Not all those who wander are lost, and yet…

- *J.R.R. Tolkien, adapted by Joyce Bosmans*

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Faculty of Medicine and Health Sciences
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The association between peripheral vestibular function, balance, and cognition: From inner ear to the brain

Het verband tussen perifere vestibulaire functie, balans, en cognitie: Van het binnenoor tot het brein

Proefschrift voorgelegd tot het behalen van de graad van doctor in de medische wetenschappen aan de Universiteit Antwerpen te verdedigen door
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Summary

The number of older adults, including those affected by dementia, continues to grow. Alzheimer's disease is the most common cause of dementia, contributing to up to 70% of all cases. Despite the epidemic scale of dementia, until now no cure or disease-modifying therapy has been identified. Therefore, the World Health Organization has recognized dementia as a public health priority.

The peripheral vestibular end-organ is located in the inner ear and codes for rotation and translation of the head whilst contribution to self-motion perception, navigation, and spatial memory. Recent evidence suggests that vestibular loss is associated with Alzheimer's disease and may even contribute to its onset. This hypothesis is known as the vestibular loss hypothesis. Impaired spatial cognition is among the most frequently observed cognitive deficits in Alzheimer's disease and is related to vestibular loss. Vice versa, people with bilateral vestibular loss have been shown to present with impaired spatial cognition. Furthermore, people with Alzheimer's disease often demonstrate an increased risk of falling potentially resulting in fractures and deficits in activities of daily life.

The vestibular loss hypothesis is supported by these observed associations between vestibular function and cognition. However, a comprehensive overview evaluating vestibular function in Alzheimer's disease and its preceding Mild Cognitive Impairment stage is currently lacking. In addition, research evaluating brain anatomical changes in people with bilateral vestibular loss in relation to brain areas involved in spatial cognition is currently very limited and is often cited exclusively. Furthermore, hearing impairment and vestibular loss are often presented jointly. Hearing impairment has been identified as the largest modifiable risk factor for dementia. Despite this substantial impact of hearing loss on cognition, current research evaluating vestibular and cognitive function often lacks the inclusion of hearing parameters. Therefore, this thesis focuses on (1) evaluating functioning of the peripheral vestibular end-organ as well as balance in older adults with Mild Cognitive Impairment and Alzheimer's disease, (2) evaluating cognition and the cognitive subdomains in older adults with bilateral vestibular loss, and (3) evaluating whole-brain and hippocampal brain morphology in older adults with bilateral vestibular loss. These three objectives are met while taking hearing status into account.

In the first part, vestibular and balance function is evaluated in older adults with Mild Cognitive Impairment and Alzheimer's disease. First, a protocol is provided. Then, a systematic review summarizes the limited amount of available literature and identifies important knowledge gaps, such as the heterogeneous methodology used and the absence of including hearing loss as a covariate. An ensuing cross-sectional study including a group with Mild Cognitive Impairment, Alzheimer's disease, and age-, sex-, and hearing-matched

healthy controls evaluates functioning of the peripheral vestibular end-organ as well as clinical balance assessments. Only the p13 latency, a measure of saccular function, is delayed in participants with Alzheimer's disease. Other measures of the sacculus or semicircular canals do not differ between groups. In addition, advancing degrees of cognitive impairment demonstrate reduced balance, mobility, stability as well as an increased fall risk as measured by clinical balance tests. In general, vestibular and balance deficits are more prevalent in groups with increasing cognitive decline.

A second part of this thesis reverses the previous association: instead of evaluating vestibular function in a population with impaired cognition, cognition is now evaluated in a population with impaired vestibular function. People with bilateral vestibular loss demonstrate a general deficit in cognition in comparison with age-, sex-, and hearing-matched healthy controls. This general deficit in cognition is most pronounced in the immediate memory, visuospatial cognition, and attention subdomains. On the other hand, the language and delayed memory subdomains remain preserved. Even more, these observed cognitive deficits are associated with balance difficulties and not with reduced functioning of the peripheral vestibular end-organ.

A third part of this thesis explores structural brain imaging in older adults with bilateral vestibular loss. The hippocampus is an important brain area because of its importance in memory and spatial navigation, two cognitive domains that are affected in people with bilateral vestibular loss. Even more, hippocampal atrophy is an important biomarker of Alzheimer's disease. Whole-brain and hippocampal volumes are compared in older adults with bilateral vestibular loss and age-, sex-, and hearing-matched healthy controls. No differences in whole-brain or hippocampal volume are observed between these two groups. When exploring whole-brain surface-based measures such as cortical thickness or sulcus depth, also no differences are observed between the two groups. People with bilateral vestibular loss are characterized by reduced semicircular canal functioning. As such, the impact of the otoliths on hippocampal volume is additionally explored in people with preserved semicircular canal functioning. However, otolith parameters are also not associated with hippocampal volume.

Finally, the main findings of this thesis are discussed and perspectives for future research are provided. The work presented in this thesis confirms and extends certain results supporting the vestibular loss hypothesis, such as observed alterations in otolith function and balance deficits in people along the Alzheimer's disease continuum together with preserved semicircular canal functioning and general as well as domain-specific cognitive difficulties in people with bilateral vestibular loss. Also results not supporting nor contradicting the vestibular loss are presented such as the observed absence of whole-brain and hippocampal volumetric alterations in people with bilateral vestibular loss. Furthermore, several recommendations for future research objectives as well as for clinical

practice are provided with the aim of preserving cognition and balance such that someone's maximum possible quality of life can be maintained for as long as possible..

Samenvatting

Het aantal oudere volwassenen, waaronder mensen met dementie, blijft groeien. De ziekte van Alzheimer is de meest voorkomende vorm van dementie en is verantwoordelijk voor tot wel 70% van alle gevallen. Ondanks de epidemische omvang van dementie is er tot nu toe nog geen genezing of therapie gevonden die de ziekte kan verbeteren. Daarom heeft de Wereldgezondheidsorganisatie dementie erkend als een prioriteit voor de volksgezondheid.

Het vestibulair orgaan bevindt zich in het binnenoor en codeert voor rotatie en translatie van het hoofd terwijl het bijdraagt aan de waarneming van zelfbeweging, navigatie, en ruimtelijk geheugen. Recent bewijs suggereert dat vestibulair verlies geassocieerd is met de ziekte van Alzheimer en mogelijk bijdraagt aan het ontstaan ervan. Deze hypothese staat bekend als de vestibulaire verlieshypothese. Verminderd ruimtelijk geheugen wordt frequent waargenomen bij de ziekte van Alzheimer en is tegelijk gerelateerd aan vestibulair verlies. Omgekeerd is aangetoond dat mensen met bilateraal vestibulair verlies een verminderde ruimtelijk geheugen vertonen. Bovendien hebben mensen met de ziekte van Alzheimer een verhoogd valrisico, wat kan leiden tot botbreuken en moeilijkheden om activiteiten van het dagelijks leven uit te voeren.

De vestibulaire verlieshypothese wordt ondersteund door deze geobserveerde associaties tussen vestibulaire functie en cognitie. Echter, een uitgebreid overzicht van de evaluatie van vestibulaire functie bij de ziekte van Alzheimer en het daaraan voorafgaande stadium van de milde cognitieve stoornis ontbreekt op dit moment. Daarnaast is onderzoek naar anatomische veranderingen in de hersenen bij mensen met bilateraal vestibulair verlies in relatie tot hersengebieden die betrokken zijn bij ruimtelijk geheugen op dit moment zeer beperkt en wordt dit vaak uitsluitend geciteerd. Bovendien presenteren gehoorverlies en vestibulair verlies zich vaak samen. Gehoorverlies is erkend als de grootste behandelbare risicofactor voor dementie. Ondanks deze substantiële impact van gehoorverlies op cognitie, worden in huidige onderzoeken naar vestibulaire en cognitieve functies vaak geen gehoorparameters meegenomen. Daarom richt dit proefschrift zich op (1) het evalueren van het functioneren van het vestibulaire orgaan en de balans bij oudere volwassenen met een milde cognitieve stoornis en de ziekte van Alzheimer, (2) het evalueren van cognitie en de cognitieve deeldomeinen bij oudere volwassenen met bilateraal vestibulair verlies, en (3) het evalueren van de morfologie van de hersenen en de hippocampus bij oudere volwassenen met bilateraal vestibulair verlies. Voor elk van deze drie doelstelling wordt rekening gehouden met de gehoorstatus.

In het eerste deel wordt de vestibulaire en balansfunctie geëvalueerd bij oudere volwassenen met een milde cognitieve stoornis en de ziekte van Alzheimer. Eerst wordt een protocol beschreven. Vervolgens vat een systematische review de beperkte beschikbare

literatuur samen en worden belangrijke hiaten in de kennis geïdentificeerd, zoals de heterogeen gebruikte methodologie en het ontbreken van het meenemen van gehoorverlies als covariaat. Een daaropvolgende cross-sectionele studie met een groep met een milde cognitieve stoornis, de ziekte van Alzheimer, en leeftijds-, geslachts- en gehoor-gematchte gezonde controles evalueert het functioneren van het vestibulaire orgaan alsook klinische balans. De systematische review en de cross-sectionele studie toonden beiden aan dat alleen de p13 latentie, een maat voor de functie van de sacculus, vertraagd is bij mensen met de ziekte van Alzheimer. Andere metingen van de sacculus of halfcirkelvormige kanalen verschillen niet tussen de groepen. Daarnaast vertonen mensen met een toenemende mate van cognitieve stoornis een verminderde balans, mobiliteit, stabiliteit en een verhoogd valrisico zoals gemeten met klinische balanstesten. In het algemeen komen vestibulaire moeilijkheden en balansstoornissen vaker voor bij groepen met een toenemende cognitieve achteruitgang.

Een tweede deel van dit proefschrift keert de vorige associatie om: in plaats van vestibulaire functie te evalueren in een populatie met verminderde cognitie, wordt cognitie nu geëvalueerd in een populatie met een verminderde vestibulaire functie. Mensen met bilateraal vestibulair verlies vertonen een globaal verminderde cognitie in vergelijking met leeftijds-, geslachts- en gehoor-gematchte gezonde controles. Deze algemene vermindering in cognitie is het meest uitgesproken in de deeldomeinen van het direct geheugen, ruimtelijk denken, en aandacht. De deeldomeinen taal en uitgesteld geheugen blijven daarentegen behouden. Bovendien zijn deze cognitieve moeilijkheden gerelateerd aan evenwichtsproblemen en niet aan een verminderd functioneren van het vestibulaire orgaan.

Een derde deel van dit proefschrift onderzoekt structurele beeldvorming van de hersenen bij oudere volwassenen met bilateraal vestibulair verlies. De hippocampus is een belangrijk hersengebied vanwege zijn rol in het geheugen en ruimtelijke navigatie, twee cognitieve domeinen die aangetast zijn bij mensen met bilateraal vestibulair verlies. Bovendien is hippocampusatrofie een belangrijke biomerker voor de ziekte van Alzheimer. Volumes van de hersenen en de hippocampus worden vergeleken tussen oudere volwassenen met bilateraal vestibulair verlies en leeftijds-, geslachts- en gehoor-gematchte gezonde controles. Er worden geen verschillen waargenomen in het volume van de hersenen of de hippocampus tussen deze twee groepen. Bij het evalueren van oppervlakte-metingen van de gehele hersenen, zoals corticale dikte of sulcusdiepte, worden ook geen verschillen waargenomen tussen de twee groepen. Mensen met bilateraal vestibulair verlies zijn gekenmerkt door een verminderd functioneren van de halfcirkelvormige kanalen. Daarom analyseert een bijkomend onderzoek de invloed van de otolieten op het hippocampale volume bij mensen met een behouden werking van de halfcirkelvormige kanalen. Hoedanook, otolietparameters blijken ook niet geassocieerd te zijn met hippocampaal volume.

Tot slot worden de belangrijkste bevindingen van dit proefschrift besproken en enkele toekomstperspectieven voor verder onderzoek belicht. Het onderzoek gepresenteerd in dit proefschrift bevestigt en breidt bepaalde resultaten die de vestibulaire verlieshypothese ondersteunen uit, zoals veranderingen in otolietfunctie en meer balansproblemen bij mensen op het continuüm van de ziekte van Alzheimer. Deze mensen vertonen tegelijk een behouden functie van de halfcirkelvormige kanalen. Daarnaast ondersteunen globale alsook domeinspecifieke cognitieve moeilijkheden bij mensen met bilateraal vestibulair verlies opnieuw de vestibulaire verlieshypothese. Er worden resultaten gepresenteerd die de vestibulaire verlieshypothese noch ondersteunen noch tegenspreken, zoals de afwezigheid van volumetrische veranderingen in de hele hersenen en de hippocampus bij mensen met bilateraal vestibulair verlies. Verder worden verschillende aanbevelingen gedaan voor toekomstige onderzoeksdoelen alsook voor de klinische praktijk, met als doel cognitie en evenwicht te behouden zodat men zo lang mogelijk een zo hoog mogelijke kwaliteit van leven kan behouden.

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ABC Scale	Activity-specific Balance Confidence Scale
ABD	Abducens nucleus
AD	Alzheimer's disease
ADD	Dementia due to Alzheimer's disease
ADL	Activities of Daily Living
ANOVA	Analysis Of Variance
BDI	Beck Depression Inventory
BLSA	Baltimore Longitudinal Study of Aging
BMI	Body mass index
BNT	Boston Naming Test
BOLD	Blood-oxygenation-level-dependent
BV	Bilateral vestibulopathy
CA	Cornu ammonis
CAEP	Cortical-Evoked Auditory Potential
CAT12	Computational Anatomy Toolbox 12
CFAI	Comprehensive Frailty Assessment Instrument
CJV	Coefficient of joint variation
COTESS	Cognitieve Testbatterij voor Senioren
COWAT	Controlled Oral Word Association Test
cVEMP	Cervical Vestibular-Evoked Myogenic Potential
dB HL	Decibel hearing level
DFNA9	DeaFNess Autosomal Dominant 9
DHI	Dizziness Handicap Inventory
DS14	Type D Scale - 14
DSMB	Data and Safety Monitoring Board
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EFC	Entropy focus criterion
EHI	Edinburgh Handedness Inventory
ENG	Electronystagmography
EQ-5D	European Quality of Life-5 Dimensions Questionnaire
FGA	Functional Gait Assessment
FI_{high}	Fletcher index high
fMRI	Functional Magnetic Resonance Imaging
GECkO	Gehoor, evenwicht en cognitie
HADS	Hospital Anxiety and Depression Scale
HC	Healthy controls
HIT	Head-Impulse Test
HUI3	Health Utilities Index Mark-3

ICH-GCP	International Conference on Harmonisation - Good Clinical Practice
IQ	Intelligence quotient
IQR	Interquartile range
IWG-2	International Working Group 2
LIST	Leuven Intelligibility Sentences Test
MAD	Median Absolute Difference
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
MRV	Mean rectified voltage
NIA-AA	National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NR	No response
OSQ	Oscillopsia Severity Questionnaire
oVEMP	Ocular Vestibular Evoked Myogenic Potentials
POMA	Performance-Oriented Mobility Assessment
POMA-B	Performance-Oriented Mobility Assessment - Balance subscale
POMA-G	Performance-Oriented Mobility Assessment - Gait subscale
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRoNTo	Pattern Recognition for NeuroImaging Toolbox
RAVLT	Rey Auditory Verbal Learning Test
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBANS-H	Repeatable Battery for the Assessment of Neuropsychological Status, adjusted for Hearing-impaired individuals
ROC	Receiver operating characteristic
ROCF	Rey-Osterrieth Complex Figure
ROI	Region of interest
SCM	Sternocleidomastoid
SD	Standard Deviation
SEM	Standard Error of the Mean
Short FES-I	Short Falls Efficacy Scale International
SNHL	Sensorineural hearing loss
SNRd	Dietrich's signal-to-noise ratio
SPIN	Speech-in-noise
SPL	Sound pressure level
SPM12	Statistical Parametric Mapping 12
SPV	Slow phase velocity
SRT	Speech reception threshold
SSQ12	Speech, Spatial and Qualities of Hearing Scale
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SVM	Support vector machine

TIV	Total intracranial volume
TUG	Timed Up-and-Go
UVH	Unilateral vestibular hypofunction
UZA	Universitair Ziekenhuis Antwerpen
V-ADL	Vestibular disorders Activities of Daily Living
VBM	Voxel-based morphometry
VCR	Vestibulocollic Reflex
VEMP	Vestibular Evoked Myogenic Potential
vHIT	Video Head Impulse Testing
VN	Vestibular nuclei
VNG	Videonystagmography
VOR	Vestibulo-ocular reflex
VOSP	Visual Object and Space Perception battery
VSR	Vestibulospinal reflex
WHO	World Health Organization
ZNA	Ziekenhuis Netwerk Antwerpen

Chapter 1. General introduction

1.1 The vestibular system

Balance is often taken for granted. Most people do not give a second thought while walking across cobblestones, looking over their shoulder when riding a bike, or getting out of bed in the middle of the night without stumbling. A properly functioning vestibular system allows us to see clearly while moving, identify orientation with respect to gravity, determine direction and speed of movement, and make automatic postural adjustments to maintain stability in our activities. However, with impaired balance such activities can be fatiguing and even dangerous.

The vestibular system can be divided into two main systems: the peripheral and central system (Goldberg et al., 2012). The peripheral system encompasses the vestibular end-organ in the inner ear and its pathways to the brainstem. The central system encompasses the brainstem, the cerebellum, the cerebral cortex, and its widespread interconnections.

1.1.1 The peripheral vestibular system

The inner ear contains two primary structures, each involved in a distinct function: the cochlea, involved in hearing, and the peripheral vestibular end-organ, involved in maintaining balance, stability and spatial orientation.

1.1.1.1 *The peripheral vestibular end-organ*

The **peripheral vestibular end-organ** is located in the inner ear. It consists of a bony labyrinth in the petrous portion of the temporal bone (Khan & Chang, 2013). This bony labyrinth consists of three **semicircular canals** (lateral, anterior, and posterior), the **vestibule**, and the cochlea. It is filled with perilymphatic fluid. Within the vestibular part of this bony labyrinth lies the membranous labyrinth, consisting of three ducts within the semicircular canals, and two **otolith organs** (the **saccule** and **utricle**) within the vestibule. The membranous labyrinth is filled with endolymphatic fluid (Kingma & Janssen, 2013). Figure 1 provides a schematic overview of the anatomy of the peripheral vestibular end-organ.

The three **semicircular canals** are oriented 90° towards each other and each canal is located in a different spatial plane (X, Y, and Z) to detect rotational acceleration in every direction (pitch, roll, and yaw). Each semicircular canal has one bulbous shaped end, called the ampulla. Within the ampulla there is a sensory receptor called the crista ampullaris, consisting of the cupula. In the cupula, multiple hair cells project up into the cupula. The hair

bundle consists of one long hair (kinocilium) and multiple short hairs (stereocilia) (Khan & Chang, 2013). These stereocilia contain cation channels at their apex and are organized by length, where the taller stereocilia are connected to the immobile kinocilium. When rotating the head in the plane in which a canal is positioned, the endolymphatic fluid within that canal – because of inertia – lags behind. This causes the cupula (including its hair cells) to bend either towards the kinocilium or away from it, resulting in either depolarization or hyperpolarization. Stereocilia moving towards the kinocilium open the cation channels, resulting in a K^+ influx and depolarization. Vice versa, stereocilia moving away from the kinocilium result in closure of the cation channels, causing a lack of K^+ influx and hyperpolarization.

Collectively, the **utricle** and **saccule** compose the vestibule (Khan & Chang, 2013). Both otolith organs consist of a macula, containing hair cells (kinocilium and stereocilia) embedded in a gelatinous and deformable material with relatively heavy calcium carbonate crystals, called otoconia, attached to its surface. The utricle is oriented largely horizontal in the head, making it possible to register accelerations in the horizontal plane, whereas the saccule is oriented largely vertical, registering accelerations in the vertical plane. With a lateral translation in the horizontal or vertical plane, the otoconia – again because of inertia – lag behind. The weight of the otoconia causes a deflection of the gelatinous material and its hair cells, leading to depolarization or hyperpolarization. The kinocilia of the macula are directed towards the striola, which is an imaginary line in the middle of each otolith membrane. Kinocilia in the utricle are oriented with their polarization direction towards the striola. Vice versa, the polarization direction of kinocilia in the saccule is oriented away from the striola. In comparison, the kinocilia of the ampulla are all oriented in one direction (Kingma & Janssen, 2013).

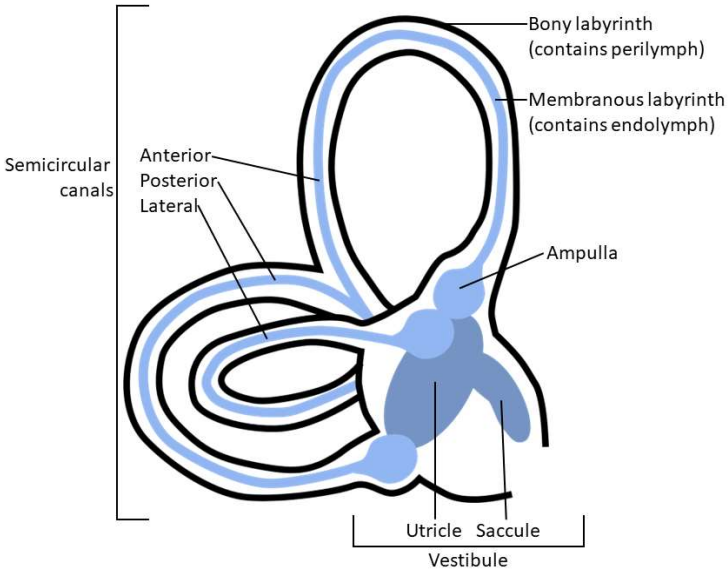

Figure 1. Anatomy of the peripheral vestibular sensor.

The depolarized or hyperpolarized signal is then sent to the brain via branches of the vestibular nerve.

1.1.1.2 *The vestibular nerve*

The **vestibulocochlear nerve**, also called cranial nerve VIII, integrates information from the five vestibular sensors together with auditory information from the cochlea. The vestibular nerve has two portions: a superior and inferior part. The superior vestibular nerve contains afferent neurons coming from the lateral and anterior semicircular canals, and the utricle. The inferior vestibular nerve contains afferent neurons coming from the posterior semicircular canal and the saccule. Vestibular information travels via the vestibular nerve to the vestibular complex in the brainstem. Vestibular efferents from the brainstem to hair cells in the vestibular inner ear are hypothesized to be involved in vestibular plasticity and compensation (Mathews et al., 2017).

1.1.2 The central vestibular system

1.1.2.1 *The brainstem*

Balance information provided by the different peripheral somatosensory organs (vestibular end-organ, eyes, muscles, and joints) is brought together in the brainstem, together with learned information provided by the cerebellum and the cerebral cortex (Goldberg et al., 2012). The cerebellum integrates information about learned automatic movements (e.g. driving a car or serving a ball). Contributions from the cerebral cortex contain previously learned information (e.g. icy sidewalks can be slippery or grass can be soggy).

The **vestibular nuclear complex (VNC)** resides in the medulla and pons of the brainstem and consists of four main nuclei: the lateral, medial, superior, and inferior vestibular nucleus. The **lateral vestibular nucleus** receives afferent fibers from the vestibulocerebellum and the vestibular end-organ. It aids in the vestibulospinal reflex to maintain proper posture and balance via the paravertebral extensor muscles and proximal extensor muscles of the limbs. The **medial vestibular nucleus** receives afferent fibers from the lateral semicircular canals. It mediates the vestibulo-ocular reflex along with the superior vestibular nucleus. It also functions to control head and neck movements to maintain balance via the medial vestibulospinal tract. The **superior vestibular nucleus** receives afferent fibers from the superior and posterior semicircular canals. It aids in coordination, postural adjustments, and related eye movements. It also plays a role in the conscious perception of movement and gravity. The **inferior vestibular nucleus** receives afferent fibers from the otolith organs. It receives information about gravity and head tilt, which affects blood flow, respiratory rate, and heart rate when standing (Hernandez E & J., 2022).

1.1.2.2 *Vestibular projections*

From the vestibular nucleus complex, widespread projections exist, contributing to the complexity of this broad central vestibular system. The sensorimotor functions can be subdivided into three major groups, but are interconnected to ensure a smooth operation.

1.1.2.2.1 Reflexive control of gaze, head, and trunk at the brainstem and cerebellar level

Three main reflexes exist to maintain gaze, head, and body stability during movement; respectively the **vestibulo-ocular reflex** (VOR), **vestibulocollic reflex** (VCR), and **vestibulospinal reflex** (VSR). When the head rotates in a certain direction, the eyes must move in an equal and opposite direction at the same speed to keep a target in focus. A deficient VOR may result in the experience of oscillopsia, where objects are blurred or dance while in motion. The VOR is driven by signals arising from the semicircular canals (Ramat et al., 2001). The VCR activates neck musculature to stabilize the head, in response to information from the otolith organs. The VSR refers to reactions below the neck to maintain posture and stabilize the body such that an upright position can be maintained (Khan & Chang, 2013).

1.1.2.2.2 Perception of self-motion and sensorimotor control of voluntary movement and balance at the cortical and subcortical level

While other senses (vision, hearing, touch, taste, and smell) have their own well-defined primary cortex, a dedicated primary vestibular cortex has not been identified to date. However, a distributed network of cortical regions responds to vestibular input. As such, a **corticocortical vestibular network** has been described including parietal opercular area OP2 as the core region for vestibular processing. Furthermore, temporo-parietal regions, the premotor cortex, and the midcingulate gyrus demonstrate direct connections and constitute a joint vestibular network (Raiser et al., 2020; zu Eulenburg et al., 2012). Perception of self-motion takes place in the **egomotion network**, stretching from cortical areas in the cingulate sulcus (CSv, PcM/pCi) and the temporo-parietal cortex (VPS, area 7a) to the cerebellum (uvula) (Ruehl et al., 2022). In addition, **balance** is achieved by a complex integration of sensorimotor control systems including input from vision, proprioception, and the vestibular system (including equilibrium, motion, and spatial orientation). All this information needs to be properly integrated and sent to the eye and body muscles for appropriate reflexes to maintain balance (Han et al., 2016).

1.1.2.2.3 Higher vestibular cognitive function at the cortical level

Spatial navigation is important for topographical orientation and interaction with our complex 3D world (Previc et al., 2014). Dr. John O'Keefe observed the hippocampus as a spatial map, where **place cells** express position and allow for spatial memory capacity. Dr. May-Britt Moser and Dr. Edvard I. Moser focused on the medial entorhinal cortex, a region neighboring the hippocampus. They discovered **grid cells**, responsible for an internal coordinate system crucial for navigation. Hippocampal place cells and entorhinal grid cells provide the foundation for maintaining a spatial map and topographical orientation. This

work has led them to win the 2014 Nobel Prize in Physiology or Medicine (The Nobel Committee for Physiology or Medicine, 2014). Because of important projections, the hippocampus together with the entorhinal cortex, posterior cingulate, parietal-temporal cortex, and nucleus caudate are often believed to be involved in spatial navigation (Coughlan et al., 2018; Previc et al., 2014). Furthermore, the vestibular organ's ability for graviception plays a crucial role in the development of cognition, orientation, and navigation (Le Gall et al., 2019). Even more, the vestibular system is involved in heading perception, which integrates visual cues (which are eye-centered) and vestibular cues (which are head-centered) in the medial superior temporal area (Moreau-Debord et al., 2014).

1.2 Bilateral vestibulopathy

Bilateral vestibulopathy (BV) is a chronic vestibular syndrome in which vestibular function is bilaterally severely reduced or absent. It is characterized by postural imbalance and unsteadiness of gait, which worsens in darkness and on uneven undergrounds. Patients often report oscillopsia and symptoms are typically absent under static conditions (Strupp et al., 2017). These symptoms lead to an increased risk of falling, imbalance, degradation in physical condition, and difficulties with navigation and spatial memory (Dobbels, Mertens, et al., 2019; Dobbels, Peetermans, et al., 2019). Even more, BV causes a decrease in health-related quality of life in 90% of all patients (Guinand, Boselie, et al., 2012). The prevalence of BV reported in literature lies between 28 and 81 in 100 000 adults. However, since BV is often missed or misdiagnosed, the actual prevalence is probably higher (Guinand, Boselie, et al., 2012; van de Berg et al., 2015; Ward et al., 2013). Various etiologies exist such as toxic or metabolic in nature (13-21%), infectious (3.8-12%), autoimmune (10%), neurodegenerative, genetic, vascular, neoplastic, traumatic, other ear pathology (e.g. Ménière's disease, otosclerosis…), congenital/syndromal, or due to another etiology (e.g. presbyvertigo, auditory neuropathy spectrum disorders…) (Lucieer et al., 2016). Unfortunately, the definite etiology cannot always be determined and remains idiopathic in 51% of all cases. Depending on the etiology, neurological symptoms can also be present (e.g. ataxia) as well as auditory symptoms (e.g. hearing loss or tinnitus) (Kim et al., 2011).

1.3 Cognition

Cognition is defined as the mental process of acquiring knowledge and understanding through experiences, thoughts, and the senses. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), cognition can be subdivided in six key neurocognitive domains, as can be seen in Figure 2 (American Psychiatric Association, 2013).

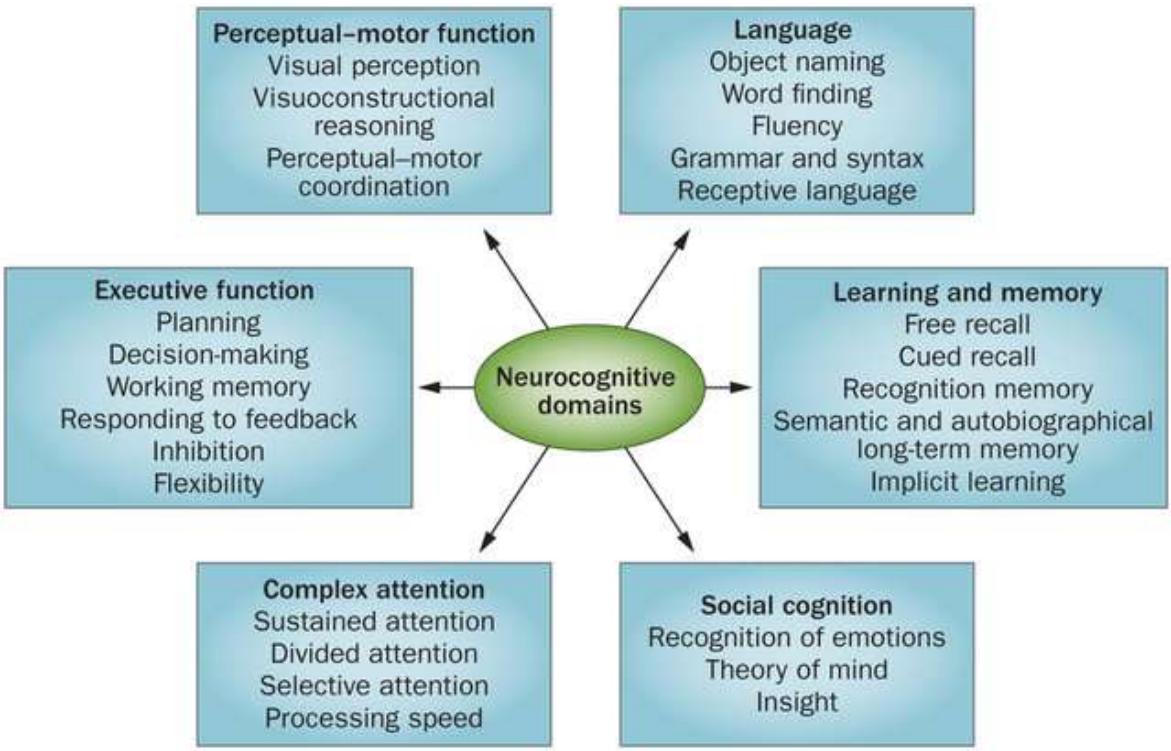

Figure 2. Six neurocognitive domains and their subdomains as defined by the DSM-5. Figure adapted from Sachdev et al. (2014). DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition (American Psychiatric Association, 2013).

1.3.1 Spatial cognition

Spatial cognition is part of the perceptual-motor function neurocognitive domain as defined by the DSM-5 (American Psychiatric Association, 2013). It is a complex, multi-dimensional concept. For example, navigating through an unknown environment does not solely rely on spatial cognition but combines multiple domains such as perception, attention, memory, and acting on this information. Designated spatial cognition processes should be able to answer the following questions (Marshall & Fink, 2001):

- Where am I, and how are my body parts oriented?
- Where are important objects in the environment in relation to me? Where are these objects located in relation to each other?
- What should I do about these objects and how?

Different domains in spatial cognition work together to answer these questions. Domains include visual perception, spatial representation, spatial memory, and visuo-spatial praxis (Kessels et al., 2016).

Visual perception encompasses the identification and location of objects. Two primary pathways or "streams" aid in visual perception: (1) the ventral "what" stream, involved in object recognition, and (2) the dorsal "where" stream, involved in recognizing where objects are in space.

Spatial representation involves the mental representation of spatial information. Two co-dependent navigation strategies exist: egocentric and allocentric spatial reference frames. A visual representation can be found in Figure 3. The egocentric reference frame is self-centred, where spatial information is encoded from the viewpoint of the person themselves, hence *ego*-centric. This reference frame is favored when the same route has been travelled frequently. By contrast, less known or novel routes prefer the use of allocentric, world-centred strategies. Here, the navigator focuses on landmark positions relative to other landmarks. These relative positions are used to update the internal cognitive map. Information is translated across egocentric and allocentric navigation frames for optimal navigational performance (Coughlan et al., 2018).

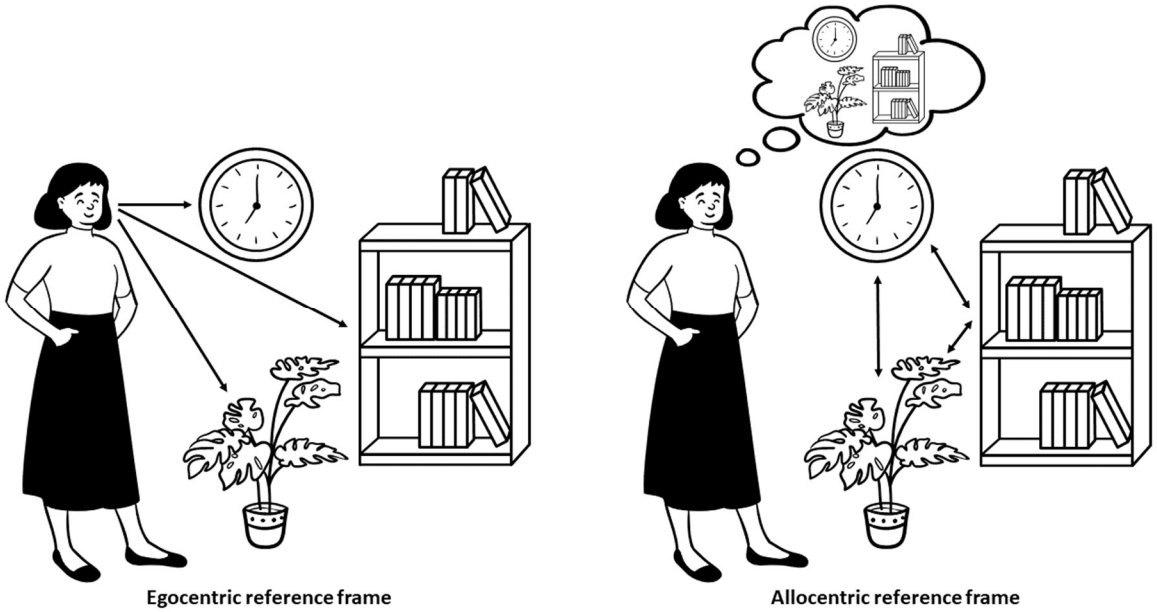

Figure 3. Egocentric and allocentric reference frames. The egocentric reference frame (left) encodes information from the viewpoint of the navigator themselves, whereas the allocentric reference frame (right) is based on the navigator's perception of landmark positions relative to each other.

Spatial memory can again be subdivided into different domains: spatial working memory, memory for object location, and learning and remembering of routes. Spatial working memory is important in short-term holding and manipulating of (visuo-)spatial memory. A simple demonstration of spatial working memory involves the mental rotation of objects.

