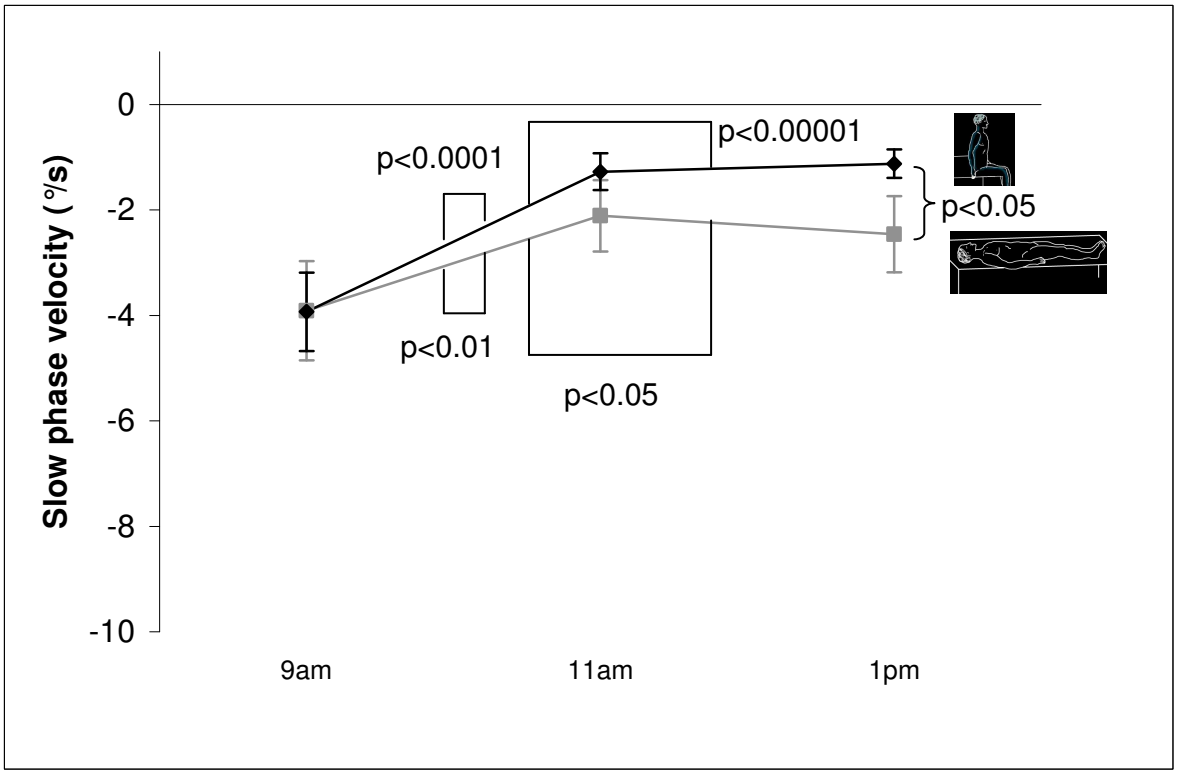


Figure 3.28 Daytime decrease in SPV between the within subjects factors interval and daytime and across both light conditions, measured in upright position with gaze straight ahead. Display of mean slow phase velocities along with the standard error bars of the mean.

Going back to the analysis that included the 9am measurements, none of the other statistical tests of this analysis became significant, neither the main effect with regard to the within subjects factor *interval*, $F(1, 9)=2.27$, $p=0.17$, nor the test for the *light times interval*

interaction, F(1, 9)=2.37, p=0.16, nor the test for the *light times interval times daytime* interaction, F(2, 18)=0.09, p=0.91. With regard to the comparison between cerebellar patients and patients with unknown aetiology, cerebellar patients had an average SPV-value of -4.71 deg/s, whilst patients with unknown aetiology had an average SPV-value of -1.905 deg/s. This descriptive difference is not significant according to the Kolmogorov-Smirnov test (p>0.05).

3.5.2.2. Second section including the within subjects factor gaze direction

As in previous analyses, it turned out that there was a main effect with respect to the within subjects factor *gaze direction*, F(2, 18)=12.42, p<0.001 (Figure 3.29), where Scheffé post-hoc tests revealed that gaze upwards (+0.19 deg/s, i.e. with a trend towards UBN) was associated with significantly lower average SPV values than gaze straight ahead (-1.84 deg/s) and gaze downwards (-1.87 deg/s), (both Scheffé post-hoc tests: p<0.01), whereas gaze straight ahead and downwards did not significantly differ from each other (p=1).

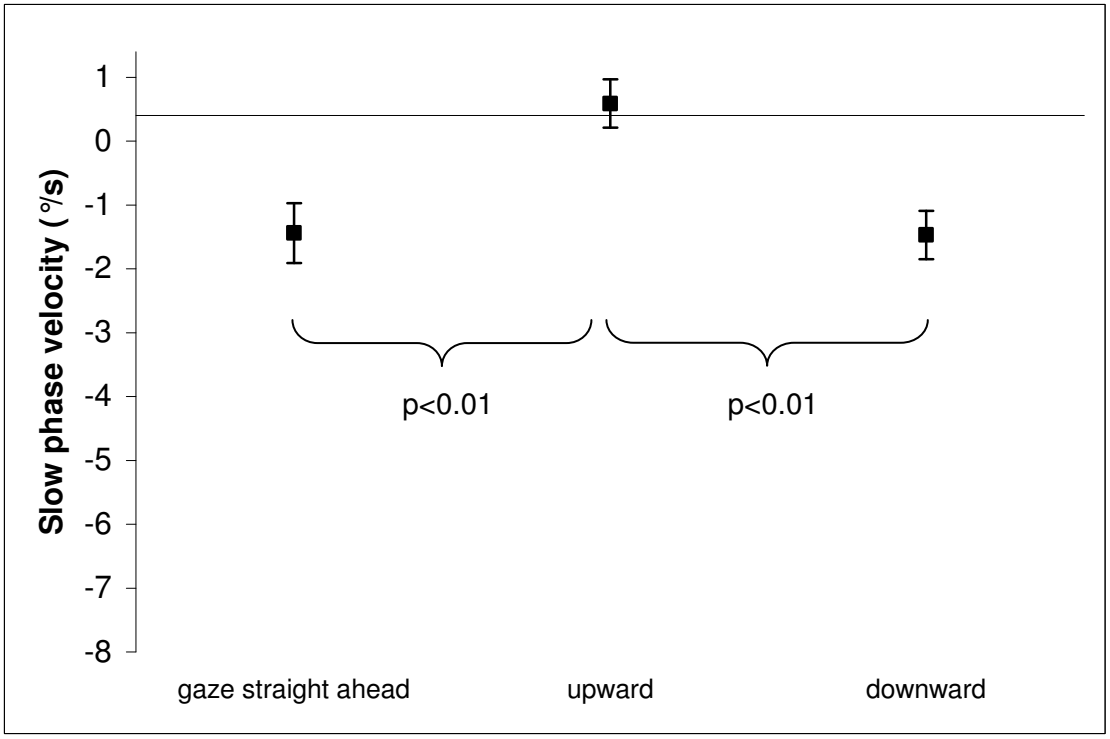
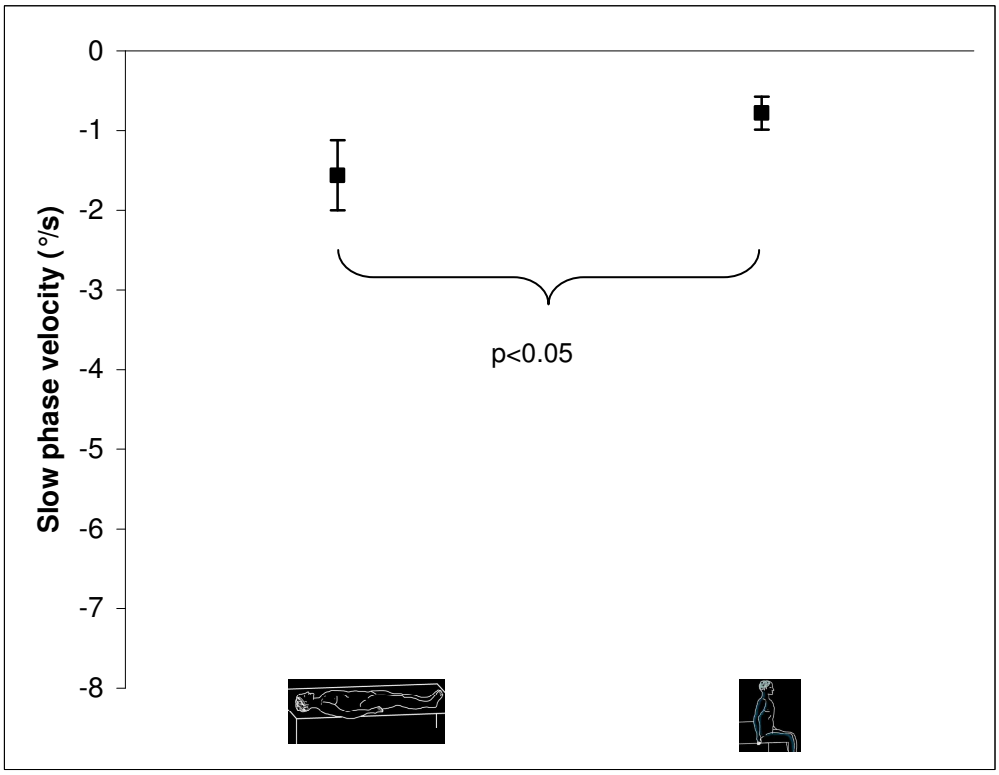


Figure 3.29 Comparing SPV across both intervals and daytime between gaze straight ahead, upward and downward, measured in upright position with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

In addition, there was a significant main effect of the within subjects factor *interval*, $F(1, 9)=6.23$, $p<0.05$ (Figure 3.30a), where having rested upright position was associated with a significantly lower average SPV (-0.78 deg/s) than having rested in supine position (-1,56 deg/s). Because the 9am measurements (before any resting intervals had taken place) have an indirect influence on the results and because they were not the same prior to the upright resting interval (-1.81 deg/s) and the supine resting interval (-2.34 deg/s), an additional analysis was carried out where the 9am measurements were skipped. This step was taken even though Scheffé post-hoc tests had not revealed a significant difference between these two 9am measurements ($p=0.59$). The analysis excluding the 9am measurements confirmed the main effect of the within subjects factor *interval*, $F(1, 9)=7.6$, $p<0.05$ (Figure 3.30b), where having rested in upright position was associated with a significantly lower average SPV (-0.27 deg/s) than having rested in supine position (-1,17 deg/s).



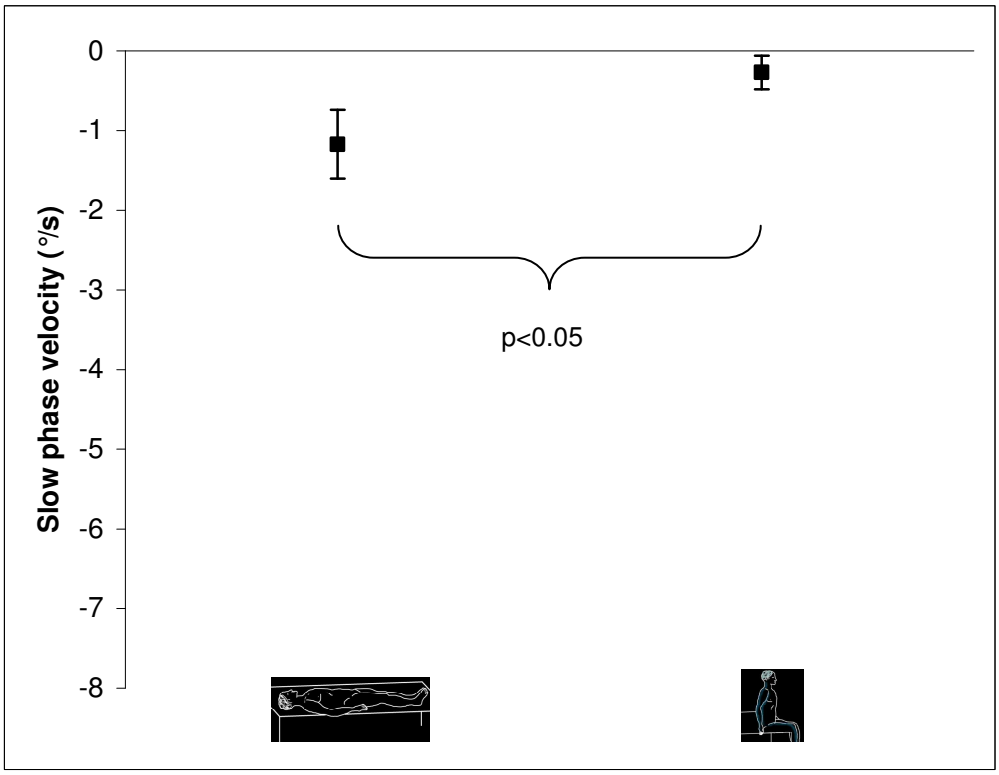


Figure 3.30a Comparing SPV between the resting intervals supine position and upright position, across all gaze directions and time (9am, 11am, 1pm), measured in upright position with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean, **b** The same comparison as 3.30a, but without the 9am measurements.

Going back to the findings where the 9am measurements were included, the analysis revealed a significant daytime decrease in SPV-values, $F(2, 18)=7.13$, $p<0.01$ (Figure 3.31), where average SPV decreased from -2.07 deg/s at 9am to -0.73 deg/s at 11am to -0.72 deg/s at 1pm. Scheffé post-hoc tests revealed that the decrease from 9am to 11am and from 9am to 1pm each had a p-value of $p<0.05$. There was no significant difference between 11am and 1pm ($p=1$).

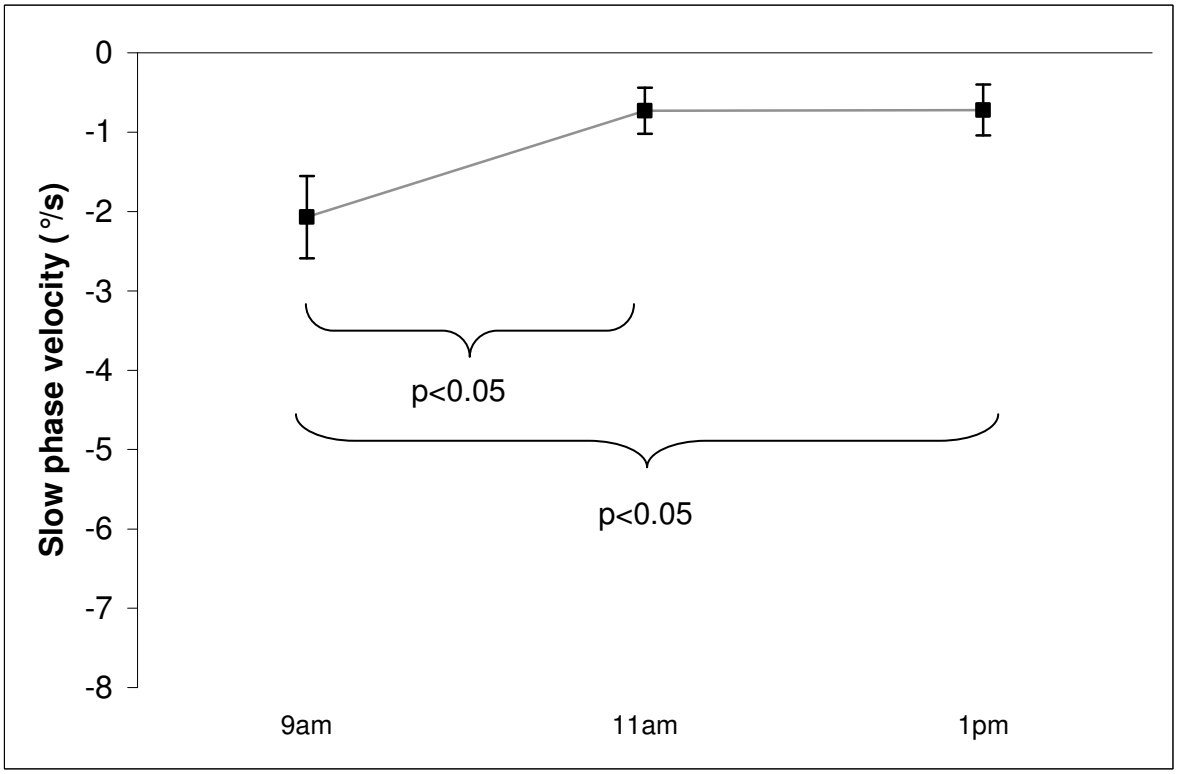


Figure 3.31 Daytime decrease in SPV across all three gaze conditions and both intervals, measured in upright position with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

There were no significant results when testing for interactions, neither for the *gaze times interval* interaction, $F(2, 18)=0.98$, $p=0.39$, nor for the *gaze times daytime* interaction, $F(4, 36)=0.77$, $p=0.55$, nor for the *interval times daytime* interaction, $F(2, 18)=0.99$, $p=0.39$, nor for the *gaze times interval times daytime* interaction, $F(4, 36)=2.08$, $p=0.1$. With regard to the comparison between cerebellar patients and patients with unknown aetiology, cerebellar

patients had an average SPV-value of -2.72 deg/s, whilst patients with unknown aetiology had an average SPV-value of -0.79 deg/s. This descriptive difference is not significant according to the Kolmogorov-Smirnov test ($p>0.05$).

3.5.2.3. Third section including the within subjects factor body orientation

Consistent with previous findings, the analysis with respect to *body orientation* resulted in a significant main effect, $F(2, 18)=8.09$, $p<0.01$ (Figure 3.32). The Scheffé post-hoc comparisons between upright (-1.84 deg/s), supine (-0.47 deg/s) and prone (-3.51 deg/s) revealed that only the difference between supine and prone position was statistically significant ($p<0.01$). Comparing upright and supine position ($p=0.22$) and upright and prone position ($p=0.12$) did not yield a significant finding.

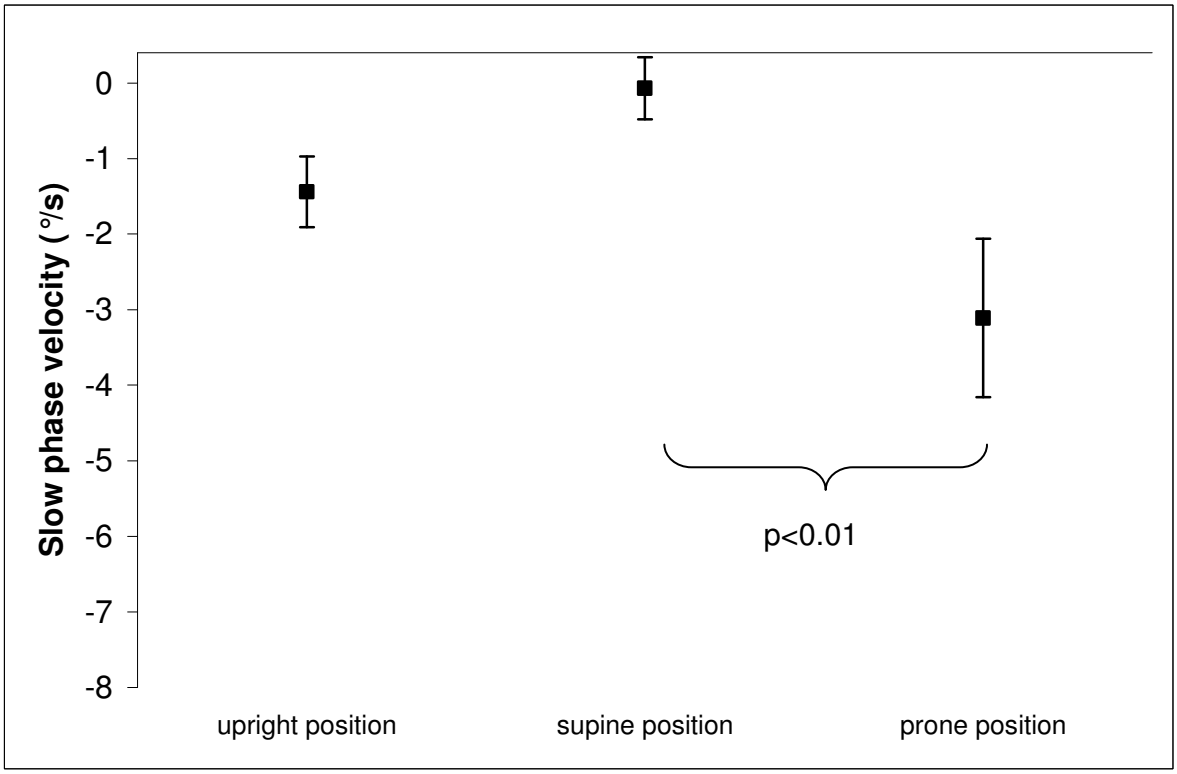


Figure 3.32 Comparing SPV between upright, supine and prone positions, across both intervals and daytime, measured in gaze straight ahead and with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

As in previous analyses, there was a significant main effect for the within-subjects factor *daytime*, F(2, 18)=9.14, p<0.01 (Figure 3.33), where average SPV decreased from -3.24 deg/s at 9am to -1.285 deg/s at 11am and -1.29 deg/s at 1pm. Scheffé post-hoc tests revealed that the difference between 9am and 11am and from 9am to 1pm were both statistically significant (p<0.01), whereas the difference between 11am and 1pm was not significant (p=1).

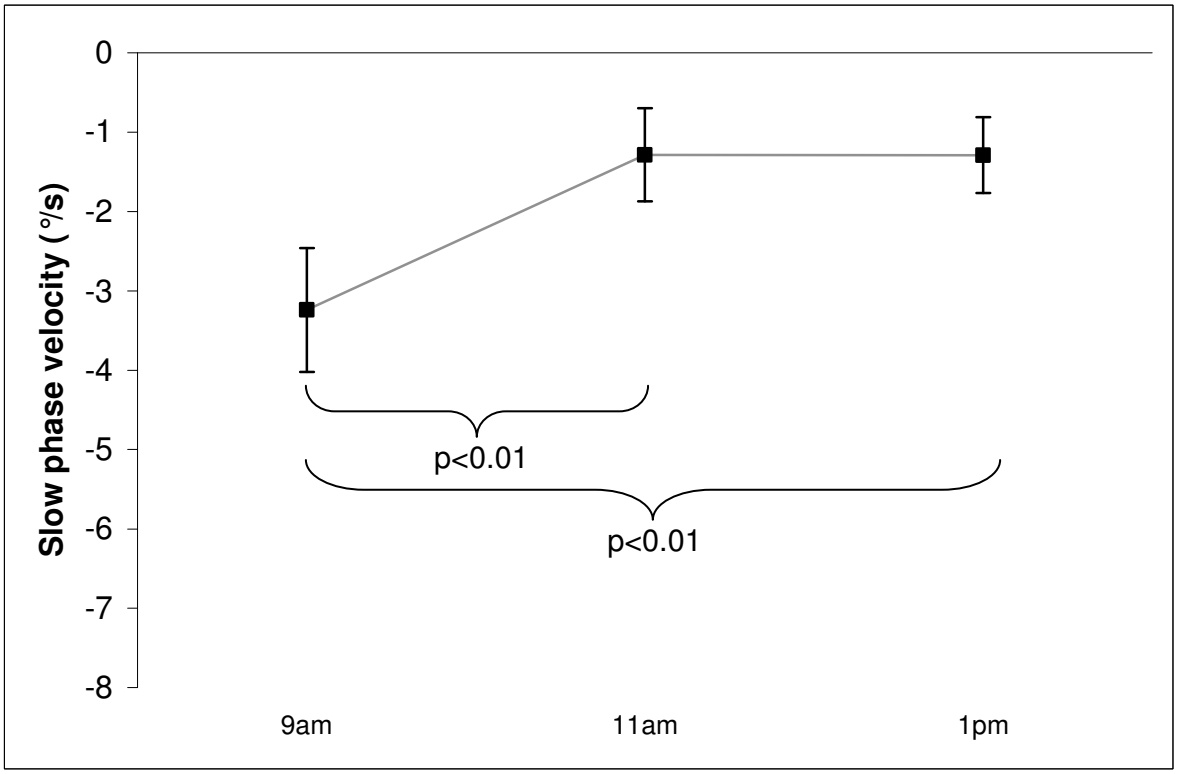


Figure 3.33 Daytime decrease in SPV across all three body positions and both intervals, measured in gaze straight ahead and with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

Among the other tests, there was no significant main effect for the within subjects factor *interval*, F(1, 9)=0.93, p=0.36. Testing possible interactions revealed a marginally significant *body orientation times interval* interaction, F(2, 18)=3.11, p=0.07, a marginally significant *body orientation times daytime* interaction, F(4, 36)=2.52, p=0.06 and a marginally significant *body orientation times interval times daytime* interaction, F(4, 36)=2.135, p=0.096. Testing

the *interval times daytime* interaction did not result in a significant finding, $F(2, 18)=0.74$, $p=0.49$. The comparison of interest in this chapter deals with the resting position during the intervals between testing. Because the *body orientation times interval* interaction was marginal and because the 9am measurements have an indirect influence on the results (even though no resting interval had taken place yet at this time of measurement), their SPV-values prior to the resting intervals were compared with each other. The 9am measurement prior to resting in supine position had an average SPV-value of -3.35 deg/s, whereas the 9am measurement prior to resting in upright position had an average SPV-value of -3.13 deg/s. Although these values are almost the same (Scheffé: $p=0.99$), they could have an indirect influence, so that a marginally significant finding may turn out significant. As a result, an additional analysis was carried out excluding the 9am measurements. This analysis ensured that only SPV-values were considered that were assessed after the resting intervals. This new analysis indeed revealed that there was a significant *body orientation times interval* interaction, $F(2, 18)=7.04$, $p<0.01$ (Figure 3.34). In upright position measurements, having previously rested in upright position is associated with a lower average SPV (-0.63 deg/s) than after having previously rested in supine position (-2.01 deg/s, Scheffé: $p<0.05$). In supine position measurements, having previously rested in supine position (-0.31 deg/s) and having rested in upright position (+0.23 deg/s) show similar average SPV-values (Scheffé: $p=0.77$). When having rested in supine position, the average SPV-values in the supine measurements (-0.31 deg/s) are significantly lower than in the upright measurements (-2.01 deg/s, Scheffé: $p<0.01$). When having rested in upright position, the average SPV-values in upright measurements (-0.63 deg/s) and in supine measurements (+0.23 deg/s) do not significantly differ from each other (Scheffé: $p=0.33$). It is interesting that having rested in upright position even shows a slight descriptive trend towards an upbeat nystagmus.

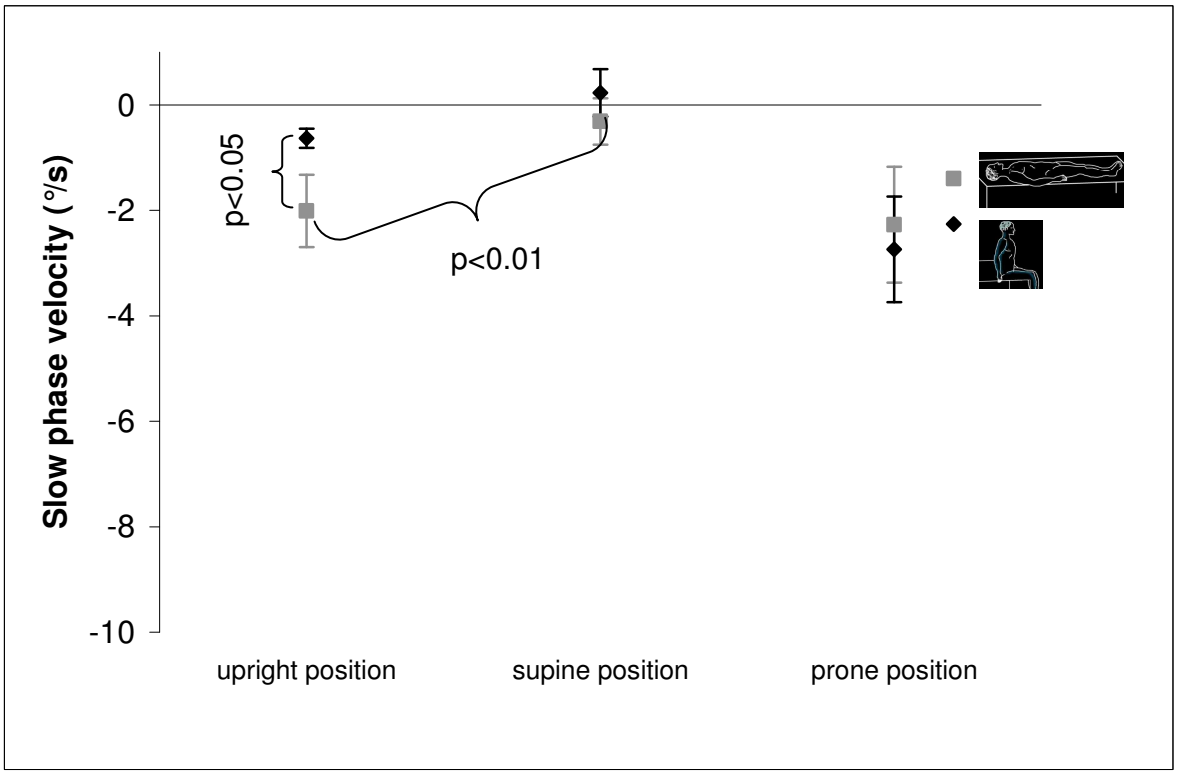


Figure 3.34 Comparing SPV differences between the within subjects factors interval and position across daytime (11am and 1pm), measured in gaze straight ahead and with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

Having rested in either supine or upright position does not seem to influence the measurements in prone position, as Scheffé post-hoc tests revealed a p-value of p=0.87 when comparing the two different resting intervals with respect to prone position measurements. With regard to the comparison between cerebellar patients and patients with unknown aetiology, cerebellar patients had an average SPV-value of -4.74 deg/s, whilst patients with unknown aetiology had an average SPV-value of -1.24 deg/s. This descriptive difference is not significant according to the Kolmogorov-Smirnov test (p>0.05).

3.5.3. Discussion

The first section of part 5 predominantly confirmed the results of earlier analyses. The possibility to fixate (i.e. when the light is turned on during the measurements) is associated

with lower SPV-values than viewing in the dark (i.e. when the light is turned off during the measurements and patients therefore lack the chance to suppress DBN by fixation). Moreover, it was shown that there is a daytime decrease of DBN intensity. New results included the *light times daytime* interaction, which was due to the fact that the 9am measurements in darkness were significantly more negative than the 9am measurements with the light switched on. After the first resting interval, this resulted in a steeper decrease of SPV-values for the measurements in darkness than for the measurements with the light switched on. When excluding the 9am measurements, however, this interaction vanished and the lines looked almost parallel. Therefore, one should not over-interpret this interaction. It could be due to chance. The explanation of sleep-inertia could also account for this interaction (see previous chapter), where it would take the Purkinje-cells up to a few hours to adapt to their full functioning. Whilst the possibility to fixate might suppress these effects, no possibility to fixate (i.e. when tested in darkness) could result in more severe DBN symptoms particularly in the morning hours. It needs to be kept in mind that, the hypothesis with regard to sleep inertia is just one possible explanation. Another significant interaction was the *interval times daytime* interaction. In this interaction, the 9am measurements prior to both resting intervals (supine versus upright) were almost identical, but the decrease in SPV was steeper following the resting interval in upright position than in supine position. This significant interaction was indirectly influenced by the 9am measurements, where no resting interval had been taken place yet. Therefore, the 9am measurements were excluded in a further analysis, which made this *interval times daytime* interaction vanish. Although the lines between resting intervals in supine and upright position looked almost parallel following this step, the exclusion of the 9am measurements did not create a significant main effect with regard to interval (though resting in upright position was associated with marginally significant lower SPV-values than resting in supine position). Consequently, there is a tentative trend towards favouring the upright position. The formerly significant *interval times daytime* interaction was

predominantly due to a steeper decrease in SPV-values following the interval in upright position. This explanation would make sense because people were measured in upright position, so an upright resting position would have resulted in a lower number of gravitational changes on the day of testing.

The second section of part 5 of this study also confirmed earlier findings. Upward gaze is associated with significantly lower SPV-values than gaze straight ahead and downward gaze, whereas gaze straight ahead and downward gaze do not differ in terms of their SPV-values. In addition, there is a daytime decrease of DBN intensity. What was only a tentative sign in the first section turned out to be a significant effect in the second section of part 5. There was a significant main effect with respect to the within subjects factor *interval*. As far as the SPV-values and therefore DBN intensity was concerned, patients had less symptoms after having rested in upright position than after having rested in supine position.

As in previous analyses, the third section of part 5 of this study revealed a significant main effect of the within subjects factor *body orientation*. From a descriptive point of view, supine position had the lowest SPV-values followed by upright position and prone position, but only the difference between supine and prone position was statistically significant. Also known from previous analyses, the intensity of DBN decreased during daytime. Although the *body orientation times interval* interaction only became marginally significant, it has to be kept in mind that the data included the 9am measurements. These measurements had taken place even before the first resting interval occurred. Consequently, an additional analysis was carried out, where the 9am measurements were not taken into consideration and where only those SPV-values were included that were assessed after the resting intervals. It turned out that there was a significant *body orientation times interval* interaction. When upright position measurements were carried out, having previously rested in upright position was associated with a lower DBN intensity than having previously rested in supine position. However, when having rested in upright position, the SPV-values in upright measurements and in supine

measurements do not differ from each other significantly. In supine position measurements, having previously rested in supine position and having rested in upright position showed a similar intensity of DBN. When having rested in supine position, however, the SPV-values in the supine measurements are significantly lower than in the upright measurements.

As hypothesised in parts 2 and 4 of this study, when being measured in upright position, it is better to have previously rested in upright position than to have previously rested in supine position. When comparing the two different resting positions prior to supine measurements, there is no significant difference, but DBN in supine measurements is less pronounced than in upright measurements when having previously rested in supine position. These results are in line with the assumption that a rotation relative to the gravitational vector makes the intensity of DBN worse than no rotation.

Only a nonparametric comparison between patients with cerebellar and unknown aetiologies was carried out, because the number of two cerebellar patients was considered too low to carry out a parametric test with the between subjectes factor *aetiology*. Although the nonparametric Kolmogorov-Smirnov tests were not significant, the descriptive trend shows that patients with cerebellar aetiology appear to have stronger symptoms of DBN.

3.6. Replicating the study on daytime dependence of downbeat nystagmus mediated by prone versus supine resting positions (part 6)

Having compared upright resting position with prone and supine resting positions individually, prone and supine resting positions will now be compared with each other.

3.6.1. Methods

The method of part 6 overlaps one to one with the method of parts 1 to 5. The only differences are with respect to the participants and the intermission between testing.

3.6.1.1. Patients

All patients were identical to the ones tested in parts 2 and 4. An overview is provided in Table 3.6. In part 6, a total number of 9 participants were tested at 9am, 11am and 1pm. In the intervals between testing, they rested in either prone or in supine position. In both cases, the light was switched off, i.e. they rested in darkness. Five of the patients were the same as in part 1, four patients had not been tested in part 1. All nine patients had also been tested in part 3. The mean duration of DBN was 6.81 years (range 3-17 years, see Table 3.6). The patients were 44 to 72 years old, with a mean of 63.67 years and a standard deviation of ± 7.92 years. Patients No. 7 and No. 8 had already participated in the study of the previous chapter. All other factors and clinical examinations were identical to parts 1 to 5.

Table 3.6 Clinical data of the patients with DBN where prone and supine positions in darkness were compared with each other

No./Sex/ Age	Neuro-ophthalmological findings	MRI findings	Aetiology	Disease duration
No. 1M, 64	Disturbed visual fixation suppression of VOR, non-existing upright opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally.	Cerebellar atrophy	Cerebellar de-generation	3 years
No. 2F, 69	Disturbed visual fixation suppression of VOR, impaired horizontal and upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally, provocation DBN.	Cerebellar atrophy	Idiopathic cerebellar ataxia	17 years
No. 3M, 69	Deviant SVV, impaired horizontal and downward pursuit, saccades with rebound after gaze to the right, provocation DBN.	Normal	Unknown	4.5 years
No. 4F, 60	Disturbed visual fixation suppression of VOR, DBN overran horizontal opto-kinetic nystagmus, non-existing upward opto-kinetic nystagmus, deviant SVV, impaired horizontal and downward pursuit.	Normal	Unknown	12 years
No. 5F, 61	Disturbed visual fixation suppression of VOR, deviant SVV, provocation DBN, vertical saccades and saccades to the left.	Normal	Unknown	5 years
No. 6M, 44	Disturbed visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and vertical pursuit.	Normal	Unknown	10 years
No. 7M, 65	Impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit, hypometric upward saccades.	Normal	Unknown	10 years
No. 8F, 69	Disturbed vertical visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit.	Normal	Unknown	3 years
No. 9F, 72	Disturbed visual fixation suppression of VOR, impaired horizontal and non-existing upward opto-kinetic nystagmus, impaired horizontal and downward pursuit.	Normal	Unknown	6 years

VOR = vestibulo-ocular reflex; SVV = subjective visual vertical axis, HTT = head-thrust test developed by Halmagyi and Curthoys (1988).

3.6.1.2. Recording of eye movements

Patients were tested three times on a single day. Each time, patients were monitored in the following sequence: (see Figure 3.35).

1. they were sitting in upright position, 2. they were lying in supine position, 3. they were lying in prone position. In the intermissions between testing, people rested in supine position and prone position, in both cases with the light switched off. The same patients were measured in prone position and supine position, i.e. they came to the hospital twice with a delay of approximately one week between these two measurements. The VOG-measurements were identical to those in the previous chapter and in parts 1 to 5 of this chapter.

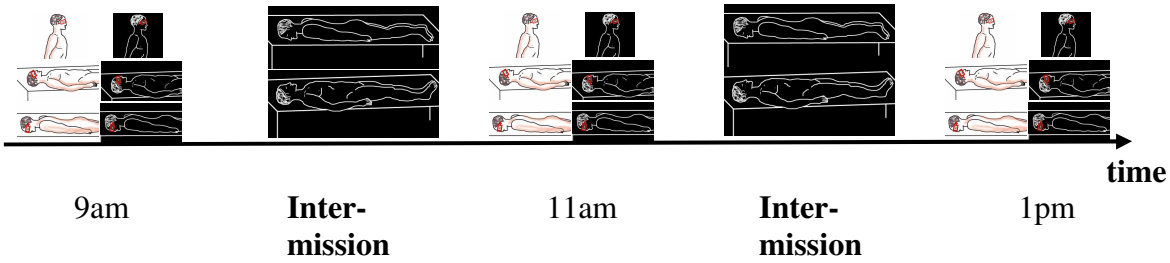


Figure 3.35. An overview describing the testing conditions for all patients. The eye movements of the patients were monitored in the following order: 1. sitting in upright position in light/dark, 2. lying in supine position in light/dark, 3. lying in prone position in light/dark. All measurements took place at 9am, 11am, and 1pm. In between the measurements, patients were lying in prone position or supine position, in both cases with the light switched off.

3.6.1.3. Data acquisition and calibration

Data acquisition and calibration was identical to the previous chapter and parts 1 to 5 of this chapter.

3.6.1.4. Statistical data analysis

The statistical analysis consisted of repeated measurement ANOVAs (Statistica 6.1, Statsoft, Tulsa OK, USA) with post-hoc Scheffé tests for individual comparisons. The dependent variable was slow phase velocity (SPV). The first analysis consisted of the within subjects factors *light* (light on = fixation is possible versus light off = viewing in the dark with no

possibility to fixate), *interval* (resting in prone position with the light switched off versus resting in supine position with the light switched off) and *daytime* (9am, 11am, 1pm). The second analysis consisted of the within subject factors *gaze condition* (straight, upwards, downwards), *interval* (resting in prone position with the light switched off versus resting in supine position with the light switched off) and *daytime* (9am, 11am, 1pm). The third analysis had the within subject factors *body orientation* (upright, supine and prone), *interval* (resting in prone position with the light switched off versus resting in supine position with the light switched off) and *daytime* (9am, 11am, 1pm). Due to the low number of patients with cerebellar symptoms, the previously mentioned nonparametric Kolmogorov-Smirnov test for two independent samples was taken as the statistical analysis. The two independent groups were the two different aetiologies (cerebellar patients versus patients with unknown aetiology). The two groups were compared with respect to their overall SPV-values.

3.6.2. Results

3.6.2.1. First section including the within subjects factor fixation versus viewing in the dark

In the first section of part 6, patient No. 4 was missing, because in prone position, she was not assessed in the dark. As a result, no comparison for the within subjects factor *light* (fixation versus viewing in the dark) was possible. Unlike the study in the previous chapter, the analysis did not reveal a significant main effect for the within-subjects factor *light*, $F(1, 7)=2.875$, $p=0.13$, although the descriptive trend was consistent with previous findings, because the possibility to fixate (= light on) resulted in an average SPV-value of -2.46, whereas no possibility to fixate (= light off) had an average SPV-value of -3.23. Consistent

with previous findings, there was, however, a significant daytime decrease in SPV-values, $F(2, 14)=7.15$, $p<0.01$ (Figure 3.36), where average SPV decreased from -4.28 deg/s at 9am to -2.28 deg/s at 11am and -1.98 deg/s at 1pm. Scheffé post-hoc tests revealed that the decrease from 9am to 11am and from 9am to 1pm each had a p-value of $p<0.05$. There was no significant difference between 11am and 1pm ($p=0.9$).

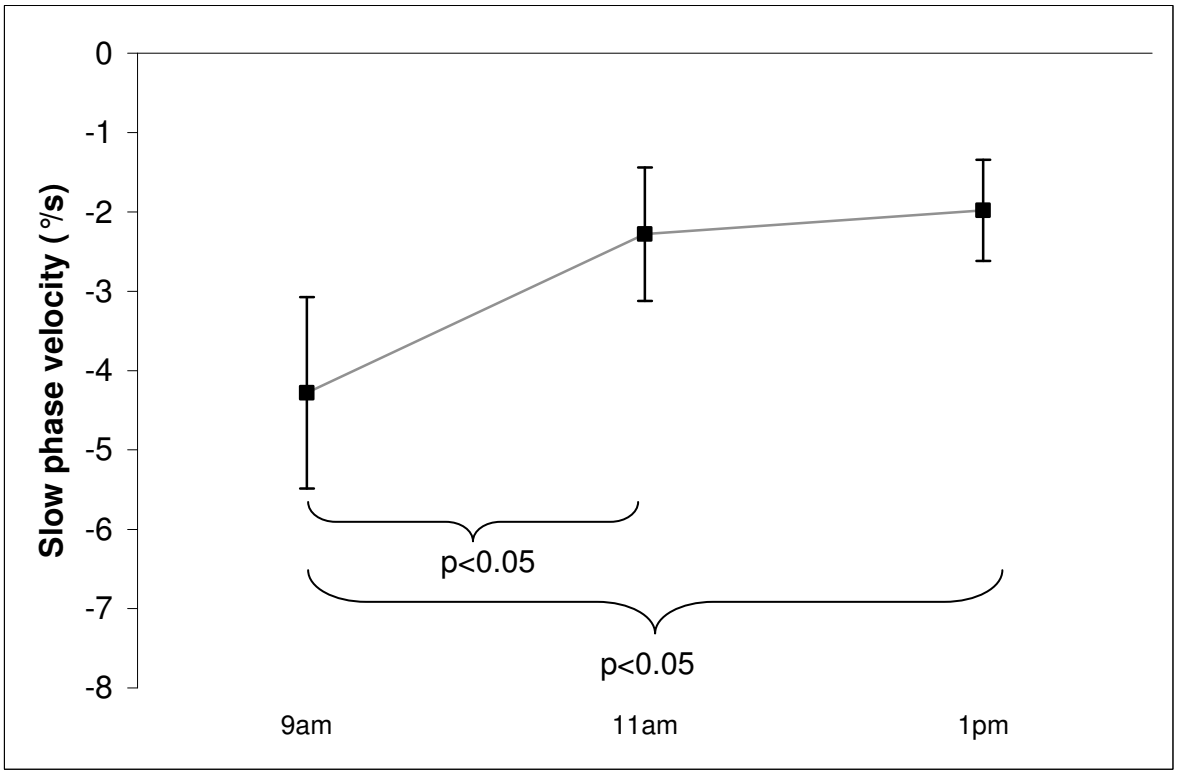


Figure 3.36 Daytime decrease in SPV across both light conditions and both intervals, measured in upright position with gaze straight ahead. Display of mean slow phase velocities along with the standard error bars of the mean.

Additional significant findings included a *light times daytime* interaction, where the SPV-decrease from 9am to 11am appeared steeper when the measurement took place with the light switched off (= with no possibility to fixate) than with the light switched on (= with the possibility to fixate), $F(2, 14)=4.5$, $p<0.05$ (Figure 3.37). As revealed by Scheffé post-hoc comparisons, the decrease from 9am to 11am an from 9am to 1pm with the light switched on (each $p<0.01$) as well as the decrease from 9am to 11am ($p<0.0001$) and from 9am to 1pm

(p<0.00001) with the light switched off were statistically significant. Whilst there was a significant difference between both 9am measurements (-3.55 deg/s with the light switched on versus -5.01 deg/s with the light switched off, Scheffé: p<0.01), the 11am and 1pm measurements did not differ from each other (Scheffé: p>0.5).

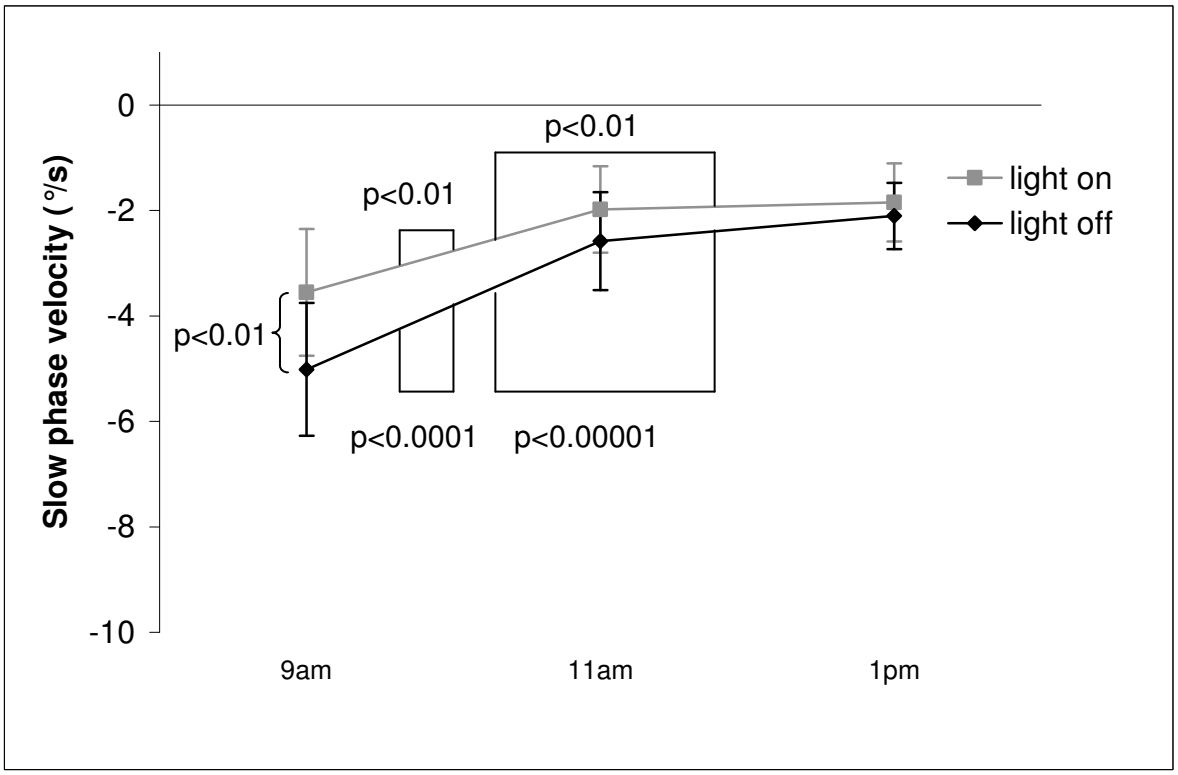


Figure 3.37 Daytime decrease in SPV between the within subjects factors light and daytime and across both intervals, measured in upright position with gaze straight ahead. Display of mean slow phase velocities along with the standard error bars of the mean.