Memory for object location is an important process in episodic memory. Not only does one need to remember the object itself, also the spatial context needs to be stored for successful object retrieval. Route learning combines all spatial memory processes. Spatial information needs to be combined with the correct temporal order and the correct location of relevant landmarks, integrating egocentric and allocentric knowledge, for successful navigation through space.

Visuo-spatial praxis combines perception, memory, and planning with the correct motor response. That way, bodily movements can be made in space and in relation to one's own body (Kessels et al., 2016).

1.3.2 Memory

Memory can be described based on different aspects. Here, time and the type of information will be used for the taxonomy of memory.

The **time** taxonomy of memory has been described by Atkinson and Shiffrin (1968), resulting in three stages. First, everything we perceive becomes part of our sensory memory. As the nomenclature implies, this **sensory memory** is based on our senses (how does information look, feel, sound, taste, and smell). Sensory memory only lasts for the first second(s). Second, the small amount of information that remains active during a limited amount of time, thus as long as attention is paid (often only the first 30 seconds), is called **working memory** or **short-term memory**. An example of working memory is holding someone's phone number in mind while entering it into your phone, and immediately forgetting this sequence of numbers afterwards. Third, information can be saved in **long-term memory** for longer periods of time or even life through rehearsing or other memorization techniques. Long-term memory contains all saved information that is currently not active in working memory.

Long-term memory can further be subdivided by the type of information. Here, a differentiation between declarative and non-declarative memory is made (Squire, 2004). **Declarative memory** contains memories that can be consciously recalled. Hence, knowing *what* has happened. Episodic memory involves recalling personal events (e.g. What did you do last Saturday?), whereas semantic memory involves recalling facts (e.g. What are the ingredients of a cake?). **Non-declarative memory** is more difficult to consciously recall and verbalize. It involves knowing *how* to do something, such as skills and habits (e.g. a ballerina's ability to perform a perfect pirouette).

1.3.3 Language

Language as a cognitive domain is a complex process involving the understanding and production of words, sentences, and entire stories.

The **understanding of spoken language** requires a correct identification of phonemes, leading to the activation of a mental lexicon that contains words fitting in this particular context. To understand a sentence, the grammatical representation needs to be comprehended. The **production of language** starts with deciding what message to communicate. First a concept is decided on, leading to activation of the corresponding mental lexicon. The message takes form by applying grammar and tone. The message is adapted to what already preceded and what will follow next. Finally, movement instructions are sent to the articulatory organs leading to production of language (Levelt, 1993). Even though the understanding and production of language sounds intuitive, this is only a very brief summary of the complex underlying processes involved.

1.3.4 Attention and executive function

Attention is the process that distinguishes relevant information from non-relevant information. Selectivity and intensity are needed for attentional processes (van Zomeren & Brouwer, 1994). The human information processing system is limited. As such, not all available information can be processed and a selection of relevant information is crucial. This selection or direction of attention can either be passive or active. Passive direction of attention (bottom-up) is automatic and involuntarily, e.g. a speeding car that suddenly appears when you are crossing a street will immediately draw your attention. Active direction of attention (top-down) focuses attention selectively and voluntarily, e.g. when you want to cross a street and you first watch left and right to see if any cars approach. A certain intensity or alertness is needed for attention. Alertness can fluctuate, e.g. having reduced attention after focussing long on a task or having a sudden increase in attention when you are startled by a dangerous situation.

Executive function involves a higher-order direction of attention. It is necessary for planning, adaptation, conflict resolution, and initiating and regulating goal-oriented task behavior. Situations are often complex and unstructured, and cannot be routinely performed (yet). Attention is needed to focus on relevant information while ignoring non-relevant information to successfully complete a task (Kessels et al., 2016).

1.3.5 Emotion and social cognition

There are three important aspects for social cognition: (1) one needs to focus attention to and perceive relevant social cues, which can be verbal or non-verbal social signals as well as contextual information, (2) one needs to interpret these cues, e.g. linking the appropriate emotion to the appropriate facial expression, and (3) one needs to react. Ideally, behavior appropriate to the social situation is selected and expressed. Emotions take an important part in social interaction. Understanding someone's emotions will guide your behavior, but your own emotions will also influence the way you perceive and act (Kessels et al., 2016).

1.4 The Alzheimer's disease continuum

Due to improved healthcare and the ensuing aging population, the number of older adults continues to grow, including those affected by dementia. Worldwide around 55 million people suffered from dementia in 2021 and by 2050 this number is expected to rise to 139 million, indicating a 2.5 times increase (World Health Organization, 2021).

Dementia is an umbrella term and multiple causes of dementia exist. Dementia is an acquired syndrome, where "acquired" implies that it is obtained throughout life (hence, one is not born with it), and "syndrome" implies that it encompasses a group of symptoms which consistently occur together. Main characteristics are a decrease from previous levels of cognitive functioning, behavioral changes, interference with the ability to perform activities of daily living, and the inability to explain these symptoms by delirium or a major psychiatric disorder. Ultimately, dementia leads to a complete loss of autonomy.

Alzheimer's disease (AD) is the most common cause of dementia and accounts for up to seventy percent of all dementia cases (World Health Organization, 2019). For a diagnosis of AD dementia, patients need to first meet the criteria for dementia. Furthermore, a slow progressive onset of symptoms over months to years must be present in addition to a decline in cognition. The amnestic presentation is the most common syndromic presentation of AD dementia, where most prominent cognitive deficits include impairment in learning and recall of recently learned information, together with evidence of cognitive dysfunction in at least one other cognitive domain (McKhann et al., 2011).

Mild Cognitive Impairment (MCI) due to AD is the symptomatic predementia phase of AD dementia. In this phase, there is evidence of a change in cognition in one or more cognitive domains that is more extensive than would be expected based on age and educational background. MCI distinguishes itself from a dementia syndrome by its independence in functional abilities. People with MCI may have mild problems with complex functional tasks. They may be less efficient and therefore take longer, and are more prone to error than in the past (Albert et al., 2011; Petersen, 2004). Impairment in episodic memory (i.e. the ability to learn and retain new information) is most often observed in MCI patients who progress to AD dementia. This subtype is called amnestic MCI and has an annual conversion rate of 12%-15% to AD dementia (Bozoki et al., 2001; Petersen, 2000).

1.5 Vestibular loss as a potential risk factor for Alzheimer's disease

A cure for dementia and AD dementia currently remains unavailable. However, identifying potentially **modifiable risk factors** for dementia is crucial to prevent or slow down further cognitive decline in individuals at risk for it. Recently, the Lancet Commission identified twelve modifiable risk factors for dementia. Risk factors in early life (<45 years; low

education), midlife (age 45-65 years; hearing loss, traumatic brain injury, hypertension, alcohol misuse, and obesity), and later life (age >65 years; smoking, depression, social isolation, physical inactivity, diabetes, and air pollution), increasing the risk of developing dementia. Modifying these twelve risk factors might prevent or delay up to 40% of all causes of dementia (Livingston et al., 2020).

An important modifiable risk factor is **hearing loss**. Hearing loss is a highly prevalent condition, occurring in 32% of individuals older than 55 years (Livingston et al., 2017). Older adults with untreated hearing loss are at risk for accelerated cognitive decline (Gallacher et al., 2012; Frank R. Lin et al., 2011; Lin et al., 2013; Livingston et al., 2020; Livingston et al., 2017). Even more, of all identified risk factors, untreated hearing loss has the highest relative risk for dementia (RR of 1.9) (Livingston et al., 2020). Because of the close anatomical relationship between auditory and vestibular structures in the inner ear, hearing loss and vestibular decline are often presented jointly. Consequently, sensorineural hearing loss and vestibular decline often coincide. According to Dobbels, Mertens, et al. (2019), 85% of adults with BV had abnormal hearing in at least one ear. Vice versa, more than half of adults with hearing loss presented with vertigo and abnormal vestibular test results (Niu et al., 2016).

Vestibular loss has recently been introduced as a possible risk factor for dementia and AD dementia in particular (Previc, 2013). Indeed, multiple findings supporting an association between vestibular function and AD dementia have been described. First, the **vestibular system projects to cortical and subcortical structures**, including to the medial-temporal cortex, in which the hippocampus and parahippocampal gyrus can be found (Burke & Fahn, 1985; Maguire et al., 1998). The hippocampus is a structure specified in memory processing and spatial memory (Manns et al., 2003; McNaughton et al., 1996; O'Keefe & Dostrovsky, 1971). Furthermore, hippocampal atrophy is an important biomarker for AD dementia. As can be seen in Figure 4, AD-related neuropathological changes in the preclinical and prodromal stage do not exclusively encompass memory centers in the brain, but also key nodes in the spatial navigation network (Coughlan et al., 2018). Second, patients in the **prodromal and symptomatic stage of AD dementia show multiple vestibular-related symptoms**. They demonstrate a decline in gait and balance, have difficulties with spatial navigation and orientation, may lose or misplace objects, experience driving difficulty, start to wander, and have a higher fall risk which often results in falls and fractures (Beauchet et al., 2008; Cipriani et al., 2014; Hamilton et al., 2009; Mazoteras Muñoz et al., 2010; Nakamagoe et al., 2015; Pettersson et al., 2005; van der Wardt et al., 2015; E. X. Wei et al., 2017). People with AD dementia have an annual incidence of falls of 60 to 80%, where the fall incidence of healthy adults is half as high (Gandhi et al., 2020; Tinetti et al., 1988). Furthermore, patients with AD dementia often get lost in familiar environments, which is in stark contrast to their peers with preserved cognition as they do not experience topographical disorientation (Lithfous et al., 2013). Third, patients with **BV demonstrate general cognitive deficits** which are most pronounced in the attention, executive function, and spatial cognitive subdomains (Dobbels, Mertens, et al., 2019; Dobbels, Peetermans, et

al., 2019). However, a minority of studies corrected for possible concomitant hearing loss, leaving the question whether vestibular loss is an independent risk factor for these observed cognitive deficits currently not yet completely resolved.

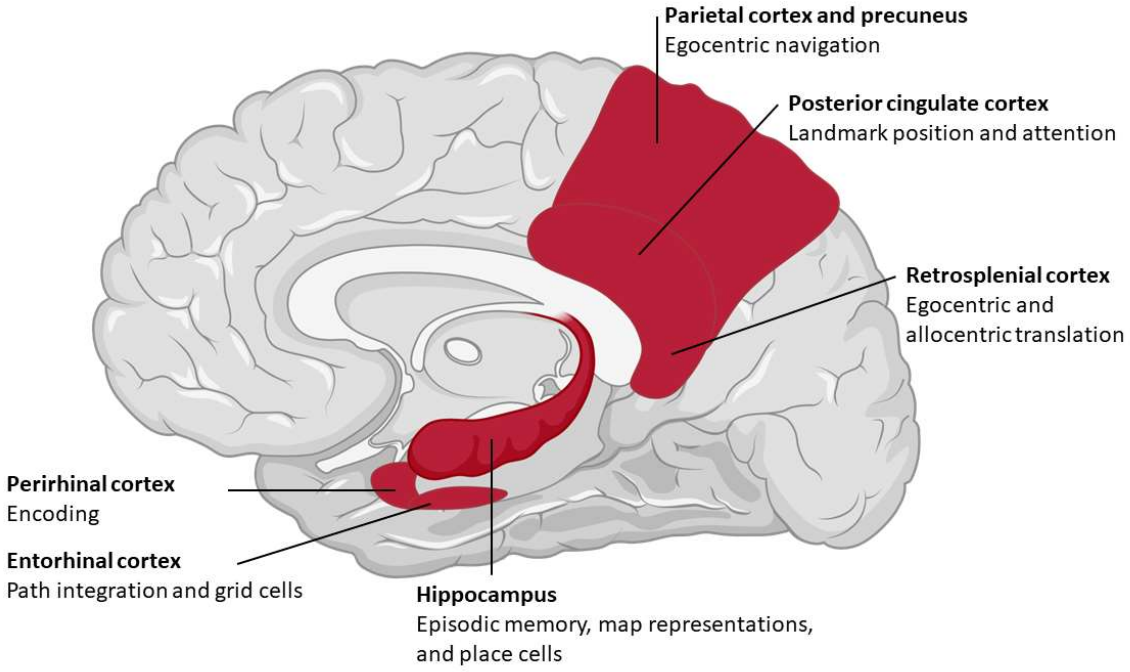

Figure 4. Anatomical illustration of neuropathological changes during the Mild Cognitive Impairment stage of the Alzheimer's disease continuum. Created with BioRender.com; Figure adapted from Coughlan et al. (2018).

1.6 Human structural neuroimaging

Magnetic resonance imaging (MRI) is used to *in vivo* visualize brain structure and integrity. When entering the MRI-scanner, a static magnetic field is permanently present, even when no scanning session is active. A proper combination of a static magnetic field, magnetic field gradients, and an oscillating radiofrequency magnetic field allows to obtain images. The precise order of pulses and gradients determines the end result, where a certain tissue can result in very bright or very dark values, resulting in a T1-, T2-, or T2*-weighted image. An example of a T1-weighted image can be seen in Figure 5. Typical field strengths used are 1.5T or 3T, and 7T is often used in research environments. Voxel-based morphometry (VBM) is a neuroimaging technique to evaluate focal anatomical changes. Images are pre-processed including tissue classification into grey matter, white matter, and cerebrospinal fluid images; warping the segmented images to a template space; and smoothing. Different and updated algorithms for pre-processing can be chosen. A voxel-wise estimation for the volume of a specific tissue compartment is provided (Ashburner & Friston, 2005). In addition to VBM, other methods of structural MRI analysis exist. For example surface-based

morphometry, which can be used to analyse cortical surface properties such as cortical thickness, the curvature, and the volume.

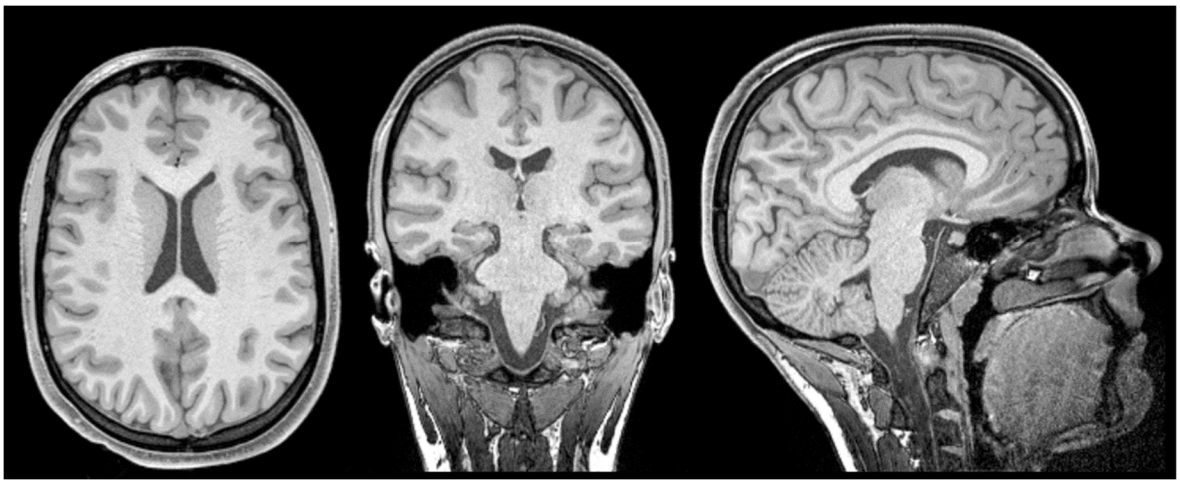

Figure 5. T1-weighted image of the brain of the PhD-defendant. The image demonstrates from left to right a slice in the horizontal, coronal, and sagittal plane.

1.7 Outline and objectives of this thesis

The aim of this doctoral thesis is to unravel the association between peripheral vestibular function, balance, and cognition while taking concomitant hearing loss into account. As such, this doctoral thesis is organized in three parts. In the first part, subjects with cognitive impairment play the leading role and vestibular function and balance are investigated. In the second part the roles are reversed and subjects with bilateral vestibular loss and their relationship with cognition is explored. The third part aims to investigate structural brain imaging of subjects with bilateral vestibular loss and compare its neural correlates with existing knowledge about AD dementia.

1.7.1 Objective 1: To evaluate vestibular function in older adults with cognitive impairment

1.7.1.1 *Step 1: To preregister and describe a protocol.*

Chapter 2 describes the prospective longitudinal study protocol of the *GECkO* study, an abbreviation for the Dutch words *Gehoor, Evenwicht, en COgnitie* (hearing, balance, and cognition). This protocol describes the methodology used to evaluate the impact of hearing loss and vestibular decline on cognition in Alzheimer's disease. By defining the methods and objectives of this study early on, the intermediate targets as well as the final goal of this study were clear and well thought out. The protocol is officially registered at ClinicalTrials.gov (identifier: NCT04385225).

1.7.1.2 *Step 2: To systematically review existing literature on peripheral vestibular function in older adults with cognitive impairment*

In Chapter 3 the literature regarding vestibular function in older adults with cognitive impairment is systematically reviewed according to the PRISMA guidelines for systematic reviews. This chapter includes a detailed overview of the inclusion and exclusion criteria, patient characteristics, and vestibular assessments subdivided per anatomical structure of the vestibular end-organ. This systematic review allows to critically evaluate the existing literature regarding vestibular function in older adults with cognitive impairment, including identifying important knowledge gaps.

1.7.1.3 *Step 3: To evaluate vestibular and balance function in older adults with cognitive impairment*

As concluded in Chapter 4 the heterogeneity of used methods and small number of studies in existing literature poses a limitation to make broad and founded inferences. Furthermore, the absence of including hearing function is another important limitation that could be a profound bias in current results. To build further on existing literature and reduce current limitations, vestibular and balance function was evaluated in older adults with cognitive impairment, more specifically MCI and AD dementia. In addition, the rate at which balance converges from normal to abnormal through the AD continuum is described in detail.

1.7.2 Objective 2: To evaluate cognitive performance in older adults with vestibular loss

Chapter 5 evaluates cognition in older adults with BV. As concomitant hearing loss could overestimate the potential cognitive function decline, hearing status was taken into account. This chapter describes alterations in global cognitive function as well as cognitive subdomains in older adults with BV compared to their matched controls. Furthermore, vestibular characteristics of patients with BV which could explain the pattern of cognitive loss were explored, including measurements of the peripheral vestibular end-organ, clinical balance testing, and questionnaires. The discussion includes a global interpretation of the cognitive pattern of patients with BV in comparison to patients with amnestic MCI. Finally, causal theories explaining the link between dementia and vestibular loss are proposed.

1.7.3 Objective 3: To evaluate structural brain imaging results in patients with bilateral vestibulopathy with respect to typical Alzheimer's disease morphologic pathology

Anatomical brain changes in Alzheimer's disease typically encompass atrophy of the medial temporal lobe, in which the hippocampus resides. As such, Chapter 6 evaluates hippocampal volume in patients with BV. To include an overview of the potential confounding impact of concomitant hearing loss, older adults with BV were compared with age-, sex-, and hearing-matched controls. To make robust inferences, multiple aspects of structural brain imaging

were evaluated, including whole-brain volumetric alterations (grey matter changes and surface-based morphometry, including cortical thickness and sulcus depth analyses) and targeted hippocampal volumetric approaches. Furthermore, the association between otolith function and hippocampal volume is explored in a population with preserved semicircular canal functioning.

Part 1

Vestibular and balance function in Mild Cognitive Impairment and Alzheimer's disease

Chapter 2. Impact of hearing loss and vestibular decline on cognition in Alzheimer's disease: A prospective longitudinal study protocol (Gehoor, Evenwicht en Cognitie, GECkO)

Published in BMJ Open

Bosmans, J., Jorissen, C., Cras, P., Van Ombergen, A., Engelborghs, S., Gilles, A., Princen, E., Moyaert, J., Mertens, G., & Van Rompaey, V. (2020). Impact of hearing loss and vestibular decline on cognition in Alzheimer's disease: a prospective longitudinal study protocol (Gehoor, Evenwicht en Cognitie, GECkO). BMJ open, 10(9), e039601. https://doi.org/10.1136/bmjopen-2020-039601

The logo of the *GECkO*-study can be found in Figure 6.

Figure 6. Logo of the GECkO-study. Figure created and provided by prof. Griet Mertens.

2.1 Abstract

Introduction: Dementia is a prevalent disease affecting a growing number of the aging population. Alzheimer's disease (AD) is the most common cause of dementia. Previous research investigated the link between hearing loss and cognition, and the effect of vestibular dysfunction on cognition. Hearing loss and, to a lesser extent, vestibular decline both result in a decreasing cognitive function. However, their interaction should not be underestimated. The aim of this study is to assess the effect of hearing loss, vestibular decline, and their interaction on cognition in people suffering from Mild Cognitive Impairment (MCI) and dementia due to AD (ADD).

Methods and analysis: We designed a prospective longitudinal study to assess the effect of hearing loss and vestibular decline on cognition. A total of 100 cognitively impaired elderly (between 55 and 84 years of age), consisting of 60 patients with MCI due to AD and 40 patients with ADD will be included. The control group will consist of individuals with preserved cognition group-matched based on age, hearing level, and vestibular function. A comprehensive assessment is performed at baseline, 12-month, and 24-month follow-up. The primary outcome measure is the change in the Repeatable Battery for the Assessment of Neuropsychological Status adjusted for Hearing-impaired individuals (RBANS-H) total score, a cognitive test battery assessing different cognitive domains. Secondary outcome measures include additional neuropsychological assessments, cortical auditory evoked potentials (CAEPs), and evaluation of general and disease-specific health-related quality of life. Variables include cognitive, audiological, and vestibular evaluation. Variance analyses will assess the effect of hearing loss and vestibular decline on cognition. More precisely, the link between hearing loss and non-spatial cognitive functioning, the effect of vestibular decline on spatial cognition, and the impact of both factors on the rate of conversion from MCI due to AD to ADD will be investigated.

Ethics and dissemination: The study protocol was approved by the ethical committee of the Antwerp University Hospital on 4 February 2019 with protocol number B300201938949 (registered at Clinicaltrials.gov (protocol number: NCT04385225). The findings will be disseminated through peer-reviewed publications and conference presentations.

Trial registration number: ClinicalTrials.gov Registry (NCT04385225).

2.2 Strengths and limitations of this study

- To our knowledge, this longitudinal study is the first to assess both hearing loss and vestibular decline in a cognitively impaired elderly population.
- Cognition will be evaluated with a neuropsychological test adapted for a potentially hearing-impaired population.
- Expected outcomes will support prospective interventional studies assessing the potential benefit of customized hearing and vestibular rehabilitation.
- Expected outcomes will support the setup of audiological and vestibular screening protocols in AD patients and those at risk.

2.3 Introduction

Cognition can be defined as the mental action of acquiring knowledge and understanding through experiences, thoughts, and the senses. According to the Diagnostic and Statistical Manual of Mental Disorders, cognition encompasses six different domains.

These domains include learning and memory, language, perceptual-motor function, executive function, complex attention, and social cognition. This article will focus on overall cognitive function and spatial cognition in particular. Spatial cognition is part of the perceptual-motor function domain. It is defined as the way the mind processes and understands two-dimensional and three-dimensional space, which includes spatial memory and spatial navigation. Spatial memory integrates information of one's environment using several different components. These components include geometry, relative position, distance, size, orientation, and coordinates (Bigelow & Agrawal, 2015). Spatial navigation involves the ability of successfully moving through one's environment. This concept encompasses head direction, which refers to the awareness of the angle and direction of one's head and path integration (Bigelow & Agrawal, 2015). Non-spatial cognition comprises the resulting cognitive domains. To assess one's cognition, multiple neuropsychological test batteries can be performed. However, available tests are often lengthy. Therefore, the Mini Mental State Examination (MMSE), a simplified cognitive mental status examination is developed. This MMSE can be used as a first screening device for cognitive impairment. Currently, the MMSE is routinely used in daily clinical practice as it only takes five to ten minutes to administer. Based on the MMSE score, a more extensive neuropsychological evaluation can be indicated. This quick screening and possible further evaluation of one's cognitive function gains importance since the world population is aging rapidly. This progressive aging of the population results in an increased amount of people suffering from dementia. Worldwide around 47 million people were affected with dementia in 2015, and this number is expected to triple by 2050 (Livingston et al., 2017). Dementia is an umbrella term for diseases characterized by a decline in multiple cognitive function domains that affects a person's ability to perform daily activities. The most common type of dementia is

Alzheimer's disease, which, according to the World Health Organization (WHO), accounts for sixty to seventy percent of all dementia cases.

A different kind of cognitive decline is Mild Cognitive Impairment (MCI). In this case a person experiences a decreased cognitive function but can still autonomously perform its activities of daily life (Albert et al., 2011). Within five years more than half of the cases progresses into a dementia syndrome (Gauthier et al., 2006). Especially the amnestic subtype of MCI could be a prodromal stage of Alzheimer's disease, because of its high risk of conversion. The diagnosis of dementia and its subtypes, like Alzheimer's disease, is currently based on the patients' medical history, physical examination, neuropsychological assessment, their performance in activities of daily life, and biomarkers. These biomarkers include (hippocampal) atrophy on brain MRI, FDG-PET, CSF biomarkers, and amyloid PET. Apart from these reliable biomarkers for diagnosing AD, other objective parameters may be of added value in the early detection of cognitive decline and the evaluation of conversion from prodromal AD to ADD (Jiang et al., 2015). One promising objective parameter is the measurement of cortical auditory-evoked potentials (CAEPs). Three major CAEPs are classified by latency from the P1-N1-P2 complex. Their latencies lie between 80 ms and 200 ms, and P300 latencies lie between 150 ms and 1000 ms (Stapells, 2009). The P1-N1-P2 complex is an obligatory CAEP response and is therefore always present in a healthy auditory system. The P300 component is obtained with an oddball paradigm, where standard stimuli are presented most of the time (80%) but occasionally (20%) a deviant stimulus is presented, which elicits the P300 response. The latency of the P300 component can be linked to processes involved in perception and cognition. Since dementia is an example of cognitive decline, it may alter the characteristics of the P300 response (Goodin et al., 1978). CAEPs provide objective information about the auditory system and reliable temporal resolution. But still little is known about its promising possibilities. Thus, CAEPs can possibly be used as an early-stage diagnostic marker for cognitive decline and may predict the conversion from prodromal AD to ADD, thus could therefore have the potential of being an important objective parameter.

Hearing loss gradually increases with old age and affects approximately a third of the aging population. Multiple studies have shown that hearing impairment is associated with an increased risk of cognitive decline (J. Wei et al., 2017). One of these studies, performed by Harrison Bush et al. (2015), states that peripheral hearing accounts for significant, but small, changes in processing speed, executive function, memory, and global cognitive status (Harrison Bush et al., 2015). Consistent with these results, multiple studies found significant, though also small, associations between hearing loss and cognitive function in older adults, independent of age, sex, education, or other confounding variables (Lin, 2011; Ray et al., 2018; Sugawara et al., 2011). Most often, these studies found an impairment in overall cognitive function, as well as a more pronounced decline in memory and executive function. However, various studies could not replicate these findings (Bucks et al., 2016; Gussekloo et al., 2005; Tay et al., 2006). A systematic review and meta-analysis performed by Loughrey

et al. found a significant association between age-related hearing loss and a decreased performance on all domains of cognitive function (Loughrey et al., 2018). Furthermore, they state that hearing loss is related to cognitive impairment and dementia, while vascular dysfunction and impaired verbal communication may also contribute to this association. Lin et al. (2013) demonstrated that hearing loss is independently associated with accelerated cognitive decline and cognitive impairment. In addition, a 24% increased risk of cognitive impairment in individuals with hearing loss was found, with more severe hearing loss resulting into an accelerated cognitive decline and greater risk of cognitive impairment (Lin et al., 2013). Furthermore, patients with dementia show greater degrees of hearing loss (Frank R. Lin et al., 2011). In summary, hearing loss is a modifiable risk factor and possible biomarker for cognitive decline, cognitive impairment, and dementia (Loughrey et al., 2018). While assessing cognitive function in subjects with hearing loss, one has to keep in mind that the subject may perform worse because of not receiving the instructions clearly. Hence, their hearing loss can bias the results of the predominantly verbal tests. A possible solution is to simultaneously present the instructions and stimuli in an oral and visual manner. An example of a cognitive test adapted for hearing-impaired subjects is the Repeatable Battery for the Assessment of Neuropsychological Status adapted for Hearing impaired persons (RBANS-H) (Claes et al., 2016). This comprehensive neuropsychological assessment investigates cognitive function in a reliable manner in hearing impaired subjects by using an accompanied PowerPoint presentation shown on an external computer screen. This presentation supports all oral instructions and stimuli with written explanations and stimuli. Therefore, the participant can understand all instructions and should be able to reproduce presented stimuli even when auditorily deprived.

In addition, vestibular decline, affecting one-third of the older population, may influence cognitive performance (Harun, Oh, et al., 2016). The vestibular apparatus, located in the inner ear, is responsible for gaze stabilization by coding rotation and translation of the head. This vestibular apparatus projects to the medial-temporal cortex, which includes the hippocampus and entorhinal cortex. These brain structures are known for their strong involvement in spatial cognition and computation of the inner neural map (Hafting et al., 2005; Hitier et al., 2014; Smith & Zheng, 2013). Bilateral vestibulopathy (BVP), characterized by a bilateral vestibular function loss, leads to hippocampal atrophy, memory impairment, and a decline of spatial cognition and attention (Brandt et al., 2005; Dobbels, Peetermans, et al., 2019; Glasauer et al., 2002; Göttlich et al., 2016; Harun et al., 2017; Kremmyda et al., 2016; Popp et al., 2017). This may suggest that vestibular dysfunction is a risk factor for dementia, more specifically for AD. In addition, vestibular decline can predict a decrease in spatial cognition in MCI and AD patients (Previc et al., 2014; Wei et al., 2018). When comparing spatially impaired AD patients to spatially normal AD patients, a significantly higher prevalence of vestibular decline is present in the former group. Furthermore, patients with vestibular dysfunction experience an increased risk of falling and deficits in daily activities (Previc et al., 2014). In addition, AD patients show more often impaired saccular function in comparison with patients with MCI and preserved cognition, while semicircular canal function remains intact (Harun, Oh, et al., 2016).

Often SNHL and vestibular decline are concomitant. According to Dobbels et al. (2019), 85% of patients with bilateral vestibulopathy had abnormal hearing in at least one ear. Compared with literature, this prevalence was relatively high (Dobbels, Mertens, et al., 2019). Vice versa, more than half of patients with hearing loss (26 – 80 dB HL of better ear) presented with vertigo and abnormal vestibular test results (including caloric irrigation and VEMP testing) (Niu et al., 2016). This underpins the importance of assessing both hearing and vestibular function in these patient groups. However, little research integrates both the scientific evaluation of hearing loss and vestibular dysfunction in their analyses. Therefore, to date this research question has not (yet) been systematically evaluated in an elderly population. The association between SNHL and cognitive impairment has been investigated thoroughly and appears to be robust. Nonetheless, vestibular decline as a potential cause of cognitive decline has been frequently overlooked (Loughrey et al., 2018; Semenov et al., 2016). Additionally, a systematic literature review evaluating the relationship between BVP and cognition concludes that the effect of vestibular decline on cognition is often established without considering hearing loss as a potential confounding variable (Dobbels, Peetermans, et al., 2019). This leaves the question whether the impact of hearing loss on cognition might be related to concomitant vestibular dysfunction (and vice versa) unanswered.

The objective of this longitudinal study is to investigate the impact of SNHL and vestibular decline on CAEPs, overall cognitive function, and spatial cognition in particular in patients with MCI due to AD and ADD. The study sample will be compared to cognitively healthy subjects group-matched based on mean age at baseline, mean hearing level of the better-hearing ear, and mean vestibular function. It is hypothesized that SNHL will result in overall cognitive dysfunction and CAEPs deficits. In addition, vestibular decline will increase the spatial cognitive load in a population with MCI due to AD and ADD. Furthermore, it is hypothesized that SNHL and vestibular decline may result in an increased rate of conversion from MCI due to AD to ADD.

2.4 Methods

2.4.1 Study setting

This study will be coordinated by the department of Translational Neurosciences of the University of Antwerp. The study will be performed at the departments of Otorhinolaryngology and Neurology of University hospital Antwerp (UZA) in collaboration with the memory clinic/department of Neurology of hospital network Antwerp (ZNA) Middelheim and Hoge Beuken, and University Hospital Brussels (UZ Brussel) in Belgium.

2.4.2 Eligibility criteria

A total of 100 cognitively impaired elderly will be included in the study. This group will consist of 60 patients with diagnosed MCI due to AD and 40 patients with diagnosed ADD, all between 55 and 84 years of age. The cut-off of 55 years was chosen because this age was

the youngest mean age in which presence of hearing loss was shown to increase dementia risk (Gallacher et al., 2012). As the prevalence of individuals with hearing loss, vestibular decline, and cognitive impairment increases with age, (Agrawal et al., 2013; Colledge et al., 1994; Fernández et al., 2015; Hebert et al., 2013; F. R. Lin, R. Thorpe, et al., 2011; Tinetti et al., 2000) and in addition in order to guarantee sufficient patient inclusion, the upper boundary of 84 years of age was chosen for patient inclusion. The control group will encompass individuals with preserved cognition group-matched based on mean age at baseline, mean hearing level of the better-hearing ear, and mean vestibular function. Inclusion and exclusion criteria are presented in Table 1. The MMSE is used as a short cognitive screening to obtain a first measurement of overall cognitive function. A total score greater than 12 is needed to enable vestibular assessment. As the MMSE is a screening tool for dementia, it may not be sensitive to MCI and preserved cognition. As such, the RBANS-H will be used. The control group will have a total score on the RBANS-H > percentile 16. Patients scoring ≤ percentile 16 on the RBANS-H total score will be classified as MCI. Patients with an additional diagnosis of AD based on IWG-2 criteria will be classified as AD (Dubois et al., 2014). The diagnostic protocol will be executed by a trained psychiatrist, geriatrician, or neurologist after proper neuropsychological examination.

Table 1. Inclusion and exclusion criteria. MMSE, Mini-Mental State Examination; IWG-2, International Working group.

Inclusion	Exclusion
● MMSE > 12	● Uncorrectable visual impairment
● between 55 and 84 years of age	● Hearing implants
● Diagnosis of MCI and dementia due to AD according to IWG-2 criteria	● Hearing aids
● Dutch-speaking	● Conductive hearing loss

Participation will be discontinued when asked by the participant. When the researchers are convinced that further participation of the participant is adverse for the research or the participant's health, participation will be terminated.

2.4.3 Sample size and power

A power calculation is performed to obtain an estimation of the needed sample size to detect significant differences in RBANS-H total score at baseline and at 24m follow-up. A two-sided paired t-test is carried out to obtain a power of 80% to detect a mean of paired differences of 4 with an estimated standard deviation of 8 and a significance level (alpha) of 0.05. A non-parametric calculation showed a proposed sample size of 34 subjects per group. These sample size calculations are based on the RBANS-H total score of cognitively healthy

participants with SNHL. As the RBANS-H total score of cognitively impaired patients is expected to result in more differentiated outcomes, a smaller sample size should be sufficient to obtain statistical significance. As one of the aims of this study is to evaluate the rate of conversion from prodromal AD to ADD, a larger number of patients with prodromal AD will be required. When covering a possible drop-out and possibility of recruitment, 60 MCI-patients due to AD and 40 ADD-patients will be recruited. In conclusion, a total of 100 cognitively impaired patients will be recruited for the study.

2.4.4 Intervention description

For this longitudinal study, an extensive protocol will be administered comprising audiologic, vestibular, and cognitive testing. The study protocol will be assessed at baseline, 12 months and 24 months. The schedule of assessment is displayed in Figure 7. Prior to any test enrolment all patients fill out an informed consent. All researchers involved in this study are International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) certificated.

	Baseline	**Follow-up**	
TIMEPOINT	**T_0**	**T_1**	**T_2**
ASSESSMENTS:			
CAEP	X	X	X
RBANS-H	X	X	X

Figure 7. Schedule of enrolment and assessments in accordance with the SPIRIT 2013 guidelines. CAEP, cortical auditory evoked potential; RBANS-H, Repeatable Battery for the Assessment of Neuropsychological Status adjusted for Hearing-impaired individuals.