If the 9am measurements were excluded, the lines looked almost parallel (see Figure 3.37). This apparent absence of a *light times daytime* interaction was confirmed in the analysis where the 9am measurements were excluded, F(1, 7)=0,84, p=0.39, and this, in turn, did not result in a main effect for the within subjects factor *light*, F(1, 7)=0.77, p=0.41. Going back to the original analysis (including the 9am measurements), none of the other statistical tests of this analysis became significant, neither the main effect with regard to the within subjects factor *interval*, F(1, 7)=0.32, p=0.59, nor the test for the *light times interval* interaction, F(1,

7)=0.34, p=0.58, nor the test for the *interval times daytime* interaction, F(2, 14)=0.355, p=0.71, nor the test for the *light times interval times daytime* interaction, F(2, 14)=2.28, p=0.14. With regard to the comparison between cerebellar patients and patients with unknown aetiology, cerebellar patients had an average SPV-value of -5.81 deg/s, whilst patients with unknown aetiology had an average SPV-value of -1.85 deg/s. This descriptive difference is not significant according to the Kolmogorov-Smirnov test (p>0.05).

3.6.2.2. Second section including the within subjects factor gaze direction

As in the other analyses of this study and the previous one, it turned out that there was a main effect with respect to the within subjects factor *gaze direction*, F(2, 16)=14.75, p<0.001 (Figure 3.38), where Scheffé post-hoc tests revealed that gaze upwards (+0.12 deg/s, i.e. a slight UBN) was associated with significantly lower SPV values than gaze straight ahead (-2.56 deg/s, Scheffé test: p<0.001) and gaze downwards (-2.35 deg/s, Scheffé test: p<0.01), whereas gaze straight ahead and downwards did not significantly differ from each other (p=0.93). Unlike the other analyses in the previous parts of this study, none of the remaining tests in this analysis revealed a significant finding, neither the test for the within subjects factor *interva*l, F(1, 8)=0.02, p=0.9, nor the marginally significant decrease of daytime SPV, F(2, 16)=3.21, p=0.07 (the descriptive trend was in line with a daytime decrease: -2.41 deg/s at 9am, -1.25 deg/s at 11am and -1.13 deg/s at 1pm), nor the tests for the interactions, where the *gaze times interval* interaction resulted in F(2, 16)=1.22, p=0.32, the *gaze times daytime* interaction in F(4, 32)=0.325, p=0.86, the *interval times daytime* interaction in F(2, 16)=0.67, p=0.52, and finally the *gaze times interval times daytime* interaction in F(4, 32)=1.4, p=0.255. Even when excluding the 9am measurements, as they had taken place before the first resting interval, none of these possible main effects and interactions resulted in a significant finding.

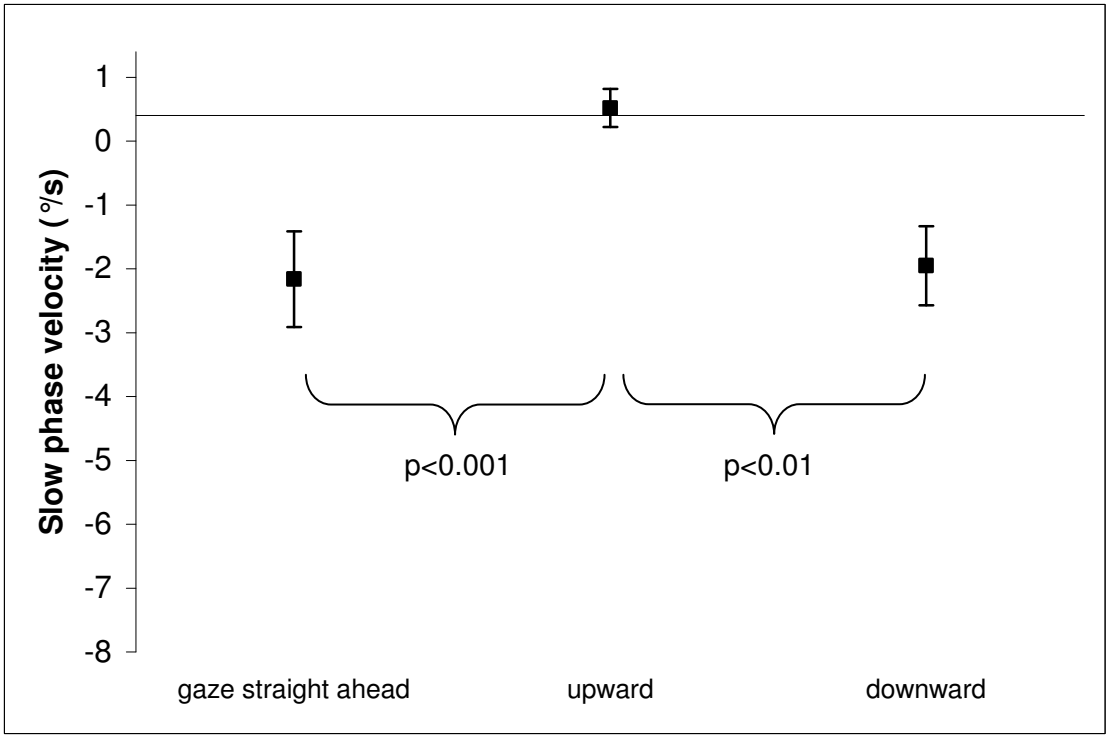


Figure 3.38 Comparing SPV between gaze straight ahead, upward and downward, across both intervals and daytime, measured in upright position and with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

With regard to the comparison between cerebellar patients and patients with unknown aetiology, cerebellar patients had an average SPV-value of -3.62 deg/s, whilst patients with unknown aetiology had an average SPV-value of -1.02 deg/s. This descriptive difference is not significant according to the Kolmogorov-Smirnov test ($p>0.05$).

3.6.2.3. Third section including the within subjects factor body orientation

Consistent with previous findings, the analysis with respect to *body orientation* resulted in a significant main effect, $F(2, 16)=4.82$, $p<0.05$ (Figure 3.39). The Scheffé post-hoc comparisons between upright (-2.56 deg/s), supine (-0.695 deg/s) and prone (-3.03 deg/s) revealed that only the difference between supine and prone position was statistically significant ($p<0.05$). Comparing upright and supine position resulted in a marginally

significant finding (p=0.094), whilst the comparison between upright and prone position (p=0.84) was not significant.

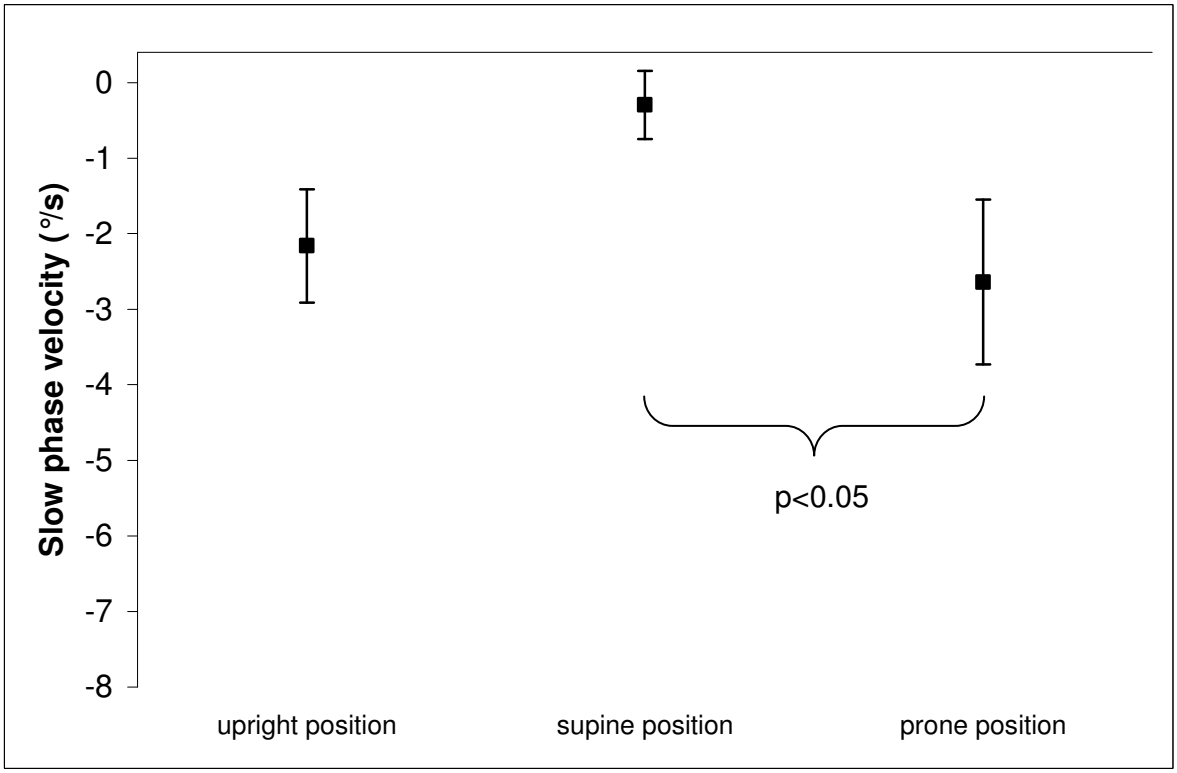


Figure 3.39 Comparing SPV between upright, supine and prone positions, across both intervals and daytime, measured in gaze straight ahead and with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

As in previous analyses, there was a significant main effect for the within-subjects factor *daytime*, $F(2, 16)=8.38$, $p<0.01$ (Figure 3.40), where average SPV decreased from -3.5 deg/s at 9am to -1.4 deg/s at 11am and -1.39 deg/s at 1pm. Scheffé post-hoc tests revealed that the differences between 9am and 11am and from 9am to 1pm were both statistically significant ($p<0.01$), whereas the difference between 11am and 1pm was not significant ($p=1$).

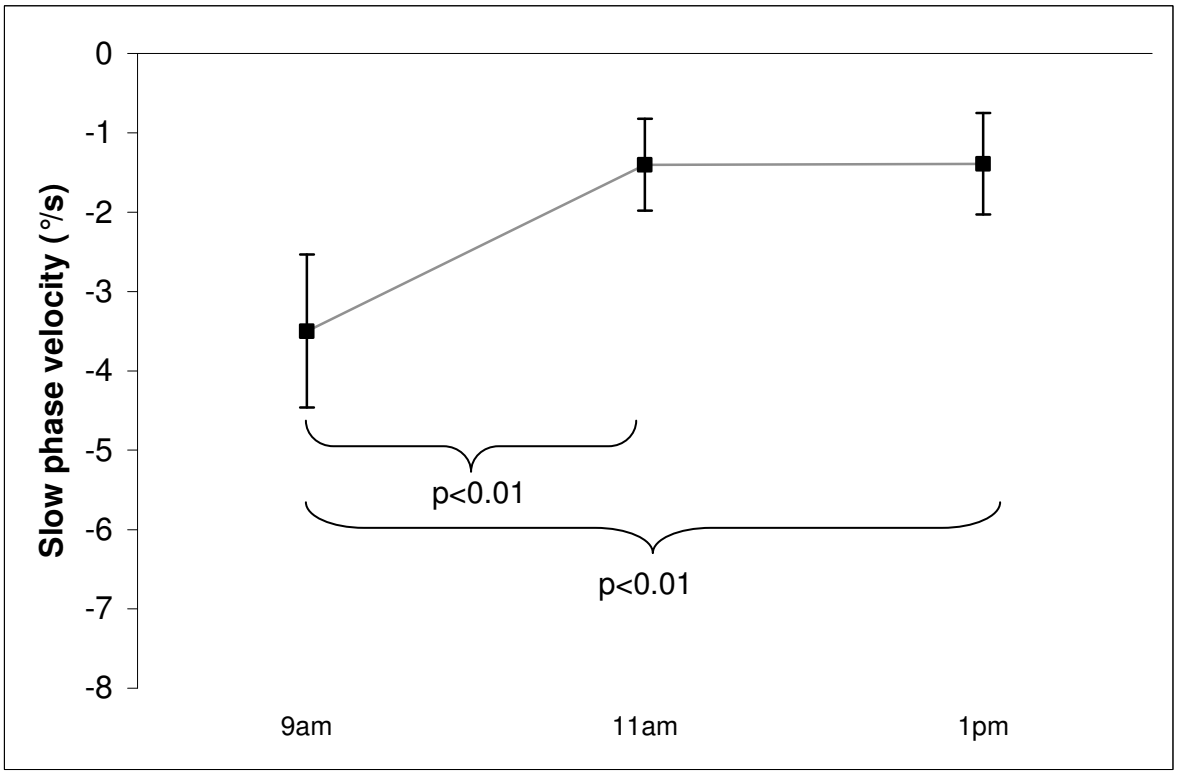


Figure 3.40 Daytime decrease in SPV across all three body positions and both intervals, measured in gaze straight ahead and with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

Among the remaining comparisons, only the *body orientation times daytime* interaction became statistically significant, $F(4, 32)=11.51$, $p<0.00001$ (Figure 3.41). At the 9am measurements, i.e. prior to the first resting interval, the average SPV-values in all three body positions (upright: -3.36 deg/s, supine: -1.56 deg/s, prone: -5.59 deg/s) were significantly different from each other, as Scheffé post-hoc comparisons revealed a difference of $p<0.01$ between upright and supine, $p<0.001$ between upright and prone and $p<0.000001$ between supine and prone. At the 11am measurements, supine and upright were significantly different from each other ($p<0.01$), at 1pm both upright and supine ($p<0.05$) and supine and prone ($p<0.05$). From the 9am measurements to the 11am measurements, the decrease of SPV in the prone measurements appears steeper than in the upright and supine measurements (i.e. see Figure 3.41). After 11am, however, the lines of all three measurements appear almost parallel. Only prone position shows a significant SPV-decrease from 9am to 11am and from 9am to

1pm (each p<0.000001). To check the influence of the 9am measurements, they were excluded in an additional analysis. In this case the significant *body orientation times daytime* interaction vanished, F(2, 16)=0.58, p=0.57 and no further tests gained statistical significance.

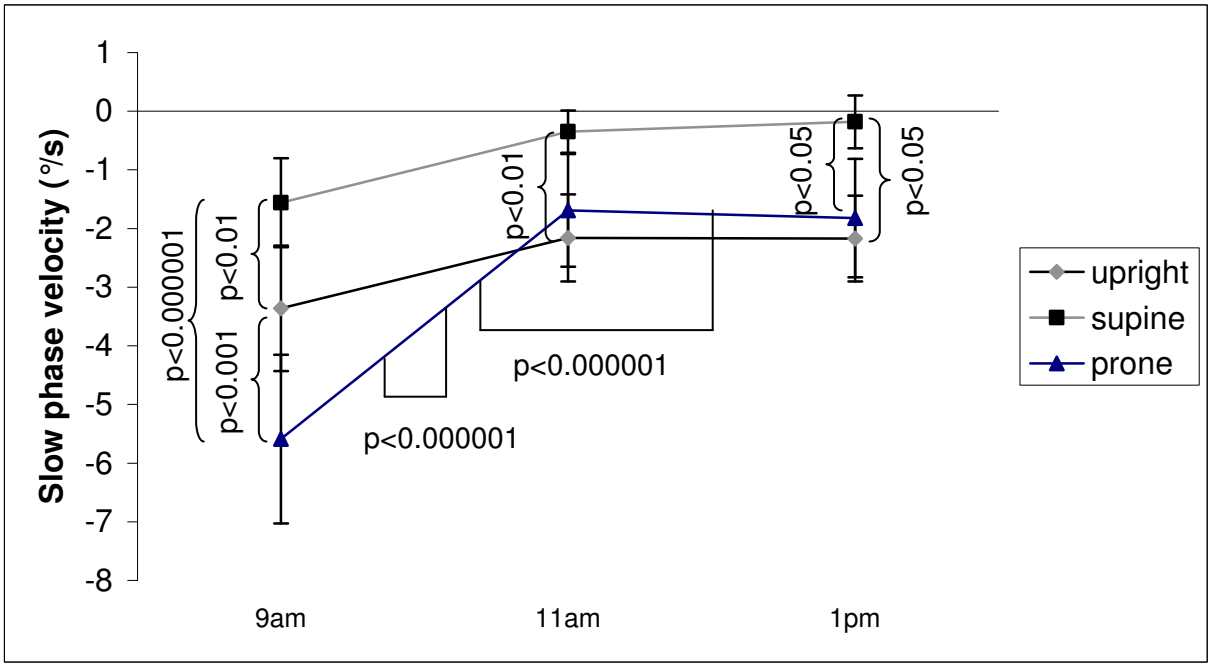
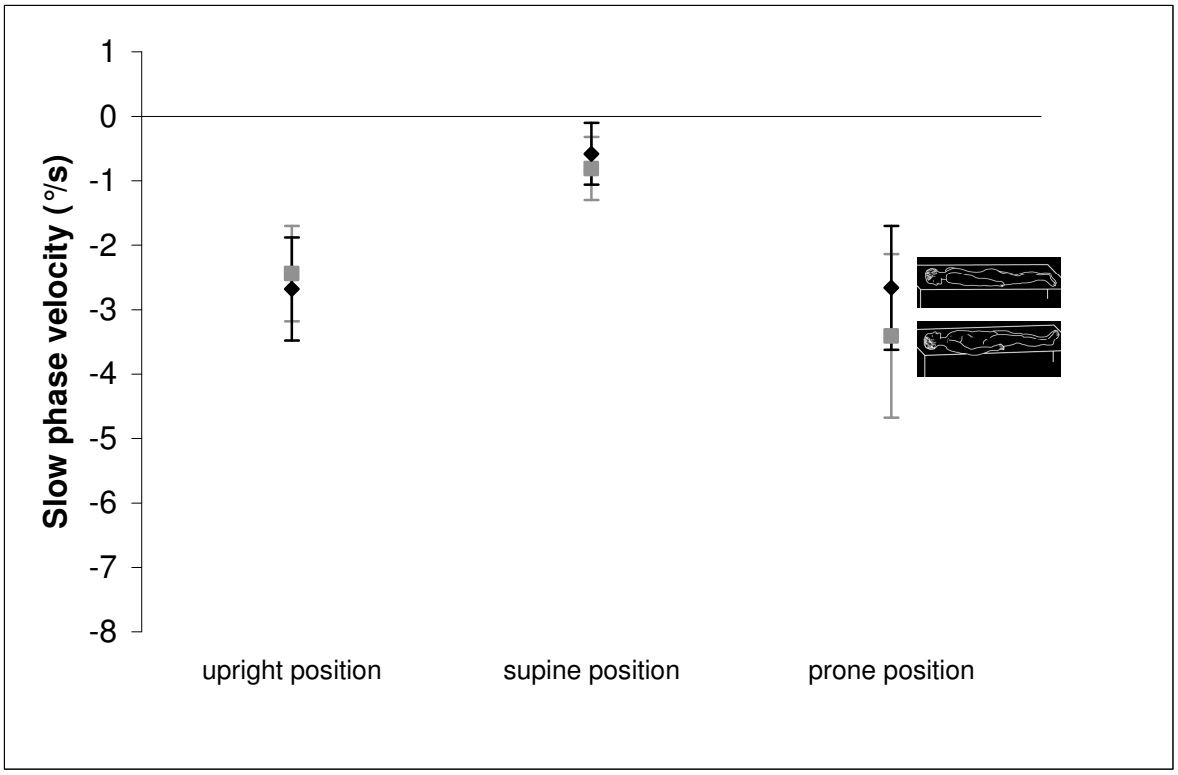


Figure 3.41 Comparing SPV differences across intervals between the within subjects factors body position and daytime, measured in gaze straight ahead and with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

Going back to the analysis that included the 9am measurements, there was no significant main effect for the within subjects factor *interval*, F(1, 8)=0.4, p=0.54. Testing possible interactions revealed a marginally significant *body orientation times interval* interaction, F(2, 16)=3.5, p=0.055, no *interval times daytime* interaction, F(2, 16)=0.29, p=0.75 and no *body orientation times interval times daytime* interaction, F(4, 32)=0.4, p=0.8. The comparison of interest in this chapter deals with the resting position during the intervals between testing. Because the *body orientation times interval* interaction was marginal and because the 9am measurements have an indirect influence on the results (even though no resting interval had taken place yet at this time of measurement), their SPV-values prior to the resting intervals were compared

with each other. The 9am measurement prior to resting in prone position had an SPV-value of -3.43 deg/s, whereas the 9am measurement prior to resting in supine position had an SPV-value of -3.57 deg/s. Although these values are almost the same (Scheffé: p=0.999), they could have an indirect influence so that a marginally significant finding may turn out significant. As a result, an additional analysis was carried out excluding the 9am measurements. This analysis ensured that only SPV-values were considered that were assessed after the resting intervals. As previously mentioned, the analysis without the 9am measurements did not reveal any significant finding. Testing the *body orientation times interval interaction* revealed an F-value of $F(2, 16)=2.55$, $p=0.11$. Although neither the analysis including the 9am measurements (Figure 3.42a), nor the analysis excluding the 9am measurements (Figure 3.42b) revealed a significant result, the descriptive trends are shown in the figures. According to these descriptive trends, when being measured in upright or supine position, it makes almost no difference whether people have rested in supine or prone position. When being measured in prone position, however, patients reveal a descriptively lower SPV after having rested in prone position as compared to having rested in supine position.

Referring to the comparison between cerebellar patients and patients with unknown aetiology, cerebellar patients had an average SPV-value of -5.19 deg/s, whilst patients with unknown aetiology had an average SPV-value of -1.21 deg/s. This descriptive difference is not significant according to the Kolmogorov-Smirnov test ($p>0.05$).



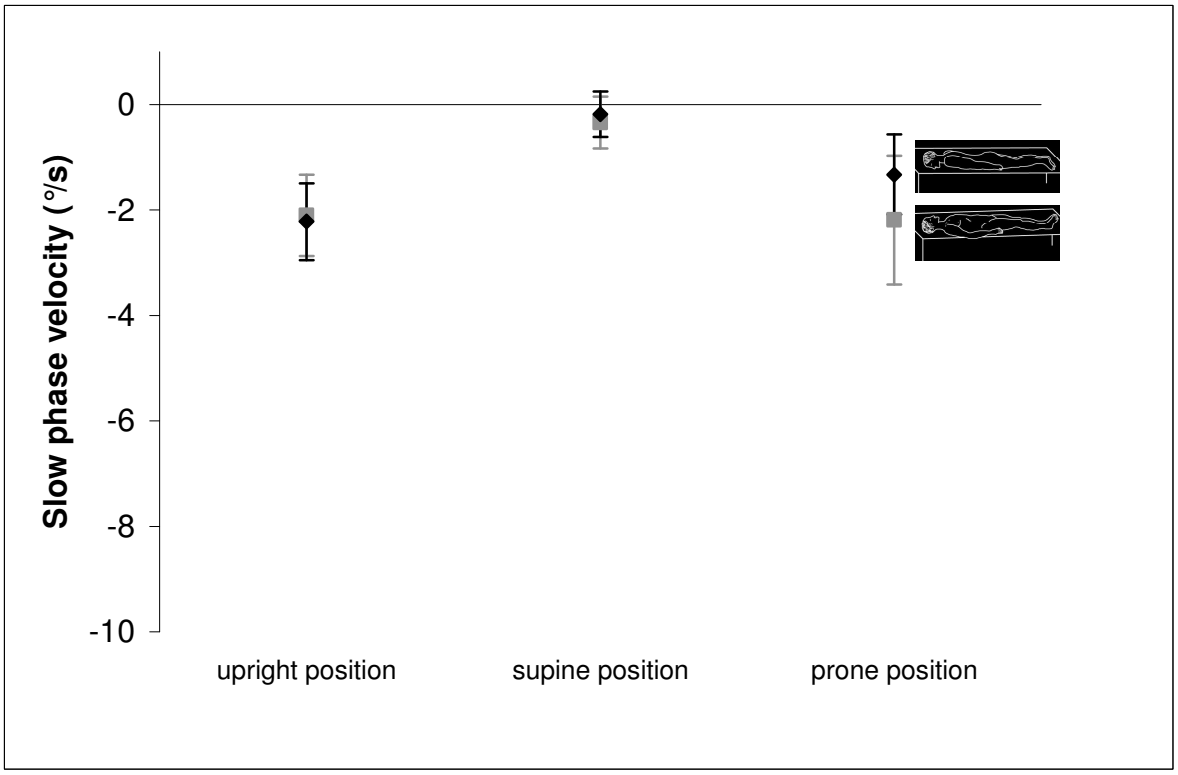


Figure 3.42a Comparing SPV differences between the within subjects factors interval and position, across daytime (9am, 11am, 1pm), measured in gaze straight ahead and with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean, **b** The same comparison as in 3.42a, but without the 9am measurements.

3.6.3. Discussion

In contrast to the previous study (chapter 2), the analysis in part 6, section 1 did not reveal a significant main effect for the within-subjects factor *light*, although it needs to be said that the descriptive trend of the results was completely in line with previous findings and the comparison was almost marginally significant. Consequently, this result did not contradict previous findings. The daytime decrease of DBN-intensity was fully in line with previous findings. As in part 5 of this study, there was a significant *light times daytime* interaction, which was due to the fact the 9am measurements in darkness were significantly more negative than the 9am measurements with the light switched on. After the first resting interval, this resulted in a steeper decrease of SPV-values for the measurements in darkness than for the measurements with the light switched on. When excluding the 9am measurements, however, this interaction vanished and the lines looked almost parallel. As mentioned in part 5 of this study, this difference could be due to chance. As an alternative, and more speculative explanation, it would also be in line with the effect of sleep inertia. Under this assumption it would take the Purkinje-cells up to a few hours to adapt to their full functioning. Whilst the possibility to fixate might suppress these effects, no possibility to fixate (i.e. when tested in darkness) could result in more severe DBN symptoms particularly in the morning hours. The absence of a fixation point and the possible effect of sleep inertia could even produce synergistic effects, which could also act as a possible explanation for this finding.

In the second section of part 6 and consistent with previous analyses, there was a main effect with respect to the within subjects factor *gaze direction*, where gaze upwards was associated with less DBN than gaze straight ahead and gaze downwards, whereas gaze straight ahead and gaze downwards did not differ in terms of their DBN. In contrast to previous analyses, testing for daytime decrease of DBN only revealed a marginally significant

finding and none of the possible interactions became statistically significant. The marginally significant daytime decrease was not in contrast to previous findings, as the descriptive trend of having a daytime decrease remained preserved in this analysis.

The third section of part 6 confirmed many previous findings, as the analysis with respect to *body orientation* resulted in a significant main effect. Being measured in supine position was again associated with the lowest intensity of DBN, though only the difference between supine and prone position was statistically significant, whereas the comparison between upright and supine position was marginally significant and the comparison between upright and prone position not significant. In addition, the *body orientation times daytime* interaction became statistically significant, which was, however, predominantly due to a high intensity of DBN in prone position prior to the first resting interval. After the first resting interval, the lines between the three body orientations appear almost parallel and the formerly significant interaction vanishes when the 9am measurements are excluded. It is difficult to interpret why the 9am measurements in prone position show a greater intensity of DBN than in the other two positions. In the previous analyses, it was shown that prone position measurements often seem to be associated with a higher intensity of DBN. It also turned out that DBN is generally highest in the morning hours. Hence, this result might be explained by synergistic effects of these two characteristics or even more than two characteristics, e.g. when taking a possible effect of sleep inertia into account as well. Because the comparison of interest in this chapter deals with the resting position during the intervals between testing, it was focused on the test of the *body orientation times interval* interaction (albeit marginally significant only). When excluding the 9am measurements due to the fact that they were carried out before the first resting interval, the marginally significant interaction even changed from marginal to not significant. Nevertheless, it is worth investigating the descriptive trends. They indicate the following: when being measured in supine position, it makes almost no difference whether people have rested in supine or in prone position. When being measured in

prone position, however, patients reveal a descriptively lower SPV after having rested in prone position as compared to having rested in supine position. Consequently, there is at least a tentative sign that the resting position has an influence during the measurements. Moreover, this descriptive trend stands in line with the significant interactions found in part 4 and part 5 of this study, where the resting position also had an influence on the position during measurement.

Finally, a nonparametric comparison between patients with cerebellar and unknown aetiologies was carried out, because the number of two cerebellar patients was considered too low to carry out a parametric comparison with the between subjects factor *aetiology*. Although the nonparametric Kolmogorov-Smirnov test did not turn out to be significant, it remains to be said, though, that the descriptive trend indicates stronger DBN symptoms in patients with cerebellar aetiology than in patients with unknown aetiology.

3.7. General discussion

This chapter revealed several main findings. First and according to part 1 of this study, it turned out that under the usual conditions during daytime (= upright position, no darkness), it makes no difference whether patients rest upright with the light switched on or upright with the light switched off, though there was a descriptive trend in terms of lower DBN being associated with the light-off condition.

The second finding under these conditions (part 2 of this study) revealed that it is better to rest upright than to rest in prone or supine position (all resting positions were in darkness). A practical application of this finding is to recommend people to rest upright.

Third, parts 3 to 6 of this study confirmed the results from the study of the previous chapter, i.e. that the intensity of DBN decreases during daytime, that fixation (= light on) suppresses the intensity of DBN, that gaze direction and body orientation have an influence

on the intensity of DBN (with upward gaze / supine position being associated with the lowest intensity of DBN). A lot of information from parts 3 to 6 may appear redundant to the previous chapter, but this information was necessary in order to show that the data from both studies and under the different conditions are coherent. It compared the same resting position (upright) between two conditions (resting with the light switched on or off). The results revealed that overall (i.e. taking together measurements in light and darkness), resting upright with the light switched off was associated with a lower intensity of DBN than resting upright with the light switched on. This result has the practical consequence that it is better to rest upright in darkness in case the daily routine of a person requires activities in both light and darkness. In addition, this result can be directly related to the discussion of the previous chapter, where it was discussed that daytime decrease could be the result of a non-visual error signal such as extraocular proprioception (Büttner-Ennever & Horn, 2002) or efference copy (Glasauer et al. 2005b; Klier et al. 2008). According to these explanations, it would be the case that DBN becomes less because patients were able to adapt throughout the day. Because patients were allowed to keep their eyes open and the light switched on during the resting intervals in the previous chapter, it was assumed that these conditions might have contributed to the adaptation process and alleviated the intensity of DBN. This interpretation stands in contrast to the current finding that DBN was less pronounced after patients rested in upright position during darkness (compared to resting in upright position with the light switched on). It needs to be kept in mind, however, that this finding alone does not contradict the explanations of extraocular proprioception or efference copy. It just implies that daytime decrease of DBN may not be due to an adaptation process that is supported by having the light switched on. In any case, more research will be necessary, and it will be desirable to not only compare light versus darkness in upright position, but also in the other resting positions (supine/prone).

Fourth, this chapter compared the influence of the three different resting orientations (each with the light switched off) on the three different measurement positions. It turned out that the positions during the resting intervals (upright, supine, prone) do at least have a tentative influence on the SPV-values of the different measurement positions (upright, supine, prone). This becomes particularly clear in part 4 of this study. After the resting positions of the patients were varied between prone position and upright position, it turned out that when being measured in upright position, having rested in upright position is associated with a significantly lower SPV-value than having rested in prone position. When being measured in prone position, having rested in prone position is associated with a marginally significant lower SPV-value than having rested in upright position.

When considering practical applications of this finding, one could, for example, recommend patients to rest in upright position when they intend to do office work after the resting period. Alternatively, one could recommend patients to rest in prone position when they intend to work in prone position, do gymnastics or swim in prone position or receive a massage after the resting period. In conclusion, the results of this study are in line with the gravitational influences that were proposed by Brandt (1990) and Marti (2002). A body rotation in relation to the gravitational vector may have an influence on the otoliths, making DBN worse in relation to not rotating. This effect occurs no matter in which direction the rotation occurs (e.g. from supine to upright or from prone to upright, as described in part 2 of this chapter).

4. Comparing 3,4-Diaminopyridine and 4-Aminopyridine in the therapy of downbeat nystagmus

As mentioned in the introduction, the aminopyridines 3,4-diaminopyridine (3,4-DAP) and 4-aminopyridine (4-AP) currently seem to be the most promising pharmacological approaches to alleviate the symptoms of DBN. For 3,4-DAP this was demonstrated in a placebo-controlled trial by Strupp et al. (2003) and for 4-AP by Kalla et al. (2007). What was missing so far was a direct comparison between both drugs. This chapter is dedicated to this comparison, where the effect of 3,4-DAP versus 4-AP in a group of patients with DBN was investigated for the first time in a double-blind study with crossover design (see Kalla et al, 2011). Thus, the purpose of this work is to analyze DBN before and after administration of 3,4-DAP / 4-AP and to determine whether both medications differ in terms of slow-phase velocity (SPV) changes. The study of this chapter has already been published in Kalla et al. (2011), where I shared the first authorship. Since I contributed, among other aspects, the text to the Kalla et al. (2011) manuscript and since I am the author of this thesis, there is a partial overlap between the text, figures, table and their legends between my thesis and the Kalla et al. (2011) article.

4.1. Methods

4.1.1. Patients

In the present study, eight patients (2 males, 6 females) with a history of DBN due to different aetiologies were analysed prior to, 45 minutes after and 90 minutes after administration of either 4-AP or 3,4-DAP. The aetiologies were cerebellar degeneration (n = 1), cerebellar degeneration with bilateral vestibulopathic failure (n = 1), cerebellar ataxia with relatively low

placement of cerebellar tonsils (n = 1), idiopathic cerebellar ataxia with cerebellar atrophy according to the MRI-scan (n = 1), and unknown DBN (n = 4), see Table 4.1, i.e. there were 4 patients with cerebellar aetiology and 4 patients with unknown aetiologies. The mean duration of DBN was 7.75 years (with a range of 3 to 24 years, see Table 4.1). The patients were 58 to 76 years old, with a mean of 68 years and a standard deviation of ± 5.93 years. Patients No. 1, No. 4, No. 7 and No. 8 had already appeared in the first study (see chapter 2), patients No. 1 and No. 7 had appeared in parts 1 and 3 of the second study (see chapter 3), and patients No. 1, No. 6 and No. 7 had appeared in parts 2, 4, 5 and 6 of the second study (see chapter 3). The effect of 3,4-DAP versus 4-AP was compared in a double-blind study with crossover design. Thus, the purpose of this work was to analyse DBN before and after administration of aminopridines and to determine whether both medications would differ in terms of slow-phase velocity (SPV) changes in our patients, i.e. the same patients received a single capsule of 10mg 3,4-DAP and 10mg 4-AP separated by a one week washout period. The patients who were administered 3,4-DAP first, received 4-AP after one week and vice versa. The assignment to capsules with 3,4-DAP and those with 4-AP was random.

On both testing occasions, patients' eye movements were recorded with 3D-videooculography prior to the administration of the capsule, which was swallowed at 9am. As mentioned before, additional recordings took place 45 minutes and 90 minutes after administration. In the intervals between the recording, patients rested in an upright position. As in previous studies (see the previous two chapters), all patients had a complete clinical examination and gave their informed consent prior to their participation. As the previous studies, this study was in accordance with the Helsinki II Declaration and approved by the local ethics committee of the Medical Faculty of Ludwig-Maximilians-University.

Table 4.1 Clinical data of the patients with DBN where 4-AP was compared to 3,4-DAP

No./Sex/ Age	Neuro-ophthalmological findings	MRI findings	Aetiology	Disease duration
No. 1M, 64	Disturbed visual fixation suppression of VOR, non-existing upright opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally.	Cerebellar atrophy	Cerebellar de-generation	3 years
No. 2F, 65	Disturbed visual fixation suppression of VOR, impaired opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally, Reboundnystagmus after gaze to the left	Normal	Cerebellar de-generation and bilateral vestibulo-pathic failure	9 years
No. 3F, 76	Disturbed visual fixation suppression of VOR, only saccades and DBN when trying to elicit opto-kinetic nystagmus, impaired horizontal and downward pursuit.	Low placement of cerebellar tonsils, malformation of the cranio-cervical transition	Cerebellar ataxia with relatively low placement of cerebellar tonsils	24 years
No. 4F, 66	Disturbed visual fixation suppression of VOR, impaired horizontal and non-existing vertical opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally.	Cerebellar atrophy	Idiopathic cerebellar ataxia	4 years
No.5M, 58	Disturbed visual fixation suppression of VOR, impaired vertical and horizontal opto-kinetic nystagmus, impaired horizontal and downward pursuit, pathological HTT bilaterally	Normal	Unknown	10 years
No. 6F, 72	Disturbed visual fixation suppression of VOR, impaired horizontal opto-kinetic nystagmus, impaired horizontal and downward pursuit.	Normal	Unknown	6 years
No. 7F, 69	Disturbed vertical visual fixation suppression of VOR, impaired upward opto-kinetic nystagmus, impaired horizontal and downward pursuit.	Normal	Unknown	3 years
No. 8F, 74	Horizontal and impaired downward opto-kinetic nystagmus with DBN when looking upwards, impaired horizontal and downward pursuit	Normal	Unknown	3 years

VOR = vestibulo-ocular reflex; HTT = head-thrust test developed by Halmagyi and Curthoys (1988). Permission for displaying the table was obtained from the publisher or my/our article.

4.1.2. Recording of eye movements

At each of the three testing sessions (before medication, 45 minutes and 90 minutes after medication), patients were monitored in upright position (see Figure 4.1).

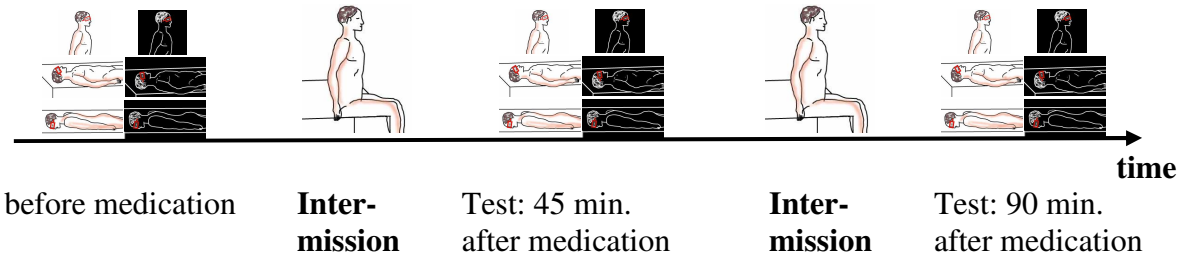


Figure 4.1 Testing conditions for all patients. Eye movements of patients were monitored in the following order: 1. sitting in upright position in light/dark, 2. lying in supine position in light/dark, 3. lying in prone position in light/dark prior to medication, 45 minutes after medication and 90 minutes after medication. In between VOG-measurements, patients were sitting upright.

As in the previous two chapters and previous publications (e.g. Spiegel et al., 2009a; Zingler et al., 2006), a 30 seconds eye movement recording with 3-D VOG took place in the following order: It started with a calibration in 8.5° position, and was followed by: 1. a gaze directed straight ahead with fixation turned on, 2. a gaze directed straight ahead in darkness (with no possibility to fixate on a fixation point), 3. 17° gaze to the right, 4. 17° gaze to the left, 5. 17° gaze upwards 6. 17° gaze downwards. The projection of the target occurred with a laser onto a white cardboard placed 60 cm in front of the patient. The horizontal gaze directions were only recorded for completeness purposes, e.g. to have a collection of these data should they be of interest for future studies, e.g. to generate possible hypotheses on gaze direction and medication.

4.1.3. Data acquisition and calibration

Data acquisition and calibration was done in exactly the same way as described in the previous two chapters, i.e. eye position was measured with 3D-VOG for 30 seconds, for details refer to the introduction of this thesis. The data were analysed off-line applying Matlab software (The Mathworks, Natick, MA, USA). The calibrated data were low-pass filtered using a digital Gaussian filter. The filter had a bandwidth of 30 Hz. Interactive software

allowed to detect and remove saccades and fast phases applying a combined velocity–acceleration criterion. Consequently, it was possible to exclude detection errors manually. The mean slow phase velocity was computed from the de-saccaded data.

4.1.4. Statistical data analysis

As in the previous two chapters, the statistical analysis consisted of repeated measurement ANOVAs (Statistica 6.1, Statsoft, Tulsa OK, USA) with post-hoc Scheffé tests for individual comparisons. Again, the dependent variable was slow phase velocity (SPV) of vertical eye movements. In line with the previous two studies, the following analyses were separated into three sections. The first section included the within subjects factors *light* (fixation = light on) versus viewing in the dark = light off with no possibility to fixate), *medication type* (3,4-DAP vs. 4-AP) and *time* (before medication vs. 45 minutes after medication vs. 90 minutes after medication), the second section the within subjects factors *gaze direction* (straight ahead, upwards, downwards), *medication type* (3,4-DAP vs. 4-AP) and *time* (before medication vs. 45 minutes after medication vs. 90 minutes after medication). In the second section, two patients (patients No. 3 and No. 5) were missing because no upward gaze and downward gaze measurements had been performed on them. Finally, the third section consisted of the within subjects factors *body orientation* (upright position vs. supine position vs. prone position), *medication type* (3,4-DAP vs. 4-AP) and *time* (before medication vs. 45 minutes after medication vs. 90 minutes after medication). In spite of the fact that there was a low number of patients with cerebellar aetiology (n = 4) or unknown aetiologies (n = 4), the between subjects factor *aetiology* was included and a parametric comparison was carried out. The inclusion of the between subjects factor stems from the fact that there is an equal number of patients in both groups and the F-test is robust to violations of its assumptions as long as there is an equal number of patients per group (Bortz, 1993; Spiegel 2002). These assumptions include normal distribution and independence of the dependent variable for each analysed

combination of values of the independent variables as well as homogenous variances across the analysed combinations (Cohen, 1988; Spiegel, 2002). Due to only 4 patients per group, the assumption that the dependent variable is normally distributed would be violated here.

4.2. Results

4.2.1. First section including the within subjects factor fixation versus viewing in the dark

Considering the *medication times time* interaction, there was a significant effect between both aminopyridines throughout time (pre vs. post 45 vs. post 90), $F(2, 14)=8.876$, $p<0.01$. Following the administration of 3,4-DAP, average SPV decreased from –5.679 deg/s (pre) to –3.29 deg/s (post 45) to –2.962 deg/s (post 90) (with Scheffé post hoc comparisons between pre and post 45 as well as between pre and post 90 each revealing a p-value of $p<0.01$, whereas post 45 and post 90 were not significantly different from each other, $p=0.98$). In 4-AP, average SPV decreased from –6.037 deg/s (pre) to –1.576 deg/s (post 45) to –1.206 deg/s (post 90), with Scheffé post hoc comparisons between pre and post 45 as well as between pre and post 90 each revealing a p-value of $p<0.00001$, whereas post 45 and post 90 were not significantly different from each other, $p=0.97$. The pre-SPV-measurements between both medications were not significantly different from each other either ($p=0.97$), but both post 45 and post 90 SPV-measurements were significantly better in 4-AP than in 3,4-DAP (each Scheffé tests revealing p-values of $p< 0.05$ for both comparisons). The result is displayed in Figure 4.2a.

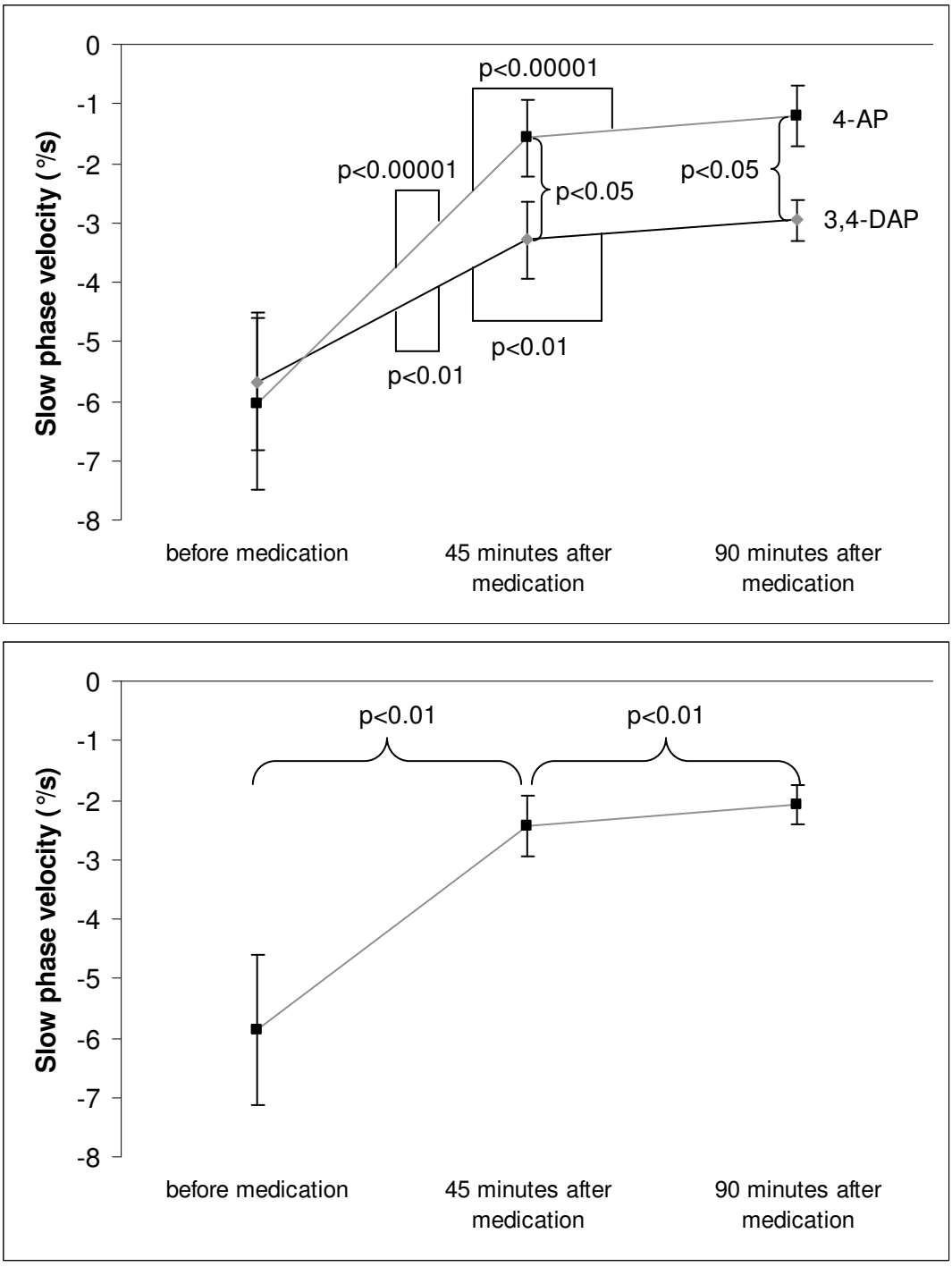


Figure 4.2a Comparing SPV between treatment with 3,4-DAP and 4-AP prior to medication, 45 minutes after administration of medication and 90 minutes after administration of medication, measured across both light conditions in upright position with gaze straight ahead, **b** SPV across both light conditions and both medications prior to medication, 45 minutes after administration of medication and 90 minutes after administration of medication, measured in upright position and gaze straight ahead. Display of mean slow phase velocities along with the standard error bars of the mean (in both 4.2a and 4.2b). Figure 4.2a was borrowed by my thesis-co-advisor Roger Kalla for research purposes (with my permission). It might have appeared on the internet after my thesis was completed (but before it has appeared on the web).

When excluding the before-medication measurements, the lines look almost parallel and the formerly significant *medication times time* interaction vanishes, $F(1, 7)=0.006$, $p=0.94$, creating a main effect for the within subjects factor *medication*, $F(1, 7)=7.07$, $p<0.05$, with 4-AP being associated with a significantly lower average SPV-value (-1.39 deg/s) than 3,4-DAP (-3.13).

Going back to the analysis that included the before-medication measurements, an additional significant finding refers to the main effect of *time* (pre vs. post 45 vs. post 90), $F(2, 14)=10.72$, $p<0.01$ (Figure 4.2b) with post-hoc Scheffé comparisons between before-medication and 45 minutes after medication and before-medication and 90 minutes after medication each resulting in p-values of $p<0.01$ (45 minutes vs. 90 minutes after medication $p=0.93$). Moreover, there was a significant main effect with respect to *light*, $F(1, 7)=14.14$, $p<0.01$ (Figure 4.3), where fixation on target (= light on) had an average SPV-value of -2.23 deg/s, whereas no fixation (= light off) had an average SPV-value of -4.69 deg/s. Other possible interactions, i.e. *light times medication type* ($F(1, 7)=0.06$, $p=0.815$), *light times time* ($F(2, 14)=2.3$, $p=0.14$), *light times medication type times time* ($F(2, 14)=0.96$, $p=0.41$)) did not result in statistically significant findings.