2.4.4.1 *Cognitive assessment*

2.4.4.1.1 Repeatable Battery for the Assessment of Neuropsychological Status adapted for Hearing impaired persons (RBANS-H)

The RBANS-H is based on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998). The RBANS is a neuropsychological test used to detect mild forms of cognitive disorders. The RBANS-H is developed in order to examine cognitive function of individuals with hearing impairment (Claes, 2016). This is done by presenting an accompanying PowerPoint presentation. Written explanations are given to support verbal instructions and to ascertain that the participant understands the instruction. Besides a visual support of the instructions, also all relevant stimuli are not only presented verbally but visually as well. All adjustments were made in accordance to the RBANS guidelines.

The RBANS-H consists of 12 subtests: 'List learning', 'Story memory', 'Figure copy', 'Line orientation', 'Picture naming', 'Semantic fluency', 'Digit span', 'Coding', 'List recall', 'List recognition', 'Story recall' and 'Figure recall'. It measures the cognitive domains of immediate memory, visuospatial/constructional, language, attention, and delayed memory.

The cognitive domain of immediate memory is examined by subtests 'List Learning' and 'Story Memory'. In 'List Learning', a list of ten words is repeated four times, while in 'Story Memory', a 12-item short story is presented twice. After each presentation, either a list of ten words or a short story, the participant is instructed to recall as much of the words or story as possible. The visuospatial/constructional domain consists of the subtests 'Figure Copy' and 'Line Orientation'. In the former, a complex geometric figure is presented and the participant needs to copy this figure as exactly as possible. In the latter, the participant needs to match two lines according to their different degrees of orientation. To assess language, participants are asked to name 10 line drawings in the subtest 'Picture Naming', while in the subtest 'Semantic Fluency', they are asked to generate as many examples as possible from a certain semantic category in one minute. The attention domain consists of the subtest 'Digit Span', where a string of digits is presented, after which the individual is asked to repeat the digits in the correct order. When doing so successfully, the string becomes longer and more digits need to be repeated. The subtest 'Coding' is also part of the attention domain, where the participant needs to complete a page of symbols as much as possible with the corresponding digits according to a key on top of the page in two minutes. To assess delayed memory, the participant needs to recall as many items as possible from the subtest 'List Learning' (free recall and recognition; where in the latter ten target words are presented from the to-be-remembered list, as well as ten distractors, and the participant needs to indicate which words needed to be remembered and which were not in the list). The participant also needs to recall as much items as possible from the subtest 'Story Memory' and is instructed to redraw the complex figure from memory which was presented in the subtest 'Figure Copy'. These subtests are called 'List Recall', 'List Recognition', 'Story Recall', and 'Figure Recall', respectively.

Total scores of the subtests are converted into index scores. These index scores are normed based on the age of the participant. The sum of all index scores is used to determine the total scale and percentile.

2.4.4.2 *Audiologic assessment*

2.4.4.2.1 Cortical Auditory Evoked Potential (CAEP)

To investigate central auditory processing, cortical auditory evoked potentials (CAEPs) are measured. CAEPs have demonstrated their usefulness in the objective evaluation of sound processing up to the level of the central auditory nervous system, including higher-order auditory-cognitive processing. Patients wear a 32-channel electroencephalography (EEG) electrode cap, with 31 silver/silver chloride (Ag/AgCl) electrodes placed according to the 10 to 20 Standard International Electrode System referenced to a chin electrode, with the

ground electrode placed on the right mastoid. While wearing this EEG-electrode cap, patients are presented an oddball paradigm. They are instructed to press a button every time a rare stimulus (2000 Hz, with a probability of 20%) is presented in between frequent stimuli (1000 Hz, with a probability of 80%). These stimuli, presented through shielded headphones (Audio Technica ATH M30x Refaeds), have a rise and fall time of both 5 milliseconds, and are delivered by use of the Software Presentation™ (Neurobehavioral Systems, Inc). The EEG is recorded (Micromed™ SD LTM 64 Express) using the interface "Gilat Medical™ Event Related Potentials system". One additional electrode is placed below the right eye to record the vertical electrooculogram (EOG), which can later be used to distinguish eye blinks. After recording, the EEG is sampled at 1024 Hz with 22-bit A/D resolution.

EEG data will be preprocessed using the Fieldtrip toolbox in Matlab (MATLAB version 9.6.0.1150989 (R2019a), The MathWorks, Inc, 1994-2019) (Oostenveld et al., 2011). First, using a default Butterworth IIR filter between 0.5 and 45 Hz, offline bandpass filtering will be applied to continuous EEG data. A channel may present excessive noise or low activity and will therefore be identified as a bad channel. Next, to detect eye blinks, an independent component analysis (ICA) will be performed and components will be identified based on their time course and localization. Components including eye blinks will be removed from the data using an inverse ICA procedure. Subsequently, data will be segmented into two-second epochs time-locked to the stimuli. Based on the amount of variance determined by visual inspection of the data, artefacts will be removed from the data set. This procedure will be performed by investigators blind to subject groups. The percentage of removed trials for each subject group will be reported. The signal of excluded channels will be interpolated based on the activity of neighboring channels using a weighted algorithm. The number of interpolated channels will be reported on a group level. Furthermore, a correction to a baseline period of 0.2 seconds preceding stimulus presentation will be applied to all epochs. Linear trends will also be removed from the data, using a detrending method. Because of the interest in differences between responses to target and non-target tones, these responses will be averaged separately.

2.4.5 Outcomes

2.4.5.1 *Primary outcome measure*

The primary outcome measure is the change in total score of the Repeatable Battery for the Assessment of Neuropsychological Status for Hearing Impaired Individuals (RBANS-H) (Claes, 2016) from baseline to follow-up at 24 months.

2.4.5.2 *Secondary outcome measures*

2.4.5.2.1 **Cortical Auditory Evoked Potential (CAEP)**

Grand averages for each subject group (MCI due to AD and ADD) and time point (baseline, 12-month, and 24-month follow-up) will be calculated. Next, differences in responses

between subjects with MCI and dementia due to AD will be detected by the Fieldtrip toolbox. The evolution of responses within the MCI and dementia due to AD subject groups from baseline to 12m and 24m follow-up will also be investigated. This will be done on a global and scalp level. Clusters with significant differences between time points or subject groups are detected with permutation testing, using the Monte Carlo method with 1000 iterations. Finally, important CAEP peaks will be located by visual inspection. Calculation of these peak values will be performed using peak finding functions provided in Matlab. Standard t-tests ($p < 0.05$, two-tailed) will be used to compare amplitudes and latencies of these peak values across subjects with MCI and dementia due to AD, and between baseline, 12m and 24m follow-up. All reporting of pre-processing steps and analysis will be done according to publication guidelines (Keil et al., 2014).

2.4.6 Variables

Next tests will be performed to assess the participants' cognitive, audiologic, and vestibular function. These variables may influence cognition, the rate of conversion to ADD, and CAEP.

2.4.6.1 *Cognitive variables*

2.4.6.1.1 Mini-Mental Status Examination (MMSE)

The MMSE is a cognitive test, which consists of 11 questions and requires 5 to 10 minutes to administer (Folstein et al., 1975). Questions cover temporal and spatial orientation, memory, attention, the ability to name, follow verbal and written commands, write a sentence spontaneously and copy interlocking pentagons. A maximum score of 30 can be obtained (Crum et al., 1993).

2.4.6.2 *Audiologic variables*

2.4.6.2.1 Pure tone audiometry

Pure-tone audiometry for air conduction will be performed at 125 Hz, 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz, 4000 Hz, 6000 Hz, and 8000 Hz using insert-earphones and a two-channel AC-40 audiometer (Interacoustics, Assens, Denmark). Bone conduction thresholds will be measured at 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz, and 4000 Hz when air conduction thresholds between 250 Hz and 4000 Hz exceed normality levels of 20 dB HL, so a distinction between sensorineural and conductive hearing loss can be made. Subsequently, the Weber test will be conducted to identify lateralization.

2.4.6.2.2 Speech-In-Noise (SPIN)

The speech audiometry in noise is assessed by the Leuven Intelligibility Sentences Test (LIST) using an adaptive procedure (van Wieringen & Wouters, 2008). This speech-in-noise test is conducted in free field using a loudspeaker at 0° azimuth at a distance of one meter. The frequency spectrum of the noise matches the long-term average frequency spectrum of the speech signal. The noise level is constant at 65 dB SPL, while the speech level is adapted according to the response of the patient. A correct repetition of the keywords of a sentence

results in a decreased speech level of 2 dB SPL, while an incorrect response results in an increased speech level of 2 dB SPL. Every list consists of ten sentences, and minimally two lists are conducted in order to acquire the speech reception threshold (SRT). This SRT is calculated by averaging the speech levels of the last five sentences of the last list and the imaginary 11th sentence.

2.4.6.3 *Vestibular variables*

2.4.6.3.1 Video Head Impulse Testing (vHIT)

The video head impulse testing (vHIT) is a vestibular test. The patients are instructed to focus on a fixation dot placed at eye-level one meter in front of them. The patients will experience short, quick head movements in the direction of all six (lateral, superior, and posterior; left and right ear) semicircular canals, performed by the researcher. The vHIT makes use of the ICS Impulse (Otometrics, Nasus), which is a lightweight pair of glasses with a built-in accelerometer and video camera pointed at the right eye so it can analyse the vestibulo-ocular reflex. The eye and head movements of patients with a working vestibular system will overlap. When patients experience vestibular loss, a corrective saccadic eye movement ("catch-up" saccade) will be present. Measurements will consist of gain, standard deviation, saccades (percentage and amplitude of covert and overt saccades), a classification of the saccades (normal, gathered, scattered), and the amplitude of the head. These measurements will be collected for all six semicircular canals.

2.4.6.3.2 Cervical Vestibular Evoked Myogenic Potentials (cVEMP)

Cervical vestibular evoked myogenic potentials are ipsilateral inhibiting muscle potentials measured at the level of the contracted sternocleidomastoid (SCM) muscle. These potentials are evoked by short tone bursts presented to the patient through insert-earphones. The patient is instructed to tilt his head to one side, thus tensioning the SCM muscle, while stimuli are presented in the contralateral ear. This procedure is repeated multiple times while decreasing the sound intensity and detecting the stimulation threshold. A typical cVEMP potential is biphasic and characterized by two distinctive peaks (p13, n23). When this cVEMP potential is present, it shows an intact reflex arc (sacculus – inferior vestibular nerve – vestibular nuclei – vestibulospinal tract). Besides a measurement of whether this reflex is present, also the threshold, the latency of p13 and n23, and the amplitude is assessed, for both the left and right ear. This test will be conducted using the validated Neuro-Audio device with electromyography (EMG) feedback (Neurosoft).

2.4.6.4 *Questionnaires*

2.4.6.4.1 Edinburgh Handedness Inventory

This inventory is a quantitative assessment of handedness. Participants need to indicate for all ten items if they prefer using their right hand, left hand or both. After calculations, it can be evaluated whether the participant is predominantly right-handed, left-handed, or ambidexter (Oldfield, 1971).

2.4.6.4.2 Beck Depression Inventory (BDI)

The BDI is used to measure symptoms and severeness of depression. Participants must answer 21 questions. Every question has four answer options, which are displayed with an ascending grade of depression. The total score is the summed item score. A higher total score indicates a higher degree of depression (0-13 = minimal, 14-19 = light, 20-28 = moderate, 29-63 = severe depression) (Van der Does, 2002).

2.4.6.4.3 Hospital Anxiety and Depression Scale (HADS)

The HADS screens states of anxiety and depression using a total of 14 questions (Spinhoven et al., 1997). Seven questions pertain to the subscale "anxiety", whereas the other seven belong to the subscale "depression". A total score of 7 or less on each subscale indicates a non-case. A score of 8 to 10 is a borderline case, and a score of 11 or more indicates a case (Zigmond & Snaith, 1983).

2.4.6.4.4 Type D Scale – 14 (DS14)

The DS14 is used to assess negative affectivity, social inhibition, and type D personality. The inventory contains seven-item negative affectivity and social inhibition subscales. A total score greater than or equal to ten on either the negative affectivity or social inhibition subscale indicates a case. A type D personality is present when both subscale scores are greater than or equal to ten (Denollet, 2005).

2.4.6.4.5 Dizziness Handicap Inventory (DHI)

This questionnaire measures self-perceived handicap resulting from dizziness and unsteadiness due to vestibular system diseases (Vereeck et al., 2006). The DHI consists of 25 questions which can be divided into three subscales: functional, emotional and physical impacts on disability. A total score is calculated and indicates the level of handicap (0-14 = no handicap, 16-34 = mild handicap, 36-52 = moderate handicap, >54 = severe handicap) (Jacobson & Newman, 1990).

2.4.6.4.6 Vestibular Disorders Activities Of Daily Living (V-ADL)

This self-rated scale quantifies the effects of vertigo and balance disorders on independence in performing activities of daily life by assessing the patient's perception about its autonomy in functional, ambulation and instrumental skills. The summed total and median is calculated for the total questionnaire, as well as for each subscale (Cohen, 2014).

2.4.6.4.7 Activity-Specific Balance Confidence scale (ABC Scale)

Senior's balance confidence in their ability to perform daily activities without falling is investigated using the ABC scale. This self-perceived handicap questionnaire includes a wider range of activity difficulty and items are described in more detail, compared to the FES-I. The average score is calculated, with a higher score indicating more confidence in not losing your balance (Powell & Myers, 1995).

2.4.6.4.8 Short Falls Efficacy Scale International (Short FES-I)

Balance confidence will also be evaluated by the short version of the FES-I. This questionnaire comprises seven statements which each are an activity of daily living commonly performed by seniors. Participants mark each item on a scale from 1 (not at all concerned about falling) to 4 (very concerned about falling). The summed total score is used to identify the degree of concern, which can be done using the 2-item gradation (7-10 = low concern, 11-28 = high concern), or the 3-item gradation (7-8 = low concern, 9-13 = moderate concern, 14-28 = high concern) (Delbaere et al., 2010).

2.4.6.4.9 Speech, Spatial and Qualities of Hearing Scale – 12 Questionnaire (SSQ12)

The SSQ12 consists of 12 questions and is a short version of the Speech, Spatial and Qualities of Hearing Scale. This questionnaire measures several aspects of hearing ability, such as: speech comprehension in quiet and noisy environments; localization of sound, distance, and movement; segregation; and listening effort. Patients rate their ability to hear or experience different situations on a 1-10 scale (1 = not at all, 10 = perfectly). An average of all 12 scores is calculated (Noble et al., 2013).

2.4.6.4.10 Oscillopsia Severity Questionnaire (OSQ)

The OSQ is a questionnaire consisting of nine questions assessing whether the patient has an unstable view while performing different activities or engaging in different situations. The patient must mark whether he always – often – sometimes – seldom – never experiences unstable vision during the described activity or situation. These answers are converted to a 5-1 scale (5 = always, 1 = never) and an average score is calculated. An average score of greater than three indicates moderate to extreme oscillopsia severity (Guinand, Pijnenburg, et al., 2012).

2.4.6.4.11 Barthel Index

The Barthel Index is a questionnaire which consists of ten questions and measures the level of independence in performing activities of daily life (ADL). The Barthel Index is also used to define the dementia stage or conversion from MCI to dementia. A higher total score describes a higher level of independence (0-4 = fully dependent, 10-14 = needs help but can perform independently, 15-19 = predominantly independent, 20 = fully independent in basal ADL and mobility) (Post et al., 1995).

2.4.6.4.12 Comprehensive Frailty Assessment Instrument (CFAI)

This self-administered instrument measures frailty in four domains (physical, psychological, social and environmental frailty). The total score is calculated by summing the scores per domain and can identify three levels of frailty: no to mild frailty, moderate frailty and severe frailty. A higher total CFAI score indicates more frailty (De Witte et al., 2013).

2.4.6.4.13 European Quality of Life-5 Dimensions Questionnaire (EQ-5D-5L)

The EQ5D-5L is a questionnaire that measures health-related and disease-specific quality of life using five dimensions (mobility, self-care, daily activities, pain/discomfort, anxiety/depression) (Balestroni & Bertolotti, 2012). Answers are converted into an EQ5D-5L profile, which is converted into an index value scaled from 0 (death) to 1 (perfect health). The questionnaire also assesses self-perceived health by using a Visual Analog Scale (VAS). Participants need to report their perceived health status on a scale ranging from 0 (worst possible health status) to 100 (best possible health status) (Economics, 1990).

2.4.6.4.14 Health Utilities Index Mark-3 (HUI3)

The HUI3 is a health-related and disease-specific quality of life measuring instrument (Feeny et al., 1995). This self-administered questionnaire comprises 15 questions, which can be divided into eight attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain). The total score ranges from 0 (dead) to 1 (perfect health).

2.4.6.4.15 Health status

A self-constructed questionnaire assessing for risk factors of hearing loss, vestibular loss, and cognitive loss was included. Patients had to fill out their weight and height, whether they have high blood pressure (>140/90 mmHg) (if yes whether they take medication for their high blood pressure), whether they have diabetes, whether they smoke, whether they experience tinnitus, and whether they wear a hearing aid (if yes: since when and how many hours per day they wear their hearing aid).

2.4.7 Data collection and management

Patient-level trial-related data will be collected using the participating site's electronic medical record and OpenClinica (v. 3.13). OpenClinica LLC is used to enter and store data in a clean, secure, and efficient manner. This software package is developed especially for electronic data management in clinical research. Only the principal investigators have access to this password-protected database. Validation checks such as range checks for data values are programmed so that the number of mistakes is minimized. The information collected in this study is kept strictly confidential. Individual information and results are coded, with only the researcher knowing which code was assigned to each participant. The data are stored for 20 years.

2.4.8 Statistical methods

Data will be analyzed using SPSS statistical software version 25 (SPSS Inc, Chicago, IL, USA). Descriptive analyses will be expressed as mean values with standard deviation or standard error of the mean (SEM). If the data is not normally distributed, median and median absolute difference (MAD) will be reported. Cross-sectional results will be studied first using intended parametric or non-parametric tests, to provide insight in the correlation between hearing, vestibular function and cognition. Longitudinal differences will be analyzed at 12 and 24

months using variance analyses (ANOVA, repeated measure design). A corresponding non-parametric test will be used to study the effect on conversion to dementia in MCI patients. A significance level of 0.05 will be applied. The Holm-Bonferroni method will be used for multiple comparison correction.

2.5 Discussion

Because of the worldwide growing prevalence of dementia, identification of possible risk factors is prioritized. First of all, hearing loss is considered to be an independent risk factor for dementia. The evidence that a vestibular decline could also be a risk factor for cognitive decline continues to rise. Because of the close anatomical relationship between auditory and vestibular structures of the inner ear, hearing loss and vestibular decline are often presented jointly. Furthermore, previous studies often subjectively assess hearing and/or vestibular function. In this respect, subjects participating in this experiment will undergo extensive testing. This way, an objective and scientifically substantiated assessment of subjects' hearing, vestibular, and cognitive function is performed.

To our knowledge, this is the first research project that will look into the effect of both hearing loss as well as vestibular decline on cognition, including their interaction. This study will go beyond the current state of art by using a neuropsychological cognitive test adapted for a potentially hearing-impaired MCI and dementia due to AD population. This way hearing-impaired subjects will be able to understand the instructions clearly and perform conform to their actual cognitive level. Furthermore, the study will be able to objectively identify the impact of hearing loss and vestibular decline on both global cognitive function, as well as on specific (spatial and non-spatial) cognitive domains. Vestibular loss is expected to decrease the level of spatial cognitive function, whereas hearing loss is expected to reduce non-spatial cognition.

The expected results will gain important insights in the identification of risk of falling, unsteadiness, driving difficulties, etc. which in turn can lead to major health concerns in people with ADD. Furthermore, vestibular rehabilitation is proven to be effective in balance improvement and reduction of fall risk in cognitively healthy subjects with vestibular deficits. On the contrary, the effectiveness of vestibular rehabilitation in cognitively impaired subjects, in this case subjects with MCI or dementia due to AD, has not yet been explored (Klatt, 2019). Future prospective interventional studies may look into the potential benefit of customized vestibular rehabilitation in subjects with varying degrees of cognitive decline, which will be supported by current research.

Hearing loss may be an early indication of ADD, and care management is primarily based on communication between the patient and its caregivers. However, the patient's hearing function is not taken into account during the diagnosis of ADD. As a result, hearing loss may be one of the most overlooked deficits in persons with ADD (Bakhos et al., 2015). The

expected results may alter this diagnostic process. In addition, current research would support future studies investigating whether individualized hearing rehabilitation could lessen cognitive decline, the rate of conversion to dementia, and/or frailty. Finally, the setup of audiologic (e.g. CAEP) and vestibular screening protocols in MCI and dementia patients due to AD and those at risk will be strengthened by current research outcomes.

Chapter 3. Vestibular function in older adults with cognitive impairment: A systematic review

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3.1 Abstract

Importance: Given the rising prevalence of patients with dementia and those at risk for it, early identification is prioritized. As vestibular dysfunction is associated with Alzheimer's disease (AD) and may contribute to its onset, vestibular assessment may yield an opportunity in early dementia screening.

Objective: This systematic review structures and compares the different raw outcome measures used to assess vestibular function while comparing older adults with preserved cognition to individuals with cognitive impairment, either suffering from Mild Cognitive Impairment (MCI) or AD.

Design: Two investigators independently and systematically searched publications on PubMed performing objectively measured vestibular testing in a patient population consisting of either MCI and/or AD, compared to a control group of older adults with preserved cognition. No limitations regarding language or publication date were applied. References of the retrieved articles were hand searched for relevant articles.

Results: Seven articles were included for analysis. A total of 235 older adults with impaired cognition (150 AD, 85 MCI) were compared with a control group of 481 older adults with preserved cognition. Evaluation of the peripheral vestibular function included video head impulse test (vHIT), videonystagmography (VNG), electronystagmography (ENG) including bithermal caloric irrigation and vestibular evoked myogenic potentials (VEMP). The VEMP test, assessing otolith function and the elicited vestibulocollic reflex (VCR), was able to differentiate subjects with AD and its prodromal stage from healthy controls, with p13 latency ($p < 0.05$) and amplitude ($p < 0.05$) having the most discriminating power. No correlation between cognitive decline and vestibulo-ocular reflex measurements in different frequency ranges of the semicircular canals (using vHIT, rotatory chair testing, and caloric irrigation) was found. Because of the limited number of available studies and the large heterogeneity in outcome measures, these results have to be interpreted with caution.

Conclusions: Measurements of the VCR, as evoked by the VEMP test, discriminate between patients with cognitive impairment (MCI and AD) and older adults with preserved cognition, whereas measurements of the VOR do not. More studies are needed to further elaborate on these findings.

3.2 Key points

Question: Which outcomes of which vestibular tests can demonstrate a difference between older adults with MCI, AD, and preserved cognition?

Findings: In this systematic review, the cVEMP test demonstrated its potential in distinguishing MCI or AD from older adults. Especially p13 latency and amplitude were the most promising parameters, compared to non-discriminatory measures of semicircular canal function. Since the search returned a limited number of results, more studies are needed to elaborate these findings.

Meaning: The VEMP test can discriminate between patients with cognitive impairment and preserved cognition. Measurements of the VOR cannot.

3.3 Introduction

As the world's population increases in age, a growing number of people are affected by dementia. Worldwide around 47 million people suffered from dementia in 2015, and this number is expected to triple by 2050 (Livingston et al., 2017). The most common cause of dementia is Alzheimer's disease (AD), which accounts for up to seventy percent of all dementia cases, according to the World Health Organization (2019). It is characterized by an episodic memory deficit and evolves from an intermediate state of cognitive decline, more specifically Mild Cognitive Impairment (MCI). Patients with MCI do not experience deficits in their activities of daily living, whereas patients with AD do. When including biomarkers in the diagnosis, the terms prodromal AD or MCI due to AD and dementia due to AD should be used instead of the more general terms such as MCI and AD, respectively. For clear writing purposes, both MCI and prodromal AD groups will be described as "MCI", and for both AD and dementia due to AD, the term "AD" will be used.

Recent evidence suggests that vestibular dysfunction is associated with AD and may contribute to its onset (Bigelow & Agrawal, 2015; Brandt et al., 2005; Previc, 2013; Schautzer et al., 2003; Semenov et al., 2016). This vestibular loss hypothesis, as described by Previc (2013), is substantiated by the evidence that vestibular decline is associated with hippocampal atrophy, which is an important biomarker for AD (Allen et al., 2017; Brandt et al., 2005; Halliday, 2017; Previc, 2013; Smith, 2016). Furthermore, impaired spatial cognition is among the most frequently observed cognitive deficits in AD (Bigelow et al., 2015; Bird et al., 2010) and is related to vestibular loss (Schautzer et al., 2003; Wei et al., 2018; Xie et al., 2017).

Moreover, recent studies found evidence of impaired spatial cognition in subjects with bilateral vestibulopathy (Dobbels, Mertens, et al., 2019; Dobbels, Peetermans, et al., 2019;

Kremmyda et al., 2016; Schautzer et al., 2003). In addition, age-related degeneration of vestibulolimbic and -cortical pathways could influence the development of AD (Previc, 2013; Smith, 2013). Given the rising prevalence of dementia, an emphasis should be put on early treatment.

The aim of this study is to systematically review the literature on vestibular function testing in populations consisting of adults older than 55 years with preserved cognition, MCI, and AD (Gallacher et al., 2012).

3.4 Materials and methods

This systematic review is performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Moher et al., 2009). The protocol was registered at the PROSPERO international prospective register of systematic reviews (PROSPERO ID: 180620).

3.4.1 Eligibility criteria

- Participants: Patients with diagnosed MCI or AD.
- Comparator: The control group consisted of older adults with preserved cognition.
- Outcomes: Assessment of peripheral vestibular function using functional tests designed to objectively evaluate vestibular function. Results must be quantifiable. Studies reporting on stabilometry, performance-based measurements, subjective assessments, drug trials, or treatment effects were excluded.
- No restrictions were imposed regarding language or publication date.

3.4.2 Search strategy

The search query was defined and ran in the databases of PubMed, Cochrane, Web of Science, and Scopus on November 4th 2020. The following search string was used: (vestibul*) AND (dementia OR Alzheimer OR Mild Cognitive Impairment). References of relevant articles were hand-searched for additional papers. Reviews on vestibular assessment in older adults with cognitive impairment were also searched for relevant articles.

The selection procedure consisted of a thorough search on title and abstract first and secondly on full-text. Two investigators (JB and CJ) independently searched publications. Discrepancies were discussed until consensus was reached. All steps of the screening procedure are presented in Figure 8.

The following information was extracted from included articles: author, year of publication, demographic characteristics, in- and exclusion criteria, population sample sizes, results of vestibular function tests, and raw data of outcome measures. Risk of bias was assessed using

the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (Health, 2014), designed by the National Institutes of Health.

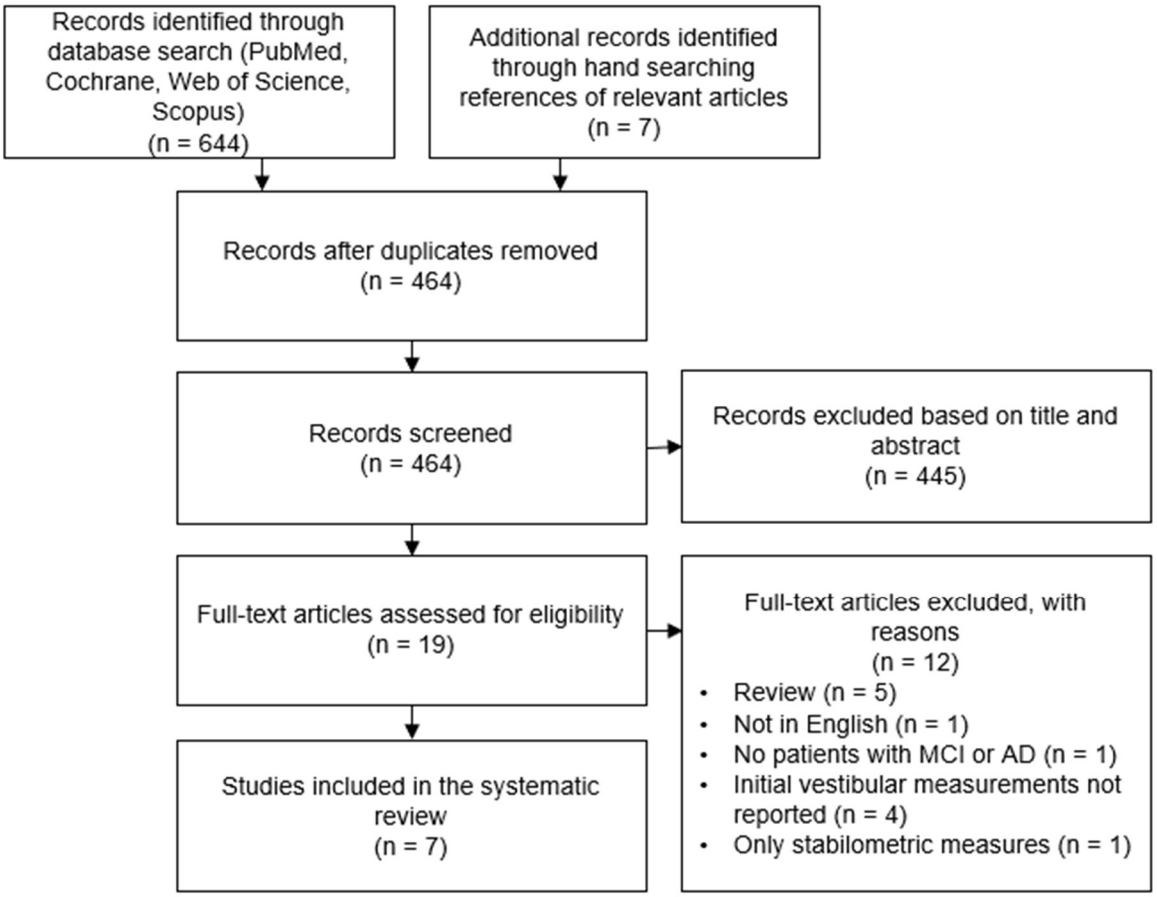

Figure 8. Flow diagram of study inclusion.

3.5 Results

Electronic database searching resulted in 457 records. After applying eligibility criteria (Figure 8), seven studies were selected for inclusion, all written in English, reporting on 235 patients with cognitive impairment (85 MCI, 150 AD). These studies all compared vestibular assessments in patients with MCI and/or AD with older adults with preserved cognition, consisting of 481 controls. Previous research elaborated on the vestibular loss hypothesis (Previc, 2013; Smith, 2013) or described ways to assess and interpret vestibular contributions to cognitive domains (Li et al., 2014; Palla & Lenggenhager, 2014). To our knowledge, this is the first systematic review on vestibular function testing in a population with cognitive impairment as compared to cognitively healthy older adults.

Baydan et al. (2020) performed VNG in 10 patients with MCI and 10 controls (Baydan et al., 2020). Birdane et al. (2012) performed cVEMP in 10 patients with MCI, 20 patients with AD,

and 30 controls (Birdane et al., 2012). Chong et al. (1999) performed rotatory chair testing in 11 patients with AD and 17 controls (Chong et al., 1999). Harun et al. (2016) performed cVEMP, oVEMP, and vHIT in 15 patients with MCI, 32 patients with AD, and 94 controls (Harun, Oh, et al., 2016). Micarelli et al. (2018a) performed vHIT in 24 patients with MCI, 24 patients with AD, and 23 controls (Micarelli et al., 2018a). Nakamagoe et al. (2015) performed bithermal caloric irrigation in 12 patients with AD and 12 controls (Nakamagoe et al., 2015). Wei et al. (2019) performed cVEMP, oVEMP, and vHIT in 26 patients with MCI, 51 patients with AD, 102 controls matched with the MCI patients, and 193 controls matched with the AD patients (Wei et al., 2019).

Different studies identified their patient groups based on different diagnostic criteria, as presented in Table 2. In one study (Baydan et al., 2020), the diagnosis of MCI was made according to the Petersen criteria (Petersen et al., 2001). In four studies (Harun, Oh, et al., 2016; Micarelli et al., 2018a; Nakamagoe et al., 2015; Wei et al., 2019), the diagnosis of MCI or AD was made according to National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for AD (NIA-AA) criteria (Albert et al., 2011; McKhann et al., 2011). In two studies (Birdane et al., 2012; Chong et al., 1999), the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS-ADRDA) were used (McKhann et al., 1984). When comparing diagnostic criteria of Petersen, NIA-AA and NINCDS-ADRDA for MCI and AD (Albert et al., 2011; McKhann et al., 1984; McKhann et al., 2011; Petersen et al., 2001), most criteria were comparable. The NIA-AA criteria are the revised version of the widely used NINCDS-ADRDA criteria, with in addition the use of biomarkers. McKhann et al. (2011) stated that all patients who were diagnosed with AD according to the NINCDS-ADRDA criteria, would also meet criteria for AD according to NIA-AA (McKhann et al., 2011).

Baydan et al. (2020) and Birdane et al. (2012) did not adjust statistical methods for age, whereas all other studies did (Baydan et al., 2020; Birdane et al., 2012). Furthermore, the study by Chong et al. (1999) was the only study that did not perform the MMSE in the control group (Chong et al., 1999). In addition, Chong et al. (1999) and Nakamagoe et al. (2015) did not ascertain the normal cognitive state of the control group by formal neuropsychological testing (Chong et al., 1999; Nakamagoe et al., 2015). Whether Harun et al. (2016) and Wei et al. (2019) performed formal neuropsychological testing in their control group remains unclear (Harun, Oh, et al., 2016; Wei et al., 2019).

3.5.1 Quality assessment

Quality assessment was performed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (Health, 2014). This checklist, designed by the National Institutes of Health, evaluates potential flaws in observational cohort and cross-sectional studies, such as sources of bias and confounding variables. All five studies were prospective cross-sectional studies and were rated as of "good" or "fair" quality, ranging between quality assessment scores of eight and ten, which can be seen in Table 2. This means that included

studies are possibly susceptible to some bias, but results are considered to be valid. No significant risks of bias were found. None of the included studies assessed vestibular function longitudinally.

3.5.2 Publication bias

Publication bias cannot be assessed due to the high heterogeneity in outcome measures of included studies.

3.5.3 Vestibular function test results

3.5.3.1 *General results*

The first noteworthy finding is that the search resulted in a small number of articles that fitted all eligibility criteria. Furthermore, the seven included articles reported on a large heterogeneity of outcome measures, which impedes comparison and makes it difficult to draw conclusions.

Harun et al. (2017) investigated the level of cognitive function required to complete standard vestibular tests (Harun et al., 2017). They suggested a threshold of cognitive impairment, more specifically a Mini-Mental State Examination (MMSE) score of 12 or less, which characterizes individuals who are too cognitively impaired to complete vestibular testing (Folstein et al., 1975). The patient population of three studies included MMSE-scores which were all greater than 12, implying that these patients should all be able to complete vestibular assessment (Baydan et al., 2020; Micarelli et al., 2018a; Nakamagoe et al., 2015). Harun et al. (2016) included patients with a MMSE-score greater than ten, of which two patients (MMSE of 12 and 12) were unable to follow vestibular testing instructions (Harun, Oh, et al., 2016). Birdane et al. (2012), Chong et al. (1999), and Wei et al. (2019) included patients with MMSE-scores less than 12 (Birdane et al., 2012; Chong et al., 1999; Wei et al., 2019). This calls into question whether these participants could adequately follow instructions for vestibular testing. Therefore, these results must be interpreted with caution. An overview of main outcome measures and its statistical significance is provided in Table 3.