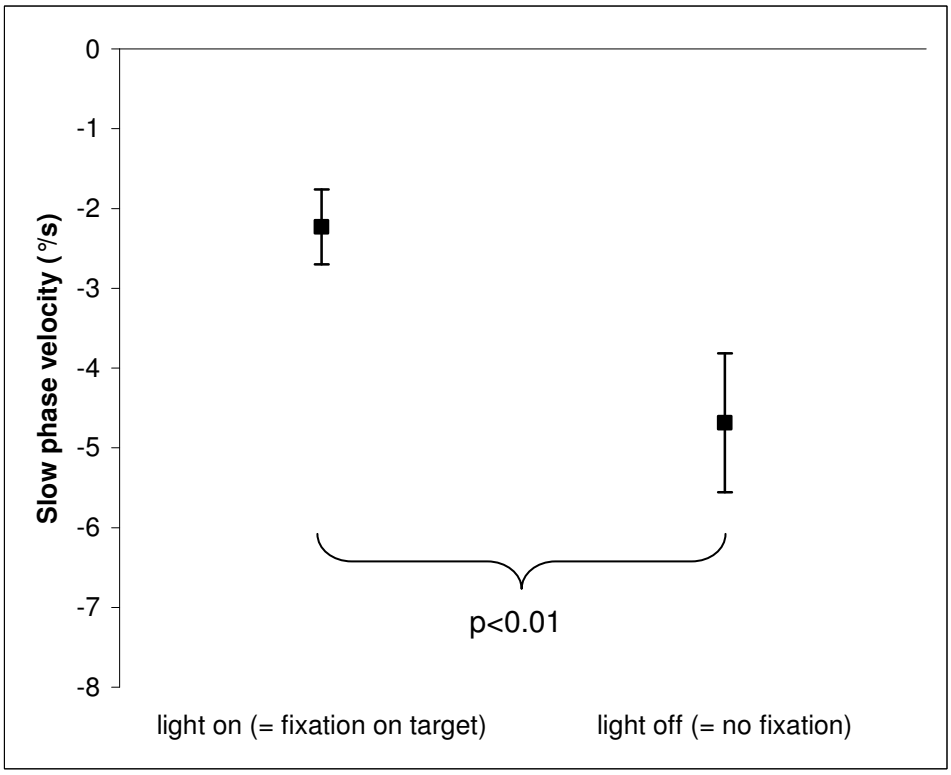


Figure 4.3 Comparing SPV between light (= fixation on target) and darkness conditions (= no fixation), across both medications and time, measured in upright position and gaze straight ahead. Display of mean slow phase velocities along with the standard error bars of the mean.

4.2.2. Second section including the within subjects factor gaze direction

Consistent with the knowledge on the influence of gaze direction (see introduction and the previous two chapters), there was a significant main effect in terms of *gaze direction*, $F(2, 10)=9.35$, $p<0.01$, where Scheffé post-hoc tests revealed that upward gaze (-1.16 deg/s) was significantly different from downward gaze (-1.89 deg/s, $p<0.05$) and gaze straight ahead (-2.16 deg/s, $p<0.01$). Downward gaze and gaze straight ahead, however, were not significantly different from each other ($p=0.54$). The results of this analysis are displayed in Figure 4.4.

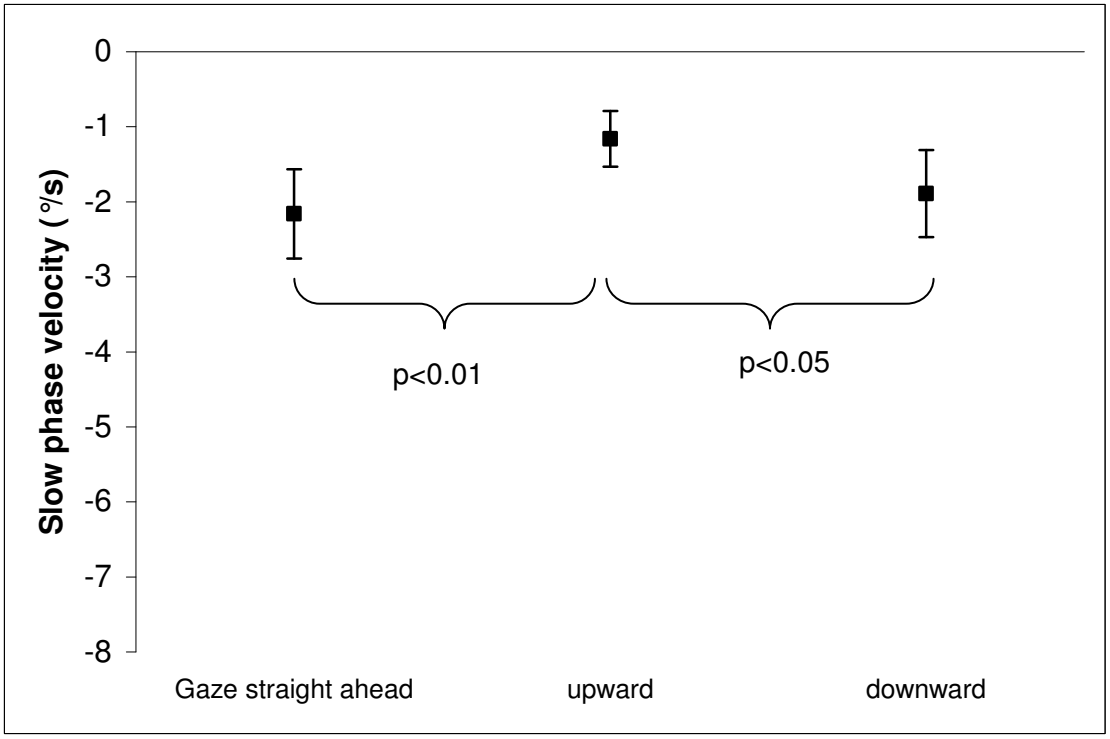


Figure 4.4 Comparing SPV between gaze straight ahead, upward gaze and downward gaze, across both medications and time, measured in upright position with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

In line with the expectation that DBN decreases after the administration of aminopyridines (see introduction), the analysis resulted in a significant main effect of *time* (pre vs. post 45 vs. post 90), $F(2, 10)=13.48$, $p<0.01$ (Figure 4.5), with significant post-hoc Scheffé comparisons between before-medication (-3.55 deg/s) and 45 minutes after medication (-1.18 deg/s, $p=0.01$) and before-medication and 90 minutes after medication (-0.49 deg/s, $p<0.01$), and no significant difference between 45 minutes and 90 minutes after medication ($p=0.56$).

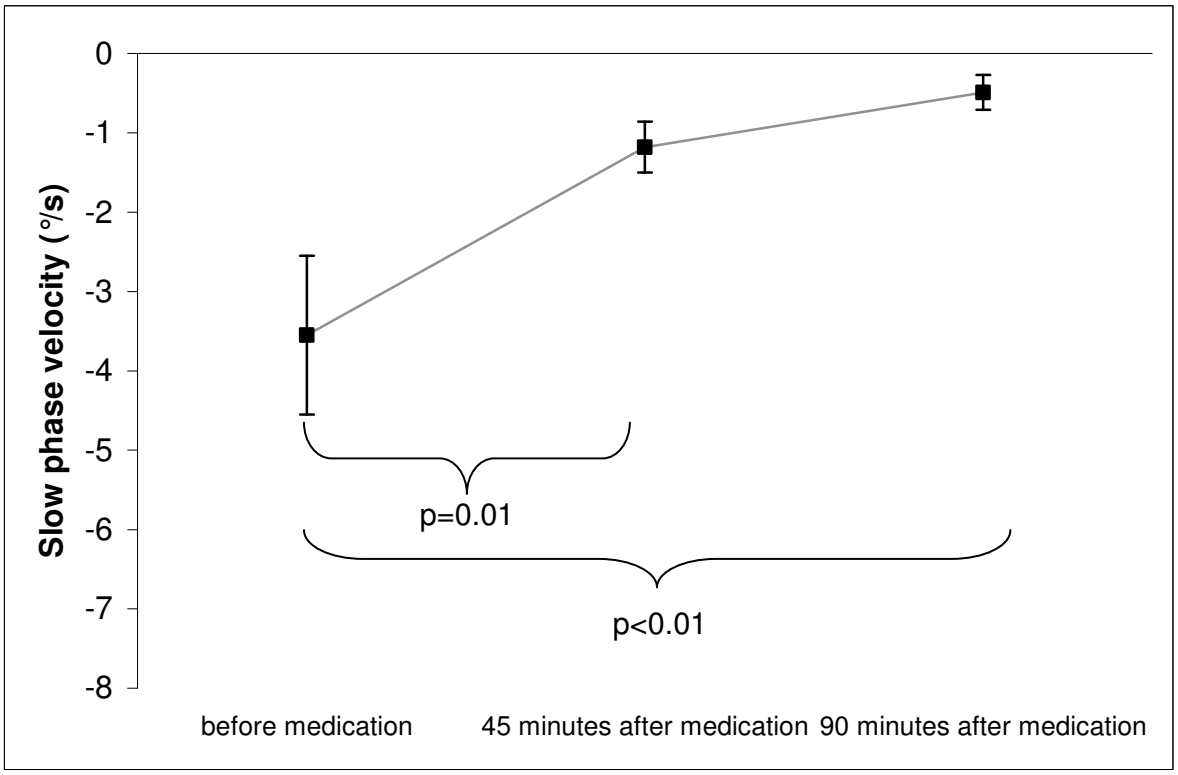


Figure 4.5 Comparing SPV across all three gaze conditions and both medications between all three measurements (before medication, 45 minutes after medication and 90 minutes after medication), measured in upright position with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

In contrast to the first section of the analysis, there was a significant main effect in terms of *medication*, $F(1, 5)=9.27$, $p<0.05$, where average SPV was lower after the administration of 4-AP (-1.22 deg/s) than after the administration of 3,4-DAP (-2.25 deg/s). The before-medication measurements in 3,4-DAP (-3.73 deg/s) and 4-AP (-3.38 deg/s) were almost identical ($p=0.99$). Figure 4.6 displays the main effect in terms of medication. This effect main effect of *medication* even remains preserved when excluding the before-medication measurements, $F(1, 5)=7.01$, $p<0.05$.

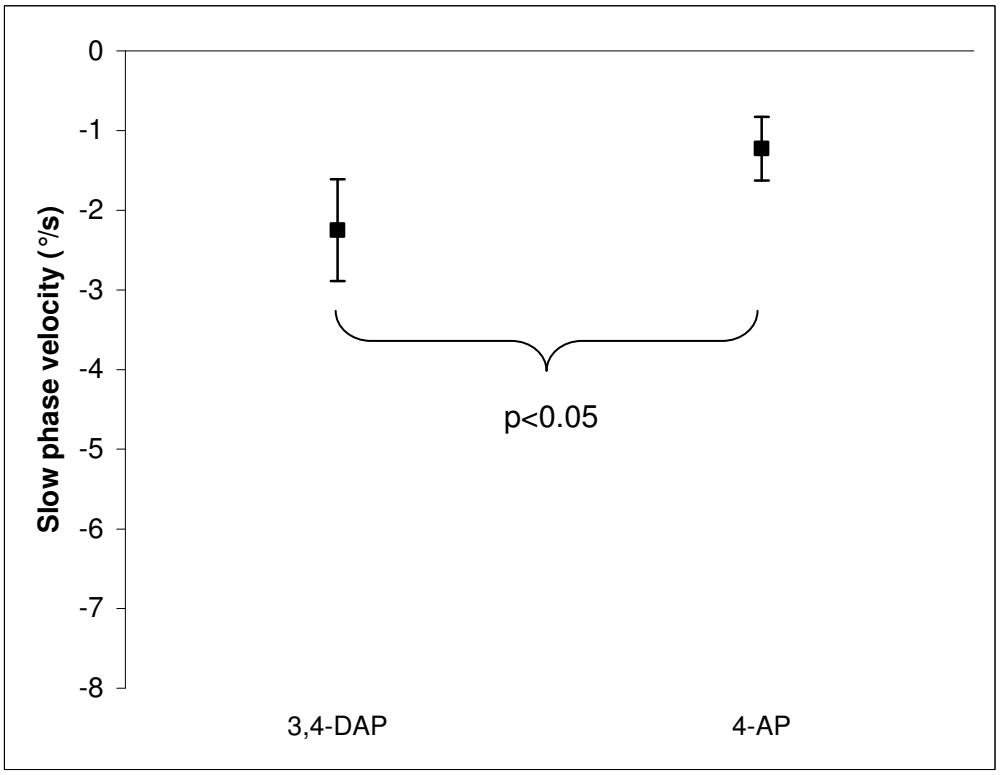


Figure 4.6 Comparing SPV between 3,4-DAP and 4-AP, across all three gaze conditions and time, measured in upright position with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

Going back to the analysis where the before-medication measurements were included, none of the tests on interactions became significant, i.e. neither *gaze times medication*, $F(2, 10)=2.12$, $p=0.17$, nor *gaze times time*, $F(4, 20)=1.14$, $p=0.365$, nor *medication times time*, $F(2, 10)=1.73$, $p=0.23$, nor *gaze times medication times time*, $F(4, 20)=0.35$, $p=0.84$.

4.2.3. Third section including the within subjects factor body orientation

Consistent with the findings from the previous two studies, the analysis with respect to *body orientation* resulted in a significant main effect, $F(2, 14)=4.54$, $p<0.05$ (Figure 4.7). The Scheffé post-hoc comparisons between upright (-2.23 deg/s), supine (-2.02 deg/s) and prone (-4.12 deg/s) led to an error probability of $p=0.96$ between upright and supine position, $p=0.08$ between upright and prone position and $p=0.0501$ between supine and prone position.

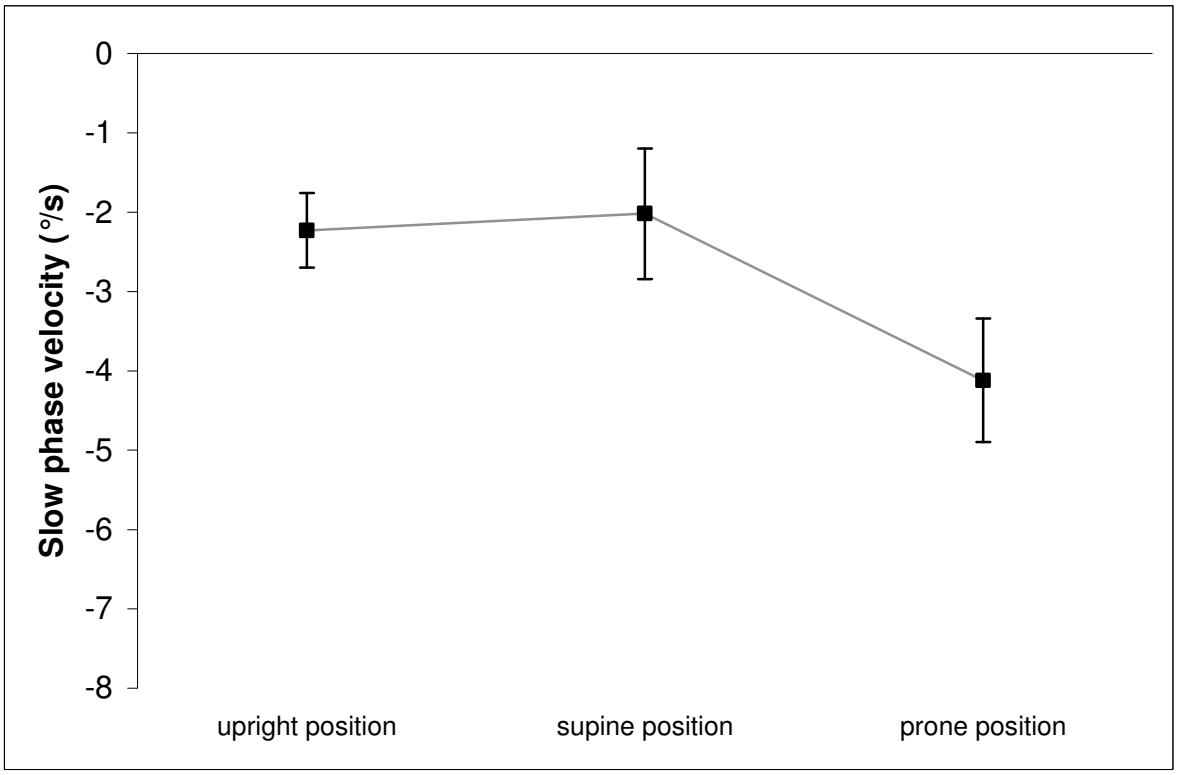


Figure 4.7 Comparing SPV between upright, supine and prone positions, across both medications and time, measured in gaze straight ahead with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

In line with the expectation that DBN decreases after the administration of aminopyridines (see the previous two chapters), the analysis resulted in a significant main effect of *time* (pre vs. post 45 vs. post 90), $F(2, 14)=13.85$, $p<0.001$ (Figure 4.8a), with significant post-hoc Scheffé comparisons before medication and 45 minutes after medication ($p<0.01$) or 90 minutes after medication ($p<0.001$), and no significant difference between 45 minutes and 90 minutes after medication ($p=0.77$). When considering the difference between both medications, there was only a marginally significant effect, $F(1, 7)=4.14$, $p=0.08$, with 3,4-DAP resulting in a mean slow phase velocity of -3.175 deg/s and 4-AP in a mean slow phase velocity of -2.41 deg/s.

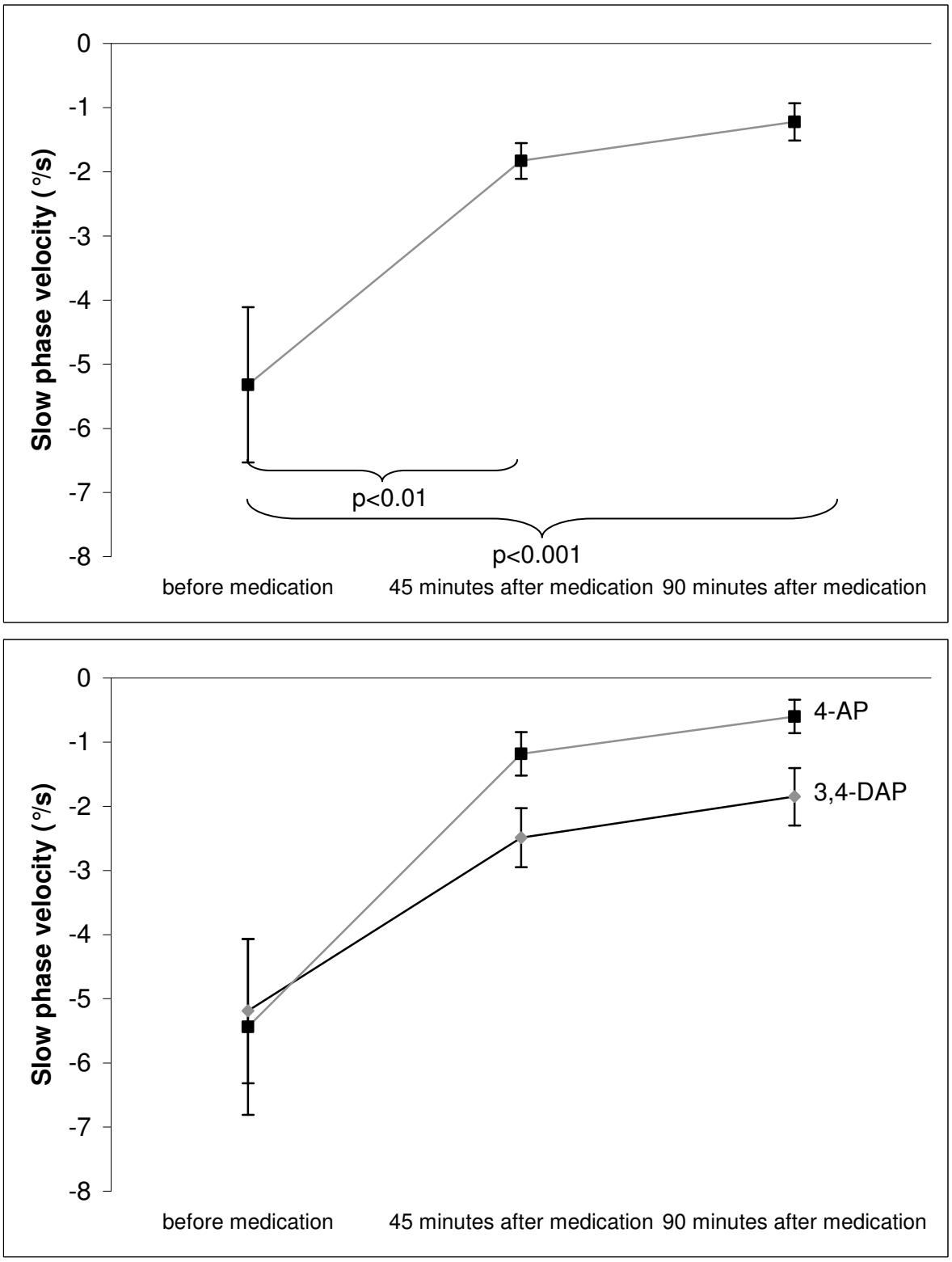


Figure 4.8a Comparing SPV between all three measurements (before medication, 45 minutes after medication and 90 minutes after medication), across all three body positions and both medications, measured in gaze straight ahead with the light switched on, **b** Comparing SPV between both medications and all three measurements (before medication, 45 minutes and 90 minutes after medication), across all three body positions, measured in gaze straight ahead with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean (in both 4.8a and 4.8b).

Likewise, the *medication times time* interaction became marginally significant, $F(2, 14)=2.87$, $p=0.09$, where both 3,4-DAP (-5.19 deg/s) and 4-AP (-5.44 deg/s) had approximately the same before-medication values ($p=0.998$), but the decrease in descriptive mean slow phase velocity values seemed weaker for 3,4-DAP (45 minutes after medication: -2.49 deg/s, 90 minutes after medication -1.85 deg/s) than for 4-AP (45 minutes after medication: -1.18 deg/s, 90 minutes after medication -0.6 deg/s), Figure 4.8b. When excluding the before-medication-measurements due to the fact that they are not exactly the same, the descriptive trend between 4-AP and 3,4-DAP in Figure 4.8b (45 minutes and 90 minutes after medication) becomes statistically different. Overall, this results in a significant main effect with respect to *medication*, $F(1, 7)=7.17$, $p<0.05$, where 3,4-DAP has an overall average SPV-value of -2.17 deg/s and 4-AP an overall average SPV-value of -0.89 deg/s.

Going back to the analysis where the before-medication measurements were included, none of the tests on interactions became significant, neither the *body orientation times medication* interaction, $F(2, 14)=2.215$, $p=0.15$, nor the *body orientation times time interaction*, $F(4, 28)=1.51$, $p=0.23$, nor the *body orientation times medication times time* interaction, $F(4, 28)=0.17$, $p=0.95$. When excluding the before-medication measurements, there are no significant interactions either.

4.2.4. Testing the influence of aetiology on the intensity of downbeat nystagmus

It was tested whether there was a significant difference in SPV-values based on the two different aetiologies. The two different aetiologies were cerebellar reasons or unknown reasons.

The first analysis neither resulted in a main effect for the between subjects factor *aetiology,* $F(1, 6)=0.1$, $p=0.76$, nor an *aetiology times light* interaction, $F(1, 6)=3.09$, $p=0.13$,

nor an *aetiology times medication* interaction, F(1, 6)=2.71, p=0.15, nor an *aetiology times time* interaction F(2, 12)=0.1, p=0.91, nor an *aetiology times light times medication* interaction F(1, 6)=0.04, p=0.84, nor an *aetiology times light times time* interaction F(2, 12)=0.61, p=0.56, nor an *aetiology times medication times time* interaction F(2, 12)=0.3, p=0.75, nor an *aetiology times light times medication times time* interaction, F(2, 12)=0.6, p=0.56. Overall, cerebellar patients even had a descriptively lower average SPV-value (-3.245 deg/s) than the patients with unknown aetiologies (-3.67 deg/s). The inclusion of the between subjects factor *aetiology* did not make any difference with respect to the overall interpretation of the results, as the same within subjects factors (light and time) and the same interaction (medication times time) were present in the analysis where no between subjects factor had been included.