3.5.3.2 *Vestibular physiologic function results*

3.5.3.2.1 Cervical VEMP (cVEMP) and ocular VEMP (oVEMP)

Birdane et al. (2012), Harun et al. (2016), and Wei et al. (2019) used the cVEMP and oVEMP to assess vestibular function (Birdane et al., 2012; Harun, Oh, et al., 2016; Wei et al., 2019). CVEMPs are measurements of saccular function using electromyographic activity of the contracted sternocleidomastoid muscle contralateral from the auditory stimulated ear. The cVEMP test is performed while patients lie in the supine position. A typical cVEMP tracing consists of a biphasic waveform, showing two distinctive peaks (p13, n23) (Li et al., 2014; Rosengren et al., 2019). Outcome measures are the latencies of p13 and n23 and their amplitude. Birdane et al. (2012) used rarefaction clicks of 0.1 ms of duration and frequency

of 5 Hz at 110 dB, while Harun et al. (2016) and Wei et al. (2019) used 500 Hz, 125 dB SPL tone bursts. The prevalence of bilaterally absent cVEMPs are recorded, which is marked when the characteristic waveform was missing (Birdane et al., 2012; Harun, Oh, et al., 2016). More specifically, Birdane et al. (2012) accepted prolongation of latency period according to average latency of the control group or the absence or decrease of cVEMP response as a pathological result. Harun et al. (2016) defined an absent response if the characteristic waveform did not occur per published guidelines, i.e. waveforms lacking the definable p13 wave (Li et al., 2015). Wei et al. (2019) marked vestibular function as abnormal when function was unilaterally or bilaterally absent (Wei et al., 2019).

OVEMPs measure utricular function using vibration-evoked extraocular myogenic responses. A typical oVEMP potential is also biphasic and characterized by two distinctive peaks (n10, p16) (Li et al., 2014). Outcome measure is the amplitude of the ear with better vestibular function and abnormal oVEMPs (Harun, Oh, et al., 2016; Wei et al., 2019). Both Birdane et al. (2012) and Harun et al. (2016) found the amplitude to be significantly ($p < 0.05$) decreased in patients with cognitive impairment compared with healthy controls (Birdane et al., 2012; Harun, Oh, et al., 2016). A smaller amplitude was associated with increased odds of AD (Harun, Oh, et al., 2016). Harun et al. (2016) reported no significant difference in amplitude between healthy controls and patients with MCI (Harun, Oh, et al., 2016).

In contrast, results provided by Birdane et al. (2012) demonstrated no statistically significant difference in amplitude when comparing patients with MCI to patients with AD, but rather a discrepancy between patients with cognitive impairment and older adults with preserved cognition ($p < 0.05$) (Birdane et al., 2012). Furthermore, they demonstrated that a prolonged p13 latency was associated with cognitive impairment ($p < 0.05$), where n23 latency was not (Birdane et al., 2012). In addition, patients with AD had a significantly higher prevalence of bilaterally absent or abnormal cVEMPs compared to controls ($p \leq 0.01$) (Harun, Oh, et al., 2016; Wei et al., 2019). According to Wei et al. (2019), patients with MCI had a significantly higher prevalence of abnormal cVEMPs and oVEMPs compared to controls ($p < 0.05$). However, this difference is less outspoken than the prevalence of abnormal cVEMPs and oVEMPs in AD patients in comparison to controls ($p < 0.001$) (Wei et al., 2019). Harun et al. (2016) stated that bilaterally absent cVEMPs increased the odds of AD by over three times. Harun et al. (2016) controlled for adequate contraction of the sternocleidomastoid muscle during cVEMP testing, whereas Birdane et al. (2012) and Wei et al. (2019) did not, which calls the validity of these results into question.

3.5.3.2.2 Vestibulo-Ocular Reflex (VOR)

Harun et al. (2016), Micarelli et al. (2018a), and Wei et al. (2019) used the vHIT (Halmagyi et al., 2017) to assess VOR gain by horizontally rotating patients' heads with a small amplitude and high velocity in order to stimulate the horizontal semicircular canals (Harun, Oh, et al., 2016; Micarelli et al., 2018a; Wei et al., 2019). Only Wei et al. (2019) demonstrated a

significant difference in VOR gain between MCI and controls (p = 0.008), however, this difference was absent between AD and controls. Both other studies did not find a significant difference in VOR gain between controls, MCI, and AD. Chong et al. (1999) confirmed these results by using the rotatory chair in order to measure VOR gain (Chong et al., 1999). During this test, subjects' eye movements were recorded while a moveable chair rotated from side to side. This measurement was performed in the dark as well as with lights on. Baydan et al. (2020) also confirmed these results by using VNG. Using goggles with a built-in camera, they recorded eye movements during saccadic and smooth pursuit, as well as spontaneous nystagmus. They found no significant differences in overall VOR between MCI and controls. They measured VOR by comparing the right and left saccade peak velocity, accuracy, and latency between MCI and controls, of which none were statistically significant (p > 0.05) (Baydan et al., 2020).

3.5.3.2.3 **Caloric response and visual suppression**

To induce caloric nystagmus, patients experience bithermal caloric irrigation in each ear sequentially. Nakamagoe et al. (2015) reported no significant difference in nystagmus parameters of caloric stimulation before and during visual suppression between older adults with cognitive impairment or preserved cognition. Only the suppression rate was significantly lower in patients with AD, compared to age-matched controls (p = 0.022) (Nakamagoe et al., 2015).

Table 2. Overview of the patient and control population of all included studies. MCI, Mild Cognitive Impairment; AD, Alzheimer's disease; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related disorders Association; NIA-AA, National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease; UVH, unilateral vestibular hypofunction.

Author, Year	**Inclusion criteria patient group**	**Use of biomarkers?**	**Sample size patient group (number of females)**	**Mean age patient group in years**	**Inclusion criteria control group**	**Sample size control group (number of females)**	**Mean age control group in years**	**Quality assessment score**
Baydan et al., 2020	Diagnosis MCI according to Petersen criteria Age > 65 years No communication problems (e.g. severe hearing loss)	No	MCI: 10 (5)	MCI: 78.8	Age-appropriate cognitive function	10 (5)	80.9	8 = fair
Birdane et al., 2012	Diagnosis MCI or AD according to criteria of NINCDS-ADRDA	Yes	Patient: 30 (15)	Patient: 67.5	No neurological	30 (12)	61.0	8 = fair

			MCI: 10	Age MCI and AD not specified	or otological disease			
			AD: 20					
			Sex MCI and AD not specified					
Chong et al., 1999	Diagnosis AD according to criteria of NINCDS-ADRDA	No	AD: 11 (5)	AD: 73.0	Age matched	17 (8)	65.0	8 = fair
Harun et al., 2016	Age ≥ 55 years	?	Patient: 47 (33)	Patient: 75.1	Age, gender, education matched	94 (66)	75.0	10 = good
	Diagnosed MCI or AD according to criteria of NIA-AA		MCI: 15 (9)	MCI: 74.3				
	MMSE ≥ 11		AD: 32 (24)	AD: 75.7				
	Fluent in English							
	Ability to obtain informed consent from the participant or							

	legally authorized representative							
Micarelli et al., 2018	UVH	?	Patient: 48 (27)	Patient: 75.2	Age, gender, education matched	23 (12)	75.5	10 = good
	Age ≥ 55 years		MCI: 24 (14)	MCI: 74.4				
	Diagnosed MCI or AD according to criteria of NIA-AA		AD: 24 (13)	AD: 75.9	Age-appropriate cognitive function			
	MMSE ≥ 11							
	Fluency in Italian							
	Ability to obtain informed consent from the participant or legally authorized representative							
Nakamagoe et al., 2015	Diagnosed AD according to criteria of NIA-AA	Yes	AD: 12 (6)	AD: 78.0	Age matched	12 (6)	75.8	9 = fair

Wei et al., 2019	Diagnosed MCI or AD according to criteria of NIA-AA	?	Patient: 77 (51)	MCI: 72.5	Age, sex, education matched	Controls: 295 (191)	Matched with MCI: 72.7	9 = fair
	Age ≥ 55 years		MCI: 26 (15)	AD: 76.0		Matched with MCI: 102 (58)	Matched with AD: 75.4	
	Fluency in English		AD: 51 (36)			Matched with AD: 193 (133)		
	Ability to obtain informed consent from the participant or a legally authorized representative							

Table 3. Results of tests structured by method of vestibular assessment. Grey colors indicate a statistical significantly impaired outcome in the MCI or AD patient group. cVEMP, cervical vestibular evoked myogenic potentials; oVEMP, ocular vestibular evoked myogenic potentials; vHIT, video head impulse testing; VNG, videonystagmography: VOR, vestibulo-ocular reflex; MCI, Mild Cognitive Impairment; AD, Alzheimer's disease; HC, healthy controls.

Tests	Measures	Outcomes	P-value	Sample size	Study
cVEMP	Latency p13	(AD & MCI) > HC	$p < 0.05$	60, 104 ears	Birdane et al., 2012
	Latency n23	(AD & MCI) = HC	$p > 0.05$	60, 104 ears	
	Amplitude	(AD & MCI) < HC	$p < 0.05$	60, 104 ears	
		AD < HC	$p = 0.039$	126	Harun et al., 2016
		MCI = HC	not specified	109	
	Prevalence bilateral absent cVEMPs	AD > HC	$p = 0.01$	126	
		MCI = HC	not specified	109	
	Abnormal cVEMPs	MCI > HC	$p = 0.03$	261	Wei et al., 2019

		AD > HC	p < 0.001	283	
oVEMP	Amplitude	AD < HC	p = 0.036	126	Harun et al., 2016
		MCI = HC	not specified	109	
	Abnormal oVEMPs	MCI > HC	p = 0.008	266	Wei et al., 2019
		AD > HC	p < 0.001	282	
vHIT	VOR gain	AD = MCI = HC	not specified	141	Harun et al., 2016
		AD = MCI = HC	not specified	71	Micarelli et al., 2018
		MCI < HC	p = 0.008	244	Wei et al., 2019
		AD = HC	p = 0.53	259	
Rotatory testing	VOR gain	AD = HC	p = 0.09	28	Chong et al., 1999

VNG		VOR	MCI = HC	p > 0.05	20	Baydan et al., 2020
Caloric irrigation	Caloric nystagmus	Amplitude, velocity, nystagmus frequency	AD = HC	p > 0.05	24, 48 ears	Nakamagoe et al., 2015
	Visual suppression test during caloric nystagmus	Amplitude, velocity, nystagmus frequency	AD = HC	p > 0.05	24, 48 ears	
		Suppression rate	AD < HC	p = 0.022	24, 48 ears	

3.6 Discussion

This study aimed to systematically review the literature on vestibular function testing in populations of older adults with preserved cognition, MCI and AD. The search resulted in seven included studies reporting heterogeneous outcome measures.

Overall, a higher prevalence of vestibular loss has been observed among individuals with cognitive impairment relative to older controls with preserved cognition. Supporting evidence demonstrated a balance decline when aging, being more pronounced in individuals with MCI (Liu-Ambrose et al., 2008; Nascimbeni et al., 2015; Pettersson et al., 2002; Pettersson et al., 2005; Shin et al., 2011) and even greater in individuals with AD (Jensen et al., 2003; Leandri et al., 2009). More precisely, this simultaneous presentation of cognitive impairment and a decline in balance appears to be associated with loss of otolith function, as measured by c- and oVEMP for saccular and utricular function, respectively, hence involving the VCR. On the other hand, the VOR -resulting from semicircular canal stimulation-, as measured by rotatory testing, bithermal caloric irrigation, and vHIT, is mainly preserved (Harun, Oh, et al., 2016). Therefore, VEMPs could be the most promising outcome measure related to vestibular function in discriminating between AD and its prodromal stage. More specifically, p13 latency and amplitude are the parameters of interest. In contrast, measures of semicircular canal function are generally not different in patients with normal or impaired cognition. In addition, the suppression rate during visual suppression of the caloric nystagmus also showed a significant differentiation between AD patients and healthy controls. This may indicate parietal lobe dysfunction due to AD and decreased blood flow in the inferior parietal lobule. Furthermore, a lower suppression rate was associated with a higher tendency to fall in patients with AD (Nakamagoe et al., 2015).

The VEMP test has plenty of advantages for utilisation in clinical practice. It is non-invasive, reliable, and safe. However, some factors may influence its results, such as muscle weakness, obesity, and age. E.g. 5-15% of individuals older than 60 years demonstrated absent cVEMP responses (Rosengren et al., 2019). Furthermore, results could be operator dependent, as no fixed criteria for the tracings exist, and interpretation may be complicated.

In order to explain why otolith function declines with cognitive impairment, while semicircular canal function is preserved, one may look at underlying neuronal pathways. Vestibular afferents transfer vestibular information to the vestibular nuclei (VN), which are connected to multiple brain areas, including the contralateral VN, the abducens nucleus (ABD) -responsible for VOR production-, higher brain centers involved in cognitive processing (such as spatial orientation), and the spinal cord motor neurons that produce the vestibulospinal reflex to maintain posture (Figure 9) (Cullen, 2012; Hitier et al., 2014). Considerable evidence exists that neurons in the VN that project to motoneurons involved in the VOR, are distinct from those which transmit vestibular information to higher brain areas, as they do not ascend to the thalamus and do not project cortically (Cullen, 2012;

Harun, Oh, et al., 2016; Smith, 2013). Neurons in higher brain structures that respond to vestibular stimulation are insensitive to eye movement, further supporting a segregation between pathways to higher areas of the brain and pathways involved in the VOR (Smith, 2013; Smith & Zheng, 2013). However, Harun et al. (2016) propose a hypothesis why the VCR decreases simultaneously with cognitive decline, whereas the VOR remains intact. They hypothesize that vestibular -specifically saccular (Miyamoto et al., 2007; Schlindwein et al., 2008) - projections to the higher brain structures undergo anterograde degeneration in cognitive impairment, resulting in an impaired VCR (Harun, Oh, et al., 2016). These patients also suffer from profound deficits in spatial awareness and spatial memory but do not exhibit VOR deficits, as these distinct pathways would be left intact (Smith, 2013). Therefore, a failure in finding VOR deficits in patients with cognitive impairment does not contradict the vestibular loss hypothesis as described by Previc (Lakshminarayanan et al., 1986; Previc, 2013; Smith, 2013). Would VOR changes still be observed, they would mainly be due to physiological aging (Nakamagoe et al., 2015). One must keep in mind that otolith-cervical and otolith-ocular projections that underlie the VEMP responses are distinct from the otolith-cortical projections (Harun, Oh, et al., 2016).

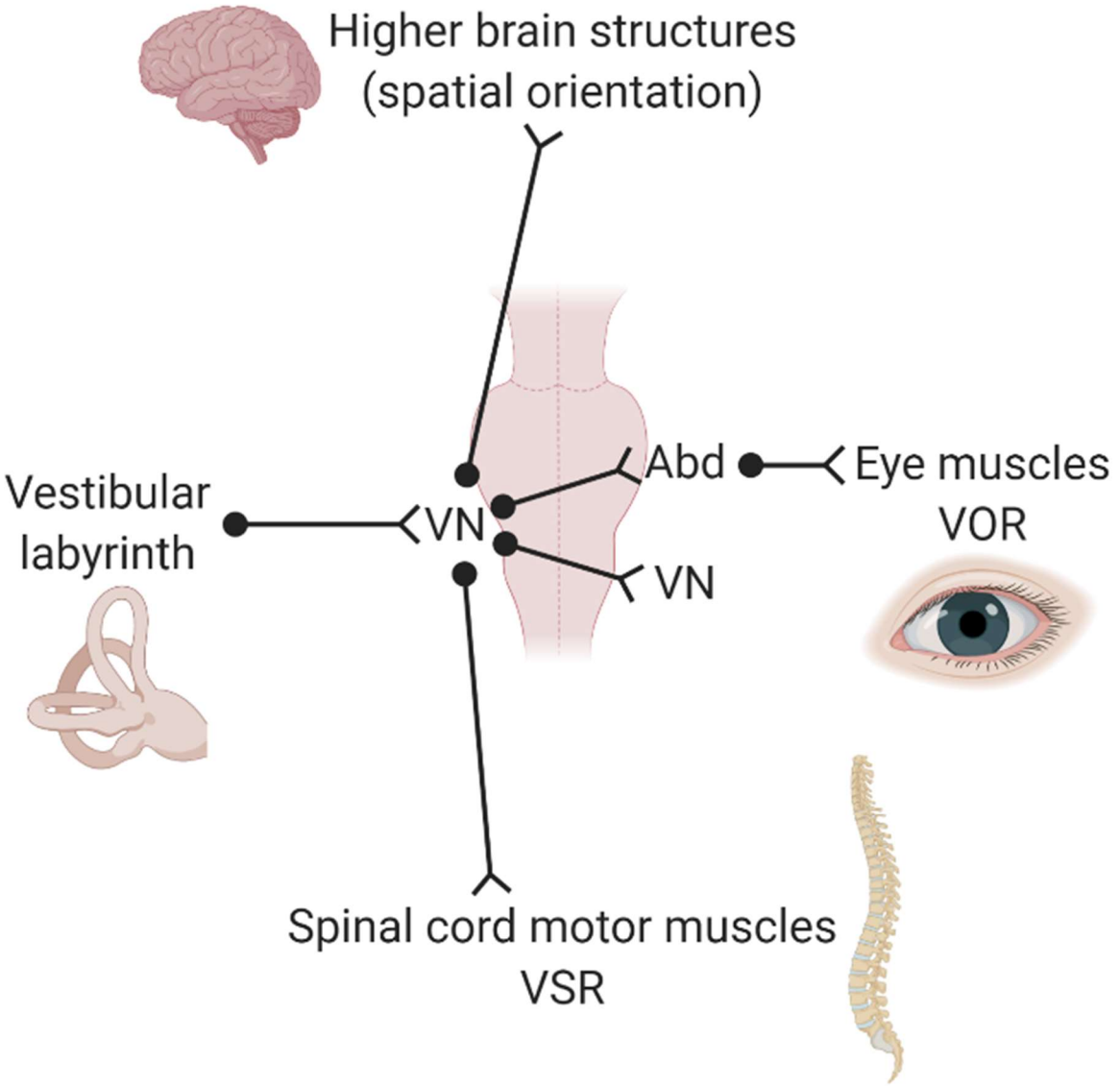

Figure 9. Neuronal pathways involved in transmitting vestibular information. Vestibular afferents project to the brainstem vestibular nuclei. These vestibular nuclei project to higher brain structures, eye muscles, and spinal cord muscles. ABD, abducens nucleus; VCR, vestibulocollic reflex; VOR, vestibulo-ocular reflex; VN, vestibular nuclei; VSR, vestibulospinal reflex.

An additional explanation for the observed association between vestibular dysfunction and cognitive impairment includes the hypothesis of a 'spatially impaired' subtype of AD. This specific subtype can be characterized by spatial disorientation and impaired spatial navigation, with symptoms such as losing or misplacing objects, driving difficulty, wandering and falls (Cipriani et al., 2014; Hamilton et al., 2009; van der Wardt et al., 2015; E. X. Wei et al., 2017). Wei et al. (2018) observed a significantly higher prevalence of vestibular loss in patients with 'spatially impaired' AD, supporting this hypothesis (Wei et al., 2018). The rationale behind this hypothesis of a specific 'spatially impaired' subtype of AD is comparable

to the vestibular loss hypothesis posited by Previc (2013). It focuses on the loss of vestibular (in particular saccular) input, leading to neurodegeneration of spatial processing networks, including the hippocampus (Agrawal et al., 2020). Therefore, in these patients, vestibular loss would impair specifically spatial cognition, independently of the more general cognitive decline associated with AD (Wei et al., 2018).

Balance impairment can also be assessed using stabilometry and gait analysis. Stabilometric results in patients with AD have demonstrated difficulties in maintaining balance while concurrently having to suppress incongruent visual and somatosensory information (Leandri et al., 2009; Liu-Ambrose et al., 2008; Micarelli et al., 2018a; Shin et al., 2011), even in case of normal peripheral vestibular function (Chong et al., 1999). Studies on gait analysis show a greater than expected balance impairment in patients with AD (Micarelli et al., 2018a; Nakamagoe et al., 2015; Pettersson et al., 2002; Pettersson et al., 2005). Gait disorders are not only more prevalent in dementia compared to normal aging, they are also related to the severity of cognitive decline (Beauchet et al., 2008; Gras et al., 2015; O'Keeffe et al., 1996). As such, patients with AD show a decreased walking speed and disturbances in dual-tasks, with the latter possibly being a specific marker of falling at a preclinical dementia stage (Beauchet et al., 2008; Pettersson et al., 2005), though contradictory results exist (Nascimbeni et al., 2015). Studies reporting on stabilometry or gait analysis were not included in this review as they do not specifically assess vestibular dysfunction.

Hearing loss, affecting around a third of the older population, is independently associated with dementia (Deal et al., 2017; Fritze et al., 2016; Gallacher et al., 2012; Lin, 2011; F. R. Lin, L. Ferrucci, et al., 2011; F. R. Lin, E. J. Metter, et al., 2011). Furthermore, hearing loss has been recognized as one of the most important modifiable risk factors for dementia (Livingston et al., 2017). Vestibular decline, however, is often overlooked as a potential concomitant risk factor for dementia (Cushing et al., 2008; Jacot et al., 2009; Loughrey et al., 2018; Semenov et al., 2016). Within vestibular research, data on hearing level are generally lacking (Dobbels, Peetermans, et al., 2019). This trend is also present in included studies. Three studies failed to mention any kind of audiological assessment (Chong et al., 1999; Harun, Oh, et al., 2016; Nakamagoe et al., 2015). One study excluded patients with hearing loss because of a possible false negative in VEMP responses (Birdane et al., 2012), and one study performed pure-tone audiometry but did not report on audiologic outcomes or findings (Micarelli et al., 2018a). Some recent studies investigating vestibular function and cognitive impairment did control for hearing loss. Evidence shows that cognitive impairment related to vestibular loss cannot be fully explained by hearing loss (Bigelow et al., 2016; Kremmyda et al., 2016; Semenov et al., 2016).

Given the limited number of included studies, the significant heterogeneity of outcome measures, and the heterogeneity with regard to inclusion criteria (use of biomarkers, formal neuropsychological testing of controls), further research is required to establish the association between vestibular function tests and cognitive impairment, with inclusion of

the assessment of hearing levels. In addition, the evaluation of anxiety should also be assessed, as this is a common problem in patients with vestibular impairment (MacDowell et al., 2018), could contribute to cognitive dysfunction (Gulpers et al., 2019), and is frequently overlooked. Indeed, none of the included studies evaluated participants' level of anxiety. Statistical methods should be adjusted for age, which is crucial when comparing vestibular, hearing and cognitive function, as all decline with age (Fischer et al., 2016; Iwasaki & Yamasoba, 2015). As current International Working Group (IWG) -2 criteria, a refined and simplified diagnostic framework involving the use of biomarkers in the diagnosis of AD, can quite reliably diagnose AD and MCI (Dubois et al., 2014) evaluation of peripheral vestibular function might allow for early detection of at-risk individuals. Furthermore, the potential treatment or rehabilitation of vestibular dysfunction might slow or even adverse cognitive decline. However, there is a need for longitudinal studies. Thus, even when vestibular function testing has shown promising results, further research is encouraged.

3.7 Conclusion

Measurements of the VCR, using the VEMP test, may suggest a discrimination between patients with cognitive impairment (MCI and AD) and older adults with preserved cognition, whereas measurements of the VOR, using vHIT or ENG, may not. Given the heterogeneity of VEMP testing and the small number of included studies, more studies are needed to corroborate these findings. Furthermore, more studies on vestibular function testing in older adults with and without cognitive impairment, including the assessment of hearing function and anxiety, are needed.

Chapter 4. Evidence of vestibular and balance dysfunction in patients with Mild Cognitive Impairment and Alzheimer's disease

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4.1 Abstract

Objectives: Given the expected rise in dementia prevalence, early diagnosis is vital. As a growing body of literature has identified a potential association between vestibular function and cognition, vestibular assessment may aid in early screening. This study aims to better comprehend the proposed association between vestibular function and Alzheimer's disease (AD) by comparing vestibular parameters (vestibular function testing and clinical balance measures) between a group with Mild Cognitive Impairment (MCI), AD, and healthy controls with age-normal cognition.

Design: Cross-sectional analysis of the *GECkO*-study, an ongoing prospective single-centre longitudinal cohort study. This study included 100 older adults (55-84 years). A total of 33 participants with MCI, 17 participants with AD, and 50 age, sex, and hearing-matched healthy controls were included.

Results: Participants with AD demonstrated a delayed latency of the p13 component measured by cervical Vestibular-Evoked Myogenic Potentials (cVEMP) compared to healthy controls and participants with MCI. Other measures including n23 latency, presence of intact responses, rectified amplitude, mean rectified voltage (measured by cVEMP) and lateral vestibulo-ocular reflex gain (measured by video Head Impulse Test (vHIT)) did not differ between groups. The Timed Up-and-Go (TUG), Performance-Oriented Mobility Assessment – Balance subscale (POMA-B), and Functional Gait Assessment (FGA) differed significantly between the three groups. Here, more cognitively impaired groups were associated with worse clinical balance scores.

Conclusions: Vestibular and balance deficits were more prevalent in groups with increasing cognitive decline. Regarding vestibular function testing, p13 latency as measured by cVEMP was delayed in participants with AD. Other cVEMP or vHIT measures did not differ between groups. All three clinical balance assessments (TUG, POMA-B, and FGA) resulted in worse scores along the AD continuum. Future research integrating vestibular parameters that add value (including otolith function testing, balance, and spatial navigation) is recommended to validate the association between vestibular function and cognition while avoiding redundant testing.

4.2 Introduction

The number of older adults, including those affected by dementia, continues to grow. Worldwide around 55 million people suffered from dementia in 2021 and by 2050 this number is expected to rise to 139 million (World Health Organization, 2021). Alzheimer's disease (AD) is the leading cause of dementia and accounts for up to seventy percent of all dementia cases, according to the World Health Organization (2019) (World Health Organization, 2019). Because of its daunting economic, social, and psychological burden, dementia -including AD - is considered to be a public health priority.

People with AD generally evolve from an intermediate state of cognitive decline, namely Mild Cognitive Impairment (MCI). Daily life activities are preserved in people with MCI, but disturbed in people with AD. When including biomarkers in the diagnostic process, the terms prodromal AD or MCI due to AD and dementia due to AD should be used instead of the more general terms MCI and AD, respectively. However, for precision, both MCI and prodromal AD will be described as "MCI" and both AD and dementia due to AD will be described as "AD".

When diagnosing AD from a neuropsychological point of view, episodic memory loss is still the go-to strategy despite its low sensitivity and specificity (Coughlan et al., 2018). However, difficulties with spatial navigation, such as getting lost in familiar places, losing or misplacing objects, and disorientation, are often reported to be one of the first cognitive losses observed in AD (Tu et al., 2015; Yew et al., 2013). Indeed, neuropathology of AD begins in brain structures crucial for successful navigation, such as the medial temporal lobe (including the hippocampus and entorhinal cortex) and parietal structures (Coughlan et al., 2018; Ghosh et al., 2022). Therefore, including navigation and orientation in the diagnostic process may help in differentiating AD from other types of dementia (Tu et al., 2015; Yew et al., 2013). Note that orientation in familiar environments remains preserved in healthy aging, in contrast to AD (Coughlan et al., 2018; Serino et al., 2015). As such, spatial navigation might be a more sensitive and specific cognitive fingerprint in addition to recent episodic memory deficits during the neuropsychological diagnostic process of AD.

The importance of accentuating spatial navigation in AD gains awareness, but it may be of interest to expand this scope further and explore vestibular function in the broad sense in AD, because of important interactions between spatial cognition, peripheral vestibular end-organ function, and balance. A recent systematic review structured measurements of the vestibular system in patients with MCI or AD, compared with a healthy control group with age-normal cognition (Bosmans et al., 2021). A higher prevalence of vestibular loss has been observed with increasing cognitive loss along the AD continuum. This cognitive loss was mainly associated with loss of otolith function, whereas semicircular canal function remained preserved. In particular, p13 latency and amplitude as measured by the Vestibular-Evoked Myogenic Potentials (VEMP) test were the most promising parameters

(Bosmans et al., 2021). An included study by Wei et al. (2019) observed a dose-response relationship between vestibular loss and the level of cognitive impairment. A note of caution is due here since the number of available studies in the systematic review was limited (n = 7), and outcome measures and inclusion criteria were heterogeneous. As such, the authors stressed the need for further research (Bosmans et al., 2021). A recent retrospective study by Cohen et al. (2022) included measures of vestibular function in patients with MCI and AD. They described more vestibular impairments in patients with MCI and AD compared to healthy controls, particularly on Dix-Hallpike manoeuvres and cervical VEMP (cVEMP), supporting previous literature (Cohen et al., 2022). In addition to peripheral vestibular end-organ dysfunction, imbalance can also be associated with AD. People with AD carry a higher incidence of imbalance, gait abnormalities and falls, often resulting in fractures (Biju et al., 2022a; Dev et al., 2021; Dyer et al., 2020). A recent study observed patients with AD to fall twice as frequently as their non-AD peers (Dev et al., 2021). Wandering, related to spatial disorientation, is a common complaint of AD patients (Alzheimer's Association, 2020). Thus, the association between vestibular function in the broad sense and the AD continuum is supported by many studies, but the interactions between the different aspects of vestibular function (spatial navigation, peripheral vestibular end-organ function, and balance) within the AD continuum remain currently underexplored and unreplicated.

We hypothesize a dose-response-type relationship of vestibular function loss and clinical decreased balance performance with progression of cognitive impairment in our groups. This study aims to better comprehend the proposed association between vestibular function and AD. The main objective is to compare vestibular parameters (vestibular function testing and clinical balance measures) between a group with MCI, AD, and healthy controls with age-normal cognition. Additionally, the suitability of vestibular and balance parameters to predict cognition was explored.

4.3 Materials and methods

4.3.1 Participants

Participants were recruited from the *GECkO*-study. This is an ongoing prospective longitudinal cohort study evaluating the effect of hearing loss and vestibular decline on cognitive functioning in older adults (Bosmans et al., 2020). The current study included cross-sectional data of the *GECkO*-study. Participant recruitment was performed at the departments of Otorhinolaryngology and Neurology of University Hospital Antwerp (UZA). The ethical committee of the University Hospital Antwerp (EC number B300201938949) approved this protocol. All participants gave their written informed consent per the Declaration of Helsinki before participation. The study protocol builds upon the Clinical Trials protocol with identifier NCT04385225.

4.3.1.1 *People with cognitive impairment*

Inclusion criteria were 1) age between 55-84 years; 2) diagnosis of MCI or AD; 3) fluent in Dutch; 4) ability to obtain informed consent from the participant or a legally authorized representative. A diagnosis of MCI or AD was based on the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria (Albert et al., 2011; McKhann et al., 2011). A formal neuropsychological exam was performed at the beginning of testing to support the diagnosis of MCI and AD. This neuropsychological exam included the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and Repeatable Battery for the Assessment of Neuropsychological Status for Hearing Impaired Individuals (RBANS-H) (Claes et al., 2016; Randolph et al., 1998). For more information about the RBANS-H, please refer to Claes et al. (2016). Participants with an RBANS-H total score ≤ percentile 16, which means that they scored 1 SD or lower from the mean, were considered patients with MCI. A formal diagnosis of AD was made by the attending neurologist based additionally on (hetero)anamnesis (in all patients), brain MRI (in all patients), additional formal extensive neuropsychological exam (in all patients), blood analysis (in all patients), brain FDG-PET scan (in 16/17 patients), and cerebrospinal fluid AD biomarker analysis (in 7/17 patients). All exams needed to be suggestive of AD and should not be indicative of an alternative diagnosis.

Patients were excluded if MMSE score ≤ 12 to ensure reliable understanding and following of instructions (Harun et al., 2017).

4.3.1.2 *Healthy controls*

For each subject with cognitive impairment, a healthy control was matched based on age, sex, and hearing function (based on pure tone audiometry averaged unaided threshold of 1 kHz, 2 kHz, and 4 kHz in the best hearing ear). In addition, to ensure preserved cognitive function, a neuropsychological test battery (RBANS-H) was performed at the beginning of testing (Claes et al., 2016). Participants with an RBANS-H total score above percentile 16 were included in the healthy control group.

4.3.2 Vestibular function testing

4.3.2.1 *Testing of the peripheral vestibular end-organ*

4.3.2.1.1 Cervical Vestibular Evoked Myogenic Potentials (cVEMPs)

cVEMPs measured function of the sacculus and intactness of the vestibulocollic reflex (VCR) using the Neuro-Audio device with electromyography feedback (Neurosoft, DIFRA). Participants lay in supine position and lifted and rotated their head to one side, thus tensioning the contralateral sternocleidomastoid (SCM) muscle, while short 500 Hz tone bursts were presented in the ipsilateral ear through insert-earphones at suprathreshold level (95 dB nHL). A typical cVEMP potential was biphasic and characterized by two distinctive peaks (p13, n23). The presence of an intact VCR was measured based on normative ranges as described by Li et al. (2014). Outcome measures included presence of intact responses (none, 1 ear, or both ears), and for each present response p13 latency (ms),

n23 latency (ms), rectified amplitude (µV), and SCM muscle contraction level (mean rectified voltage, MRV, µV).

4.3.2.1.2 Video Head Impulse Test (vHIT)

The vHIT measured semicircular canal function and the accompanying vestibulo-ocular reflex (VOR) using the ICS Impulse (Otometrics, Natus, Pleasanton, California, USA). Participants focused on a fixation dot at eye level 1 meter in front of them. The researcher performed short, high-velocity head thrusts in the direction of all six (lateral, superior, and posterior; left and right ear) semicircular canals. Lateral VOR gains were measured, resulting in two values per participant (left and right lateral VOR gain).

4.3.2.1.3 Primary and secondary outcome measures

Based on the systematic review by Bosmans et al. (2021), the latency of the p13 as measured by the cVEMP was chosen as the primary outcome measure for the peripheral vestibular end-organ function. Secondary outcome measures were cVEMP presence, n23 latency, rectified amplitude, MRV, and lateral VOR gains measured by the vHIT.

4.3.2.2 *Clinical balance assessments*

4.3.2.2.1 Timed Up-and-Go (TUG)

The TUG evaluated balance, walking pattern, fall risk, and mobility (Shumway-Cook et al., 2000). Participants started in a chair with their backs against the back of the chair. Then, they were instructed to rise from the chair, walk 3 meters, turn, walk back to the chair, and sit down again. They were encouraged to do this as quickly as possible but safely. This task was repeated 3 times and the mean time to complete this task was measured. In addition, individual mean completion times were categorized as "normal" or "abnormal". This classification was based on age- and sex-specific normative scores published by Steffen et al. (2002). For our analyses, a score was abnormal when it exceeded the mean plus one SD, hence 10" for people in their sixties, 12" for men in their seventies, 11" for women in their seventies, 11" for men in their eighties, and 14" for women in their eighties.

4.3.2.2.2 Performance-Oriented Mobility Assessment (POMA) by Tinetti

The POMA test evaluated balance abilities in a chair and while standing (POMA-B) and dynamic balance during gait on an even walkway (POMA-G) (Köpke & Meyer, 2006; Tinetti, 1986). Higher scores indicate more independence, with a maximum score of 16 for the POMA-B. A cut-off score of ≤ 14 for the POMA-B was chosen for abnormal scores (Harada et al., 1995).

4.3.2.2.3 Functional Gait Assessment (FGA)

The FGA evaluated postural stability and balance during walking. Participants crossed a 6-meter long walkway with different instructions each time. Instructions included changing walking speed, walking with horizontal or vertical head turns, performing a 180° turn, walking up and down stairs, stepping over an obstacle, walking with arms folded across the

chest and with feet aligned heel to toe in tandem, walking with closed eyes, and walking backwards (Beninato et al., 2014; Wrisley & Kumar, 2010). A maximum score of 30 could be obtained. A cut-off score of ≤ 22 for the FGA was chosen for abnormal scores, indicating an increased fall risk (Beninato et al., 2014; Wrisley & Kumar, 2010).

4.3.2.2.4 Primary and secondary outcome measures

Because of its time efficiency, simplicity for use in clinical practice, and feasibility to conduct in a small consulting room, the primary outcome measure for balance was the mean TUG score. Secondary outcome measures included the POMA-B total score and FGA total score and classification of individual normal and abnormal scores for the TUG, POMA-B, and FGA. The POMA-G was not included in further analyses because of an expected and observed ceiling effect.

4.3.3 Demographic characteristics

The MMSE is a routinely used screening device for cognitive impairment and takes 5-10 minutes to administer (Folstein et al., 1975). Based on the MMSE score, a more extensive neuropsychological assessment can be indicated.

The RBANS-H is a comprehensive neuropsychological evaluation of cognitive function as well as its subdomains, including immediate memory, visuospatial/constructional cognition, language, attention, and delayed memory (Claes et al., 2016; Randolph et al., 1998). Because of its accompanying slideshow presentation, cognitive function can be adequately evaluated in individuals with hearing impairment.

Hearing function was evaluated using the Fletcher index high of the best hearing ear, unaided (FI_{high}; average threshold of 1 kHz, 2 kHz, and 4 kHz). To resemble real-world hearing status more closely, the best-aided speech-in-noise (SPIN) test in free field was assessed by the Leuven Intelligibility Sentences Test (van Wieringen & Wouters, 2008). Analysis included the best-aided condition, where participants wore their hearing aid(s) if they had them.

Education level was calculated as the number of years spent in school, starting from the age of 6 years old.

4.3.4 Statistical analysis

Levene's tests and data visualisation using histograms confirmed equal variances for all measures and a normal data distribution. Continuous variables and outcome measures were compared between the three groups (healthy controls, MCI, and AD) with ANOVA. Results of continuous data were further clarified using post-hoc comparisons with the Tukey-Kramer method, with *eta squared* (η^2) indicating the effect size of the full model (with ≥ .01 indicating small, ≥ .06 medium, and ≥ .14 large effect size) and *Cohen's d* (with 95%

confidence interval) indicating the effect size of each pairwise comparison (with ≥ .2 indicating small, ≥ .5 medium, and ≥ .8 large effect size). The Pearson's Chi-squared statistic was used for categorical variables, with *phi* (*w*) indicating the effect size (with ≥ .1 indicating small, ≥ .3 medium, and ≥ .5 large effect size). Post-hoc comparisons were made by performing pairwise comparisons for all combinations. In addition, a multiple linear regression model using the backward elimination technique was used to explore the suitability of vestibular and balance parameters to predict cognitive status (RBANS-H percentile score) for individuals. A *p*-value of <.05 was used as the stopping rule. For all statistical analyses, the program JMP Pro 15 (Medmenham, UK) was used.

4.4 Results

4.4.1 Study population

Demographic characteristics of people with cognitive impairment (MCI and AD) and healthy controls matched on age, sex, and hearing level can be found in Table 4. Hearing loss is a recognized risk factor for dementia and is often associated with vestibular dysfunction (Livingston et al., 2020; Lucieer et al., 2016; Santos et al., 2015). Therefore, the matching procedure used the Fletcher index high of the best hearing ear, unaided. To resemble real-world hearing status more closely, the best-aided speech-in-noise (SPIN) test in free field was included in the analysis of participant characteristics. The three groups did not differ in hearing level. Education level was included as a demographic characteristic, resulting in a significant difference. This needs to be considered when interpreting results. For transparency reasons, cognitive measurements including the RBANS-H total percentile score and MMSE are also included. MMSE scores only serve as an exclusionary criterion. Median [range] for the RBANS-H total percentile were 62 [18, 95] for healthy controls, 9 [1, 16] for MCI, and 0.2 [0, 2] for AD ($p < .0001$). Median [range] for the MMSE were 29 [24, 30] for healthy controls, 27 [23, 30] for MCI, and 19 [14,25] for AD ($p < .0001$).

Table 4. Demographic, hearing, and cognitive characteristics of people with cognitive impairment (Mild Cognitive Impairment and Alzheimer's disease) and healthy controls. p-Values in *italics* are the result of the Pearson's Chi-squared statistic, whereas all other p-values reflect results of ANOVA. Education level indicates the number of years spent in school, starting from 6 years old. SD, standard deviation; FI_{high}, Fletcher index high; dB HL, decibel hearing level; SPIN, speech-in-noise; SRT, speech reception threshold; RBANS-H, Repeatable Battery for the Assessment of Neuropsychological Status for Hearing Impaired Individuals; MMSE, Mini-Mental State Examination.

	Healthy Controls (n = 50)	**Mild Cognitive Impairment (n = 33)**	**Alzheimer's disease (n = 17)**	**p-Value**
Age (year: mean (SD))	74 (6.3)	74 (6.0)	76 (5.3)	.5206
Sex (n: M/F)	28/22	17/16	11/6	*.6729*
Education level (year: mean (SD))	13.7 (0.4)	12.4 (0.6)	11.6 (0.8)	.0319
Hearing level				
FI_{high} best ear (unaided dB HL: mean (SD))	43.0 (17.0)	43.3 (20.1)	39.4 (13.3)	.7194
SPIN (best-aided SRT: mean (SD))	-0.8 (4.0)	0.1 (3.9)	-0.2 (2.1)	.5358
Cognition				
RBANS-H total percentile (mean (SD))	59.4 (20.6)	8.5 (4.8)	0.3 (0.5)	<.0001
MMSE (mean (SD))	28.5 (1.6)	26.8 (1.9)	19.5 (3.4)	<.0001

4.4.2 Vestibular function testing

An overview of the vestibular function tests, their mean scores and standard deviations per group, their p-values, effect sizes, and post-hoc comparisons can be found in Table 5. A visual overview represented by boxplots can be found in Figure 10. Regarding the primary outcome measure of vestibular function testing, participants with AD demonstrated a significantly delayed latency of the p13 component measured by cVEMP in comparison with the MCI and healthy control group, who did not differ in p13 latency (p = .001; η^2 = .13, medium effect; difference in means healthy controls vs. AD = 1.02; 1.10 SD). Secondary outcome measures of vestibular function testing (including n23 latency, presence of intact responses, rectified amplitude, and MRV as measured by cVEMP; and lateral VOR gain as measured by vHIT) demonstrated no significant differences between the three groups. Effect sizes for these variables ranged from trivial to small effects. In 98 out of a total of 200 ears, an intact cVEMP response was found (healthy controls: 49/100; MCI: 34/62; AD: 15/30).

Regarding clinical balance assessments, the primary outcome measure mean TUG scores demonstrated a significant difference between healthy controls and people with cognitive impairment (participants with MCI and AD combined) (p <.0001; η^2 = .26, large effect). People with cognitive impairment took longer to complete this task successfully. Post-hoc comparisons indicated that the TUG time-to-complete was able to differentiate healthy controls from the MCI group in a significant way (p = .0014; d = 0.8, large effect; difference in means healthy controls vs. AD = 4.33; 1.96 SD). A similar pattern was observed in the total score of the FGA (p = .0001; η^2 = .18, large effect). People with cognitive impairment obtained lower scores in comparison to healthy controls. Here, a differentiation between healthy controls and the MCI group was significant (p = .0049; d = 0.7, medium effect). On the other hand, the MCI and AD groups obtained equivalent scores (p = .3734; d = 0.4, small effect; difference in means healthy controls vs. AD = 5.15; 1.22 SD). Last, the POMA-B score was significantly decreased in participants with AD compared with the MCI and healthy control group (p = .0031; η^2 = .12, medium effect). Here, equivalent scores were obtained for the healthy control and MCI group (p = .4581; d = 0.3, small effect). However, the MCI and AD groups differed significantly (p = .0461; d = 0.7, medium effect; difference in means healthy controls vs. AD = 1.45; 1.28 SD).

Similar results were obtained when individually classifying each balance result as "normal" or "abnormal". Again, the TUG demonstrated a significant difference between healthy controls and people with cognitive impairment (p <.0001; w = .42, medium effect). The POMA-B classification differentiated in a significant way between the AD group and the healthy control and MCI group combined (p = .0019; w = .31, medium effect). Finally, the FGA classification differed significantly between groups (p = .0494; w = .21, small effect). Post-hoc comparisons did not reveal significant differences between pairwise comparisons.

Table 5. Results of vestibular function tests in healthy controls, Mild Cognitive Impairment, and Alzheimer's disease. Degrees indicate an interpretation of effect size (° = small, °° = medium, °°° = large). The Pearson's Chi-squared statistic was used for categorical variables, with phi (w) indicating the effect size. Categorical post-hoc comparisons were made by performing pairwise comparisons for all combinations. Here, phi (w) is reported as a measure of effect size. cVEMP, cervical Vestibular-Evoked Myogenic Potentials; MRV, mean rectified voltage; vHIT, video Head Impulse Test; VOR, vestibulo-ocular reflex; TUG, Timed Up-and-Go; POMA-B, Performance-Oriented Mobility Assessment Balance subscale; FGA, Functional Gait Assessment; HC, healthy controls; MCI, Mild Cognitive Impairment; AD, Alzheimer's disease.

	HC	**MCI**	**AD**	**p-Value**	**η^2**	**Post-hoc comparison**	**Cohen's d [95% CI]**
Peripheral vestibular end-organ							
cVEMP: p13 latency	13.4 (0.9)	13.7 (0.9)	14.4 (0.7)	.0010	.13°°	(HC = MCI) < AD	HC – AD: 1.1 [0.5,1.7]°°° HC – MCI: .3 [-0.2,0.7]° MCI – AD: .9 [0.2,1.5]°°
cVEMP: n23 latency	21.4 (1.7)	21.6 (1.6)	22.3 (1.9)	.1991	.03°	HC = MCI = AD	HC – AD: .5 [-0.1, 1.1]°° HC – MCI: .1 [-0.3, 0.6] MCI – AD: .4 [-0.2, 1.0]°
cVEMP: presence	0: 15 1: 21 2: 14 NA: 0	0: 9 1: 10 2: 12 NA: 2	0: 4 1: 7 2: 4 NA: 2	Chi-square (df=3): .8177	w: .09	HC = MCI = AD	HC – AD: w = .03 HC – MCI: w = .08 MCI – AD: w = .10°
cVEMP: rectified amplitude	0.6 (0.2)	0.7 (0.3)	0.7 (0.3)	.3579	.02°	HC = MCI = AD	HC – AD: .3 [-0.3, 0.8]° HC – MCI: .3 [-0.1, 0.7]° MCI – AD: .0 [-0.6, 0.7]
cVEMP: MRV	158.1 (33.9)	150.5 (37.9)	136.9 (32.9)	.0684	.05°	HC = MCI = AD	HC – AD: .6 [0.1, 1.1]°° HC – MCI: .2 [-0.2, 0.6]° MCI – AD: .4 [-0.2, 0.9]°
vHIT:	1.0 (0.2)	1.0 (0.3)	1.1 (0.3)	.1049	.02°	HC = MCI = AD	HC – AD: .4 [-0.0,0.8]°

Lateral VOR gain							HC – MCI: .3 [-0.1,0.6]° MCI – AD: .1 [-0.3,0.5]
Clinical balance assessments							
TUG: mean (SD)	8.8 (2.2)	11.1 (3.3)	13.1 (3.4)	<.0001	.26°°°	HC < (MCI = AD)	HC – AD: 1.5 [0.9,2.1]°°° HC – MCI: 0.8 [0.4,1.3]°°° MCI – AD: 0.7 [0.1,1.3]°°
TUG: classification	Normal: 43 Abnormal: 4 NA: 3	Normal: 19 Abnormal: 13 NA: 1	Normal: 7 Abnormal: 10	Chi-square (df=2): <.0001	w: .42°°	HC < (MCI = AD)	HC – AD: w = .50°°° HC – MCI: w = .38°° MCI – AD: w = .15°
POMA-B: total score	15.3 (1.1)	14.9 (1.6)	13.8 (1.9)	.0031	.12°°	(HC = MCI) > AD	HC – AD: 1.0 [0.4,1.6]°°° HC – MCI: .3 [-0.2,0.7]° MCI – AD: .7 [0.1,1.3]°°
POMA-B: classification	Normal: 38 Abnormal: 9 NA: 3	Normal: 24 Abnormal: 9	Normal: 6 Abnormal: 11	Chi-square (df=2): .0019	w: .31°°	(HC = MCI) > AD	HC – AD: w = .38°° HC – MCI: w = .09 MCI – AD: w = .31°°
FGA: total score	24.4 (4.2)	21.1 (4.8)	19.3 (4.9)	.0001	.18°°°	HC < (MCI = AD)	HC – AD: 1.1 [0.6,1.7]°°° HC – MCI: .7 [0.3,1.2]°° MCI – AD: .4 [-0.2,1.0]°
FGA: classification	Normal: 32 Abnormal: 15 NA: 3	Normal: 17 Abnormal: 16	Normal: 6 Abnormal: 11	Chi-square (df=2): .0494	W: .21°	HC = MCI = AD	HC – AD: w = .25° HC – MCI: w = .14° MCI – AD: w = .13°

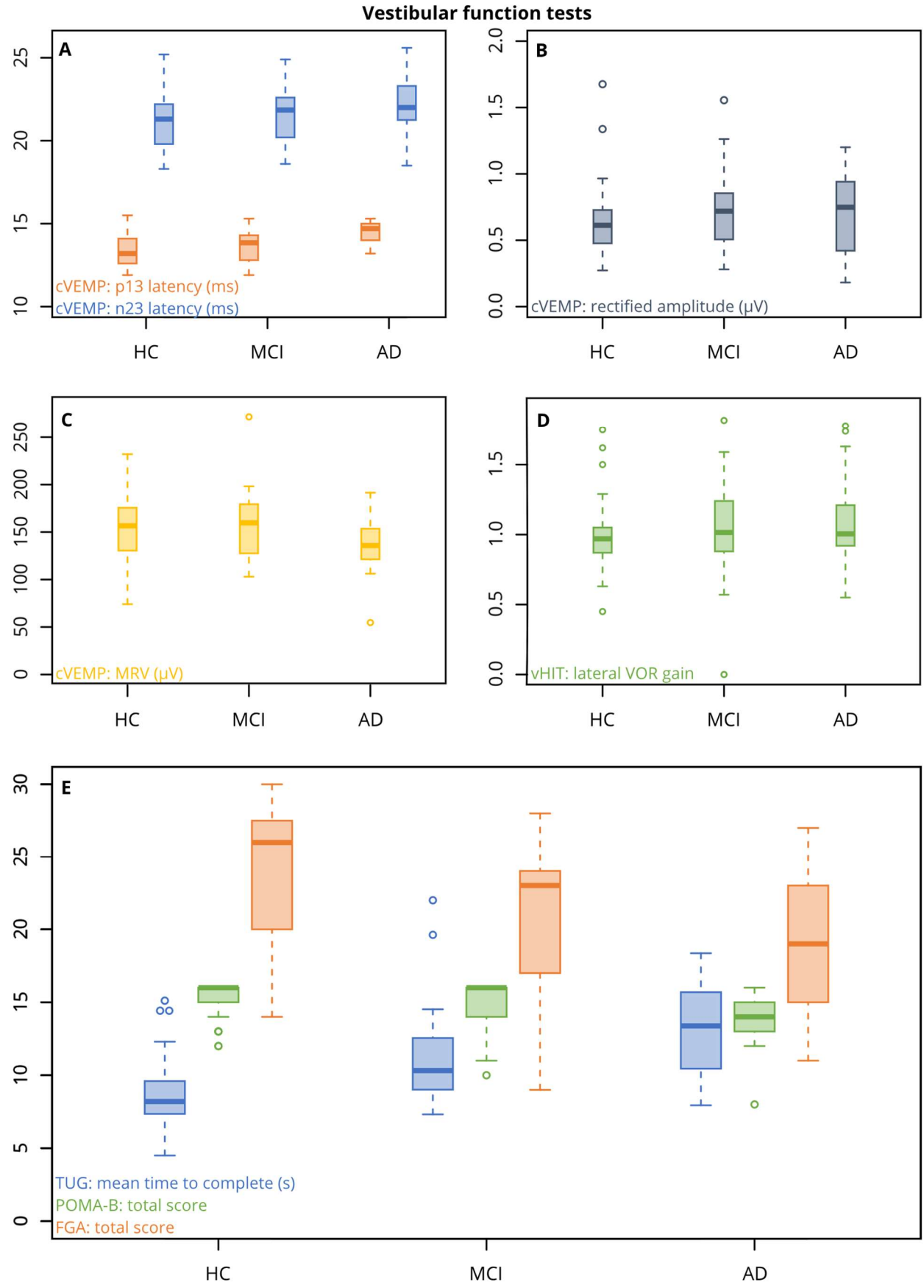
Vestibular function tests
A
cVEMP: p13 latency (ms)
cVEMP: n23 latency (ms)
HC
MCI
AD
B
cVEMP: rectified amplitude (μV)
C
cVEMP: MRV (μV)
D
vHIT: lateral VOR gain
E
TUG: mean time to complete (s)
POMA-B: total score
FGA: total score

Figure 10. Visual overview of vestibular function tests, including testing of the peripheral vestibular end-organ and clinical balance assessments. A) cVEMP: p13 and n23 latency, B) cVEMP: rectified amplitude, C) cVEMP: MRV, D) vHIT: lateral VOR gain, E) clinical balance assessments. Whiskers indicate range; boxes, IQR; bold line, median. As different parameters are expressed in various units, the appropriate unit is defined between brackets. cVEMP, cervical Vestibular-Evoked Myogenic Potentials; MRV, mean rectified voltage; vHIT, video Head Impulse Test; HC, healthy controls; MCI, Mild Cognitive Impairment; AD, Alzheimer's disease; FGA, Functional Gait Assessment; POMA-B, Performance-Oriented Mobility Assessment Balance subscale; TUG, Timed Up-and-Go.

To explore whether vestibular and balance parameters were suitable to predict cognition in this population, a multiple linear regression model using the backward elimination technique was conducted. Input of the initial model included demographic parameters (age, sex, and years of education), hearing function (Fletcher index high of the best hearing ear), peripheral vestibular end-organ parameters (cVEMP: p13 latency, n23 latency, rectified amplitude, MRV; vHIT: lateral gain), and clinical balance (TUG, POMA-B, FGA) to predict RBANS-H total scaled score. We used the RBANS-H total scaled score instead of the percentile score as this scaled score was more accurate in describing distinctly low scores (e.g.: percentile <0.1 reflected scaled scores 47 through 54 in the current dataset). This scaled score followed the distribution of the Wechsler IQ scale (100[SD,15]) (Weiss et al., 2006). A backward elimination regression model was able to reduce to five parameters which were: TUG, sex, and cVEMP: p13 latency, n23 latency, and rectified amplitude. These five final predictors added significance to the final equation (TUG, $p < .0001$, $\eta^2 = .3078$; sex, $p = .0291$, $\eta^2 = .0265$; cVEMP p13 latency, $p = .0006$, $\eta^2 = .0683$; cVEMP n23 latency, $p = .0047$, $\eta^2 = .0453$; cVEMP rectified amplitude, $p = .0364$, $\eta^2 = .0243$). The final equation was statistically significant ($F(5,89) = 19.3093$, $p < .0001$) with an R^2 of .5203. The equation for predicting cognition via the RBANS-H total scaled score is established as follows:

$$\begin{aligned}\text{RBANS-H total scaled score} &= 157.37 + (\text{Sex})\begin{pmatrix}\text{female} \rightarrow -3.31\\ \text{male} \rightarrow +3.31\end{pmatrix} - 3.65 * (\text{TUG mean}) - 6.24 \\ &* (\text{cVEMP p13 latency}) + 2.73 * (\text{cVEMP n23 latency}) - 12.08 \\ &* (\text{cVEMP rectified amplitude})\end{aligned}$$

4.5 Discussion

This study aimed to better comprehend the proposed association between vestibular function and AD by comparing vestibular parameters (vestibular function testing and clinical balance assessments) between a group with MCI, AD, and healthy controls with age-normal cognition. These groups were matched on age, sex, and hearing level. In general, vestibular and balance deficits were more prevalent in the groups with increasing cognitive decline. Regarding vestibular function testing, only p13 latency as measured by cVEMP

demonstrated an increase in latency in participants with AD compared to the MCI and healthy control groups. Other variables of the cVEMP (measuring saccular function) or vHIT (measuring semicircular canal function) demonstrated no difference among the three groups. This implied that saccular function, rather than semicircular canal function, may underlie the association between vestibular loss and cognitive impairment. In addition, saccular function testing (in particular p13 latency as measured by cVEMP) may allow for early detection of individuals at risk for MCI and AD with a potential fall risk. These results support and extend previous literature on this topic (for a review, see Bosmans et al. (2021) and Agrawal et al. (2020)). Hence, this manuscript was able to confirm and replicate what existing literature has shown. A note of caution is due here as in the current study, intact cVEMP responses needed to have p13 and n23 latencies within the latency ranges defined by Li et al. (2014) (p13: 11.81-15.59 ms; n23: 18.15-25.64 ms). However, multiple studies reporting cVEMP latencies applied different criteria. A recent systematic review with meta-analysis by Macambira et al. (2017) provided an overview of mean p13 and n23 latencies of studies comparing young and older adults. However, multiple mean p13 and n23 latencies in both young and older adult groups of this meta-analysis fell outside the ranges defined by Li et al. (2014), complicating comparisons across studies. This emphasizes the need for generally-accepted latency ranges and reporting of cVEMP variables to guarantee reliable interpretations and implications.

Regarding clinical balance assessment, participants with AD showed poorer performance on all three included tests (TUG, POMA-B, and FGA). The TUG and FGA were able to differentiate healthy controls from participants with cognitive impairment (MCI and AD combined). On the other hand, the POMA-B differentiated in a later stage along the AD continuum (healthy control and MCI versus AD). Caution should be exercised, however, when extrapolating the results of balance tests in order to assess vestibular function. In principle, static balance tasks are more appropriate to get an idea of vestibular function (sensory organization test) through changes in sensory test conditions (Cohen et al., 2019; Verbecque et al., 2021). Balance tasks including locomotion provide a better idea about the functional impact of a vestibular problem (Vereeck et al., 2007), but one should be aware that additional aspects such as non-vestibular sensory inputs, motor and executive functions may be involved in locomotion. This must be kept in mind, especially in a population with cognitive impairment.

Figure 11 provides a schematic overview of actual clinical balance assessment data and how they change with cognitive decline. People with age-normal cognition demonstrated little deficits in any of the three clinical balance assessments. More than half of participants with AD demonstrated abnormal clinical balance function in all assessments. However, included balance assessments converge from normal to abnormal at different rates, resulting in heterogeneous outcomes in the MCI stage. The combination of these three clinical balance assessments could give the impetus to construct a timeline and aid in pinpointing where a subject with cognitive impairment is located on the AD continuum, based on their balance

function. Future research can extend this concept by integrating the vestibular-related parameters that add value and step away from redundant testing. As a recommendation, otolith function testing (including saccular and utricular function), spatial cognition, clinical balance, and subjective balance measurements (fear of falling, balance confidence, etc.) should be further investigated, whereas horizontal semicircular canal testing (by means of VOR testing) appears to be less relevant in a population with cognitive impairment. However, an important side note is that topographical memory has been related to horizontal semicircular canal functioning (Previc et al., 2014). Another important side note is that one study observed significantly reduced VOR gains in the anterior and posterior semicircular canals in patients with MMSE scores < 21 in comparison to healthy controls, while observing no significant differences in VOR gains of the horizontal semicircular canals (Yargholi et al., 2018). By plotting these parameters on a timeline covering the AD continuum, we may gain a more extensive understanding about the gradual changes of the vestibular system and its associated regions. This may increase our knowledge about the potential of vestibular rehabilitation or other vestibular interventions such as a vestibular implant to slow the progression of AD.

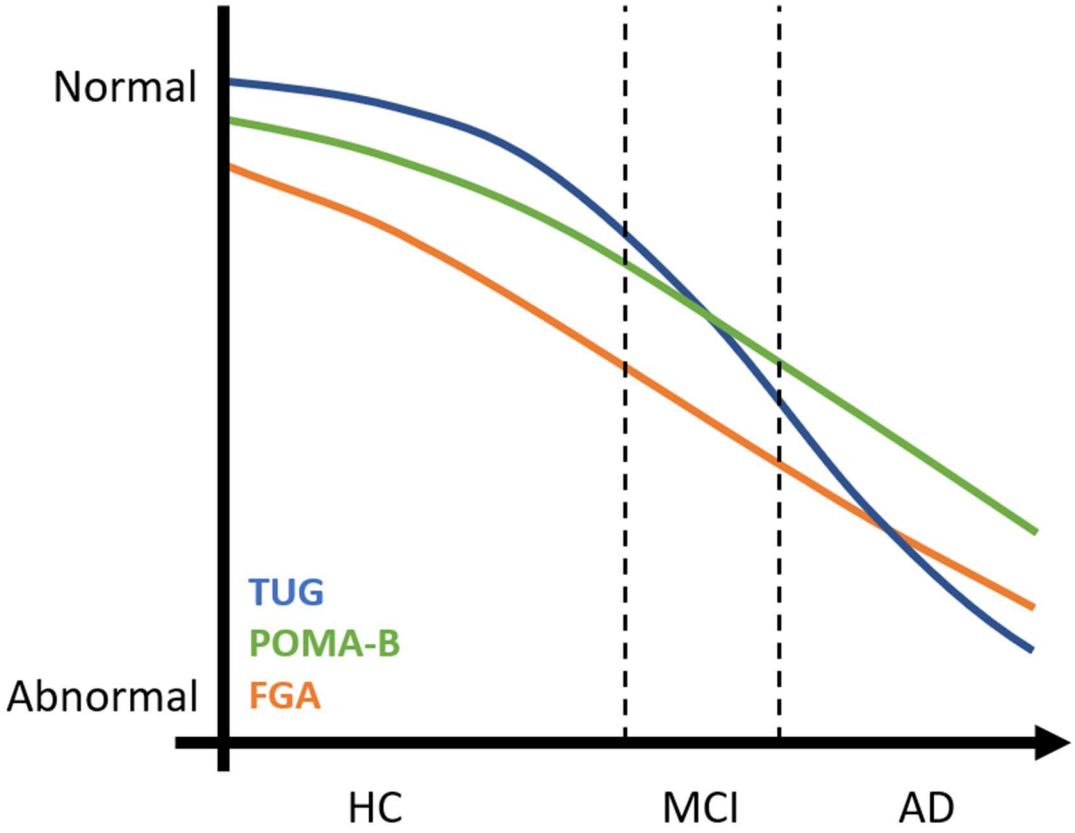

Figure 11. Schematic overview of changes in balance through the Alzheimer's disease continuum. Each clinical balance result was per subject classified as "normal" or "abnormal". This classification was plotted against the RBANS-H total score. Each coloured line represents the logistic fit of a clinical balance assessment by the RBANS-H total score. HC,

healthy controls; MCI, Mild Cognitive Impairment; AD, Alzheimer's disease; TUG, Timed Up-and-Go; POMA-B, Performance-Oriented Mobility Assessment – Balance subscale; FGA, Functional Gait Assessment.

A first limitation of the current study is that we considered participants with an RBANS-H total score ≤ percentile 16 (hence ≤ 1 SD from the mean) as patients with MCI. According to guidelines by Albert et al. (2011), cognitive scores are typically 1 to 1.5 SD below the mean for the appropriate normative data. Our study uses the less stringent approach regarding inclusion of participants with MCI, which has to be taken into account. Furthermore, biomarkers were not routinely tested in our MCI group, resulting in a heterogeneous group consisting of MCI due to AD as well as other causes of MCI. Another limitation of the current study is the absence of caloric irrigation, rotatory chair, and ocular VEMP (oVEMP) data to fully map peripheral vestibular end-organ function. Future research untangling vestibular function and its association with cognitive decline should include a complete and complementary battery of vestibular function tests, with special focus on cVEMP and oVEMP testing. We hypothesize that measures of horizontal semicircular canal function (vHIT, rotatory chair, and caloric irrigation) will demonstrate no change in people with advancing degrees of AD. This hypothesis is based on considerable evidence describing distinct pathways for motoneurons involved in the vestibulo-ocular reflex (VOR; associated with semicircular canal function) and saccular pathways (involved with the vestibulocollic reflex; VCR) transmitting vestibular information to higher brain areas. Here the VCR decreases simultaneously with cognitive decline, whereas the VOR gain would remain intact (Bosmans et al., 2021). However, this distinction should be nuanced as there is a large semicircular canal projection to the hippocampus in the form of head-direction cells so a higher-order semicircular canal influence should not be completely dismissed (Previc, 1998, 2013). Keeping that in mind, otolith function (as measured by both oVEMP for the utriculus and cVEMP for the sacculus) may underlie the association between vestibular function and cognitive impairment and would therefore be interesting to further explore in a population with varying degrees of AD.

4.6 Conclusion

This cross-sectional study included participants with MCI, AD, and healthy controls and found that vestibular and balance deficits were more prevalent in groups with increasing cognitive decline. P13 latency as measured by cVEMP was delayed in participants with AD. Other cVEMP or vHIT measures did not differ between groups. All three included clinical balance assessments (TUG, POMA-B, and FGA) resulted in worse scores in participants with AD. However, included balance assessments converged from normal to abnormal at different rates, resulting in heterogeneous outcomes in the MCI stage. Future research integrating a complete assessment of otolith function testing, balance, and spatial cognition is recommended to fully comprehend the gradual changes of the vestibular system and its associated regions in advancing degrees of cognitive decline.

Part 2

Cognitive performance in bilateral vestibulopathy

Chapter 5. Associations of bilateral vestibulopathy with cognition in older adults matched with healthy controls for hearing status

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5.1 Abstract

Importance: Recent literature suggests there may be a significant effect of the vestibular system on cognition and visuospatial processing. Given the increasing prevalence of dementia and individuals at risk for it, exploring possible modifiable risk factors, including vestibular dysfunction, is vital.

Objectives: To explore the association of bilateral vestibulopathy (BV) with cognitive function in older adults, taking hearing status into account, and to explore multiple vestibular characteristics and their potential associations with cognition in patients with BV.

Design, setting, and participants: This cross-sectional study assessed older adults (age 55-84 years) with diagnosed BV from a single center using baseline measurements from the Gehoor, Evenwicht en Cognitie (*GECkO*) study, an ongoing prospective longitudinal cohort study. Each participant was individually matched with a healthy control based on age, sex, and hearing performance. Data were analyzed in January 2022.

Main outcomes and measures: The primary outcome measure was cognition, measured by the Repeatable Battery for the Assessment of Neuropsychological Status for Hearing-Impaired Individuals (RBANS-H).

Results: A total of 68 patients were assessed, including 34 patients with BV (mean [SD] age, 63.3 [6.0] years; 18 [53%] men) matched with 34 control individuals without BV. Overall, participants with BV had a clinically meaningful lower score on the RBANS-H total scale compared with those without BV (mean [SD] score, 98.62 [12.70] vs 105.91 [11.03]). This decline was most pronounced in the subdomains of immediate memory (mean [SD] score, 107.74 [10.66] vs 112.26 [10.66]), visuospatial cognition (mean [SD] score, 90.06 [13.34] vs 100.47 [13.91]), and attention (mean [SD] score, 94.79 [16.39] vs 102.06 [12.97]). There were no differences in language or delayed memory subdomains. Within the BV population, 1 vestibular parameter (the Performance-Oriented Mobility Assessment, in particular the balance subscale) was associated with lower cognitive scores ($r_{32} = 0.51$; 95% CI, 0.20 to 0.72; $\eta 2 = 0.26$). Other vestibular parameters, including measurements of the peripheral vestibular end-organ and questionnaires, showed no association.

Conclusions and relevance: These findings suggest there was an association between vestibular loss and cognitive impairment. Further research on the causal mechanisms underlying this association and the possible impact of vestibular rehabilitation on cognition is needed.

5.2 Key Points

Question: Is bilateral vestibulopathy (BV) associated with cognitive function in older adults?

Findings: In this cross-sectional study including 34 participants with BV and 34 age-, sex-, and hearing performance–matched controls, participants with BV had worse cognitive function in general, which was most pronounced in the subdomains of immediate memory, visuospatial cognition, and attention.

Meaning: These findings support existing evidence on an association between vestibular loss and cognitive impairment.

5.3 Introduction

The peripheral vestibular end-organ is located in the inner ear and codes for rotation and translation of the head. Because of its numerous projections to the central nervous system, including the brainstem, cerebellum, and widespread cortical connections, the vestibular system is involved in gaze stability, self-motion perception, orientation, navigation, and balance. An evolving body of literature suggests a significant impact of the vestibular system on cognitive function, particularly visuospatial processing. Visuospatial cognition encompasses navigation, spatial memory, mental rotation, and mental representation of 3-dimensional space (Bigelow & Agrawal, 2015).

Substantial preclinical research has demonstrated long-term spatial memory deficits in animals with vestibular lesions (Smith & Zheng, 2013). Vestibular damage often leads to ataxia or oscillopsia because of vestibulospinal or vestibulo-ocular reflex (VOR) deficits, respectively. Although some compensation for these reflex deficits occurs over time, spatial memory deficiencies remain (Baek et al., 2010; Smith et al., 2015; Zheng et al., 2007, 2009). An important limitation in animal studies is that chemical or surgical lesions of the vestibular end-organ often unintentionally also damage the cochlea. Therefore, the cognitive effects of these lesions may be due to iatrogenic hearing loss. To control for this limitation, tympanic membranes of sham control animals are often removed so that sound is no longer transmitted effectively (Smith & Zheng, 2013). Nonetheless, these sham animals (intact vestibular function but removed tympanic membrane) have been observed to consistently perform better in spatial tasks than animals with vestibular lesions (Baek et al., 2010; Smith et al., 2015; Zheng et al., 2007, 2009). This implies that vestibular loss, not hearing loss, is the major cause of spatial memory deficits.

These animal findings are consistent with results from human studies (Brandt et al., 2005; Dobbels, Mertens, et al., 2019; Dobbels, Peetermans, et al., 2019). Profound evidence exists that people with bilateral vestibulopathy (BV) experience impaired spatial cognition, in

addition to impairments on other cognitive domains (eg, processing speed, immediate memory, and executive function) (Brandt et al., 2005; Dobbels, Mertens, et al., 2019; Dobbels, Peetermans, et al., 2019). Vice versa, an overall higher prevalence of vestibular loss has been observed among people with cognitive impairment (eg, Mild Cognitive Impairment [MCI] and Alzheimer disease [AD]) (Bosmans et al., 2021). When examining brain volumetry, studies have described significant hippocampal atrophy in the BV population, with spatial memory and navigation deficits closely matching the pattern of hippocampal volume loss (Brandt et al., 2005; Smith, 2016). Therefore, a direct association between hippocampal volume (a biomarker associated with AD), vestibular decline, and impaired (spatial) cognition has been observed (Brandt et al., 2005). Hence, the question of how and to what extent vestibular loss is associated with cognitive impairment remains unanswered.

This study aims to explore the associations of BV with cognitive function, both cognition in general and different cognitive domains, in older adults. We hypothesize that individuals with BV will perform worse than healthy controls on cognition in general and on the visuospatial subdomain in particular. The secondary aim of this study is to explore multiple vestibular characteristics and their possible associations with cognition. While animal studies often discuss the possibility that concomitant hearing loss could exacerbate cognitive function decline in addition to vestibular loss, human studies investigating cognition in people with vestibular loss taking hearing status into account are limited (Dobbels, Peetermans, et al., 2019; Van Rompaey et al., 2021). Nonetheless, the prevalence of sensorineural hearing loss in people with BV ranges from 31% to 44% (Lucieer et al., 2016; Zingler et al., 2007). Therefore, this study will include hearing status when matching its control participants.

5.4 Methods

This cross-sectional study uses data from a longitudinal study approved by the ethical committee of the University Hospital of Antwerp. The study protocol has been published previously (Bosmans et al., 2020). All participants provided written informed consent. This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (von Elm et al., 2007).

5.4.1 Study design

This study is a single-center, prospective, longitudinal study recruiting from November 2019 until January 2022 at the Antwerp University Hospital, Belgium. All participants were assessed during 1 baseline visit of approximately 3 hours by 2 International Conference on Harmonization Good Clinical Practice–accredited clinical researchers (J.B. and H.G.).

5.4.2 Study participants

5.4.2.1 *Participants with BV*

Participants with a diagnosis of BV according to the Bárány Society criteria (Strupp et al., 2017) were recruited from the Department of Otorhinolaryngology–Head and Neck Surgery at the Antwerp University Hospital, Belgium. Inclusion criteria for participants with BV were bilaterally reduced or absent angular VOR function documented by bilaterally pathological horizontal angular VOR gain less than 0.6 (measured by the video head impulse test [vHIT] or scleral-coil technique), reduced horizontal angular VOR gain less than 0.1 on sinusoidal stimulation on a rotatory chair (0.1 Hz, Vmax=50°/s), or reduced caloric response (sum of bithermal maximum peak slow-phase velocity on each side <6°/s).