The second analysis neither resulted in a main effect for the between subjects factor *aetiology,* F(1, 4)=0.0001, p=0.99, nor an *aetiology times gaze* interaction, F(2, 8)=0.54, p=0.6, nor an *aetiology times medication* interaction, F(1, 4)=1.46, p=0.29, nor an *aetiology times time* interaction F(2, 8)=0.02, p=0.98, nor an *aetiology times gaze times medication* interaction F(2, 8)=1.19, p=0.35, nor an *aetiology times gaze times time* interaction F(4, 16)=0.87, p=0.5, nor an *aetiology times medication times time* interaction F(2, 8)=0.23, p=0.8, nor an *aetiology times gaze times medication times time* interaction, F(4, 16)=1.06, p=0.41. Overall, cerebellar patients had almost the same average SPV-value (-1.73 deg/s) as the patients with unknown aetiologies (-1.74 deg/s). The inclusion of the between subjects factor *aetiology* did not make any difference with respect to the overall interpretation of the results, as the same within subjects factors (gaze, medication and time) and a complete absence of interactions were also present in the analysis where no between subjects factor had been included.

The third analysis neither resulted in a main effect for the between subjects factor *aetiology,* F(1, 6)=0.37, p=0.56, nor an *aetiology times time* interaction F(2, 12)=0.08, p=0.92,

nor an *aetiology times body orientation times medication* interaction F(2, 12)=1.06, p=0.38, nor an *aetiology times body orientation times time* interaction F(4, 24)=0.955, p=0.45, nor an *aetiology times medication times time* interaction F(2, 12)=0.01, p=0.99, nor an *aetiology times body orientation times medication times time* interaction, F(4, 24)=1.97, p=0.13. Overall, cerebellar patients had a more pronounced average SPV-value (-3.15 deg/s) as the patients with unknown aetiologies (-2.435 deg/s). Although there was no main effect with respect to the between subjects factor *aetiology*, the inclusion of this factor made a difference with respect to the overall interpretation of the results. Prior to the inclusion of the between subjects factor, there were main effects with respect to *body orientation* and *time* and marginally significant effects with respect to *medication* and the *medication times time* interaction. After inclusion of the between subjects factor, there were still significant main effects with respect to the within subjects factors *body orientation,* F(2, 12)=8.44, p<0.01, and *time*, F(2, 12)=12.03, p<0.01, but the marginally significant effect for *medication* now turned out significant, F(1, 6)=10.91, p<0.05 (average SPV of 3,4-DAP: -3.175 deg/s versus average SPV of 4-AP: -2.41 deg/s, see Figure 4.9). No exclusion of the before-medication measurements were necessary, as 3,4-DAP had even less pronounced average SPV-values at the before-medication measurements (-5.19 deg/s) than 4-AP (-5.44 deg/s), so in spite of the fact that 4-AP was disadvantaged due to a lower before-medication measurement, the main effect nevertheless turned out significant.

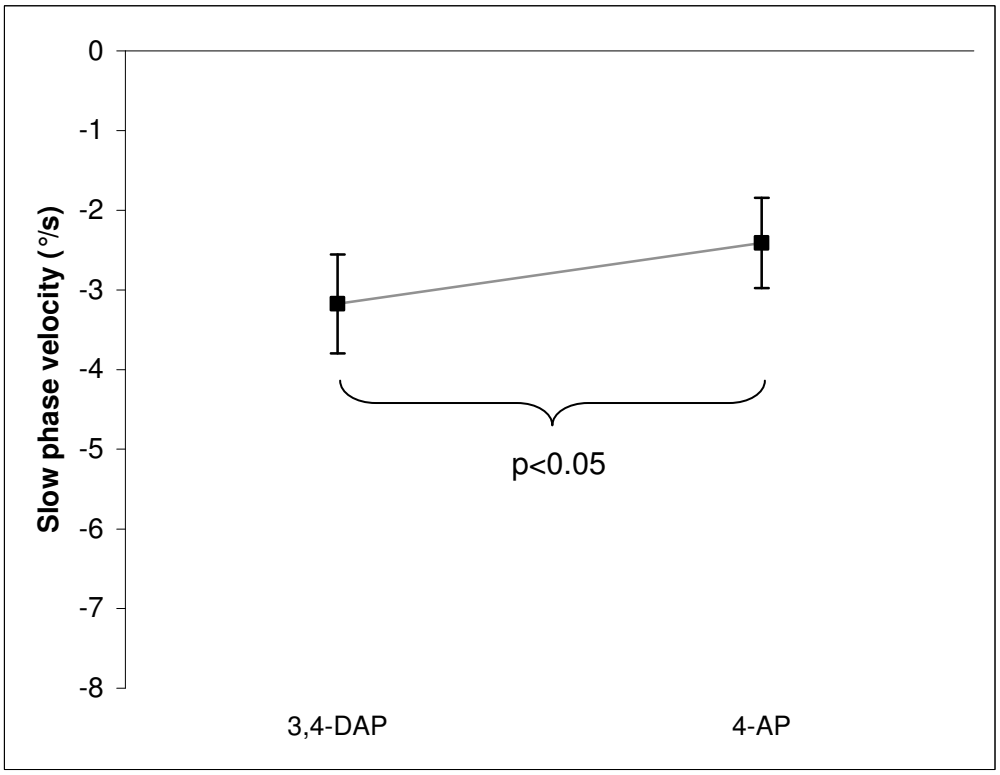


Figure 4.9 Comparing SPV between 3,4-DAP and 4-AP, across aetiology, body orientation and time, measured in gaze straight ahead with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

Another finding that differed from the analysis without the between subjects factor is that the marginally significant *medication times time* interaction switched from marginally significant to not significant when the between subjects factor was included, $F(2, 12)=2.46$, $p=0.13$. Furthermore, there were significant interactions involving the between subjects factor *aetiology*. The *aetiology times body orientation* interaction became significant, $F(2, 12)=7.01$, $p<0.01$ (Figure 4.10), where the cerebellar patients replicated the trend (upright: -2.52 deg/s, supine: -1.36 deg/s, prone: -5.56 deg/s) of the analysis without the inclusion of *aetiology* as a between subjects factor (see Figure 4.7), whereas patients with unknown aetiologies showed a completely different pattern of results, with upright position even having a less pronounced average SPV-value (-1.94 deg/s) than supine (-2.69 deg/s) and prone (-2.68 deg/s). None of the post-hoc Scheffé-tests comparing the two aetiologies in the three different body positions

became significant. The only significant post-hoc test was the difference between supine position and prone position among cerebellar patients ($p<0.01$).

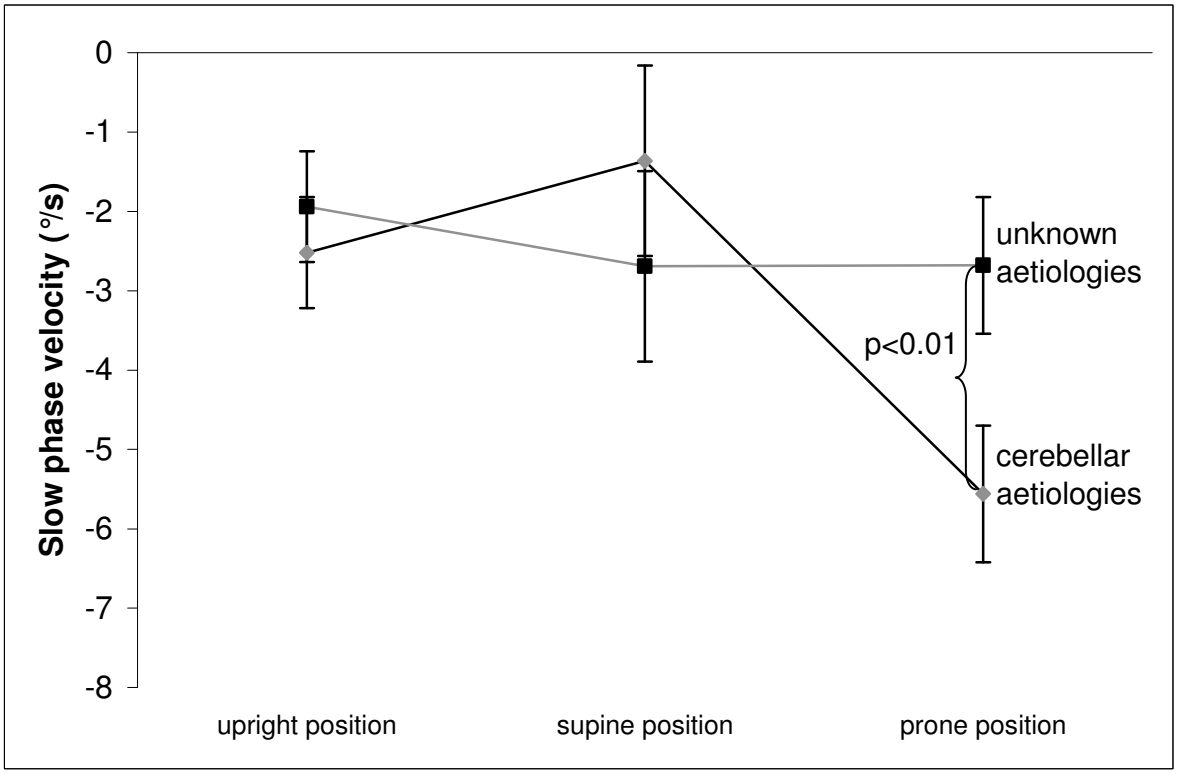


Figure 4.10 Comparing SPV between patients with cerebellar and unknown aetiologies of DBN in the three different body positions. The comparison is across medication and time, measured in gaze straight ahead with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

The *aetiology times medication* interaction also turned out significant, $F(1, 6)=12.45$, $p<0.05$ (Figure 4.11), where the average SPV-value was only more pronounced in 3,4-DAP (-3.94 deg/s) than in 4-AP (-2.35 deg/s) when patients had cerebellar aetiology (Scheffé: $p<0.05$), whereas 3,4-DAP (-2.41 deg/s) and 4-AP (-2.46 deg/s) had approximately equal average SPV-values (Scheffé: $p=1$) when patients had unknown aetiologies. Other post-hoc comparisons did not become significant ($p>0.5$).

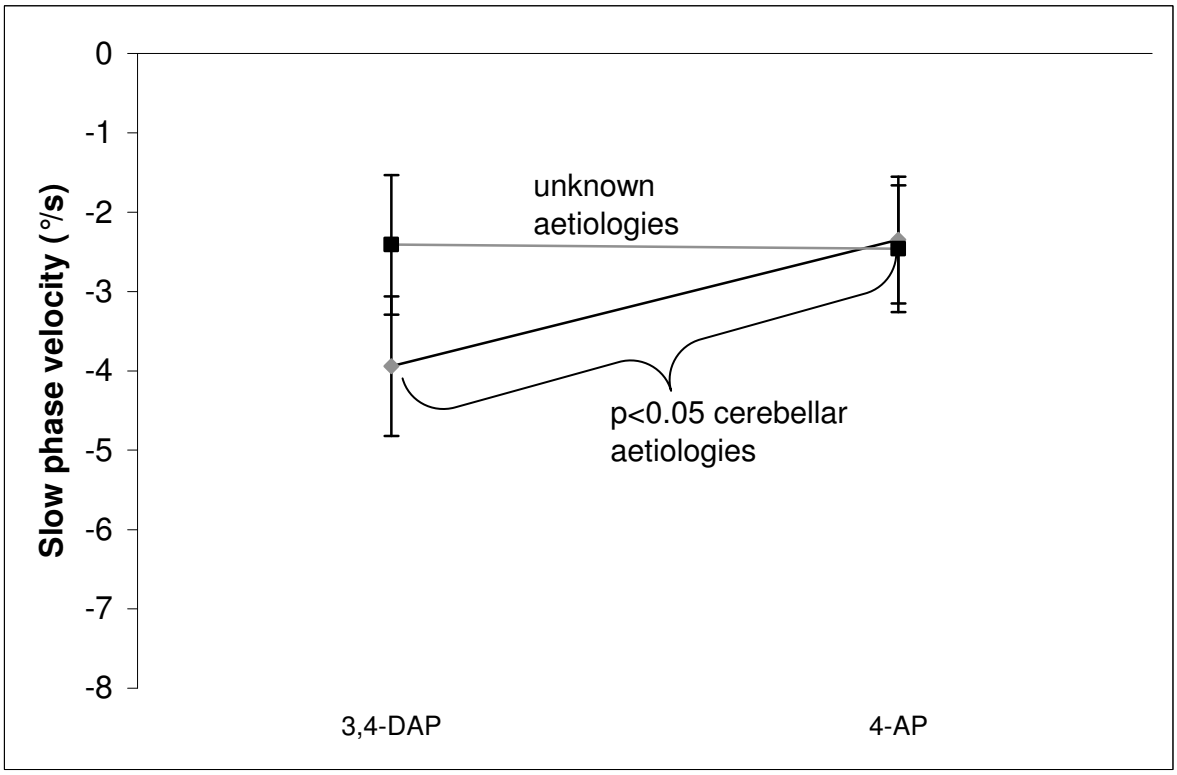


Figure 4.11 Comparing the two different medications in terms of SPV-values between patients with cerebellar and unknown aetiologies of DBN. The comparison was across body orientation and time, measured in gaze straight ahead with the light switched on. Display of mean slow phase velocities along with the standard error bars of the mean.

The previously mentioned absence of interactions in terms of *body orientation times medication*, *body orientation times time*, *body orientation times medication times time* overlapped with the analysis where the between subjects factor aetiology was included and the one where it was not included.

4.3. Discussion

Although both 4-AP and 3,4-DAP had previously shown symptom alleviation in DBN, in particular an improvement of slow-phase velocity (SPV) over a placebo, both drugs had not been compared in terms of their treatment efficacy yet. Consequently, they were compared in a double-blind study with crossover design. It turned out that both aminopyridines resulted in a significant SPV-decrease, because SPV had become less in both measurements 45 minutes

and 90 minutes after administering the medications. This was no new finding, as the previously mentioned placebo-controlled trials by Strupp et al. (2003) and Kalla et al. (2007) had already shown that 3,4-DAP and 4-AP were associated with a decreased intensity of DBN. What is new about this study is that it showed a decreased intensity of DBN even 90 minutes after the ingestion of the capsule. This complements earlier findings by Strupp et al. (2003), who observed a U-shaped curve in terms of DBN intensity, with DBN having the lowest intensity from 30 minutes to 45 minutes after ingestion of a 20 mg 3,4-DAP capsule and a higher intensity later on (e.g. 90 minutes after ingestion). In the present study, a 10 mg ingestion of 3,4-DAP was associated with no higher DBN intensity 90 minutes after ingestion than 45 minutes after ingestion. Hence, it is a new finding, but it does not contradict Strupp et al. (2003), because the medication was not administered in the same dose, and the U-shaped curve in Strupp et al. (2003) was based on a single case, whilst the results in the present study were based on 8 patients. Moreover, DBN was assessed by mean peak slow phase velocity in Strupp et al. (2003), whereas it was assessed by average slow phase velocity here. What is also new about this study is that it is the first that compared both aminopyridines to find out whether one is better suited to treat DBN than the other. In the first section including the within subjects factor *light* (fixation versus viewing in the dark), the difference in terms of mean SPV was revealed by Scheffé post-hoc comparisons following the significant *medication* (4-AP vs. 3,4-DAP) times *time* (pre-med vs. post 45 vs. post 90) interaction. These significant post-hoc comparisons showed that the decrease in SPV was significantly more pronounced for 4-AP than for 3,4-DAP (in both 45 minutes and 90 minutes post-medication-measurements). At this stage, it is only possible to speculate about the nature of this difference. It might be due to a better ability of 4-AP to cross the blood-brain barrier as well as a longer half-life (Hayes, 1994; Hayes et al., 2003; Judge & Bever, 2006; Kalla et al., 2009, Kalla et al., 2011; Leigh, 2003). In order to find supporting evidence for this assumption, however, further placebo-controlled studies are necessary, in particular a

therapeutic trial over more than 2 post-medication measurements and a detailed pharmacological drug-monitoring (e.g. determining the concentration of both medications in the serum) including a comparison between both medications with dose efficacy curves. There were additional results in the first section of the statistical analysis. The main effect of *time* indicated that across both medications, DBN as indexed by the slow phase velocity decreased with time. This was an expected finding, because both Strupp et al. (2003) and Kalla et al. (2007) had individually shown in placebo-controlled trials that both medications decrease DBN after the medication was administered. Moreover, the effect in this study seems to be an effect of medication rather than a mere effect of time (as it used to be in Spiegel et al., 2009a), because the decrease occurs very rapidly (45 minutes after drug administration) and the time interval between the before-medication VOG and the next VOG was only 45 minutes, as compared to 2 hours in the study on daytime dependence of DBN (Spiegel et al., 2009a). This main effect was also seen in the second and third section of this analysis.

When referring to the influence of fixation, the intensity of DBN was less pronounced in light, where people were able to fixate. The ability to fixate is known to be associated with a lower intensity of DBN, which was also found in the first two studies of this thesis (chapters 2 and 3) and appeared in the literature before (e.g. Spiegel et al., 2009a). As a result, this finding is consistent with current knowledge. It is important to note that this is a mere main effect, i.e. due to the absence of a *light times medication* interaction, the fixation effect was in no way differentially influenced by the two drugs. All other possible interactions in the first section of the analysis (*light times time* or *light times medication type times time*) did not become significant either. Furthermore, it made no difference to the general interpretation of the results whether the between subjects factor *aetiology* was included or not.

The second section of this analysis included the within subjects factor *gaze direction*. As explained in the introduction and the first two studies, there was a significant main effect of *gaze direction*, where upward gaze was associated with significantly lower mean slow

phase velocity values than downward gaze or gaze straight ahead. Although this finding is consistent with Alexander's law, it is interesting that downward gaze and gaze straight ahead did not significantly differ from each other. Considering the descriptive findings, downward gaze even had a less pronounced mean slow phase velocity than gaze straight ahead, which is consistent with the first study of this thesis (chapter 1), but not with Alexander's law, where slow phase velocity decreases when gaze moves away from the direction of the fast phase (Jeffcoat et al., 2008; Robinson et al., 1984), i.e. it should be lower instead of higher in gaze straight ahead when compared with downward gaze. As in the first section of this analysis, DBN significantly decreased from the before-medication measurements to the measurements after drug administration (across all three gaze directions). In contrast to the first section of the analysis, however, there was a significant main effect in terms of *medication*, where SPV was lower after the administration of 4-AP than after the administration of 3,4-DAP in spite of the fact that the before-medication measurements in 3,4-DAP and 4-AP did not differ from each other. This underlines that 4-AP seems better suited to alleviate the symptoms of DBN than 3,4-DAP. Given that none of the gaze-related interactions in the second section of this analysis became significant, the improvement over time and the difference between both medications was not affected by gaze-direction. Moreover, it made no difference to the general interpretation of the results whether the between subjects factor *aetiology* was included or not.

The third section of this analysis included the within subjects factor body orientation. In line with Brandt (1990), Marti et al. (2002) and the first two studies of this thesis, there was a significant main effect with respect to body orientation. However, post-hoc analyses revealed that the differences between supine position and prone position and between upright position and prone position were only marginally significant, whilst supine and upright position did not significantly differ from each other. Hence, the general finding on gravitational influence through different body positions on DBN from the previous two

studies was confirmed, but the detailed individual comparisons between the different body positions lacked confirmation when taking the conventional type one error probability level of five percent. Similar to the first two sections of this analysis, DBN decreased after administration of the medication, as there was a main effect of *time*, i.e. irrespective of gaze direction and type of medication, DBN was lower after than before aminopyridine administration. Turning to a potential difference between both aminopyridines next, a marginally significant finding revealed no proof but a descriptive trend that 4-AP was associated with lower mean slow phase velocity values than 3,4-DAP. Likewise, the *medication times time* interaction became marginally significant, where the decrease in mean slow phase velocity values seemed weaker for 3,4-DAP than for 4-AP after before-medication values did not significantly differ from each other. Hence, this finding is not in contrast to the findings of the first two sections of this analysis, where advantages of 4-AP over 3,4-DAP were raised in terms of DBN alleviation. When excluding the before-medication measurements, there was even a significant main effect with regard to *medication*, where 4-AP was associated with a lower intensity of DBN than 3,4-DAP. It made sense to exclude the before-medication measurements, because they were associated with a descriptively (though not significantly) higher DBN intensity for 4-AP than for 3,4-DAP, i.e. the exclusion of the before-medication measurements gave 4-AP a fairer comparison with 3,4-DAP. Because none of the body-positional interactions in the third section of this analysis became significant (neither with nor without the before-medication measurements), the improvement over time and the difference between both medications was not affected by body position.

The third section was the only section where it made a difference to the interpretation of the results when the between subjects factor *aetiology* was included. Although there was no main effect with respect to *aetiology* (with a descriptive trend that average SPV-values were more pronounced for cerebellar patients than for patients with unknown aetiologies) and even though the majority of interactions including *aetiology* did not turn out significant, the

presence of this between subjects factor nevertheless had important consequences. After including the factor *aetiology*, there was a significant main effect of *medication* (with 4-AP being associated to a lower intensity of DBN). This effect had only been marginally significant prior to the inclusion of the between subjects factor. In addition, there were two interactions of interest that included the between subjects factor *aetiology*. The *aetiology times body orientation* interaction indicated that cerebellar patients replicated the trend from Marti et al. (2002), which was hypothesised for cerebellar patients in particular, where supine position had the lowest intensity of DBN, upright position took the medium position and prone position was associated with the highest intensity of DBN. Patients with unknown aetiologies showed an entirely different pattern of results, where, from a descriptive point of view, upright position was associated with the lowest intensity of DBN, prone position was in the middle and supine position had an equal or even vaguely higher intensity of DBN than prone position. It is difficult to interpret this type of interaction, as this interaction did not turn out significant in previous analyses, e.g. in the first study of this thesis (see chapter 1). Moreover, none of those post-hoc tests that compared the three different body positions between the two aetiologies became significant. Hence, this interaction might be due to chance. It is particularly surprising that the cerebellar patients replicated the pattern of results that were mostly achieved with patients not having a cerebellar aetiology in the two previous studies, whist the patients with unknown aetiologies showed a different pattern of results. Nevertheless, it shows that as far as this analysis is concerned, aetiology made a difference to this analysis. This difference becomes even clearer when considering the *aetiology times medication* interaction, where the intensity of DBN was only more pronounced after the administration of 3,4-DAP than after the administration of 4-AP in case patients had a cerebellar aetiology, whereas administration of 3,4-DAP and 4-AP showed equal effects for the unknown aetiologies. Hence, 4-AP might have a particularly positive effect in cerebellar patients that is not reflected by 3,4-DAP, although it needs to be kept in mind that both

medications show a significant improvement over before-medication DBN and have been shown to be better than placebo by Strupp et al. (2003) for 3,4-DAP and by Kalla et al. (2007) for 4-AP. Hence, 4-AP might have an additional effect on cerebellar aetiology of DBN, e.g. because it is better able to cross the blood-brain barrier (e.g. Hayes, 1994; Hayes et al., 2003; Judge & Bever, 2006; Kalla et al., 2009; Kalla et al., 2011; Leigh, 2003). However, due to the low number of patients per group (n = 4), one should be cautious and avoid making strong claims about aetiology and its effect on the two medications. Nevertheless, there is an additional study where 4-AP worked best when DBN was associated with cerebellar atrophy (Kalla et al., 2007), so it seems worth to further investigate this issue in the future.

5. Conclusion

In this thesis, three aspects of DBN were examined: first, the effects of daytime on the changes of its intensity, second the effects of body position on the changes of its intensity during daytime, and third, the differential effects of 3,4-DAP versus 4-AP. So far, a cure for DBN is not in sight, as there can be many underlying causes, most of them cause a progressive loss of cells with cerebellar atrophy.