5.4.2.2 *Healthy controls*

Healthy control participants were recruited from the Gehoor, Evenwicht, Cognitie (*GECkO*) (Bosmans et al., 2020) and the Repeatable Battery for the Assessment of Neuropsychological Status for Hearing Impaired Individuals (RBANS-H) before and after cochlear implantation study (Claes et al., 2016). Both protocols were approved by the ethical committee of the University Hospital of Antwerp, Belgium. Each participant with BV was individually matched to a control based on age, sex, and hearing performance (best-aided speech in noise [SPIN]). All healthy controls underwent the vHIT to confirm vestibular function within reference range.

For both participants with BV and healthy controls, the following additional inclusion criteria were applied: age 55 to 84 years, Dutch as native language, no history of neurological diseases (eg, MCI or dementia), no implanted hearing aid device, and provided written informed consent. As screening for early stages of cognitive impairment may reasonably start at the age of 55 years, this age cut-off was chosen (Lu et al., 2021). Low education, hearing loss, obesity, smoking, and depression are risk factors associated with dementia and may negatively affect cognition (Livingston et al., 2020). Although tinnitus has not been identified as a risk factor for dementia, research is ongoing to assess associations of tinnitus with cognition (Cardon et al., 2019). Therefore, these variables were included in the demographic and clinical characteristics of both groups.

5.4.3 Cognitive assessment

The RBANS-H is based on the Repeatable Battery for the Assessment of Neuropsychological Status (Randolph et al., 1998) and was developed to examine cognitive function of individuals with hearing impairment (Claes et al., 2016). The RBANS-H is conducted by presenting an accompanying slide presentation with written explanations, which are given to support verbal instructions and to ascertain that the participant understands the instruction. In addition to visual support of the instructions, all relevant stimuli are not only presented verbally but visually as well.

The RBANS-H consists of 12 subtests: list learning, story memory, figure copy, line orientation, picture naming, semantic fluency, digit span, coding, list recall, list recognition, story recall, and figure recall. It measures the cognitive domains of immediate memory, visuospatial, language, attention, and delayed memory. Total scores of the subtests are converted into index scores per cognitive domain. These index scores are normed based on the age of the participant. The sum of all index scores is used to determine the RBANS-H total scaled score (following the distribution of the Wechsler IQ scale, 100 [SD, 15]) (Weiss et al., 2006). A scaled score (index score for each cognitive domain or RBANS-H total scaled score) of 85 or lower indicates a lower-than-expected cognitive result. Therefore, the cut-off of 85 is used for cognitive impairment (Albert et al., 2011; Cassel, 1963).

5.4.4 Vestibular assessment

5.4.4.1 *Video Head Impulse Test (vHIT)*

The vHIT is a vestibular test measuring semicircular canal function and the VOR. For this study, we used ICS Impulse (Natus). Participants are instructed to focus on a fixation dot at eye level 1 m in front of them. They experience short, high-velocity head thrusts in the direction of all 6 (lateral, superior, and posterior; left and right ear) semicircular canals.

5.4.4.2 *Cervical Vestibular–Evoked Myogenic Potentials (cVEMP)*

Cervical vestibular–evoked myogenic potentials are ipsilateral inhibiting muscle potentials measured at the level of the contracted sternocleidomastoid (SCM) muscle using the validated Neuro-Audio device with electromyography feedback (Neurosoft). Short tone bursts presented through insert-earphones evoke these potentials. Participants lie in a supine position and are instructed to lift and rotate their head to 1 side, thus tensioning the SCM muscle, while stimuli are presented in the contralateral ear. A typical cervical vestibular–evoked myogenic potential is biphasic and characterized by 2 distinctive peaks (p13, n23). Normative ranges are applied (Li et al., 2014).

5.4.4.3 *Rotatory chair testing*

Rotatory chair testing is a midfrequency test of the lateral semicircular canals testing a range of different frequencies, from 0.01 Hz to 0.64 Hz. Participants are tested with their eyes closed by means of electronystagmography. The sinusoid method oscillates the chair in yaw at varying frequencies, typically with peak velocities that remain constant at 50 or 60 °/s (Gimmon & Schubert, 2019).

5.4.4.4 *Caloric irrigation*

Bithermal caloric irrigation (33 °C/44 °C) stimulates each lateral semicircular canal independently. It can identify the extent to which the vestibular system is responsive and how symmetric the responses are, between left and right.

5.4.5 Clinical balance testing

The Timed Up-and-Go (TUG) balance test evaluates mobility, fall risk, balance, and walking pattern (Shumway-Cook et al., 2000). Participants start in a seated position on a chair. They are then instructed to stand up, walk 3 m, turn around, walk back to the chair, and sit down again. This task is repeated 3 times, and the mean time needed to complete this task is measured.

The Performance-Oriented Mobility Assessment (POMA) test consists of 2 parts (Köpke & Meyer, 2006; Tinetti, 1986). The first test evaluates balance abilities in a chair and while standing (POMA-B). The other part assesses dynamic balance during gait on an even walkway (POMA-G) (Köpke & Meyer, 2006; Tinetti, 1986).

In Belgium according to the National Institute for Health and Disability Insurance (RIZIV), to obtain reimbursement of gait rehabilitation (age ≥65 years), an increased risk of falling needs to be objectified. This is done by performing the TUG (completion time, >20 seconds), POMA (total score, <20/28), and/or the timed chair stands (score, >14 seconds). Based on these criteria, the TUG and POMA are included in current study.

The Functional Gait Assessment is used to evaluate postural stability and balance during walking tasks. Participants are asked to cross a 6 m long walkway, each time with a different instruction, including: changing walking speed, walking with horizontal head turns, walking with vertical head turns, performing a 180° turn, stepping over an obstacle, walking with arms folded across the chest and with feet aligned heel to toe in tandem, walking with eyes closed, walking backward, and walking up and down stairs (Beninato et al., 2014; Herssens et al., 2020; Wrisley & Kumar, 2010; Wrisley et al., 2004).

Additionally, we assessed 3 patient-reported outcomes: dizziness, balance confidence, and oscillopsia. The Dizziness Handicap Inventory questionnaire quantifies self-perceived handicap resulting from dizziness and unsteadiness due to vestibular system diseases (Vereeck et al., 2006). Balance confidence was evaluated using the Short Falls Efficacy Scale International. Seven activities of daily living commonly performed by older adults are presented and are scored based on their concern about falling (Delbaere et al., 2010). The Oscillopsia Severity Questionnaire assesses the feeling of oscillopsia while performing different activities or engaging in different situations (Dobbels et al., 2020; Guinand, Pijnenburg, et al., 2012).

5.4.6 Hearing assessment

Unaided pure-tone audiometry was performed to calculate the Fletcher Index high (mean threshold of 1000 Hz, 2000 Hz, and 4000 Hz) (Smoorenburg, 1992). In addition to the pure-tone audiometry, speech audiometry in noise was evaluated by the Leuven Intelligibility

Sentences Test using an adaptive procedure (van Wieringen & Wouters, 2008). The SPIN test is conducted in free field using a loudspeaker at a distance of 1 m at 0° azimuth. The frequency spectrum of the noise matches the long-term average frequency spectrum of the speech signal. The noise level is constant at 65 dB sound pressure level (SPL), while the speech level is adapted according to the response of the patient. A correct repetition of the keywords of a sentence decreases speech level of 2 dB SPL, while an incorrect response increases speech level of 2 dB SPL. Each list comprises 10 sentences and two lists are conducted to acquire the speech reception threshold. This threshold is calculated by calculating the mean speech levels of the last 5 sentences of the last list and the imaginary 11th sentence. To most closely resemble real-world hearing status, the best-aided SPIN results were used.

5.4.7 Statistical analysis

All data were stored in OpenClinica electronic data capture software. For all statistical analyses, JMP Pro statistical software version 15 (JMP Statistical Discovery) was used.

To obtain an estimation of the sample size needed to detect significant differences in the primary outcome variable, RBANS-H total score, a 2-tailed paired t test was performed on previously collected in-house validation data of the RBANS-H. The proposed sample size is 34 participants per group, which holds a power of 80% to detect a minimum clinically important difference of 4 with an estimated SD of differences of 8 and a significance level of $\alpha = .05$.

The objectives of this study were to evaluate cognition (in general and the different cognitive domains) of participants with BV in comparison with healthy controls and to determine whether cognition was correlated with vestibular characteristics. The Levene test was used to evaluate the assumption of equal variances. Normality was determined by visualizing the data in histograms. Equal variances and the normality of the reported data were confirmed. Therefore, parametric tests with the mean and SD of the variables are reported. For the first objective, RBANS-H subtest index scores and the total scale score were compared between matched participants with BV and healthy controls using paired effect size metrics. Effect sizes (Cohen *d*) and 95% CIs are presented, with *d* of 0.2 indicating a small effect; 0.5, a medium effect; and 0.8, a large effect (Cohen, 1988). For the second objective, associations between different vestibular variables and cognition within the BV population were explored by performing the $\eta 2$ effect size metric, with $\eta 2$ of 0.01 indicating a small effect; 0.06, a medium effect; and 0.14, a large effect (Cohen, 1988). Data were analyzed in January 2022.

5.5 Results

5.5.1 Study population

A total of 68 individuals were assessed, including 34 participants with BV (mean [SD] age, 63.3 [6.0] years; 18 [53%] men) matched with 34 healthy controls. The groups did not differ in the relevant demographic and clinical characteristics in any clinically meaningful way (Table 6).

Table 6. Demographic characteristics of people with bilateral vestibulopathy and healthy controls. BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); dB HL, decibel hearing level; FI_{high}, Fletcher index high (mean 1, 2, and 4 kHz); NA, not available; SPIN, speech-in-noise; SRT, speech reception threshold.

Characteristic	Participants, No. (%)	
	Bilateral vestibulopathy (n = 34)	**Healthy controls (n = 34)**
Sex		
Men	18 (52.9)	18 (52.9)
Women	16 (47.1)	16 (47.1)
Age, mean (SD), y	63.3 (6.0)	63.5 (5.7)
Hearing level		
$FI_{high,}$ best ear unaided, mean (SD), dB HL	45.4 (22.6)	39.0 (22.4)
SPIN, best aided SRT, mean (SD)	−0.01 (5.7)	−1.7 (3.3)
Hearing aid ownership		
Yes	16 (47.1)	14 (41.2)
No	17 (50.0)	20 (58.4)
NA	1 (2.9)	0
Education level, mean (SD), y[a]	13.3 (3.4)	14.3 (2.2)
BMI, mean (SD)	26.8 (3.8)	25.7 (4.1)
Smoking		
Yes	5 (14.7)	2 (5.9)
No	25 (73.5)	31 (91.2)
NA	4 (11.8)	1 (2.9)
Tinnitus		
Yes	11 (32.4)	13 (54.2)
No	5 (14.7)	9 (26.5)
NA	18 (52.9)	12 (35.3)
Depression, mean (SD)[b]	8.9 (7.0)	7.5 (7.1)

a Education level indicates the number of years spent in school, starting from the age of 6 years old.

b Measured using Beck Depression Inventory.

To confirm the diagnosis of BV, the Bárány Society criteria needed to be met (Strupp et al., 2017). All 3 criteria (bilaterally reduced response of vHIT, rotatory chair test, and caloric testing) were met by 13 individuals (38.2%) with vestibular loss. In 11 individuals (32.4%), 2 of 3 criteria were fulfilled, and the remaining 10 individuals (29.4%) met 1 criterion. Of all 34 individuals with BV, 11 individuals had a variation in the *COCH* gene causing DFNA9, an autosomal dominant disorder causing both progressive hearing loss and bilateral vestibular loss (Janssens de Varebeke et al., 2021a, 2021b). An additional analysis comparing demographic variables between participants with BV with and without DFNA9 resulted in an expected significant difference in hearing status (SPIN best aided, $p < .0001$; FI_{high} best hearing ear, $p = .0002$; tinnitus presence, $p = .0126$). No significant difference was observed regarding age, sex, education level, or depression.

5.5.2 Vestibular loss and cognitive performance

All 34 participants with BV and their matched healthy controls completed the RBANS-H. Overall, participants with BV obtained a clinically meaningful lower score on the RBANS-H compared with health controls (mean [SD] total score, 98.62 [12.70] vs 105.91 [11.03]; difference, 7.3; 95% CI, 0.14 to 1.22; d=0.68). Participants with BV scored worse than healthy controls on all subscales (Figure 12). The magnitudes of the difference in performance between BV and healthy controls were greatest on visuospatial cognition (mean [SD] score, 90.06 [13.34] vs 100.47 [13.91]; d=0.98), attention (mean [SD] score, 94.79 [16.39] vs 102.06 [12.97]; d=0.68), and immediate memory (mean [SD] score, 107.74 [10.66] vs 112.26 [10.66]; d=0.42) (Table 7).

Table 7. Results of the RBANS-H total and index scores including effect size in people with BV and their matched HC. BV, bilateral vestibulopathy; HC, healthy control; RBANS-H, Repeatable Battery for the Assessment of Neuropsychological Status for Hearing-impaired individuals.

RBANS-H index score	Mean (SD)		Cohen da	Interpretation effect
	BV	HC		
Immediate memory	107.74 (10.66)	112.26 (10.66)	.42	Small
Visuospatial	90.06 (13.34)	100.47 (13.91)	.98	Large
Language	100.41 (11.82)	103.35 (9.95)	.28	Small
Attention	94.79 (16.39)	102.06 (12.97)	.68	Medium
Delayed memory	103.56 (9.68)	104.32 (7.19)	.07	Trivial
Total scale	98.62 (12.70)	105.91 (11.03)	.68	Medium

a As data are paired, the Cohen d resembles the effect size for the sum of the magnitude of the difference in each of the RBANS-H index paired scores.

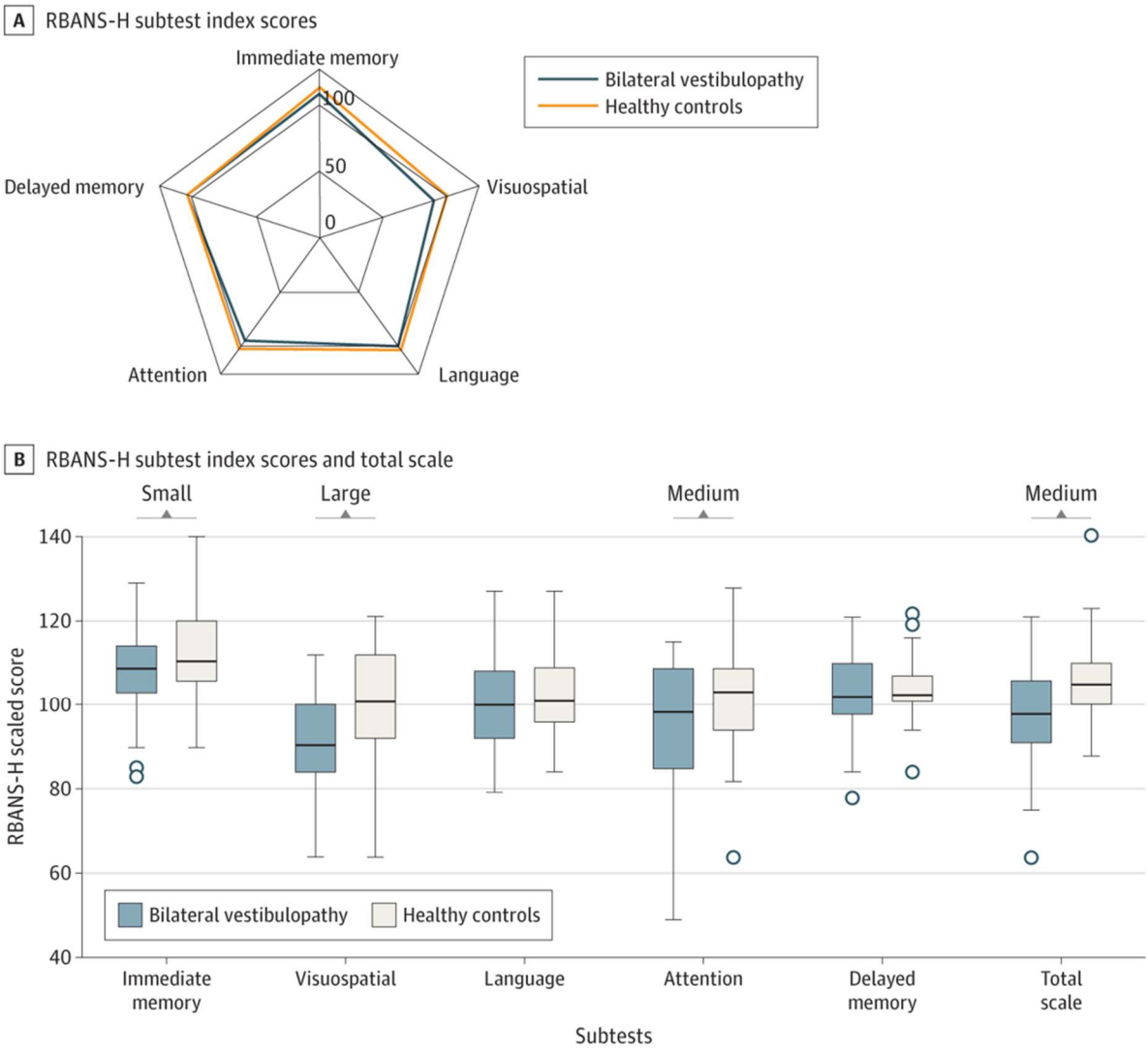

Figure 12. Comparison of Repeatable Battery for the Assessment of Neuropsychological Status for Hearing-Impaired Individuals (RBANS-H) scores between individuals with bilateral vestibulopathy and their matched healthy controls. B, Whiskers indicate range; boxes, IQR; bold line, median. Small, medium, and large indicate clinically meaningful Cohen *d* effect sizes.

5.5.3 Vestibular characteristics and cognition

Despite results showing worse cognitive scores in participants with BV, it remains unknown which vestibular characteristics could explain this pattern of cognitive loss. Possible vestibular characteristics include measurements of the peripheral vestibular end-organ, clinical balance testing, and questionnaires documenting self-perceived handicap, balance confidence, and oscillopsia. An overview can be found in Table 8. These analyses only include data of participants with BV, excluding healthy controls.

Table 8. Vestibular characteristics and association with the RBANS-H total scale scores. CVEMP, cervical vestibular evoked myogenic potentials; DHI, Dizziness Handicap Inventory; FGA, Functional Gait Assessment; OSQ, Oscillopsia Severity Questionnaire; POMA, Performance-Oriented Mobility Assessment; Short FES-I, Short Falls Efficacy Scale International; TUG, Timed Up-and-Go; vHIT, Video Head Impulse Test; VOR, vestibulo-ocular reflex.

Test	Outcome	η2	Interpretation effect
Peripheral vestibular end-organ: sacculus			
Presence of intact cVEMP responses, No.			
0	21[a]	.06	Small
1	11[a]		
Both	2[a]		
Peripheral vestibular end-organ: lateral semicircular canals			
VOR gain, mean (SD)			
vHIT, mean (SD)[b]	0.39 (0.33)	.01	Small
Rotatory chair	0.15 (0.18)	.05	Small
Caloric response: bithermal maximum peak slow-phase velocity on each side, mean (SD)[b]	2.80 (2.71)	.02	Small
Peripheral vestibular end-organ			
Bárány criteria met, No.			
1	10[a]	.01	Trivial
2	11[a]		
3	13[a]		
Clinical balance testing			
TUG score, mean (SD)	9.13 (2.20)	.03	Small
POMA total score, mean (SD)	25.15 (4.10)	.20	Large
FGA total score, mean (SD)	18.09 (6.88)	.02	Small
Questionnaires			
DHI total score, mean (SD)	37.19 (24.37)	<.01	Trivial
Short FES-I total score, mean (SD)	13.72 (5.48)	.01	Trivial
OSQ score, mean (SD)	2.74 (1.02)	.02	Small

a Presented as number of participants in category.

b For the vHIT and caloric response, each person had 2 values (left and right lateral VOR gain and sum of bithermal maximum peak slow-phase velocity per ear, respectively). For the analyses of these variables, each side/ear was analyzed, resulting in 68 ears (instead of 34 people).

Measurements of the peripheral vestibular end-organ and questionnaires included in this study demonstrated no clinically meaningful association with RBANS-H total scores. Regarding clinical balance assessments, only the POMA demonstrated a clinically meaningful

positive correlation with RBANS-H total scores (r32=0.45; 95% CI, 0.13 to 0.68; η2=0.20). Here, more impaired POMA scores indicate worse balance ability and are associated with worse RBANS-H total scores. Since the POMA test includes 2 subscales (balance and gait), correlations for both subscales were calculated. Results indicated that the balance subscale (r32=0.51; 95% CI, 0.20 to 0.72; η2=0.26) but not the gait subscale (r32=0.15; 95% CI, –0.19 to 0.47; η2=0.02) demonstrated a clinically meaningful positive correlation with the RBANS-H total scores.

As participants with BV demonstrated different degrees of cognitive function on different cognitive subdomains, an additional analysis including vestibular characteristics and the cognitive subdomains was performed. Figure 13 provides a heat map of the effect sizes (η^2) and its interpretation per cognitive subdomain and per vestibular characteristic. The same vestibular characteristics as defined in Table 8 were used. Results indicated that the POMA demonstrated a clinically meaningful positive correlation with the RBANS-H subdomains of visuoconstruction and attention. In addition, the additional clinical balance assessments (TUG and FGA) also demonstrated a clinically meaningful positive correlation with the RBANS-H attention subdomain.

		RBANS-H					
	η^2	Immediate memory	Visuo-construction	Language	Attention	Delayed memory	Total scale
Peripheral vestibular end-organ	cVEMP presence	0,052	0,022	0,034	0,039	0,106	0,059
	vHIT	0,030	0,022	0,001	0,014	<0,0001	0,013
	Rotatory chair	0,015	0,062	0,005	0,058	0,052	0,047
	Caloric response	0,016	0,034	0,002	0,019	0,001	0,017
	Barany criteria	0,020	0,022	0,030	0,090	0,013	0,009
Clinical balance testing	TUG	0,002	<0,001	0,011	0,267	0,011	0,032
	POMA	0,081	0,216	<0,001	0,322	0,135	0,199
	FGA	0,002	0,001	0,001	0,181	0,024	0,024
Questionnaires	DHI	0,001	0,001	0,055	<0,0001	0,018	0,002
	Short FES-I	0,010	0,013	0,036	0,025	0,063	0,006
	OSQ	0,015	0,037	0,069	0,001	<0,001	0,024

Figure 13. Heat map of the effect sizes (η^2) of vestibular characteristics as defined in Table 8 per RBANS-H cognitive subdomain as well as the RBANS-H total scale. Background colors indicate an interpretation of the effect size, with white indicating a trivial effect ($\eta^2 \leq 0.01$), light blue indicating a small effect ($\eta^2 > 0.01$), medium blue indicating a medium effect ($\eta^2 > 0.06$), and dark blue indicating a large effect ($\eta^2 > 0.14$).

To explore possible associations of demographic, psychological, and hearing covariates with this correlation, a general linear model analysis was performed. No significant associations of sex, age, years of education, anxiety (measured by the Hospital Anxiety and Depression Scale), depression (measured by the Hospital Anxiety and Depression Scale and Beck Depression Inventory), or hearing (best-aided SPIN and unaided Fletcher Index high: best ear) were observed.

5.6 Discussion

The primary aim of this cross-sectional study was to investigate the association of BV with cognitive function in older adults. Overall, participants with BV had a clinically meaningful lower score on the RBANS-H total scale, indicating a cognitive decline in general. This cognitive decline was most pronounced in the subdomains of immediate memory, visuospatial cognition, and attention. Moreover, even though no participant had a history of neurological disease, 3 participants with BV had a total score worse than expected when compared with a normative group (total scaled score ≤85), which could be indicative of cognitive impairment. As the RBANS-H is a cognitive screening test and more information is needed to make a formal diagnosis, a referral to the neurology department or memory clinic was suggested to closely monitor progressive cognitive decline. Despite animal studies emphasizing the importance of accounting for possible concomitant hearing loss, human studies, including data or corrections for hearing status, are often lacking (Dobbels, Peetermans, et al., 2019; Smith, 2022). As such, this study included hearing status in the individual matching procedure.

Our secondary aim was to explore vestibular characteristics and their potential associations with cognitive performance in participants with BV. A 2020 study by Pineault et al. found bilateral saccular and semicircular canal vestibular impairments were associated with impairment of various domains of cognition (Pineault et al., 2020). Surprisingly, we were unable to detect an association between measurements of the peripheral vestibular end-organ (including saccular and semicircular canal measurements) and cognition. However, this claim cannot be made unambiguously as, in our study, most participants with BV met more than 1 criterion of the Bárány Society. Therefore, an interaction effect between saccule and semicircular canal dysfunction may be present. On the other hand, 1 clinical balance assessment (the POMA, balance subscale) was the only vestibular assessment parameter associated with cognition in BV in a clinically meaningful way. Previous literature on the association between the POMA and cognitive function found that older adults at risk for falls had reduced cognitive function scores, supporting our findings (Dobbels, Mertens,

et al., 2019; Koo et al., 2012; Taylor et al., 2021; Teixeira-Leite & Manhães, 2012). However, studies are limited, and future studies examining the predictive value of the POMA (and its balance subscale) in cognitive decline are warranted. Furthermore, we hypothesize a dissociation between peripheral vestibular end-organ function versus balance, mobility, and fall risk. Patients with BV all demonstrated a bilaterally reduced or absent VOR, as this is the key criterion for diagnosis according to the Bárány Society guidelines. However, not every patient with BV demonstrated the same balance skill, as some had worse balance and mobility and thus a higher fall risk. The hypothesis is that the amount of central compensation that has occurred may drive the association between POMA and cognition. Furthermore, we argue that the TUG may be relatively too easy for patients with BV, and the FGA may be relatively too difficult. As such, we would recommend the POMA, and in particular the balance subscale to include in practice when evaluating balance and cognition in BV. Furthermore, no clinically meaningful associations of demographic, psychological, or hearing status covariates were observed. This supports evidence of a link between vestibular dysfunction and cognitive impairment, regardless of hearing status.

5.6.1 Vestibular loss as a risk factor for Alzheimer's disease

There is evolving evidence of an association between vestibular loss and cognitive impairment, in particular AD (Bigelow & Agrawal, 2015; Brandt et al., 2005; Previc, 2013; Semenov et al., 2016; Smith, 2021). From a neuropsychological point of view, the cognitive profile of BV and the early stages of AD appear to overlap. Of particular interest is a comparison with MCI. People with MCI are characterized by cognitive impairment out of proportion to the age and educational level of the individual, without impeding activities of daily life. Different subtypes of MCI exist, where amnestic MCI has the highest conversion rate to AD (annual conversion rate, 12%-15%) and is therefore considered the most relevant group to compare with people with BV (Bozoki et al., 2001; Petersen, 2000).

As the nomenclature implies, people with amnestic MCI demonstrate a prominent episodic memory loss, in which they have difficulty with learning and retaining new information. After a delay interval, people with amnestic MCI have trouble with free recall tasks. Moreover, people with amnestic MCI who convert to AD also struggle with a recognition task, whereas people who do not convert benefit from these cues (De Simone et al., 2019; Yanhong et al., 2013). In this study, participants with BV also demonstrated episodic memory loss, but their delayed memory remained intact. Other patterns of cognitive impairment, such as visuospatial loss, may still be consistent with underlying AD pathological mechanisms and may therefore be observed in amnestic MCI (Albert et al., 2011). Regarding language, impairment is atypical and often only present in more severe AD. Taken together, the visuospatial and language patterns in amnestic MCI agree with the cognitive patterns of BV. Finally, people with amnestic MCI often have mild problems performing complex functional tasks (eg, planning, finances, cooking). They may be less efficient, make more mistakes, and take longer to finish a task, but they are still able to do so independently (Albert et al., 2011). People with BV demonstrated difficulties in the attention subdomain, which encompasses

executive function (Galvin et al., 2020). Therefore, people with BV may struggle with planning and performing complex functional tasks, generally matching the cognitive profile of amnestic MCI. In summary, an overlap between the cognitive profile of BV and amnestic MCI can be found (Table 9). These results further support and extend evidence of an association between vestibular loss and cognitive impairment, in particular AD.

Table 9. Cognitive Profile of Individuals With BV and Amnestic MCI. BV, bilateral vestibulopathy; MCI, Mild Cognitive Impairment.

Cognitive domain	BV	Amnestic MCI
Immediate memory	Impaired	Impaired
Delayed memory	Preserved	Impaired
Visuospatial	Impaired	Impairments possible
Language	Preserved	Atypical but possible
Attention	Impaired	Mild problems performing complex functional tasks

Although the association between vestibular loss and cognitive impairment is gaining evidence, a causal relationship has not been established. Several causal theories have been proposed to explain the link between dementia and hearing loss, the largest modifiable risk factor for dementia (Livingston et al., 2020; Mitchell et al., 2020; Rizk et al., 2020). These theories can also be applied to vestibular loss being a modifiable risk factor for dementia and, in particular, AD. A first hypothesis is the cognitive load hypothesis, which states that cognitive resources are diverted to maintain balance at the expense of other cognitive processes (Bigelow & Agrawal, 2015). Second, the deprivation hypothesis or cascade hypothesis describes that vestibular loss, and therefore reduced vestibular input, leads to accelerated brain atrophy, which then leads to dementia. Previously observed hippocampal atrophy (a biomarker of AD) in people with vestibular loss strengthens this hypothesis (Brandt et al., 2005; Göttlich et al., 2016). A third hypothesis focuses more on psychosocial aspects of vestibular loss, namely the social isolation hypothesis. People with vestibular loss often experience living in fear and anxiety because they feel unsafe and fearful of falling. Therefore, they restrict their participation in activities and travel, leading to living a more socially isolated life (Harun, Li, et al., 2016; Kirby & Yardley, 2012). Finally, the common cause hypothesis assumes that both vestibular loss and cognitive impairment are the result of a common neurodegenerative process. Both vestibular loss and dementia are heterogeneous and involve many factors. Risk factors may vary and coexist (Previc, 2013). The exploration and identification of causal mechanisms underlying the association between vestibular loss and cognitive impairment may allow for early detection of people at risk for AD. Furthermore, identification may prevent or slow down progression along the AD continuum through proper treatment of vestibular loss.

5.6.2 Treating vestibular loss

Given the association between vestibular function and cognition, one may hypothesize that restoration of vestibular function (by either vestibular rehabilitation, vestibular implant, or vibrotactile feedback) may increase or preserve cognition (Brown et al., 2001; Guyot & Perez Fornos, 2019; Kingma et al., 2019; Kundakci et al., 2018; Whitney et al., 2016). A study by Sugaya et al. trained 60 people with intractable dizziness to perform a 30-minute vestibular rehabilitation program by themselves (Sugaya et al., 2018). They demonstrated a significant improvement in cognition (visuospatial cognition, attention, and executive function, as measured by the Trail Making Test). Furthermore, vestibular rehabilitation should encompass balance exercises and training people to not stop walking while talking. Improvement in balance performance will decrease the cognitive load associated with balance performance itself. More studies examining the effect of restoration of vestibular function on cognition (including >1 cognitive test) in a population with vestibular loss are warranted. This may provide interesting results in future research, including potential treatment options within dementia research.

5.6.3 Limitations

This study has some limitations. The inclusion of 34 participants per group was the lower limit of the proposed sample size. Although this number is estimated to be sufficient, a larger sample size would benefit the analysis and interpretation of results. A second limitation is the use of the RBANS-H as the neuropsychological assessment. This test is able to provide an estimation of total cognition and multiple relevant cognitive domains while only taking 30 minutes to administer. However, an extended formal neuropsychological evaluation would be beneficial to obtain a more in-depth assessment of cognition and would be able to detect more subtle differences. In addition, the RBANS-H is normed based on age, whereas neuropsychological tests, which are also normed based on sex and education level, would be preferable.

5.7 Conclusions

This cross-sectional study found that individuals with BV demonstrated cognitive deficits compared to healthy controls. These deficits were most pronounced in the cognitive subdomains of immediate memory, visuospatial cognition, and attention. However, language and delayed memory subdomains remained preserved. This cognitive loss was found to be independent of concurrent hearing loss. In individuals with BV, cognitive deficits were associated with 1 clinical balance assessment, namely the POMA, and more specifically, the balance subscale. Other vestibular parameters, such as measurements of the peripheral vestibular end-organ and questionnaires, showed no clinically meaningful association. These results support and extend previous literature on an association between vestibular loss and cognitive impairment, in particular AD. However, further research

investigating causal mechanisms and the impact of vestibular treatment on cognition is recommended.

Part 3

Structural brain imaging in bilateral vestibulopathy

Chapter 6. Is vestibular function related to human hippocampal volume?

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6.1 Abstract

Background: Recent studies implicate the effect of vestibular loss on cognitive decline, including hippocampal volume loss. As hippocampal atrophy is an important biomarker of Alzheimer's disease, exploring vestibular dysfunction as a risk factor for dementia and its role in hippocampal atrophy is of interest.

Objective: To replicate previous literature on whole-brain and hippocampal volume in semicircular canal dysfunction (bilateral vestibulopathy; BV) and explore the association between otolith function and hippocampal volume.

Methods: Hippocampal and whole-brain MRI volumes were compared in adults aged between 55 and 83 years. Participants with BV (n=16) were compared to controls individually matched on age, sex, and hearing status (n=16). Otolith influence on hippocampal volume in preserved semicircular canal function was evaluated (n=34).

Results: Whole-brain and targeted hippocampal approaches using volumetric and surface-based measures yielded no significant differences when comparing BV to controls. Binary support vector machines were unable to classify inner ear health status above chance level. Otolith parameters were not associated with hippocampal volume in preserved semicircular canal function.

Conclusions: No significant differences in whole-brain or hippocampal volume were found when comparing BV participants with healthy controls. Saccular parameters in subjects with preserved semicircular canal function were not associated with hippocampal volume changes.

6.2 Key points

- Recent research suggests an association between vestibular function and cognition.
- Hippocampal atrophy is an important biomarker of Alzheimer's disease.
- Bilateral vestibular loss did not modulate hippocampal or whole-brain volume.

6.3 Introduction

Bilateral vestibulopathy (BV) is a severe chronic vestibular disorder of the labyrinth or the eighth cranial nerve characterized by postural imbalance, unsteadiness of gait which worsens in darkness and/or on uneven ground, and oscillopsia during head movements. Symptoms are typically absent under static conditions (Strupp et al., 2017). Multiple possible etiologies for BV exist, including but not limited to ototoxicity, bilateral Menière's disease, bilateral vestibular schwannoma, genetic, or infectious causes (Lucieer et al., 2016).

There is evolving evidence suggesting that vestibular loss is associated with cognitive impairment and may even contribute to the onset of Alzheimer's disease (Bigelow & Agrawal, 2015; Bosmans et al., 2022; Bosmans et al., 2021; Harun, Oh, et al., 2016; Previc, 2013; Semenov et al., 2016).

When zooming in on the anatomical level, structural brain changes have been reported in patients with BV over the past twenty years in cross-sectional manual segmentation studies, specifically at the level of the hippocampus (Brandt et al., 2005; Hüfner et al., 2007). The hippocampus is a seahorse-shaped structure necessary for memory processing (encoding, consolidation, and retrieval) (Manns et al., 2003; Scoville & Milner, 1957) and spatial memory function (McNaughton et al., 1996; O'Keefe & Dostrovsky, 1971). These cognitive functions have been identified to be impacted in BV patients (Bosmans et al., 2022; Brandt et al., 2005; Dobbels, Mertens, et al., 2019; Dobbels, Peetermans, et al., 2019). Previous studies have compared hippocampal volumes between subjects with and without BV. Brandt et al. (2005) observed a significant selective shrinkage of hippocampal volume by 16.9% in people with BV relative to controls. A study by Kremmyda et al. (2016) described a significant reduction in grey-matter mid-hippocampal and posterior parahippocampal volume in long-standing BV patients compared to healthy controls. On the other hand, other studies observed a lack of hippocampal volumetric differences when comparing patients with BV and healthy controls (Dordevic et al., 2021; Göttlich et al., 2016; Schöne et al., 2022).