As known from previous research (Jeffcoat et al.; 2008, Marti et al., 2008; Robinson et al., 1984; for a summary, see Spiegel et al., 2009a), the intensity of DBN is generally weaker in gaze upward. As reported in Spiegel et al. (2009a), it is also weaker when people are able to fixate (e.g. during daylight or when the light is switched on). In daily life, most activities are carried out under conditions where people are able to fixate. However, people rarely perform upwards directed gaze all the time. As shown in the first two studies of this thesis, however, there are additional characteristics that alleviate the symptoms. The intensity of DBN decreases in the course of the day (chapter 1 and Spiegel et al., 2009a). Hence, it would be possible to recommend patients to do activities such as office work later during the day (after 11am). In the morning hours, one could engage in activities that are less dependent on gaze holding. If it is nevertheless necessary to do office work in the morning hours, one might recommend to the patients to arrange the screen and the keyboard of the computer in such a way that it could be done in supine position (with slight gaze upward), because the studies in this thesis confirmed that body position has a significant influence on the intensity of DBN. As it turned out, however, the intensity of DBN in various body positions is also mediated by the body resting positions prior to the measurement (chapter 2 of this thesis). This became particularly clear when patients were tested in upright position (Spiegel et al., 2010). Had they previously rested in upright position, their DBN was lower than if they had previously rested in prone position. When tested in prone position, their DBN tended to be lower if they had

previously rested in prone position as compared to having rested in upright position. This indicates that not only the body positions are relevant with respect to DBN intensity, but also the changes from previous body position to current body position. As a practical application, one could recommend people to rest in upright position if they intend to do office work in upright position following the resting period. Alternatively, it is better for them to rest in prone position prior to activities in prone position, e.g. prior to gymnastics or swimming. As far as resting in upright position is concerned, there was a tentative trend that people should rather rest in darkness than with the light switched on, i.e. in contrast to the finding that the possibility to fixate suppresses the intensity of DBN, resting should be done with no fixation. These results are limited to resting periods in upright position, though, as no comparison between resting under light and darkness conditions has been carried out for supine or prone position thus far.

According to literature reviews (e.g. Kalla et al., 2008; Spiegel et al., 2009b; Strupp & Brandt, 2006; Strupp et al., 2011a), there also exist pharmacological ways to achieve symptom alleviation. Among the most promising pharmacological approaches up to the present date are the two aminopyridines 4-AP and 3,4-DAP. This was first demonstrated in double-blind and placebo-controlled studies with cross-over design for 3,4-DAP (Strupp et al., 2003) as well as for 4-AP (Kalla et al., 2007). The two aminopyridines, however, had not been compared thus far. Hence, it was the aim to compare both aminopyridines in terms of their efficacy in a double-blind study with cross-over design. In the previous chapter of this thesis and Kalla et al. (2011), where I shared the first-authorship, it had been shown in detail that 4-AP is more effective than 3,4-DAP. In addition, there was a tentative trend that it was particularly effective for cerebellar patients. This is no surprising result, though, as it had been reported to better cross the blood-brain barrier and to have a longer half-life than 3,4-DAP (Hayes, 1994; Hayes et al., 2003; Judge & Bever, 2006; Kalla et al., 2009; Kalla et al, 2011; Leigh, 2003). One should, however, avoid drawing bold conclusions on the basis of this

result, as the number of eight patients in this study was relatively low (with four cerebellar patients and four patients with DBN due to other aetiologies). Further studies with more patients would be necessary to confirm this finding, especially a placebo-controlled trial with more than two post-medication measurements and a detailed pharmacological drug monitoring. Nevertheless and in spite of the low number of patients having been involved in this study, there seems to be a clear effect favouring 4-AP over 3,4-DAP. Until further clinical trials have been completed, one could recommend patients with DBN to take 4-AP. According to a literature review (Judge & Bever, 2006) it is still unclear whether one of the two aminopyridines shows more toxicity, but clinical observations have revealed that 4-AP is associated with less adverse side effects than 3,4-DAP (personal communication, Andreas Sprenger, 26 March 2009). Hence, it makes sense to recommend 4-AP to patients with DBN as long as no new findings on adverse reactions or toxicity are reported.

To derive further insights on what could be recommended to patients, additional studies will be necessary. It has to be kept in mind, though, that only a small number of patients have DBN-symptoms, so it is difficult to conduct large clinical trials with many patients. Moreover, it would be too stressful for many patients to undergo a large number of different trials. For that reason, this thesis focused on different alternatives with as many patients as were available. Based on the results obtained so far, a number of recommendations can already be made to these patients. In spite of the fact that larger trials with additional variations are necessary, the discussion of the main results in each chapter has shown that many findings were quite robust to variations, especially the daytime improvement of DBN, the effect of fixation as well as the effect of gaze direction and body orientation. There was also some evidence that gravity has an influence on DBN, as the intensity of DBN in the different body positions was mediated by the body positions during the resting intervals. This could have been the result of the patients' otoliths exerting a stabilizing influence on otolith-related central vestibular neurons (Spiegel et al., 2010). Hence, these three clinical studies

along with their sub-studies have added a few insights. They also gave rise to new hypotheses that can be tested in future studies on DBN-treatment. One promising new way of treating DBN is 4-AP in its sustained released form (Ampyra^{TM}, Biogen Idec, Cambridge MA, USA) and case studies on individual patients under the supervision of Michael Strupp have already provided positive effects on the reduction of slow phase velocity and the improvement of ataxia. The sustained released form had been thoroughly tested in patients with multiple sclerosis by Goodman et al. (2008). Based on the case observations by Strupp and his colleagues, there is a good chance that it will also successfully alleviate symptoms in patients with DBN.

6. References

Alviña, K. & Khodakhah, K. (2010). The therapeutic mode of action of 4-aminopyridine in cerebellar ataxia. *Journal of Neuroscience*, 30(21): 7258-7268.

Angelaki, D.E. (2004). Eyes on target: what neurons must do for the vestibuloocular reflex during linear motion. *Journal of Neurophysiology*, 92(1):20-35.

Averbuch-Heller, L., Tusa, R.J., Fuhry, L., Rottach, K.G., Ganser, G.L., Heide, W., Büttner, U., & Leigh, R.J. (1997). A double-blind controlled study of gabapentin and baclofen as treatment for acquired nystagmus. *Annals of Neurology*, 41(6): 818-825.

Baloh, R.W. & Spooner, D.W. (1981). Downbeat nystagmus: a type of central vestibular nystagmus. *Neurology*, 31(3): 304–310.

Baloh, R.W., Yue, Q., & Demer, J.L. (1995). The linear vestibulo-ocular reflex in normal subjects and patients with vestibular and cerebellar lesions. *Journal of Vestibular Research: equilibrium & orientation*, 5(5): 349-361. [cited by Marti et al., 2002]

Barin, K. (2004). Calculating slow phase velocity of nystagmus. *Audiology online*, 13 Sep. 2004, http://www.audiologyonline.com/askexpert/display_question.asp?question_id=244

Bense, S., Best, C., Buchholz, H.G., Wiener, V., Schreckenberger, M., Bartenstein, P., & Dieterich, M. (2006). 18F-fluorodeoxyglucose hypometabolism in cerebellar tonsil and flocculus in downbeat nystagmus. *Neuroreport*, 17(6): 599-603.

Böhmer, A. & Straumann, D. (1998). Pathomechanisms of mammalian downbeat nystagmus due to cerebellar lesion: a simple hypothesis. *Neuroscience Letters*, 250(2): 127-130.

Bortz, J. (1993). *Statistik für Sozialwissenschaftler* (4. Aufl.). Berlin: Springer.

Brandt, T. (1990). Positional and positioning vertigo and nystagmus. *Journal of the Neurological Sciences*, 95(1): 3-28.

Brandt, T. (2000). *Vertigo. Its multisensory syndromes*. London: Springer.

Brandt, T. (2003). *Vertigo. Its multisensory syndromes*. New York: Springer.

Brandt, T. & Dieterich, M. (1994). Vestibular syndromes in the roll plane: topographic diagnosis from brainstem to cortex. *Annals of Neurology*, 36(3): 337-347.

Brandt, T. & Dieterich, M. (1995). Central vestibular syndromes in the roll, pitch, and yaw planes: topographic diagnosis of brainstem disorders. *Neuroophthalmology*, 15: 291-303.

Bronstein, A.M. (2004). Vision and vertigo: some visual aspects of vestibular disorders. *Journal of Neurology*, 251(4): 381-387.

Büttner-Ennever, J.A. & Horn, A.K. (2002). The neuroanatomical basis of oculomotor disorders: the dual motor control of extraocular muscles and its possible role in proprioception. *Current Opinion in Neurology*, 15(1): 35-43.

Chambers, B.R., Ell, J.J., & Gresty, M.A. (1983). Case of downbeat nystagmus influenced by otolith stimulation. *Annals of Neurology*, 13(2): 204-207.

Cohen, J. (1988). *Statistical power analysis for the behavioural sciences* (2nd ed.). Hillsdale, N.J.: Erlbaum.

Crane, B.T., Tian, J.R., & Demer, J.L. (2000). Initial vestibulo-ocular reflex during transient angular and linear acceleration in human cerebellar dysfunction. *Experimental Brain Research*, 130(4): 486-496. [cited by Marti et al., 2002]

Crawford, J.D., & Vilis, T. (1991). Axes of eye rotation and Listing's law during rotations of the head. *Journal of Neurophysiology*, 65(3): 407-23.

Currie, J.N., & Matsuo, V. (1986). The use of clonazepam in the treatment of nystagmus-induced oscillopsia. *Ophthalmology*, 93(7): 924-932.

Davies, A., Hendrich, J., Van Minh, A.T., Wratten, J., Douglas, L., & Dolphin, A.C. (2007). Functional biology of the alpha(2)delta subunits of voltage-gated calcium channels. *Trends in Pharmacological Sciences*, 28(5): 220-228.

Dieterich, M., Straube, A., Brandt, T., Paulus, W., & Büttner, U. (1991). The effects of baclofen and cholinergic drugs on upbeat and downbeat nystagmus. *Journal of Neurology, Neurosurgery, and Psychiatry*, 54(7): 627-632.

Encyclopaedia Britannica (1987). “Sensory reception: human vision: structure and function of the human eye" Chicago: Encyclopaedia Britannica.

Eron, J.N., Cohen, B., Raphan, T., & Yakushin, S.B. (2008). Adaptation of orientation vectors of otolith-related central vestibular neurons to gravity. *Journal of Neurophysiology*, 100(3): 1686-1690.

Etzion, Y., & Grossman, Y. (2001). Highly 4-aminopyridine sensitive delayed rectifier current modulates the excitability of guinea pig cerebellar Purkinje cells. *Experimental Brain Research*, 139(4): 419-425.

Ferrara, M. & De Gennaro, L. (2000). The sleep inertia phenomenon during the sleep-wake transition: theoretical and operational issues. *Aviation, Space, and Environmental Medicine*, 71(8): 843-848.

Glasauer, S., Hoshi, M., Kempermann, U., Eggert, T., & Büttner, U. (2003). Three-dimensional eye position and slow phase velocity in humans with downbeat nystagmus. *Journal of Neurophysiology*, 89(1): 338-354.

Glasauer, S., Strupp, M., Kalla, R., Büttner, U., & Brandt, T. (2005a). Effect of 4-aminopyridine on upbeat and downbeat nystagmus elucidates the mechanism of downbeat nystagmus. *Annals of the New York Academy of Sciences*, 1039: 528-531.

Glasauer, S., Schneider, E., Jahn, K., Strupp, M., & Brandt, T. (2005b). How the eyes move the body. *Neurology*, 65(8): 1291-1293.

Goodman, A.D., Brown, T.R., Cohen, J.A., Krupp, L.B., Schapiro, R., Schwid, S.R., Cohen, R., Marinucci, L.N., Blight, A.R.; Fampridine MS-F202 Study Group. (2008). Dose

comparison trial of sustained-release fampridine in multiple sclerosis. *Neurology*, 71(15): 1134-1141.

Grasse, K.L., & Lisberger, S.G. (1992). Analysis of a naturally occurring asymmetry in vertical smooth pursuit eye movements in a monkey. *Journal of Neurophysiology*, 67(1): 164-179.

Gresty, M., Barratt, H., Rudge, P., & Page, N. (1986). Analysis of downbeat nystagmus. Otolithic vs semicircular canal influences. *Archives of Neurology*, 43(1): 52-55.

Halmagyi, G.M. & Curthoys, I.S. (1988). A clinical sign of canal paresis. *Archives of Neurology*, 45(7): 737-739.

Halmagyi, G.M., Rudge, P., Gresty, M.A., & Sanders, M.D. (1983). Downbeating nystagmus. A review of 62 cases. *Archives of Neurology*, 40(13): 777-784.

Hayes, K.C. (1994). 4-aminopyridine and spinal cord injury: a review. *Restorative Neurology and Neuroscience,* 6(4): 259-270.

Hayes, K.C., Katz, M.A., Devane, J.G., Hsieh, J.T., Wolfe, D.L., Potter, P.J., & Blight, A.R. (2003). Pharmacokinetics of an immediate-release oral formulation of Fampridine (4-aminopyridine) in normal subjects and patients with spinal cord injury. *Journal of Clinical Pharmacology*, 43(4): 379-385.

Heide, W. & Kömpf, D. (2005). Augenbewegungsstörungen. In C.W. Wallesch (Hrsg.): Neurologie: Diagnostik und Therapie in Klinik und Praxis, pp. 273-289. München: Urban & Fischer.

Helmchen, C., Sprenger, A., Rambold, H., Sander, T., Kömpf, D., & Straumann, D. (2004). Effect of 3,4-diaminopyridine on the gravity dependence of ocular drift in downbeat nystagmus. *Neurology*, 63(4): 752-753.

Hille, B. (2001). Ionic channels of excitable membranes. 3rd edition. Sunderlang, MA: Sinauer.

Hüfner, K., Stephan, T., Kalla, R., Deutschländer, A., Wagner, J., Holtmannspötter, M., Schulte-Altedorneburg, G., Strupp, M., Brandt, T., & Glasauer, S. (2007). Structural and functional MRIs disclose cerebellar pathologies in idiopathic downbeat nystagmus. *Neurology*, 69(11): 1128-1135.

Jeffcoat, B., Shelukhin, A., Fong, A., Mustain, W., & Zhou, W. (2008). Alexander's law revisited. *Journal of Neurophysiology*, 100(1): 154-159.

Jewett, M.E., Wyatt, J.K., Ritz-De Cecco, A., Khalsa, S.B., Dijk, D.J., & Czeisler, C.A. (1999). Time course of sleep inertia dissipation in human performance and alertness. *Journal of Sleep Research*, 8(1): 1-8.

Judge, S.I., & Bever, C.T. Jr. (2006). Potassium channel blockers in multiple sclerosis: neuronal Kv channels and effects of symptomatic treatment. *Pharmacology & Therapeutics*, 111(1): 224-259.

Kalla, R., Deutschländer, A., Hüfner, K., Stephan, T., Jahn, K., Glasauer, S., Brandt, T., & Strupp, M. (2006). Detection of floccular hypometabolism in downbeat nystagmus by fMRI. *Neurology*, 66(2): 281-283.

Kalla, R., Glasauer, S., Büttner, U., Brandt, T., & Strupp, M. (2007). 4-aminopyridine restores vertical and horizontal neural integrator function in downbeat nystagmus. *Brain*, 130(9): 2441-2451.

Kalla, R., Glasauer, S., Schautzer, F., Lehnen, N., Büttner, U., Strupp, M., & Brandt, T. (2004). 4-aminopyridine improves downbeat nystagmus, smooth pursuit, and VOR gain. *Neurology*, 62(7): 1228-1229.

Kalla, R., Spiegel, R., Rettinger, N., Glasauer, S., & Strupp, M. (2009). Therapy of downbeat nystagmus: 4-aminopyridine versus 3,4-diaminopyridine. *Klinische Neurophysiologie*, 40(1): 69.

Kalla, R., Spiegel, R., Claassen, J., Bardins, S., Hahn, A., Schneider, E., Rettinger, N., Glasauer, S., Brandt, T., & Strupp, M. (2011). Comparison of 10 mg doses of 4-aminopyridine and 3,4-diaminopyridine for the treatment of downbeat nystagmus. *Journal of Neuro-Ophthalmology*, 31(4): 320-325.

Kalla, R., Spiegel, R., Wagner, J., Rettinger, N., Jahn, K., & Strupp, M. (2008). Pharmakotherapie zentraler Nystagmusformen. *Nervenarzt*, 79(12): 1380-1385.

Klier, E.M., Hess, B.J., & Angelaki, D.E. (2008). Human visuospatial updating after passive translations in three-dimensional space. *Journal of Neurophysiology*, 99(4): 1799-1809.

Leigh, R. J. (2003). Potassium channels, the cerebellum, and the treatment of downbeat nystagmus. *Neurology*, 61(2): 158-159.

Leigh, R.J. & Zee, D.S. (2006). *The neurology of eye movements*. New York: Oxford University Press.

Leigh, R.J., Burnstine, T.H., Ruff, R.L., & Kasmer, R.J. (1991). Effect of anticholinergic agents upon acquired nystagmus: a double-blind study of trihexyphenidyl and tridihexethyl chloride. *Neurology*, 41(11): 1737-1741.

Löhle, M., Schrempf, W., Wolz, M., Reichmann, H., & Storch, A. (2008). Potassium channel blocker 4-aminopyridine is effective in interictal cerebellar symptoms in episodic ataxia type 2 - A video case report. Movement Disorders, 23(9): 1314-1316.

Marti, S., Palla, A., & Straumann, D. (2002). Gravity dependence of ocular drift in patients with cerebellar downbeat nystagmus. *Annals of Neurology*, 52(6): 712-721.

Marti, S., Straumann, D., Büttner, U., & Glasauer, S. (2008). A model-based theory on the origin of downbeat nystagmus. *Experimental Brain Research*, 188(4): 613-631.

Mosby's Medical Dictionary (2009). 8th edition. St. Louis: Elsevier.

Paige, G.D. & Seidman, S.H. (1999). Characteristics of the VOR in response to linear acceleration. *Annals of the New York Academy of Sciences*, 871: 123-135. [cited by Marti et al., 2002]

Pierrot-Deseilligny, C. & Milea, D. (2005). Vertical nystagmus: clinical facts and hypotheses. *Brain*, 128(6): 1237-1246.

Precht, W., Volkind, R., Maeda, M., & Giretti, M.L. (1976). The effects of stimulating the cerebellar nodulus in the cat on the responses of vestibular neurons. *Neuroscience*, 1(4): 301-312. [cited by Marti et al., 2002]

Rucker, J.C. (2005). Current treatment of nystagmus. *Current Treatment Options in Neurology*, 7(1): 69-77.

Robinson, D. A., Zee, D.S., Hain, T.C., Holmes, A., & Rosenberg, L.F. (1984). Alexander's law: its behaviour and origin in the human vestibule-ocular reflex. *Annals of Neurology*, 16(6): 714-722.

Rubin-Preminger, J.M., & Englert, U. (2007). 3,4-Diaminopyridine. *Acta Crystallographica Section E*, 63(2): 757-758.

Schneider, E., Glasauer, S., & Dieterich, M. (2002). Comparison of human ocular torsion patterns during natural and galvanic vestibular stimulation. *Journal of Neurophysiology*, 87(4): 2064-2073.

Schneider, E., Glasauer, S., Brandt, T., & Dieterich, M. (2003). Nonlinear nystagmus processing causes torsional VOR nonlinearity. *Annals of the New York Academy of Sciences*, 1004: 500-505.

Shinmey, Y., Yamanobe, T., Fukushima, J., & Fukushima, K. (2002). Purkinje cells of the cerebellar dorsal vermis: simple-spike activity during pursuit and passive whole-body rotation. *Journal of Neurophysiology*, 87(4): 1836-1849.

Snyder, L.H. & King, W.M. (1996). Behavior and physiology of the macaque vestibulo-ocular reflex response to sudden off-axis rotation: computing eye translation. *Brain Research Bulletin*, 40(5-6): 293-302. [cited by Marti et al., 2002]

Spiegel, R. (2002). *Human and machine learning of spatio-temporal sequences: an experimental and computational investigation*. Ph.D. Thesis, University of Cambridge, UK.

Spiegel, R., & McLaren, I.P.L. (2006). Associative sequence learning in humans. *Journal of Experimental Psychology: Animal Behavior Processes*, 32(2), 150-163.

Spiegel, R., Rettinger, N., Kalla, R., Lehnen, N., Straumann, D., Brandt, T., Glasauer, S., & Strupp, M. (2009a). The intensity of downbeat nystagmus during daytime. *Annals of the New York Academy of Sciences*, 1164: 293-299.

Spiegel, R., Kalla, R., Rettinger, N., Brandt, T., & Strupp, M. (2009b). Die medikamentöse Therapie des Nystagmus bei zentralen Augenbewegungsstörungen. *pleoptik - orthoptik*, 32: 24-30.

Spiegel, R., Kalla, R., Rettinger, N., Schneider, E., Straumann, D., Marti, S., Glasauer, S., Brandt, T., & Strupp, M. (2010). Head position during resting modifies spontaneous daytime decrease of downbeat nystagmus. *Neurology*, 75: 1928-1932.

Sprenger, A., Rambold, H., Sander, T., Marti, S., Weber, K., Straumann, D., & Helmchen, C. (2006). Treatment of the gravity dependence of downbeat nystagmus with 3,4-diaminopyridine. *Neurology*, 67(5): 905-907.

Sprenger, A., Zils, E., Rambold, H., Sander, T., & Helmchen, C. (2005). Effect of 3,4-diaminopyridine on the postural control in patients with downbeat nystagmus. *Annals of the New York Academy of Sciences*, 1039: 395-403.

Stephan, T., Kalla, R., Marti, S., Straumann, D.,& Glasauer, S. (2005). Asymmetric cerebellar flocculus activation for vertical smooth pursuit eye movements. In Abstract for the 11th OHBM meeting, Toronto.

Straube, A. (2007). Therapeutic considerations for eye movement disorders. *Developments in Ophthalmology*, 40: 175-192.

Straube, A., Leigh, R.J., Bronstein, A., Heide, W., Riordan-Eva, P., Tijssen, C.C., Dehaene, I., & Straumann, D. (2004). EFNS task force – therapy of nystagmus and oscillopsia. *European Journal of Neurology*, 11(2): 83-89.

Straumann, D., Zee, D.S., & Solomon, D. (2000). Three-dimensional kinematics of ocular drift in humans with cerebellar atrophy. *Journal of Neurophysiology*, 83(3): 1125-1140.

Strupp, M., & Brandt, T. (2006). Pharmacological advances in the treatment of neuro-otological and eye movement disorders. *Current Opinion in Neurology*, 19(1): 33-40.

Strupp, M., Kalla, R., Dichgans, M., Freilinger, T., Glasauer, S., & Brandt, T. (2004). Treatment of episodic ataxia type 2 with the potassium channel blocker 4-aminopyridine. *Neurology*, 62(9): 1623-1625.

Strupp, M., Kalla, R., Claassen, J., Adrion, C., Mansmann, U., Klopstock, T., Freilinger, T., Neugebauer, H., Spiegel, R., Dichgans, M., Lehmann-Horn, F., Jurkat-Rott, K., Brandt, T., Jen, J.C., Jahn, K. (2011b). A randomized trial of 4-aminopyridine in EA2 and related familial episodic ataxias. *Neurology*, 77(3): 269-275.

Strupp, M., Schüler, O., Krafczyk, S., Jahn, K., Schautzer, F., Büttner, U., & Brandt, T. (2003). Treatment of downbeat nystagmus with 3,4-diaminopyridine: a placebo-controlled study. *Neurology*, 61(2): 165-170.

Strupp, M., Thurtell, M.J., Shaikh, A.G., Brandt, T., Zee, D.S., & Leigh, R.J. (2011a). Pharmacotherapy of vestibular and ocular motor disorders, including nystagmus. *Journal of Neurology*, 2 April 2011, Epub ahead of print. DOI: 10.1007/s00415-011-5999-8.

Tassi, P. & Muzet, A. (2000). Sleep inertia. *Sleep Medicine Reviews*, 4(4): 341-353.

Toutenburg, H., Heumann, C., & Schomaker, M. (2008). *Induktive Statistik*. Berlin: Springer.

Wagner, J.N., Glaser, M., Brandt, T., & Strupp, M. (2008). Downbeat nystagmus: aetiology and comorbidity in 117 patients. *Journal of Neurology, Neurosurgery, and Psychiatry*, 79(6): 672-677.

Wirtz, P.W., Verschuuren, J.J., van Dijk, J.G., de Kam, M.L., Schoemaker, R.C., van Hasselt, J.G., Titulaer, M.J., Tjaden, U.R., den Hartigh, J., & van Gerven, J.M. (2009). Efficacy of 3,4-diaminopyridine and pyridostigmine in the treatment of Lambert-Eaton myasthenic syndrome: a randomized, double-blind, placebo-controlled, crossover study. *Clinical Pharmacology and Therapeutics*, 86(1): 44-48.