A study by Kamil et al. (2018) took a different approach and evaluated hippocampal volume in healthy older adults (≥ 60 years) from the Baltimore Longitudinal Study of Aging (BLSA). They observed that a larger cervical vestibular-evoked myogenic potential (cVEMP) amplitude was significantly associated with a larger mean hippocampal volume (p = .003). They proposed that lower cVEMP amplitude, implying reduced saccular function, is

significantly associated with a lower mean volume of the hippocampus. Jacob et al. (2020) included healthy older adults (≥ 60 years) from the BLSA cohort. They investigated the relation between vestibular function (using cVEMP) and the volume of structures comprised of or connected to the vestibular cortex. They observed smaller volumes of the hippocampus and entorhinal cortex associated with reduced vestibular function. A review by Smith (2019) supports these findings, stating that reduced saccular function can be associated with poorer spatial memory, Alzheimer's disease, and reduced hippocampal volume.

There is a high risk of concomitant sensorineural hearing loss (SNHL) in patients with vestibular dysfunction and vice versa (Lucieer et al., 2016; Zingler et al., 2007). As concomitant hearing loss could exacerbate a potential effect of vestibular dysfunction on brain volume, the hippocampus being of main interest, hearing levels should be included in these analyses. Previously mentioned studies comparing hippocampal volumes between BV patients and healthy controls generally lack a detailed description of hearing performance and did not include hearing performance in their methodological approach to the topic.

We are interested in evaluating the impact of semicircular canal dysfunction (in this case: BV) and otolith function (in this case: saccular function) on hippocampal volume. We hypothesize that the effect of BV will not result in significant hippocampal volume differences when compared to controls because of the adjustments made for hearing level. In addition to hippocampal and whole-brain volumetric analyses, we will also evaluate surface-based morphometry including cortical thickness and sulcus depth analyses. A second aim of this study is to delineate otolith (saccular) influence on hippocampal volume in a population with preserved semicircular canal function.

6.4 Materials and methods

6.4.1 Participant characteristics

All participants were recruited from the *GECkO*-study (Gehoor, Evenwicht, COgnitie), an ongoing prospective longitudinal cohort study of the effect of hearing loss and vestibular decline on cognitive function in older adults (Bosmans et al., 2020). This protocol was approved by the ethical committee of the University Hospital of Antwerp, Belgium (EC number B300201938949) and all participants gave their written informed consent in accordance with the Declaration of Helsinki prior to participation. The study protocol builds upon the Clinical Trials protocol with identifier NCT04385225.

6.4.1.1 *BV population*

The diagnosis of BV was made according to the Bárány Society criteria and was defined as (1) a bilaterally pathological horizontal angular VOR gain (<0.6) measured by the vHIT, and/or (2) reduced horizontal angular VOR gain (<0.1) upon sinusoidal stimulation on a rotatory

chair (0.1 Hz, Vmax = 50°/sec), and/or (3) reduced caloric response (sum of bithermal (30°C/44°C) maximum peak SPV on each side <6°/sec) (Strupp et al., 2017).

6.4.1.2 *Healthy controls*

BV participants were matched based on age, sex, and best aided speech audiometry in noise. All participants underwent vHIT to confirm normal vestibular function (bilateral horizontal VOR gain > 0.6). For all participants (BV and healthy controls) the following inclusion criteria were applied (1) age 55 – 84 years, (2) Dutch as native language, (3) right-handed as defined by the Edinburgh Handedness Inventory (Oldfield, 1971), and (4) preserved cognitive function. A neuropsychological exam including a Mini-Mental State Examination (MMSE) and Repeatable Battery for the Assessment of Neuropsychological Status for Hearing impaired individuals (RBANS-H) was performed in all participants (Claes et al., 2016; Folstein et al., 1975). Participants were considered having preserved cognitive function when scoring ≥ 24/30 on the MMSE as well as ≥ percentile 16 on the RBANS-H total score (Albert et al., 2011; Folstein et al., 1975). Participants with lower cognitive scores were excluded as cognitive impairment can affect hippocampal volume and confound our results. People with an implanted hearing aid device (e.g., cochlear implant or bone-anchored hearing aid) were also excluded from this study.

6.4.2 MRI volumetry

6.4.2.1 *Acquisition protocol*

All subjects were investigated in a clinical 3.0 T scanner (Siemens Magnetom Prisma, Erlangen equipped with a 32-channel receiver head coil, 24 subjects in total, being 11 with BV and 13 healthy controls; Siemens Magnetom Vida, Erlangen equipped with a 64-channel receiver head coil, 8 subjects in total, being 5 with BV and 3 healthy controls). A high-resolution T1-weighted image (GRAPPA sequence, 256 slices, slice thickness = 0.75 mm, voxel size = 0.75 x 0.75 x 0.75 mm, TR = 2060 ms, TE = 2.17 ms) was obtained in sagittal orientation.

6.4.2.2 *MRI data processing*

Neuroimaging data quality control was performed via MRIQC version 0.15.1 (Esteban et al., 2017). Structural images were pre-processed and automatically segmented by the Computational Anatomy Toolbox (CAT12 Version 1980) (Figure 14, Panel A) (Gaser et al., 2022), an extension within the framework of Statistical Parametric Mapping software (SPM12) in MATLAB. Atlas-based segmentation for regions-based morphometry included the entire hippocampus as well as the volume of its substructures (CA1, CA2, CA3, dentate gyrus, and subiculum) taken from the cytoarchitectonic representation in the Julich Brain atlas (Amunts et al., 2020). In addition, total intracranial volume (TIV) was estimated and used (together with age and scanner type) as a covariate for all the voxel- and region-based, but not for surface-based analyses (Hutton et al., 2009).

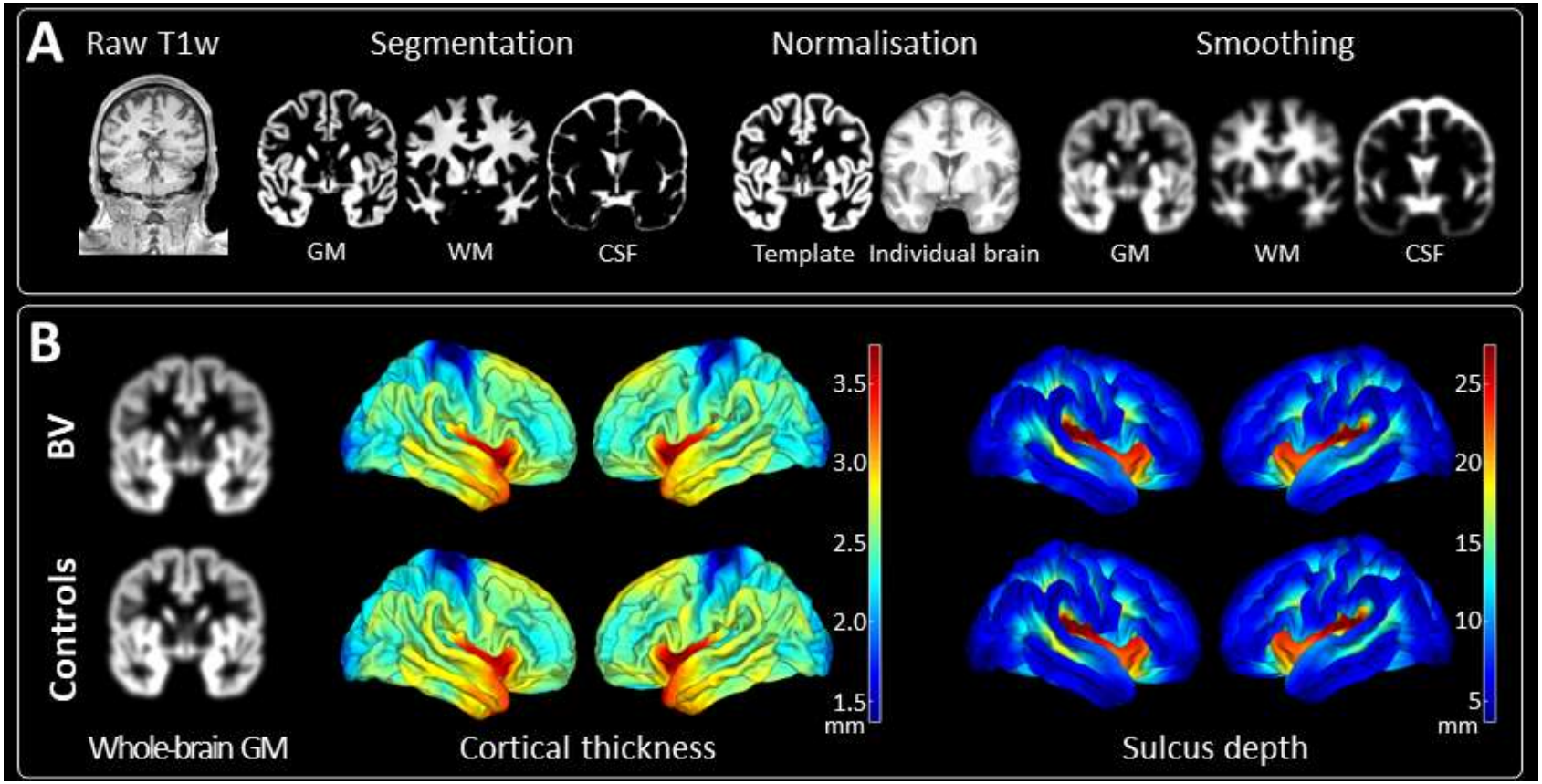

Figure 14. (A) Flowchart of the structural MRI preprocessing pipeline. All presented images are derived from the same control participant. The MNI152 NLIN 2009c 1mm template is used for normalisation. A smoothing kernel of 6mm full width at half maximum is applied. (B) Results of whole-brain comparisons between patients with BV (n=16) and their matched controls (n=16). Whole-brain comparisons encompassed whole-brain grey matter volumetric analyses and surface-based measures including cortical thickness and sulcus depth analyses. No significant differences were found in any of the comparisons. GM, grey matter; WM, white matter; CSF, cerebrospinal fluid; BV, bilateral vestibulopathy.

6.4.3 Otolith function evaluation of the saccule

Saccular function was investigated via the vestibulocollic reflex (VCR) using cVEMP with the validated Neuro-Audio device incorporating electromyography feedback (Neurosoft, DIFRA). While participants lay in a supine position, they lifted and rotated their head to one side, contracting the sternocleidomastoid (SCM) muscle. Short 500 Hz tone bursts were presented in the contralateral ear at suprathreshold level (95 dB nHL). Present responses were biphasic and had two distinctive peaks (p13 and n23). Normative ranges were applied, with the p13 occurring 11.81–15.59 ms after stimulus onset, and with the n23 occurring 18.15–25.64 ms after stimulus onset (Li et al., 2014). Intact responses needed to be elicited at least twice to confirm presence of the VCR. Outcome measures included presence of intact responses (0, 1 ear, or both ears), and for each present response outcome measures included p13 latency (ms), n23 latency (ms), P-N amplitude (μV), rectified amplitude (μV), and SCM muscle contraction level (mean rectified voltage, MRV, μV).

6.4.4 Hearing assessment

Unaided pure-tone audiometry was measured over a frequency range from 125 Hz to 8 kHz (specifically 0.125, 0.25, 0.5, 1, 2, 3, 4, 6, 8 kHz). Hearing thresholds were measured separately for each ear using a 2-channel Interacoustics AC-40 audiometer with insert earphones. Speech audiometry in noise (speech-in-noise; SPIN) was evaluated by the Leuven Intelligibility Sentences Test (LIST) with an adaptive procedure (van Wieringen & Wouters, 2008) in free field using a loudspeaker at a distance of 1 meter at 0° azimuth. The noise level was constant at 65 dB sound pressure level (SPL) while the speech level was adapted according to a correct (decreased speech level of 2 dB SPL) or incorrect (increased speech level of 2 dB SPL) response. Two lists of ten sentences each were conducted to acquire the speech reception threshold (SRT in dB SNR; averaged speech levels of the last five sentences and the imaginary 11^{th} sentence), both in an unaided and aided condition. The mean value of the best aided condition was used for analyses.

6.4.5 Statistical analysis

For demographic and region of interest (ROI) based analyses (by use of the Julich-Brain atlas (Amunts et al., 2005)), JMP Pro 15 (Medmenham, UK) was used. Levene's tests and visualization of data using histograms confirmed equal variances and the normality of reported data. However, because of the small sample size, nonparametric tests with the median and range are reported. Continuous patient characteristics were compared using Kruskal-Wallis ANOVA, for nominal patient characteristics, the Pearson Chi-squared statistic was used. For voxel-based morphometry analyses, the CAT12 toolbox and SPM12 were used. For each aim, a two-sample t-test was performed. Whole-brain changes were investigated by an F-contrast, with age, TIV, and scanner type as covariates. Similar statistics were performed for surface analyses (cortical thickness and sulcus depth), with only age and scanner type as covariates. Regarding *p*-value adjustment, the Monte-Carlo method for

permutation testing (10.000 permutations) was applied using the TFCE toolbox (Version 224), with correction for multiple comparisons via false discovery rate ($p < .05$). In addition, machine learning in the form of multi-voxel pattern analysis is performed to increase the sensitivity to detect differences in each pairwise comparison by use of the Pattern Recognition for Neuroimaging Toolbox v3.0 (PRoNTo) (Schrouff et al., 2016). Classification was performed using a binary support vector machine (SVM) with one subject per class left out as the cross-validation scheme and 10.000 permutations. A Spearman correlation (and its 95% confidence interval) was performed for saccular analyses. *P*-values are reported, as well as *eta squared* (η^2) indicating the effect size. The Pearson Chi-squared statistic was used for ordinal parameters, with *w* indicating its effect size. Between-scanner type differences were examined by a two-sample t-test of quality control parameters derived from MRIQC.

6.5 Results

6.5.1 Patient characteristics

Demographic and clinical details as well as neuroimaging data quality of included participants can be found in Table 10. The median [range] disease duration for the BV population was 8 years [2, 22]. Among the etiologies of BV, 6 patients had a genetic risk (DFNA9), 1 patient autoimmune, 2 patients infectious (meningitis, varicella zoster), 1 patient ototoxic, 2 patients due to trauma, 1 patient with unknown etiology, and 3 patients idiopathic. All patients with idiopathic etiology had undergone an MRI internal auditory canal, tonal audiometry, and (hetero)anamnesis to exclude other causes. To confirm the diagnosis of BV, patients must meet at least one out of three of the Bárány Society criteria (Strupp et al., 2017). All three criteria (bilaterally reduced vHIT response, rotatory chair, and caloric testing) were met by 25% (n = 4) of people with vestibular loss. In 37.5% (n = 6), two out of three criteria were fulfilled, and the remaining 37.5% (n = 6) of people met one criterion. Based on the unaided tonal audiometry of the best hearing ear, 6 subjects with BV demonstrated age-normal hearing function, 4 had moderate SNHL, and 6 had severe SNHL.

Age, sex, hearing level, education level, obesity, smoking status, tinnitus presence, and depression may affect hippocampal volumes (Campbell et al., 2004; Cherbuin et al., 2015; Nobis et al., 2019; Profant et al., 2020). Therefore, age, sex, Fletcher index high (FI_{high}; average threshold of 1 kHz, 2 kHz, and 4 kHz), SPIN, hearing aid ownership, years of education (number of years spent in school, starting from the age of 6 years old), body mass index (BMI), smoking status, tinnitus presence, and the total score of the Beck Depression Inventory were included in the demographic characteristics. No significant demographic or patient characteristic differences were observed (Table 10).

Neuroimaging data quality control encompassed image quality metrics for structural images including Dietrich's signal-to-noise ratio (SNRd) (Dietrich et al., 2007), entropy focus criterion (EFC) (Atkinson et al., 1997), and coefficient of joint variation (CJV) (Ganzetti et al., 2016).

Neuroimaging data quality control was blinded for diagnostic categories and afterwards tested for group differences. The parameters EFC and CJV were included to control for the potential head motion differences between the groups during structural neuroimaging. None of the pairwise comparisons resulted in a significant difference on any of the image quality metrics (Table 10).

Table 10. Demographic characteristics of people with BV and its age-, sex-, and hearing-matched controls. Education level indicates the number of years spent in school, starting from 6 years old. NA indicates the amount of missing data. SD, standard deviation; FI_{high}, Fletcher index high (mean 1 – 2 – 4 kHz); dB HL, decibel hearing level; SPIN, speech-in-noise; SRT, speech reception threshold; BMI, body mass index; SNRd, Dietrich's signal-to-noise ratio; EFC, entropy focus criterion; CJV, coefficient of joint variation.

	Bilateral vestibulopathy (n = 16)	**Healthy controls (n = 16)**	**p-Value**
Age (year: median [range])	63 [56, 74]	64 [57, 74]	.4486
Sex (n: M/F)	10/6	10/6	1
Hearing level			
FI_{high} best ear (unaided dB HL: median [range])	40 [10, 78.3]	33.3 [6.7, 68.5]	.7395
SPIN (best aided SRT: median [range])	-2.8 [-5, 14.3]	-3 [-5.7, 1.7]	.1867
Hearing aid ownership (n: YES/NO)	8/8	8/8	1
Tinnitus presence (n: YES/NO/NA)	10/4/2	10/6	.6048
Education level (year: median [range])	13 [8, 20]	14.5 [12, 32]	.1030
BMI (median [range])	26 [24.2, 32.8]	25.8 [21, 36.6]	.2991
Smoking (n: YES/NO/NA)	2/12/2	0/16/0	.1176
Depression (Beck Depression Inventory: median [range])	4 [0, 22]	5.5 [0, 15]	.6813
Neuroimaging data quality control			
SNRd (median [range])	66.0 [46.4, 105.7]	66.3 [49.3, 96.6]	.6338
EFC (median [range])	0.6 [0.5, 0.7]	0.6 [0.5, 0.7]	.8893
CJV (median [range])	0.7 [0.6, 0.8]	0.7 [0.6, 0.9]	.8706

6.5.2 Effect of semicircular canal dysfunction on brain volumes

To evaluate the effect of semicircular canal dysfunction on brain tissue compartments and to exclude a potential confounding effect of concomitant hearing loss, modulated grey and white matter tissue volumes of people with BV were compared with matched healthy controls. Whole-brain grey matter comparisons yielded no significant differences between these two groups ($p > .05$) (Figure 14, Panel B). A ROI analysis of the hippocampus proper found no significant morphometric changes between these two groups (total hippocampus proper: $p = .7806$; left hippocampus proper: $p = .7200$; right hippocampus proper: $p = .8958$; see Table 11; Figure 15). Surface-based analyses (cortical thickness and sulcus depth) also gave no significant differences between these two groups ($p > .05$) (Figure 14, Panel B). The SVM model resulted in an area under the ROC curve value of 0 ($p = 1$, total accuracy of 40.62%), reflecting at random classification of people with BV versus their matched healthy controls.

Table 11. ROI volumes of the hippocampus proper and its subdomains. The hippocampus proper is calculated as the sum of CA1, CA2, and CA3. BV, bilateral vestibulopathy; CA, cornu ammonis.

	Bilateral vestibulopathy: Median [range]	**Healthy controls: Median [range]**	**p-Value BV vs healthy controls**
Left hippocampus proper	3.3 [1.3, 3.8]	3.2 [2.6, 3.8]	.7200
Right hippocampus proper	3.9 [3.1, 4.6]	3.9 [3.4, 4.7]	.8958
Hippocampus proper	7.3 [5.1, 8.2]	7.2 [6.0, 8.5]	.7806
CA1	5.2 [3.7, 5.9]	5.2 [4.2, 6.0]	.8675
CA2	1.1 [0.7, 1.3]	1.1 [0.9, 1.3]	.6336
CA3	1.0 [0.6, 1.1]	1.0 [0.8, 1.2]	.6027
Dentate gyrus	2.2 [1.3, 2.5]	2.2 [1.8, 2.5]	.5573
Subiculum	1.5 [1.0, 1.7]	1.5 [1.2, 1.8]	.9777

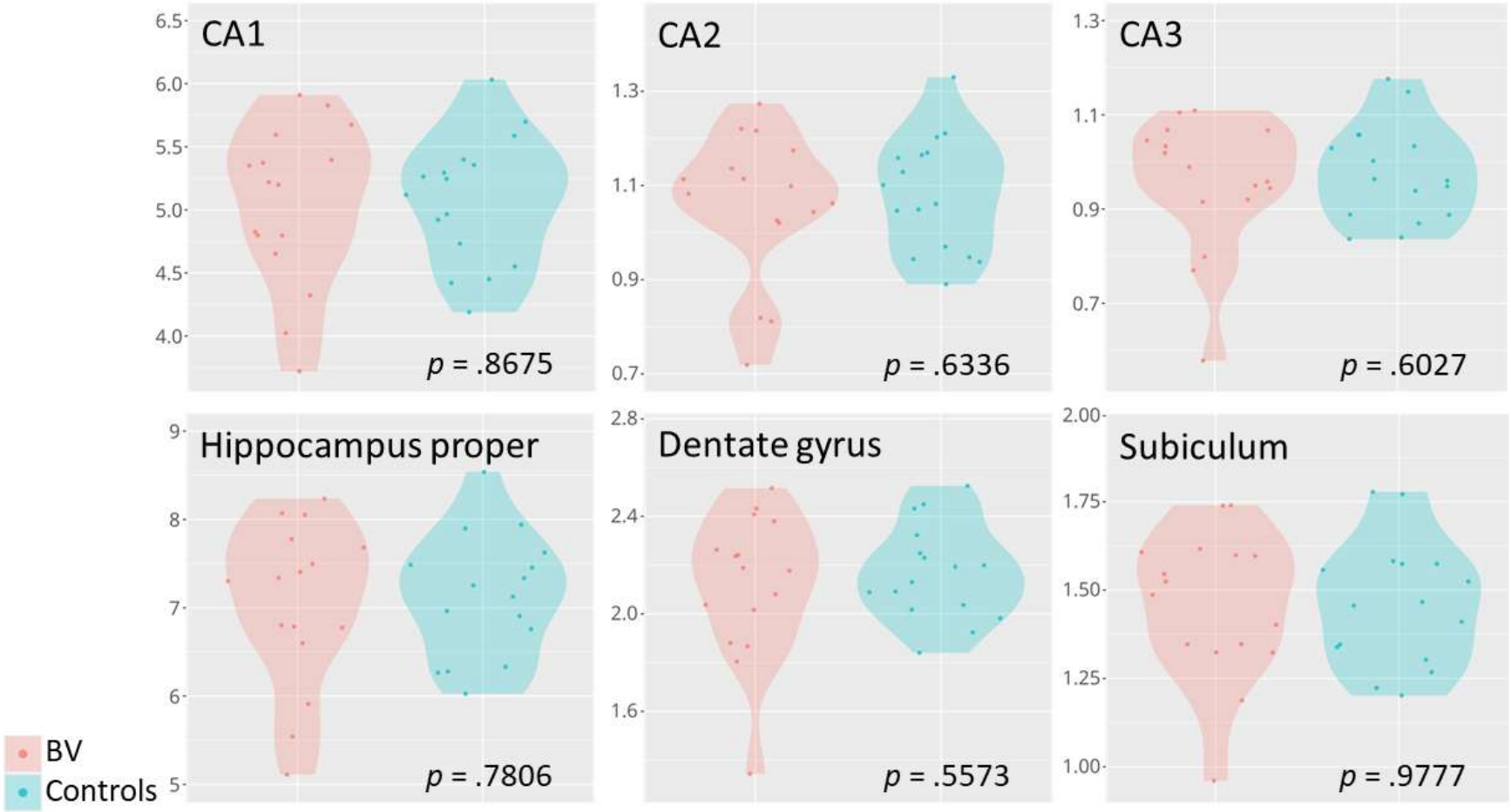

Figure 15. Targeted hippocampal volumetric measurements. Violin plots of the hippocampal subfields (in ml) of patients with BV (n=16) in comparison with their matched controls (n=16). The hippocampus proper is calculated as the sum of CA1, CA2, and CA3. BV, bilateral vestibulopathy; CA, cornu ammonis.

6.5.3 Otolith (saccular) function and hippocampal volumes

To explore whether hippocampal volume correlates with saccular function in a population with preserved vestibular function, cVEMP parameters of participants without BV were analysed (Table 12). These analyses included a total of 34 participants (15 with sensorineural hearing loss and 19 controls with preserved hearing). Out of all 68 ears, 43 ears demonstrated an intact saccular response. However, the presence of intact responses was not significantly associated with the volume of the hippocampus proper ($X^2(2, N = 34) = .0804$, $p = .9606$). Of the ears with intact responses, P-N amplitude, rectified amplitude, and n23 latency demonstrated no significant nor clinically meaningful effect ($r(1) = -0.07$, $p = .643$; $r(1) = 0.01$, $p = .966$;$r(1) = 0.11$, $p = .472$; respectively). Muscle tension of the SCM as measured by MRV also demonstrated no significant effect ($r(1) = 0.16$, $p= .304$). P13 latency on the other hand was significantly associated with hippocampal volume ($r(1) = 0.34$, $p = .028$) with a medium effect ($\eta^2 = .1129$). Even though cVEMP testing does not depend on hearing level but to correct for SNHL, p13 latency was correlated with unaided FI_{high}-values of the best hearing ear (Rosengren et al., 2019). As expected, this correlation was not significant ($r(1) = -0.001$, $p = .995$) with a trivial effect size ($\eta^2 < .001$). There are heterogeneous results on the effect of age on p13 latency, but p13 latency is generally known to be associated with age (Macambira et al., 2017). Indeed, when including age and p13 latency as independent variables with total hippocampal volume as the dependent variable, this model was significant ($F(2, 40) = 5.8485$, $p = .006$). Parameter estimates were $p = .020$ for age and $p = 0.107$ for p13 latency. When removing p13 latency from this model, thus resulting in the correlation between total hippocampal volume and age, this model was significant ($r(1) = -0.310$, $p = .010$).

Table 12. Saccular characteristics and their association with volume of the hippocampus proper. Latencies are expressed in milliseconds, amplitude and muscle tension are expressed in microvolts. Significant results are indicated with an asterisk (*: *p*<.05). *p*-Values and effect sizes (uncorrected) are presented together with *p*-values and effect sizes corrected for age as a confounder. cVEMP, cervical vestibular-evoked myogenic potentials; MRV, mean rectified voltage.

cVEMP parameter	Median [range]	Correlation with hippocampal volume (95% confidence interval)	p-Value uncorrected	p-Value corrected for age	Uncorrected effect size η^2	Effect size η^2 corrected for age
Presence of intact responses (n = 34)	No responses: n=6 (18%) One ear: n=13 (38%) Both ears: n=15 (44%)	Chi-Square (df=2): .0804	.9606	.9382	w = .0486 (trivial)	w = <.0001 (trivial)
P-N amplitude (n=43)	102.5 [38.5, 195.2]	0.07 (-0.23, 0.37)	.6429	.8124	.0053 (trivial)	.0012 (trivial)
Rectified amplitude (n=43)	0.69 [0.36, 1.47]	0.01 (-0.29, 0.31)	.9660	.7502	.00004 (trivial)	.0021 (trivial)
p13 latency (n=43)	13.4 [12, 15.2]	0.34 (0.04, 0.58)	.0276*	.1071	.1129 (medium)	.0526 (small)
n23 latency (n=43)	22 [18, 25.3]	0.11 (-0.19, 0.40)	.4718	.3754	.0127 (small)	.0163 (small)
MRV (n=43)	149.9 [90.5, 204.7]	0.16 (-0.15, 0.44)	.3039	.2173	.0258 (small)	.0312 (small)

6.6 Discussion

This study aimed to evaluate the impact of semicircular canal and otolith function on hippocampal volume. As such, this study evaluated hippocampal and whole-brain volumetric differences when comparing BV participants with healthy controls whilst adjusting for hearing level, as previous studies on this inner ear topic did not control for the confounding effects of altered hearing levels. However, we were unable to find any structural differences: neither using whole-brain grey matter analyses, nor using an ROI analysis of the hippocampus proper, nor using surface-based analyses, nor using the SVM model as a more sensitive machine learning technique.

In addition, we aimed to delineate otolith influence on hippocampal volume in a population with preserved semicircular canal function. An intact cVEMP response was elicited in at least one ear in 82% of the cases. The p13 latency was positively correlated with hippocampal volume, where longer latencies within normal ranges indicated larger hippocampal volumes. However, when correcting for age, this significant correlation disappeared and could thus be explained by age as a confounding variable. Other saccular parameters at suprathreshold level (95 dB nHL) including the number of intact responses, P-N amplitude, rectified amplitude, n23 latency, and MRV did not demonstrate a significant correlation with the volume of the hippocampus proper.

This study used the normative ranges of Li et al. (2014) to indicate the presence of intact cVEMP responses (p13: 11.81-15.59 ms; n23: 18.15-25.64 ms). However, different latencies can be observed in the literature, with some diverging from the normative ranges of Li et al. (2014) (for a recent systematic review with meta-analysis, see Macambira et al. (2017)). For transparency reasons, an overview per subject of saccular parameters and additional relevant data can be found in the supplemental content, Table 13.

The emerging theory of the association between vestibular loss and cognitive decline would be supported by associated hippocampal atrophy in BV. As such, positive studies by Brandt et al. (2005) and Kremmyda et al. (2016) are often cited exclusively to substantiate this hypothesis. However, the role of the replication crisis should not be underestimated and these current null findings, together with those observed by Dordevic et al. (2021), Göttlich et al. (2016), and Schöne et al. (2022) need to be taken into account to correct earlier underpowered findings using less reliable segmentation approaches to avoid future false understandings of this association. However, one can question whether the present study's absence of significant findings can completely disprove the association between hippocampal atrophy and BV? Not necessarily. First of all, BV is a broad and heterogeneous condition. Therefore, one might consider subdividing the BV population by etiology or duration since onset. Second, multiple tests exist to assess peripheral vestibular end-organ functioning. The current study included older adults diagnosed with BV. Diagnostic criteria for this condition all rely on semicircular canal function. However, measurements of otolithic

organs may be of added value. They may provide interesting new insights because of their association with spatial learning and memory (Smith, 2019). Therefore, this study included saccular characteristics and their association with hippocampal volume. Even though no association between saccular function and brain volumetry was observed, a previous systematic review described longer p13 latencies and smaller VEMP amplitudes with increasing cognitive decline along the Alzheimer's disease continuum (Bosmans et al., 2021). It appears that the association between vestibular dysfunction and an increased risk of cognitive dysfunction may remain on a behavioral level and may not be expressed at the anatomical level.

One thing that must be kept in mind is the sample size. Our research included 16 participants with BV and 16 healthy controls. Although as a rule of thumb, it is recommended that each subgroup should include at least 20 participants (Gaus & Rainer, 2013). However, we believe that the obtained data quality and stringency of the employed processing pipeline together with the application of full permutation testing makes our findings robust.

A minor limitation is the difference in disease duration for the current BV population. Our study's median [range] disease duration was 8 [2-22] years. Comparable studies have a variable disease duration of 5-10 years (Brandt et al., 2005), 13.6 ± 17.4 years (Kremmyda et al., 2016), and 3 months to 20 years (Göttlich et al., 2016). The high variation in disease duration might hamper a direct comparison between studies.

Ideally, the impact of isolated otolith dysfunction (i.e. abnormal otolith function with preserved semicircular canal function) on hippocampal and whole-brain volume should be evaluated. However, there is no consensus on defining otolith symptoms, standardized assessment of laboratory otolith function testing, and diagnostic criteria with structured definitions of isolated otolith dysfunction (Chua et al., 2022). This often leads to mis- or underdiagnosing. Future studies should evaluate hippocampal and whole-brain volume in those participants with isolated otolith dysfunction, once a consensus regarding this pathology has been reached.

6.7 Conclusion

Neither whole-brain nor hippocampal volume differences were observed when comparing subjects with BV and healthy controls. Saccular function testing in subjects with preserved semicircular canal function resulted in no significant correlations with hippocampal volume. The association between vestibular dysfunction and an increased risk of cognitive dysfunction may only be present on the behavioral level and may not be expressed at the anatomical level.

Table 13. Supplemental content. Overview per subject of sex, age, hearing level, saccular parameters, and hippocampal volume. All cVEMP latencies lying between the normative ranges of Li et al. (2014) and therefore included in the analyses are shaded in grey. NR indicates no response was found. FI_{high}, Fletcher index high (mean 1 – 2 – 4 kHz, unaided, best hearing ear); cVEMP, cervical vestibular-evoked myogenic potential; MRV, mean rectified voltage; NR, no response.

ID	Sex	Age	FI_{high} best ear	cVEMP right ear					cVEMP left ear					Hippocampal volume
				P13 latency	N23 latency	P-N amplitude	Rectified amplitude	MRV	P13 latency	N23 latency	P-N amplitude	Rectified amplitude	MRV	
1	Female	76-80	43.33	12.3	19.6	165.0	1.10	149.8	13.4	18.0	66.1	0.43	153.4	5.35
2	Female	71-75	21.67	13.2	25.3	159.3	1.20	132.8	14.6	24.1	172.4	1.47	117.4	7.29
3	Female	61-65	33.33	14.3	22.0	62.1	0.51	121.6	15.0	21.9	80.7	0.57	142.5	6.76
4	Female	61-65	33.33	NR	NR	NR	NR	NR	14.0	24.1	107.1	0.69	155.0	6.26
5	Male	76-80	21.67	15.2	22.0	146.7	0.77	190.1	11.6	15.7	67.5	0.38	175.9	9.10
6	Male	66-70	30.00	14.7	24.7	101.6	0.77	131.9	NR	NR	NR	NR	NR	7.07
7	Male	61-65	31.67	16.0	25.2	178.1	1.12	158.5	14.2	24.0	85.7	0.53	162.7	7.13
8	Male	76-80	31.67	14.0	23.8	99.2	0.66	151.4	13.1	19.5	64.3	0.48	132.7	7.98
9	Female	71-75	28.33	NR	NR	NR	NR	NR	12.8	20.8	38.5	0.37	103.5	6.23
10	Male	56-60	6.67	14.0	23.0	130.5	0.88	148.0	14.4	19.7	78.1	0.43	180.5	7.25
11	Female	51-55	15.00	15.7	23.4	71.3	0.53	134.2	12.2	16.9	68.9	0.58	119.1	7.06
12	Female	56-60	21.67	14.8	20.7	62.0	0.56	111.3	13.4	21.0	100.5	0.77	131.3	7.49
13	Female	71-75	15.00	19.3	25.4	71.5	0.48	147.6	15.6	24.3	65.0	0.54	121.4	5.57
14	Male	66-70	25.00	11.2	18.6	108.4	0.69	156.5	14.0	23.4	59.8	0.61	147.9	7.90
15	Male	71-75	28.33	NR	NR	NR	NR	NR	13.2	21.6	69.4	0.77	90.5	5.83
16	Male	56-60	16.67	14.9	21.4	136.3	0.90	150.7	13.1	20.0	140.9	0.69	204.7	7.33

17	Female	66-70	20.00	12.3	23.4	154.8	0.99	156.6	13.1	22.6	184.3	1.02	180.7	6.34
18	Female	66-70	16.67	12.4	22.2	100.5	0.64	156.1	13.4	24.9	163.8	0.98	167.6	7.23
19	Male	81-85	26.67	12.3	20.5	102.5	0.58	176.5	12.7	19.7	151.8	0.84	180.9	5.92
20	Male	71-75	15.00	15.2	21.2	112.0	0.67	168.2	17.3	21.8	84.7	0.54	156.3	6.33
21	Male	61-65	18.33	12.6	22.2	106.2	0.61	173.2	12.0	20.5	128.0	0.81	157.8	7.45
22	Male	61-65	45.00	13.8	22.5	99.6	0.97	103.1	14.0	22.0	148.3	1.08	137.0	6.28
23	Male	81-85	46.67	12.7	22.9	141.0	0.96	147.2	13.1	23.2	97.8	0.59	164.4	5.60
24	Male	71-75	55.00	13.4	23.3	85.0	0.61	139.0	12.7	23.2	130.6	0.87	149.9	6.91
25	Male	56-60	53.33	13.2	20.4	104.6	0.70	149.9	NR	NR	NR	NR	NR	7.94
26	Female	76-80	53.33	12.7	23.0	112.9	0.76	149.2	23.0	30.2	81.3	0.57	141.8	5.40
27	Female	56-60	53.33	13.4	20.8	195.2	1.20	162.7	18.4	24.5	71.2	0.44	161.9	7.63
28	Male	71-75	65.00	14.8	25.3	70.5	0.51	138.0	26.2	35.6	101.4	0.63	160.8	6.41
29	Female	71-75	76.67	16.8	27.9	121.2	0.44	273.2	17.8	24.9	70.3	0.29	241.3	8.54
30	Male	71-75	75.00	12.8	19.1	42.9	0.36	117.7	20.1	28.7	89.5	0.69	129.5	6.34
31	Female	76-80	73.33	15.2	24.9	94.2	0.57	163.9	12.6	20.6	78.3	0.49	160.5	6.96
32	Male	61-65	63.33	19.4	26.7	112.2	0.77	144.9	10.6	18.0	90.2	0.58	155.4	6.03
33	Female	71-75	65.00	9.1	16.7	55.0	0.36	153.6	NR	NR	NR	NR	NR	6.96
34	Male	66-70	73.33	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	6.55

Chapter 7. General discussion

7.1 Research outcomes: synopsis

This doctoral thesis provided important insights in the association between vestibular function, balance, and cognition. An overview of the research outcomes related to the objectives presented in the introduction is provided below.