Yang, F.J., Fang, X., Yu, H.Y., & Wang, J.D. (2008). 4-Aminopyridine-κN^1)(phthalocyaninato-$\kappa^4 N$)zinc(II) tetrahydrofuran disolvate. *Acta Crystallographica Section C*, 64(11): 375-377.

Young, Y.H., & Huang, T.W. (2001). Role of clonazepam in the treatment of idiopathic downbeat nystagmus. *Laryngoscope*, 111(8): 1490-1493.

Zee, D.S., Friendlich, A.R., & Robinson, D.A. (1974). The mechanism of downbeat nystagmus. *Archives of Neurology*, 30(3): 227-237.

Zee, D.S., Walker, M.F., & Ramat, S. (2002). The cerebellar contribution to eye movements based upon lesions: binocular, three-axis control and the translational vestibulo-ocular reflex. *Annals of the New York Academy of Sciences*, 956: 178-189. [cited by Marti et al., 2002]

Zee, D.S., Yamazaki, A., Butler, P.H., & Gücer, G. (1981). Effects of ablation of flocculus and paraflocculus of eye movements in primate. *Journal of Neurophysiology*, 46(4): 878-899.

Zingler, V.C., Kryvoshey, D., Schneider, E., Glasauer, S., Brandt, T., & Strupp, M. (2006). A clinical test of otolith function: static ocular counterroll with passive head tilt. *Neuroreport*, 17(6): 611-615.

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8. Lebenslauf

Zur Person:

Name:	Dr. Rainer Christian Spiegel
Anschrift:	Witellikerstr. 22, c/o BK 203 8008 Zürich
Geburtsdatum:	6. September 1971
Geburtsort:	Würzburg
Staatsangehörigkeit:	deutsch
Familienstand:	ledig

Schulische Ausbildung:

Grundschule:	August 1978 bis Juli 1979: Grundschule Köln-Porz-Wahn August 1979 bis Juli 1982: Grundschule Köln-Porz-Langel
Gymnasium:	August 1982 bis Mai 1991: Kopernikus-Gymnasium Niederkassel, Abschluss mit der allgemeinen Hochschulreife am 29.05.1991.
Sprachschule:	Juni 1991 bis August 1991: Spanischkurs am Colegio Sagasta in Madrid (Spanien)
Berufsausbildung:	September 1991 bis Juni 1993: Berufsausbildung bei der Bayerischen Vereinsbank AG in München. Abschluss des Ausbildungsberufs zum Bankkaufmann am 28.06.1993.

Erststudium:

10/1993 bis 04/1998:	Psychologiestudium an den Universitäten Fribourg (Schweiz) und Trier. Abschluss mit dem Titel Diplom-Psychologe von der Universität Trier am 08.04.1998.
Übergangszeit:	April 1998 bis Juli 1998: Werkvertrag an der Universität Trier zur Softwareentwicklung für das Forschungsinstitut für Psychobiologie und Psychosomatik.

Graduiertenstudium:

10/1998 bis 12/1998:	Graduiertenstudium am Department of Experimental Psychology der Oxford University (UK).
01/1999 bis 04/1999:	Graduiertenstudium am Department of Experimental Psychology der University of Cambridge (UK).
04/1999 bis 07/2003:	Doktorand am Department of Experimental Psychology der University of Cambridge (UK). Erlangung des Doktortitels (Ph.D) im Fach *Experimental Psychology* (Faculty of Biology) am 19.07.2003 von der University of Cambridge (UK). Titel: Human and Machine Learning of Spatio-temporal sequences: an Experimental and Computational Investigation.

Berufstätigkeit:

10/2002 bis 10/2004:	"Junior Research Fellow in Experimental Psychology" am Wolfson College, University of Cambridge (England).
01/2003 bis 10/2004:	Hochschuldozent (= Lecturer) am Department of Computing des Goldsmiths College, University of London (England).

Zweitstudium:

10/2004 bis 03/2011:	Medizinstudium an der Ludwig-Maximilians-Universität München mit jeweils einmonatigen Famulaturen (= Praktika) in den Semesterferien in den Fächern Rheumatologie (Innere Medizin), Augenheilkunde, Neurologie, Paraplegiologie und Psychiatrie. Mein praktisches Jahr fand in den Fächern Innere Medizin, Neurologie und Chirurgie statt. Approbation als Arzt am 22.12.2010.

Ärztliche Berufstätigkeit:

Seit 01/2011:	Assistenzarzt an der Psychiatrischen Universitätsklinik Zürich.

Ausgewählte Veröffentlichungen (Rainer Spiegel):

- Spiegel, R., Kalla, R., Claassen, J., Bardins, S., Anciães da Silva, F., Farahmand, P., Hahn, A., Schneider, E., Rettinger, N., Jahn, K., Brandt, T., & Strupp, M. (zur Veröffentlichung angenommen). Aminopyridine treatment in a patient with bilateral vestibular failure and cryptogenic downbeat nystagmus. Erscheint im *Journal of Neuro-Ophthalmology* [ISSN 1536-5166]

- *Anagnostopoulos, A., *Spiegel, R., Palmer, J., & Brugger, P. (in press). A left-hand superiority for the implicit detection of a rule. Erscheint in der Fachzeitschrift *Cortex* [ISSN 0010-9452] *[geteilte Erstautorschaft]

- Spiegel, R., Farahmand, P., Anciães da Silva, F., Claassen, J., & Kalla, R. (2012). Preventing road injuries in children by applying feedback devices. *Traffic Injury Prevention*, *13*, 49-54. [ISSN 1538-9588]

- *Kalla, R., *Spiegel, R., Claassen, J., Bardins, S., Hahn, A., Schneider, E., Rettinger, N., Glasauer, S., Brandt, T., & Strupp, M. (2011). 10 mg doses of aminopyridines in downbeat nystagmus therapy: 4-Aminopyridine is more effective than 3,4-Diaminopyridine. *Journal of Neuro-Ophthalmology*, *31*, 320-325. [ISSN 1536-5166] *[geteilte Erstautorschaft]

- Kalla, R., Muggleton, N., Spiegel, R., Bueti, D., Claassen, J., Walsh, V., & Bronstein, A. (2011). Adaptive visual processing in bilateral vestibular failure. *Journal of Neurology, Neurosurgery and Psychiatry, 82*, 1212-1216. [ISSN 0022-3050]

- Strupp, M., Kalla, R., H., Claassen, J., Adrion, C., Mansmann, U., Klopstock, T., Freilinger, T., Neugebauer, Spiegel, R., Dichgans, M., Jurkat-Rott, K., Brandt, T., & Jahn, K. (2011). A randomized trial of 4-aminopyridine in EA2 and related familial episodic ataxias. *Neurology, 77*, 269-275. [ISSN 0028-3878]

- *Kalla, R., *Claassen, J., *Spiegel, R., Foldon, M., Kennard, C., Danchaivijitr, C., Bardins, S., Dera, T., Rettinger, N., Schneider, E., Glasauer, S., Brandt, T., Bronstein, A., & Strupp, M. (2011). A dual centre, double-blind, cross-over trial of 4-aminopyridine in the downbeat nystagmus syndrome – effects of the drug on slow phase eye velocity. *Journal of Neurology, 258*, Suppl. 1: S. 40. [ISSN: 0340-5354], *[geteilte Erstautorschaft]

- Claassen, J., Bardins, S., Spiegel, R., Schneider, E., Kalla, R., Jahn, K., Strupp, M. (2011). Body position and direction of moving object modulate visual motion perception. *Journal of Neurology, 258*, Suppl. 1: S144. [ISSN: 0340-5354]

- Spiegel, R., Kalla, R., Rettinger, N., Schneider, E., Straumann, D., Marti, S., Glasauer, S., Brandt, T., & Strupp, M. (2010). Head position during resting modifies spontaneous daytime decrease of downbeat nystagmus. *Neurology, 75, 1928-1932*. [ISSN 0028-3878]

- Spiegel, R., Kalla, R., Spiegel, F., Brandt, T. & Strupp, M. (2010). Motivating motorists to voluntarily slow down. *Journal of Prevention & Intervention in the Community, 38, 332-340* [ISSN 1085-2352]

- Kalla, R., Brandt, T., Rettinger, N., Spiegel, F., Strupp, M., & Spiegel, R. (2010). Evaluating a community-based intervention to enhance road safety. *Journal of Prevention & Intervention in the Community, 38, 306-315* [ISSN 1085-2352]

- Spiegel, R. (2010). Introduction: Community-based applications to enhance road safety. *Journal of Prevention & Intervention in the Community, 38, 261-262* [ISSN 1085-2352]

- Spiegel, R. (2010). Guest Editor: Theme issue on community-based applications to enhance road safety. *Journal of Prevention & Intervention in the Community, 38,* 261-340. [ISSN 1085-2352]

- Spiegel, R., Kalla, R., Rettinger, N., Schneider, E., Straumann, D., Marti, S., Claassen, J., Glasauer, S., Brandt, T., & Strupp, M. (2010). The influence of positional effects on the spontaneous decrease of downbeat nystagmus in the course of the day. *Klinische Neurophysiologie, 41*, 41-42 [ISSN 1434-0275]

- Spiegel, R., Kalla, R., Rettinger, N., Schneider, E., Straumann, D., Claassen, J., Glasauer, S., Marti, S., Brandt, T., & Strupp, M. (2010). The influence of resting in light or darkness on the spontaneous decrease of downbeat nystagmus. *Klinische Neurophysiologie, 41*, 42 [ISSN 1434-0275]

- Spiegel, R., Kalla, R., Muggleton, N., Bueti, D., Claassen, J., Walsh, V., & Bronstein, A. (2010). Adaptive mechanisms in visual motion processing and a possible link to evolution. *Klinische Neurophysiologie, 41*, 42 [ISSN 1434-0275]

- v. Stülpnagel, C., Plischke, H., Zill, P., Bäumel, C., Spiegel, R., Gruber, R. & Kluger G. (2009). Lack of association between MDR1 polymorphisms and pharmacoresistance to anticonvulsive drugs in patients with childhood onset epilepsy. *Epilepsia, 50,* 1835-1837 [ISSN 0013-9580]

- Spiegel, R., Rettinger, N., Kalla, R., Lehnen, N., Straumann, D., Brandt, T., Glasauer, S. & Strupp, M. (2009). The intensity of downbeat nystagmus during daytime. *Annals of the New York Academy of Sciences, 1164,* 293-299 [ISSN 00778923]

- Spiegel, R., Kalla, R., Rettinger, N., Brandt, T. & Strupp, M. (2009). Die medikamentöse Therapie des Nystagmus bei zentralen Augenbewegungsstörungen. *pleoptik - orthoptik, 32,* 35-42 [ISSN 0947-8698]

- Kalla, R., Spiegel, R., Rettinger, N., Glasauer, S. & Strupp, M. (2009). Therapy of downbeat nystagmus: 4-aminopyridine versus 3,4-diaminopyridine. *Klinische Neurophysiologie, 40*, 69 [ISSN 1434-0275]

- Spiegel, R., Kalla, R., Spiegel, F. & Strupp, M. (2008). Testing a new intervention to enhance road safety. Available from *Nature Precedings* http://precedings.nature.com/documents/2231/version/1

- Kalla, R., Spiegel, R., Wagner, J., Rettinger, N., Jahn, K., Strupp, M. (2008). Pharmakotherapie zentraler Augenbewegungsstörungen. *Nervenarzt*, *79*, 1377-8, 1380-2, 1384-5. [ISSN 0028-2804]

- Kuon, W., Pfeiffer, T., Kirsch, S., Körner, D., Spiegel, R., Stöcker, W., Schulze-Koops, H., Steller, U. (2008). Genotyping Of Five Single Nucleotide Polymorphisms (SNP) Of Human NAT2 Gene By A Novel Diagnostic Microarray Platform Reveals An Increased Allele Frequency Of Slow Acetylation In Rheumatoid Arthritis Patients. Poster presentation at the 2008 Annual Scientific Meeting of the American College of Rheumatology, San Francisco, and publication as a supplement of *Arthritis & Rheumatism, 58* [ISSN 1529-0131]

- Spiegel, R. (2007). Bayesian statistics as an alternative to gradient descent in sequence learning. *International Journal of Emerging Technologies in Learning*, 2(3), 1-6. [ISSN 1863-0383]

- Spiegel, R. (2007). A Hybrid Model Simulating Sensory-Motor Learning as a Tool to Enhance Knowledge in Medicine and Psychology. *Dynamics of Continuous, Discrete and Impulsive Systems, Series A: Mathematical Analysis, 14*, 354-363 [ISSN 1201-3390]

- Spiegel, R., Naqvi, S., Ohene-Djan, J., Moore, D.R. & Hsiao, E. (2007). A Neuropsychological Perspective on Measuring Sign Language Learning and Comprehension. *International Journal of Emerging Technologies in Learning, 2*, 1-5. [ISSN 1863-0383]

- Spiegel, R. & McLaren, I.P.L. (2006). Associative Sequence Learning in Humans. *Journal of Experimental Psychology: Animal Behavior Processes*, *32*, 150-163. [ISSN 0097-7403]

- Spiegel, R. & McLaren, I.P.L. (2006). A Hybrid Cognitive-Associative Model to Simulate Human Learning in the Serial Reaction Time Paradigm. T. Kovacs & J.A.R. Marshall (Eds.), *Proceedings of AISB 06, Adaption in Artificial and Biological Systems, 1,* 74-90. [ISBN 1-90295-697-5]

- Spiegel, R. (2006). A Search Engine inspired by Natural Language and Human Memory. *WSEAS Transactions on Information Science and Applications, 3*, 56-63. [ISSN 1790-0832]

- Spiegel, R. (2005). A Machine Learning Approach towards Improving Internet Search with a Question-Answering-System. In L. Zadeh & K. Grigoriadis (Eds.), *4th International Conference on Computational Intelligence, Man-Machine Interaction and Cybernetics (CIMMACS 2005),* pp. 270-275. [ISSN: 1790-5117]

- Naqvi, S., Ohene-Djan, J. & Spiegel, R. (2005). Testing the Effectiveness of Digital Representations of Sign Language with Children. Paper presented at the Instructional Technology and Education of the Deaf Symposium, pp. 1-7. National Technical Institute for the Deaf. Rochester, N.Y., USA, June 2005.

- Spiegel, R. & Nenh, Y.P. (2004). An Expert System Supporting Diagnosis in Clinical Psychology. *WIT Transactions on Information and Communication Technologies, 31*, 145-154 [ISSN: 1743-3517].

- Spiegel, R. & McLaren, I.P.L. (2003). Abstract and associatively-based representations in human sequence learning. *Philosophical Transactions of the Royal Society, Series B (=Biological Sciences)*, *358*, 1277-1283. The Royal Society of London. [ISSN 0962-8436]

- Spiegel, R. & McLaren, I.P.L. (2003). Computational Modeling of Human Performance in a Sequence Learning Experiment. *Proceedings of the IEEE International Joint Conference on Neural Networks (IJCNN)*, *Vol. 1*, pp. 212-217. Piscataway, N.J.: IEEE. [ISSN 1098-7576]

- Spiegel, R. (2003). Finger Tapping on the Keyboard. Rhythmic Patterns, Rule-based or Associative Processes? *Cambridge Music Processing Colloquium 2003*, pp. 57-62. Cambridge University Engineering Department, Signal Processing Group, University of Cambridge.

- Spiegel, R. (2003). A Novel Computational Approach to Extract Rules from Sequences of Phonemes. Special issue of the *Cambridge First Postgraduate Conference in Language Research (CamLing).* Cambridge Institute of Language Research, University of Cambridge. Session on Computational Linguistics, pp. 494-500 [ISSN: 1741-6655]

- Spiegel, R. (2003). Relating Bayesian Learning to Training in Recurrent Networks. *Proceedings of the IEEE International Joint Conference on Neural Networks (IJCNN)*, *Vol. 2*, pp. 908-913. Piscataway, N.J.: IEEE. [ISSN 1098-7576]

- Spiegel, R. (2003). Cognitive Modeling of Symbolic-like Relationships with the Adaptive Neural Network Associator (ANNA). *Proceedings of the IEEE International Joint Conference on Neural Networks (IJCNN)*, *Vol. 4*, pp. 2746-2751. Piscataway, N.J.: IEEE. [ISSN 1098-7576]

- Spiegel, R., Le Pelley, M.E., Suret, M. & McLaren, I.P.L. (2002). Combining Fuzzy Rules and a Neural Network in an Adaptive System. *Proceedings of the IEEE World*

Congress on Computational Intelligence. Section: IEEE International Conference on Fuzzy Systems (FuzzIEEE), pp. 340-345. Piscataway, N.J.: IEEE. [ISBN: 0-7803-7281-6]

- Spiegel, R., Suret, M., Le Pelley, M.E. & McLaren, I.P.L. (2002). Analyzing State Dynamics in a Recurrent Neural Network. *Proceedings of the IEEE World Congress on Computational Intelligence. Section: International Joint INNS/IEEE Conference on Neural Networks (IJCNN), pp. 834-839*. Piscataway, N.J.: IEEE. [ISSN 1098-7576]

- Spiegel, R. & McLaren, I.P.L. (2001). Human Sequence Learning: Can Associations Explain Everything? In J.D. Moore & K. Stenning (Eds.): *Proceedings of the Twenty-Third Annual Conference of the Cognitive Science Society, pp. 976-981.* Mahwah, N.J.: Erlbaum. [ISBN: 0-8058-4152-0]

- Spiegel, R. & McLaren, I.P.L. (2001). SARAH: Modeling the Results of Spiegel and McLaren (2001). In J.D. Moore & K. Stenning (Eds.): *Proceedings of the Twenty-Third Annual Conference of the Cognitive Science Society, p. 1239* [CD-Rom]. Mahwah, N.J.: Erlbaum. [ISBN: 0-8058-4152-0]

- Spiegel, R. & McLaren, I.P.L. (2001). Recurrent Neural Networks and Symbol Grounding. *Proceedings of the IEEE International Joint Conference on Neural Networks (IJCNN), Vol. 1, pp. 320-325.* Piscataway, N.J.: IEEE [ISSN 1098-7576]

- Spiegel, R. & McLaren, I.P.L. (2001). A Hybrid Model Approach to Generalization in Sequence Learning. *Proceedings of the IEEE International Joint Conference on Neural Networks (IJCNN), Vol. 4, pp. 2393-2398.* Piscataway, N.J.: IEEE [ISSN 1098-7576]

- Spiegel, R., Jones, F.W. & McLaren, I.P.L. (2001). The Prediction-Irrelevance Problem in Grammar Learning. *Proceedings of the IEEE International Joint Conference on Neural Networks (IJCNN), Vol. 1, pp. 314-319.* Piscataway, N.J.: IEEE [ISSN 1098-7576]

- Spiegel, R.; Buchner, A. & Laessle, R. (1998). Gaining Knowledge About Cognitive Mechanisms of Restrained Eaters in Order to Prevent Eating Disorders. In R. Schwarzer (Ed.): *Advances in health psychology research.* [Proceedings of the European Health Psychology Society (EHPS) Conference. Berlin: Freie Universität. ISBN 3-00-002776-9]

Diplom- bzw. Doktorarbeiten

- Spiegel, R. (1998). Kognition und Essverhalten: Gibt es differentielle Gedächtniseffekte zwischen gezügelten und ungezügelten Esserinnen? Diplomarbeit in Allgemeiner Psychologie, Universität Trier, D. Publiziert in: Spiegel, R. (1998). Kognition und Essverhalten: Gibt es differentielle Gedächtniseffekte zwischen gezügelten und ungezügelten Esserinnen? In R. Schwarzer (Ed.): Advances in health psychology research. [CD-ROM]. Berlin: Verlag der Freien Universität. [ISBN 3-00-002776-9]

- Spiegel, R. (2003). Human and Machine Learning of Spatio-temporal Sequences: An Experimental and Computational Investigation. PhD-thesis in the Department of Experimental Psychology. University of Cambridge, UK.

Kapitel in einem Herausgeberwerk

- Leichtman, M.D.; Morse, M.B.; Dixon, A. & Spiegel, R. (2000). Source-Monitoring and Suggestibility: An Individual Differences Approach. In K. Roberts & M. Blades (Eds.): Children's Source Monitoring, pp. 257-287. Mahwah, N.J.: Erlbaum. [ISBN 0-8058-3326-9]

Manuale für klinisch-psychologische Software

- Bodenmann, G.; Bourquard, E.; Perrez, M. & Spiegel, R. (1995). *CAOS. Computer Aided Observation System.* [Manual] Université de Fribourg (Switzerland).

- Spiegel, R.; Adam, T. & Laessle, R. (1999). From EMIL to BEFEE: The interface between a diagnostic technique and its application for treatment. University of Trier (Germany). (Software zur Erfassung und Therapie von Eßstörungen)

Ausgewählte Software

- Abdi, M. & Spiegel, R. (2004). Museum Store Database project. Department of Computing, Goldsmiths College, University of London.

- Butt, R. & Spiegel, R. (2004). Music Lyrics Search Engine. Department of Computing, Goldsmiths College, University of London.

- Nenh, Y.P. & Spiegel, R. (2004). Psychological Diagnosis Expert System. Department of Computing, Goldsmiths College, University of London.

- Nesarajah, C. & Spiegel, R. (2004). Virtual Museum Store Database and E-commerce project. Department of Computing, Goldsmiths College, University of London.

- Ocampo, S. & Spiegel, R. (2004). Leamington Parents' Centre Database Charity project. Department of Computing, Goldsmiths College, University of London.

- Sogules, M. & Spiegel, R. (2004). An Expert System supporting Medical Diagnosis. Department of Computing, Goldsmiths College, University of London.

- Spiegel, R. (2010). Software development for the *colordice* experiment, Neuropsychology-Unit, Neurologische Klinik, UniversitätsSpital Zürich.

- Spiegel, R. (2007). Software development for the paper *A Hybrid Model Simulating Sensory-Motor Learning as a Tool to Enhance Knowledge in Medicine and Psychology*. It appeared in the journal Dynamics of Continuous, Discrete and Impulsive Systems, Series A: Mathematical Analysis.

- Spiegel, R. (2006). Software development for the paper *Associative Sequence Learning in Humans*, having appeared in the Journal of Experimental Psychology: Animal Behavior Processes. [ISSN 0097-7403].

- Spiegel, R. (2006). Software development for the paper *A Hybrid Cognitive-Associative Model to Simulate Human Learning in the Serial Reaction Time Paradigmm* having appeared in the Proceedings of the AISB 2006 Conference on Adaption in Artificial and Biological Systems Convention.

- Spiegel, R. (2006). Software development for the paper *A Search Engine inspired by Natural Language and Human Memory*. The paper was published in WSEAS Transactions on Information Science and Applications, 3, 56-63. [ISSN 1790-0832]

- Spiegel, R. (2003). Software development for the paper *Computational Modeling of Human Performance in a Sequence Learning Experiment*, having appeared in the Proceedings of the IEEE International Joint Conference on Neural Networks (IJCNN), Vol. 1, pp. 212-217. Piscataway, N.J.: IEEE. [ISSN 1098-7576]

- Spiegel, R. (2003). Software development for the paper *A Novel Computational Approach to Extract Rules from Sequences of Phonemes*, having appeared in the special issue of the Cambridge First Postgraduate Conference in Language Research (CamLing). Cambridge Institute of Language Research, University of Cambridge. Session on Computational Linguistics, pp. 494-500. [ISSN: 1741-6655]

- Spiegel, R. (2003). Software development for the paper *Relating Bayesian Learning to Training in Recurrent Networks*, having appeared in the Proceedings of the IEEE International Joint Conference on Neural Networks (IJCNN), Vol. 2, pp. 908-913. Piscataway, N.J.: IEEE. [ISSN 1098-7576]

- Spiegel, R. (2003). Software development for the paper *Cognitive Modeling of Symbolic-like Relationships with the Adaptive Neural Network Associator (ANNA)*, having appeared in the Proceedings of the IEEE International Joint Conference on Neural Networks (IJCNN), Vol. 4, pp. 2746-2751. Piscataway, N.J.: IEEE. [ISSN 1098-7576]

9. Ehrenwörtliche Erklärung

Diese Dissertation wurde durch mich alleine angefertigt, d.h. selbständig sowie ohne unerlaubte Hilfe bzw. ohne unerlaubte Hilfsmittel. Ich habe diese Dissertation selbst geschrieben.

München, den 22.12.2012

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(Dr. Rainer Spiegel)

Einreichungsdatum der Dissertation: 28.06.2011