7.1.1 Objective 1: To evaluate vestibular function in older adults with cognitive impairment

Before evaluating vestibular function in older adults with cognitive impairment, two important preparatory steps were undertaken. First, a study protocol was described and preregistered at ClinicalTrials.gov, providing a detailed description of this prospective longitudinal study on which this dissertation is based. By defining the methods and objectives of this study early on, the intermediate targets as well as the final goal of this study were clear and well thought out.

A second preparatory step involved conducting a systematic review of vestibular function in MCI and AD to provide an overview of previous studies, the knowledge already available, and the resulting knowledge gap. This systematic review included seven articles for analysis, reporting on a total of 235 older adults with impaired cognition (85 subjects with MCI, 150 subjects with AD) and a control group of 481 older adults with preserved cognition. Included articles measured peripheral vestibular end-organ function by use of vHIT, VNG, ENG, cVEMP, and oVEMP. Only the VEMP test demonstrated significantly different results in subjects with AD, more specifically p13 latency and amplitude. Included VOR measurements demonstrated no significant association with cognitive (dys)function. However, the limited number of available studies and the large heterogeneity of outcome measures underscored the importance of reproducing these research outcomes to increase the reliability of its implications.

These two preparatory steps led to the construction of a comprehensive background of available information and knowledge gaps as well as the setup of the final methodology to answer if and how vestibular function is affected in subjects with cognitive impairment, more specifically MCI and AD. Adding clinical balance to this association was a deliberate choice because of its interaction with peripheral vestibular end-organ function, known incidence of imbalance and falls in subjects with AD, and applicability of clinical balance testing in general clinical practice. This study included 33 subjects with MCI, 17 subjects with AD, and 50 age-, sex-, and hearing-matched controls and observed peripheral vestibular end-organ results consistent with the previously conducted systematic review. More

precisely, an increased p13 latency as measured by cVEMP in participants with AD and a preserved horizontal VOR gain as measured by vHIT was observed. As was expected, balance deficits were increasingly prevalent in MCI and AD. Patients with a stronger degree of cognitive impairment demonstrated a reduction in balance, stability, and mobility, as well as an increase in fall risk. A multiple linear regression model to predict cognition (here: RBANS-H total scaled score) was constructed, resulting in sex, cVEMP parameters (p13 latency, n23 latency, and rectified amplitude) and TUG mean time-to-complete adding significantly to the model. Hence, sex, otolith function, and balance function are important factors in predicting cognition via the RBANS-H total scaled score in participants ranging from preserved cognition, MCI, and AD.

7.1.2 Objective 2: To evaluate cognitive performance in older adults with vestibular loss

The second part of this dissertation reversed the previously described association and therefore evaluated cognitive function in subjects with vestibular dysfunction, more precisely BV. Because concomitant hearing loss can affect cognitive function in addition to vestibular loss, hearing status was taken into account in the matching procedure to control for this effect. This cross-sectional study included 34 patients with BV and 34 age-, sex-, and hearing-matched controls. Subjects with BV demonstrated an overall lower score on the RBANS-H total score, indicating general cognitive decline in comparison to controls, most pronounced in the immediate memory, visuospatial cognition, and attention subdomains. On the other hand, language and delayed memory subdomains remained preserved.

To try and pinpoint the vestibular characteristics associated with cognition, multiple vestibular components were explored, including: saccular function (presence of intact cVEMP responses), lateral semicircular canal function (VOR gain as measured by vHIT, rotatory chair, and caloric response), peripheral vestibular end-organ function (amount of Bárány criteria met), clinical balance testing (TUG, POMA, FGA), and questionnaires (DHI, short FES-I, OSQ). Surprisingly, the association between measurements of the peripheral vestibular end-organ (including saccular and semicircular canal measurements) and cognition resulted non-significant. Nonetheless, the only vestibular characteristic significantly associated with cognition in subjects with BV was one clinical balance assessment (the POMA, balance subscale).

7.1.3 Objective 3: To evaluate structural brain imaging results in patients with bilateral vestibulopathy with respect to typical Alzheimer's disease morphologic pathology

In the third part of this dissertation, structural MRI alterations were analyzed in subjects with BV in comparison to healthy controls. To delineate the potential confounding effect of concomitant hearing loss, hearing status was included in the matching procedure. The

structural brain imaging methodology included whole-brain approaches including volumetric measures and surface-based measures, encompassing cortical thickness and sulcus depth analyses. Machine learning using a SVM model was applied as a more sensitive approach to detect differences in each pairwise comparison. In addition to whole-brain measures, dedicated ROI analyses of the hippocampus proper were evaluated. Summarized, neither whole-brain nor targeted hippocampal volume differences were observed when comparing subjects with BV with healthy controls.

Besides evaluating whether whole-brain and hippocampal volume is affected in subjects with BV, the correlation between hippocampal volume and saccular function in subjects with preserved vestibular function was explored. However, hippocampal volume was not associated with the presence of intact saccular responses, nor with cVEMP amplitude, rectified amplitude, n23 latency, or MRV. On the other hand, p13 latency was significantly, positively correlated with hippocampal volume, implying that longer p13 latencies and larger hippocampal volumes are associated with each other. This was surprising, as previous research (among them research included in this dissertation) observed prolonged p13 latencies in AD, a neurodegenerative disease characterized by hippocampal atrophy. As a result, a model was constructed correcting for age. Indeed, the significant (read: spurious) correlation disappeared and could thus be explained by age. In summary, no significant correlations were observed between saccular function testing and hippocampal volume.

7.2 Vestibular loss as a risk factor for Alzheimer's disease: a discussion on supporting and non-supporting evidence

This thesis has focused on the association between vestibular function, balance, and cognition. Recent evidence suggests that vestibular decline is associated with AD and may even contribute to its onset (Agrawal et al., 2020; Bigelow & Agrawal, 2015; Brandt et al., 2005; Semenov et al., 2016; Smith, 2022). Previc (2013) specifies this as the vestibular loss hypothesis. This hypothesis mainly targets the early stages of AD, when patients experience specific difficulties in their topographical memory and orientation. The role of vestibular loss is less clear in more advanced stages of AD, as widespread and pronounced deficits in multiple cognitive domains occurs.

In the following paragraphs, an overview of the evidence described in this thesis supporting or not supporting the vestibular loss hypothesis is provided.

7.2.1 Vestibular reflex (dys)function and Alzheimer's disease

A systematic review by Bosmans et al. (2021) summarized the limited research available on otolith and semicircular canal function measurements in older adults with MCI and AD. Based on data gathered during the *GECkO*-study, Bosmans, Gommeren, Gilles, et al. (2023) evaluated otolith and semicircular canal function in older adults with MCI and AD. A

comparison between results from the systematic review and the data gathered during the *GECkO*-study is provided below.

7.2.1.1 *Alterations in otolith function and the accompanying vestibulocollic reflex*

The systematic review by Bosmans et al. (2021) summarized research on otolith function measurements by use of the cVEMP and oVEMP in older adults with MCI and AD. Data gathered during the *GECkO*-study measured otolith, more precisely saccular, function by use of the cVEMP in older adults with MCI and AD (Bosmans, Gommeren, Gilles, et al., 2023).

The systematic review described that patients with cognitive impairment demonstrated a prolonged **p13 latency** (Birdane et al., 2012). These results were supported by the *GECkO*-study, where patients with AD demonstrated a significantly delayed p13 latency in comparison with the MCI and healthy control group (Bosmans, Gommeren, Gilles, et al., 2023).

In addition, **n23 latency** was not affected in patients with cognitive impairment (MCI and AD combined) as described by the systematic review (Birdane et al., 2012). This finding was supported by data from the *GECkO*-study (Bosmans, Gommeren, Gilles, et al., 2023).

The systematic review demonstrated a significant decrease in **amplitude** in patients with cognitive impairment (MCI and AD combined) (Birdane et al., 2012; Harun, Oh, et al., 2016). However, data from the *GECkO*-study did not find a significant difference in amplitude between healthy controls, MCI, and AD (Bosmans, Gommeren, Gilles, et al., 2023).

Finally, the systematic review observed patients with AD to have a significantly higher **prevalence of bilaterally absent or abnormal cVEMPs** (Harun, Oh, et al., 2016; Wei et al., 2019). Even more, bilaterally absent cVEMPs were described to increase the odds of AD by over three times (Harun, Oh, et al., 2016). However, data from the *GECkO*-study did not find a difference in prevalence of absent or abnormal cVEMPs between controls, MCI, or AD (Bosmans, Gommeren, Gilles, et al., 2023).

In summary, results from the systematic review and the *GECkO*-study were consistent regarding a prolonged p13 latency and a non-affected n23 latency in subjects with MCI and AD. Inconsistent results have been observed regarding amplitude and prevalence of bilaterally absent or abnormal cVEMPs, where previous literature did observe a difference in subjects with cognitive impairment, but where the *GECkO*-study was not able to reproduce these findings.

7.2.1.2 *Alterations in semicircular canal function and the accompanying vestibulo-ocular reflex*

The systematic review by Bosmans et al. (2021) summarized research on semicircular canal function measurements by use of the vHIT, rotatory chair testing, and caloric irrigation in older adults with MCI and AD. Data gathered during the *GECkO*-study measured semicircular canal function by use of the vHIT in older adults with MCI and AD (Bosmans, Gommeren, Gilles, et al., 2023).

Only Wei et al. (2019) observed a significantly lower VOR gain using vHIT in MCI patients compared to healthy controls. However, no significant difference was observed when comparing AD patients and healthy controls. They claim that MCI patients have a level of vestibular impairment that appears to be intermediate between normal cognition and AD. However, two other studies included in the systematic review using vHIT observed no alterations in VOR gain in patients with MCI or AD (Harun, Oh, et al., 2016; Micarelli et al., 2018b). In addition, data gathered during the *GECkO*-study also demonstrated no significant difference in lateral VOR gain as measured by vHIT when comparing healthy controls, MCI, and AD. In fact, a preserved VOR gain was present in all groups (Bosmans, Gommeren, Gilles, et al., 2023). Preserved VOR gains in MCI and AD were confirmed by Chong et al. (1999) using rotatory chair testing and by Nakamagoe et al. (2015) using caloric irrigation testing. In addition, two alternative methods of VOR measurements were performed. First, by comparing the right and left saccade peak velocity, accuracy, and latency between MCI and controls using videonystagmography (Baydan et al., 2020). None of these measurements resulted in significant differences between MCI and controls. Second, by evaluating the suppression rate during visual suppression during caloric irrigation (Nakamagoe et al., 2015). Here, a significantly lower suppression rate was observed in patients with AD compared to healthy controls.

In summary, alterations in VOR gain as measured by standardized tests such as vHIT, caloric irrigation, and rotatory chair testing are mainly absent when comparing healthy controls, MCI, and AD patients. Results from previous literature and the current *GECkO*-study are mostly consistent.

7.2.1.3 *A short discussion on vestibular reflex (dys)function in Alzheimer's disease*

In brief, we have observed mainly consistent results on vestibular reflex (dys)function in patients with MCI and AD in comparison with healthy controls. More precisely, we have observed a prolonged latency of the p13 component and a non-affected latency of the n23 component as measured by the cVEMP, as well as a preserved VOR gain as measured by vHIT, caloric irrigation, and rotatory chair testing. However, results regarding the amplitude and prevalence of absent or abnormal cVEMPs remain inconsistent.

Is it possible to observe alterations in the VCR while the VOR remains preserved? This question is also described in the discussion section of Bosmans et al. (2021), but will here be reviewed and explained further in short.

If vestibular dysfunction in AD was caused by vestibular hair cell loss or degeneration of the vestibular nerve, we would expect a deficient VOR together with a deficient VCR. However, succinctly, the VOR is not affected in AD. As such, we may argue that deficits occur in the afferent vestibular pathway following the vestibular nerve. We know that vestibular information transmitted from the brainstem vestibular nucleus projecting to the motoneurons involved in the VOR is segregated from vestibular information which is transmitted to higher areas of the brain (such as the thalamus, posterior insular cortex, inferior parietal cortex, intraparietal sulcus, and temporo-parietal junction) for spatial orientation and general cognitive processing (Cullen, 2012; Harun, Oh, et al., 2016; Smith, 2013). By this logic, it may be hypothesized that otolith, and in particular saccular, projections to higher brain structures undergo anterograde degeneration in AD, hence being accompanied by an impaired VCR together with difficulties in spatial awareness and spatial memory, but leaving the VOR intact (Harun, Oh, et al., 2016; Smith, 2013).

Furthermore, one may explore the brainstem and cerebellar importance in vestibular reflex (dys)function in AD. Brainstem pathology may be fairly widespread in AD and may precede cortical degeneration (Dutt et al., 2021; Grinberg et al., 2011; Previc, 2013). Baloyannis et al. (2000) observed extensive deafferentation within the cerebellum and brainstem vestibular pathways. The cerebellum together with the vestibular nucleus complex, located in the brainstem, are involved in multiple vestibular pathways projecting cortically. Hence, it may be hypothesized that this deafferentation within the cerebellum and brainstem vestibular pathways may account for anterograde degeneration. However, an exact description of where and in which of the vestibular pathways involved in cognition this anterograde degeneration occurs, has yet to be determined.

7.2.2 Balance and Alzheimer's disease

Data gathered from the *GECkO*-study evaluated clinical balance in MCI and AD participants by use of the TUG, FGA, and POMA-B (Bosmans, Gommeren, Gilles, et al., 2023). Participants with cognitive impairment (MCI and AD combined) took significantly longer to successfully complete the TUG. A similar pattern was observed in performance on the FGA, where participants with cognitive impairment (MCI and AD combined) again scored significantly worse in comparison to healthy controls. Both the TUG and FGA thus observed a decline in balance in the earlier stages of cognitive decline, hence during the conversion from preserved cognition to MCI. In contrary, significantly worse scores on the POMA-B were observed in AD participants, where the MCI and healthy control participants obtained equivalent scores. The POMA-B could thus be preferred in the more advanced stages of the AD due to its ceiling effect in preserved cognition and MCI. Overall, we have observed more prevalent balance deficits in groups with increasing cognitive decline along the AD

continuum. Hence, the more severely the AD pathology is pronounced, the more difficulties patients will have with balance, mobility, stability, together with a higher fall risk. Results from the *GECkO*-study are in line with previous literature. In general, people with AD have more trouble with maintaining balance and demonstrate gait abnormalities and falls, often resulting in fractures (Biju et al., 2022b; Dev et al., 2021; Dyer et al., 2020).

7.2.2.1 *My personal experience in evaluating balance in Alzheimer's disease*

A recent study compared performance on the TUG and its subtasks (sit-to-stand, walking forward, turn, walking back, and turn-to-sit) using kinematic data between healthy controls, MCI, and AD (Ansai et al., 2019). All subtasks were able to differentiate participants with AD from healthy controls, except the sit-to-stand subtask. Results on the sit-to-stand subtask were similar in healthy controls, MCI, and AD. The MCI group performed equivalent to AD in the walking forward subtask, and equivalent to healthy controls in the walking back, turn, and the turn-to-sit subtasks. Even though this study focused on mobility patterns and not solely on the time-to-complete as we did in the *GECkO*-study, this study supports and extends the hypothesis of a decline in mobility and gait along the AD continuum. Even more, this study substantiates my overall experience with TUG testing in participants with AD. Participants did not only take longer to complete the test, they were also observed to be more unstable. In particular during the turn-to-sit subtask, it was noticeable that AD participants did not sit down carefully and safely. On the contrary, they dropped themselves in the chair, which sometimes led to unsafe situations. It appeared that they had more trouble with correctly estimating at what distance and depth the seat of the chair was positioned relative to themselves. It felt that they often thought the seat of the chair was closer and higher, and that they could then safely sit down. However, that was often not the case and it looked like first they lowered themselves safely and then for the final centimeters fell into the chair. Even though my experience is not based on objective data, studies using kinematic data (such as the study by Ansai et al. (2019)) could provide a greater understanding on the mobility patterns along the AD continuum and could provide guidelines regarding (vestibular) physical therapy.

7.2.2.2 *(Vestibular) physical therapy in Alzheimer's disease*

Because of the increased balance impairment and vestibular alterations observed in people with AD, they could benefit from (vestibular) physical therapy or other exercise programs targeting balance and mobility aiming at reducing fall risk. However, a recent retrospective study evaluating physical and vestibular physical therapy referrals in people with AD observed that only 6.0% of individuals were referred to physical therapy and only 0.6% to vestibular physical therapy (Gandhi et al., 2020). This is an important finding and adds to the clinical relevance of this PhD dissertation. Raising awareness of vestibular and balance dysfunction as well as the importance of providing rehabilitation services in AD is important. People with AD and their caregivers would benefit from reducing balance problems to avoid unnecessary injuries a fall could cause.

7.2.3 Cognition and bilateral vestibulopathy

Data from the *GECkO*-study evaluated cognition by use of the RBANS-H in older adults with diagnosed BV. In general, participants with BV obtained lower total scores on the RBANS-H in comparison with healthy controls. In addition, participants with BV obtained lower scores on the RBANS-H subdomains of immediate memory, visuospatial cognition, and attention. No significant difference was observed on the RBANS-H subdomains of language and delayed memory between BV participants and healthy controls (Bosmans et al., 2022).

In general, these results support the hypothesis of vestibular loss as a risk factor for cognitive decline, in particular cognitive decline of the AD type as the cognitive difficulties are most pronounced in the subdomains of memory, attention, and visuospatial cognition.

7.2.3.1 *The use of the RBANS-H in a non-demented population from a neuropsychological point of view*

The RBANS-H total score was the primary outcome measure for evaluating cognition in patients with BV. In the following paragraphs, the advantages and disadvantages of using the RBANS(-H) will be discussed as a neuropsychological assessment tool in a non-demented population.

7.2.3.1.1 Advantages

A major advantage of the RBANS is that it takes **± 30 minutes to complete** and within that timeframe, an overview of global cognition and the general cognitive subdomains (immediate and delayed memory, visuoconstruction, language, and attention) is provided. In clinical practice, time is sparse so efficient testing is of utmost importance. The creator of the RBANS, prof. Randolph, felt this to be important to maximize patient cooperation and minimize effects of fatigue on performance (Randolph et al., 1998).

A second advantage of the RBANS is the availability of **parallel versions**, which are equivalent versions to avoid practice effects when repeating the test multiple times, for example during longitudinal studies, when evaluating disease progression, or screening for improvements as a result from therapeutic interventions.

A third advantage of the RBANS is the **standardization of results**. The total score is provided in scaled scores, which follow the distribution of the Wechsler IQ test with a mean of 100 and SD of 15. The total score can also be converted to percentile scores, which are often used in neuropsychological assessments in clinical practice. All total scores per subdomain are standardized in scaled scores and percentiles. Even more, this is also the case for the scores per subtask. As such, raw scores can be converted to standardized values, normed per age range.

A fourth advantage is specifically applied to the **RBANS-H**. The RBANS-H (Claes et al., 2016) is adapted from the original RBANS (Randolph et al., 1998). Most neuropsychological assessments are inappropriate in evaluating cognition in hearing-impaired individuals. However, especially when testing older adults, hearing loss is quite common. For example, if someone could only repeat 2 words out of a list of 10, is it because they could not remember the other 8 or because they did not hear them? As such, the RBANS-H was developed based on the RBANS, but adjusted to test hearing-impaired subjects. The RBANS-H uses exactly the same stimuli as the RBANS, additionally providing an accompanying slideshow presentation shown on an external computer screen. As such, oral instructions are supported by written explanations and stimuli are not only presented orally but also visually (Claes et al., 2016). As a result, if someone could only repeat 2 words out of a list of 10, we now know it is because they could not remember the other 8 words.

7.2.3.1.2 Disadvantages and suggestions

Randolph et al. (1998) wanted to design the RBANS such that the level of difficulty was appropriate for evaluating cognition in older adults ranging from preserved cognition to moderately severe dementia. They stated that existing tests are excessively difficult, while tests specific for the demented population are insensitive to detect milder forms of cognitive impairment. With the development of the RBANS, they wanted to bridge this gap. However, using the exact same test battery in preserved cognition as well as in a demented population comes with certain challenges and hence, "bridging this gap" is not that evident. The RBANS is an appropriate test in evaluating cognition when expecting a mild or moderately severe cognitive impairment, but certain subtasks may be less suitable for older adults with preserved cognition. Older adults with preserved cognition would benefit from more difficult subtasks to avoid ceiling effects and to be able to differentiate between average, better-than-average, and less-than-average cognitive performance.

For example, let's take a closer look at results from the *GECkO*-study at baseline in healthy controls (n=75) without hearing, vestibular, or cognitive impairment. A total overview can be found in Table 14. Some subtasks are suitable in evaluating cognition in older adults with preserved cognition, such as the semantic fluency subtask for evaluating language, and the digit span and coding subtasks for evaluating attention, working memory, and executive functioning. However, for some of the other subtasks, suggestions can be made. As many different tests and alternative forms exist, only one example is given to keep this discussion (relatively) succinct.

Regarding the **immediate memory** subdomain, a ceiling effect can be observed in both subtasks (list learning and story memory). To accentuate this ceiling effect, the final repetitions (4^{th} and 2^{nd}, respectively; because of the most pronounced negative skewness) and their statistics are presented in Table 14. For list learning, a list of 15 words instead of the current list of 10 words would be able to provide more interesting individual learning curves. For example, the 15 words of the Rey Auditory Verbal Learning Test (RAVLT) would

be a good alternative (Bean, 2011). For story memory, a longer story with more text elements that need to be reproduced would be of added value, for example the subtest logical memory of the Cognitieve Testbatterij voor Senioren (COTESS) (Dierick et al., 2014). These alternatives could also be applied when evaluating **delayed memory**. For example, the RAVLT also provides a recognition trial for delayed memory.

Accurately measuring **visuoconstruction/visuospatial cognition** is a challenge in pen-and-paper tasks. However, with the figure copy and line orientation subtasks, it can be argued that a decent balance between time efficiency and specificity is obtained. An alternative for the figure copy subtask could be the original Rey–Osterrieth Complex Figure (ROCF). However, due to the stringent correction method we follow, ceiling effects for the RBANS complex figure are not too pronounced. Alternatives for measuring visuoconstruction/visuoperception in general could consider subtasks from the Visual Object and Space Perception Battery (VOSP) (Warrington & James, 1991), for example the cube analysis subtask.

The most pronounced ceiling effect is present in the picture naming subtask of the **language** cognitive domain. Almost all participants (73/75 healthy controls; 97.33%) obtained a perfect score. A suggestion of using the more difficult images of the Boston Naming Test (BNT; e.g. a protractor, tripod, or sphinx) could be made (Kaplan et al., 1983). However, people with preserved cognition seldom complain from extensive word-finding problems, which may also result in a ceiling effect even when including more difficult pictures to name. It would be more interesting to compare results from semantic word fluency with phonetic word fluency. As such, I think it would be of added value to add at least one phonetic category in the test battery, for example based on the Controlled Oral Word Association Test (COWAT) (Benton et al., 1994).

As previously mentioned, subtasks included in the **attention** cognitive domain appear to be adequate in evaluating attention. Many alternatives for measuring attention exist, however there is no need to further discuss alternatives as the currently used tasks are suitable.

Table 14. Baseline data on the RBANS-H from the *GECkO*-study in healthy older adults (n=75).

Cognitive domain/subtask	Maximum score available	Range	Median	Mean	SD	Shape of distribution around the mean
Immediate memory						
List learning, 4th repetition	10	7-10	9.0	9.0	0.9	Negatively skewed
Story, 2nd repetition	12	7-12	12	11.4	1.0	Negatively skewed

Index score	NA	78-140	114	114.2	11.4	Normal
Visuoconstruction						
Figure copy	20	12-20	17	17.2	2.3	Negatively skewed
Line orientation	20	9-20	18	17.8	2.0	Negatively skewed
Index score	NA	66-131	102	101.7	14.7	Normal
Language						
Picture naming	10	9-10	10	10	0.2	Negatively skewed
Semantic fluency	NA	11-34	22	22.4	4.9	Normal
Index score	NA	85-128	102	104.3	10.0	Normal
Attention						
Digit span	16	6-16	10	10.0	1.8	Normal
Coding	NA	31-68	48	47.4	8.5	Normal
Index score	NA	72-138	103	102.3	12.5	Normal
Delayed memory						
List recall	10	0-10	7	6.9	2.1	Normal
Story recall	12	5-12	11	10.2	1.4	Negatively skewed
Figure recall	20	4-20	13	13.1	3.6	Normal
List recognition	20	18-20	20	19.7	0.5	Negatively skewed
Index score	NA	81-130	103	106.0	9.1	Normal
Total RBANS-H						
Scaled score	NA	87-141	107	107.7	10.6	Normal
Percentile	100	19-99.7	68	65.9	20.4	Negatively skewed

In general, providing alternatives for subtasks is easy but gathering the same amount of information the RBANS(-H) provides in the same amount of time is a more challenging task. As such, a trade-off between using a full existing test battery or performing a self-constructed combination of parts of neuropsychological tests needs to be made, with each having its own advantages and disadvantages regarding time to complete, standardization, target audience etc. In addition, the choice will also depend on whether the test will be used for individual neuropsychological assessments or as a standardized outcome measure in research.

7.2.4 Whole-brain and hippocampal anatomical changes and bilateral vestibulopathy

Data from the *GECkO*-study evaluated whole-brain and hippocampal volume in subjects with BV, which are known for their deficit in semicircular canal functioning. However, no significant differences were observed in volumetric or surface-based measures. Furthermore, the association between otolith function and hippocampal volume was explored in subjects with preserved semicircular canal function. Similarly, no significant differences were observed (Bosmans, Gommeren, zu Eulenburg, et al., 2023).

The absence of finding anatomical alterations in whole-brain or hippocampal volume in BV may be seen as a positive or a negative outcome. The **positive outcome** is mostly directed at the BV population themselves as no whole-brain or hippocampal atrophy was observed. Hippocampal atrophy is one of the main characteristics of AD, and observing hippocampal atrophy in BV patients would thus imply that they are at an increased risk for AD. However, cognitive deficits (global as well as immediate memory, visuospatial, and attention) were found in patients with BV. As such, it would be expected that these behavioral deficits would also translate to anatomical changes. No differences in whole-brain or hippocampal volume were found, but there is so much more to explore. As such, the **negative outcome** is that there is still a lot more to explore and that the exact location or architecture of anatomical change has yet to be determined, if there even is any.

7.2.4.1 *Structure-function dissociation*

Because of the observed absence of hippocampal atrophy in BV, the hypothesis arises that there may be a **structure-function dissociation** whereby functional changes may take place sooner or even despite any corresponding structural brain changes (Dordevic et al., 2021).

However, using fMRI and even resting-state fMRI comes with certain challenges. Structural MRI is currently used in medical practice, for example as an aid in certain diagnostic processes. The advantage of using structural MRI is that the preprocessing and analysis steps are “relatively” transparent such that different researchers will observe quite similar results when given the exact same data. However, because of the multitude of options in the set-up of the fMRI paradigm, preprocessing, dealing with artifacts, statistics, correcting for multiple comparisons, interpretation of results, and so much more, a straightforward pipeline from start to finish is not that obvious. Even though fMRI definitely has potential in aiding the diagnostic process, caution is warranted and transparency about the methods used is recommended.

7.2.5 The vestibular loss hypothesis: balancing the evidence

A succinct summary of previously described and discussed results in light of the vestibular loss hypothesis is provided below.

Results supporting the vestibular loss hypothesis:

- Alterations in otolith function (with the accompanying VCR) are observed along the AD continuum, together with a preserved semicircular canal function (with the accompanying VOR). This discrepancy is possible because of distinctive vestibular pathways and a probable anterograde deterioration of the pathways projecting to higher cortical areas involved in spatial orientation and navigation.
- Balance difficulties are observed along the AD continuum, with more pronounced balance difficulties in more advanced stages of AD. These balance difficulties result in an accompanying decrease in mobility and higher risk of falls and fractures.

- General cognitive difficulties have been observed in BV, which were most pronounced in the subdomains of immediate memory, visuoconstruction, and attention.

Results not supporting the vestibular loss hypothesis:

- Observed absence of whole-brain and hippocampal volumetric changes in patients with BV.

7.3 The importance of including hearing loss when evaluating cognition and vestibular function

The impact of hearing loss on cognition and dementia gains importance. However, what appears to be an auditory contribution to cognitive loss may actually be partly vestibular in nature and vice versa. Because of the close anatomical relationship between auditory and vestibular structures of the inner ear, hearing loss and vestibular dysfunction are often presented together. In addition, certain otological disorders may present with co-existing auditory and vestibular symptoms, such as in Ménière's disease and DFNA9. Furthermore, the auditory and vestibular systems interact in the central nervous system, for example, the brainstem vestibular nucleus and dorsal cochlear nucleus project to each other (Smith, 2012).

In this section, the importance of including hearing loss when evaluating both cognition and vestibular function will be discussed. The two-way theoretical association between hearing loss and cognition or hearing loss and vestibular function will not be discussed here, as they are already the topic of recent literature, for example the high-impact paper of Livingston et al. (2020) on hearing loss as a modifiable risk factor for dementia, and the review paper of Seiwerth (2023) on the interaction between hearing and balance.

It is important to know the degree of hearing loss that is present in our patient populations, in this case patients with cognitive impairment (MCI and AD) and patients with vestibular loss (BV). This will aid in evaluating the importance of keeping hearing loss into account for research purposes as well as in clinical practice.

7.3.1 Sensorineural hearing loss in patient populations of the *GECkO*-study

In this section, the prevalence of sensorineural hearing loss will be described in the patient populations of the *GECkO*-study, more precisely the patient population with cognitive loss (MCI and AD) as well as the patient population with vestibular loss (BV, further subdivided into BV patients with DFNA9 and BV patients without DFNA9). A summary of their hearing statistics can be found in Table 15. These patient groups were recruited based on their cognitive and vestibular function, respectively, without specifically including them based on

their hearing parameters (for full transparency: implanted hearing devices were an exclusion criterion). As such, when extrapolating information from these small groups, results are representative for the hearing status of these general patient populations.

7.3.1.1 *Sensorineural hearing loss in MCI and AD participants of the GECkO-study*

In the MCI group (n=35), based on the FI_{high} of the best hearing ear, 18 persons (51.4%) had normal hearing (≤40 dB HL), 13 persons (37.1%) had moderate SNHL (41-60 dB HL), and 4 persons (11.4%) had severe SNHL (>60 dB HL). In the AD group (n=17), 7 persons (41.2%) had normal hearing, 9 persons (52.9%) had moderate SNHL, and 1 person (5.9%) had severe SNHL. The MCI and AD groups did not differ significantly on the FI_{high} of the best hearing ear (p = .8422), SPIN in free field best aided (p = .9453), and the percentage of people wearing at least one hearing aid (p = .1530).

Hearing results of the MCI and AD groups of the *GECkO*-study can be compared to published data of United States citizens aged 50 years and older using a 4-frequency (0.5 kHz, 1 kHz, 2 kHz, 4 kHz) PTA (Goman & Lin, 2016). Hearing results of the MCI and AD groups are here recalculated to also reflect the 4-frequency PTA instead of the previously used FI_{high} to be able to make a direct comparison with the published study. Patients with MCI and AD demonstrated a general higher prevalence of moderate sensorineural hearing loss than was observed in the representative general population of older adults (normal hearing: 57.9% in US citizens versus 51.4% in MCI and 52.9% in AD; moderate SNHL: 35.0% in US citizens versus 40.0% in MCI and 47.1% in AD; and severe SNHL: 7.0% in US citizens versus 8.6% in MCI and none in AD).

The importance of taking potential hearing loss into account when working with MCI and AD patients needs to be highlighted. Neuropsychological assessments in dementia testing need to be adapted to account for this higher prevalence of hearing loss. As such, the implementation of neuropsychological tests adjusted for the hearing-impaired population such as the RBANS-H are recommended for use in clinical practice.

7.3.1.2 *Sensorineural hearing loss in BV participants of the GECkO-study*

In the BV group (n=38), 17 persons (44.7%) had normal hearing, 9 persons (23.7%) had moderate SNHL, and 12 persons (31.6%) had severe SNHL based on the FI_{high} of the best hearing ear. The etiology of BV is DFNA9 in 12 persons (31.6%). As such, evaluating hearing status in this BV population will result in an overestimation because of the high prevalence of DFNA9 patients in the *GECkO*-study. It is therefore of added interest to divide the BV group in a BV due to DFNA9 group and a BV not due to DFNA9 group when interpreting hearing status.

In the BV due to DFNA9 group (n=12), 1 person (8.3%) had normal hearing, 2 persons (16.7%) had moderate SNHL, and 9 persons (75.0%) had severe SNHL. In the BV not due to DFNA9 group (n=26), 16 persons (61.5%) had normal hearing, 7 persons (26.9%) had moderate

SNHL, and 3 persons (11.5%) had severe SNHL. As was expected, the BV due to DFNA9 group presented with a considerable higher severity of hearing loss. However, the BV not due to DFNA9 group was also not exempt from hearing loss. As such, when evaluating cognition in a BV population, either with or without DFNA9, concomitant hearing loss needs to be taken into account.

7.3.2 How to disentangle the individual impact and interaction of both hearing and vestibular loss on cognition?

It would be very interesting to delineate to which extent cognition is affected by hearing loss, vestibular dysfunction, and their interaction. To answer this question, the DFNA9 population is the ideal candidate because of their known and well-described decline in both hearing and vestibular function (Janssens de Varebeke et al., 2021a, 2021b). In ideal circumstances, the sole effect of hearing loss could be evaluated by comparing DFNA9 patients to healthy controls additionally matched on their vestibular function, vice versa the sole effect of vestibular loss could be evaluated by comparing DFNA9 patients to healthy controls additionally matched on their hearing function. However, this proposed study design comes with certain challenges. It is for example very difficult to match a healthy control subject to a DFNA9 patient on either hearing or vestibular function because of the fast age-related decline in hearing and vestibular function. Very little healthy controls will present with such severe degrees of acquired hearing or vestibular loss at such young ages, making it extremely difficult to recruit eligible control subjects. As Gommeren et al. (2022) discussed, our current best option is to rely on available literature reporting on the separate effect of hearing loss or vestibular decline on cognition. Another option is to look at longitudinal data, such as the current *GECkO*-project of which currently only baseline data are published, as well as the upcoming results from the longitudinal study by Danneels et al. (2020). In any case, it is paramount for forthcoming studies to always include hearing level as a covariate when evaluating vestibular function and cognition.

Table 15. Hearing parameters in patient populations. Patients with cognitive impairment encompass the MCI and AD groups. Patients with BV are presented as one total group as well as divided into the DFNA9 subgroup and the non-DFNA9 subgroup. For transparency reasons, results from the SPIN best aided in free field as well as the use of at least one hearing aid are presented. MCI, Mild Cognitive Impairment; AD, Alzheimer's disease; BV, bilateral vestibulopathy; DFNA9, DeaFNess Autosomal Dominant 9; FI_{high}, Fletcher Index high; dB HL, decibel hearing level; SD, standard deviation; SPIN, Speech-In-Noise; SRT, speech reception threshold.

Hearing parameter	MCI (n=35)	AD (n=17)	BV (n=38)	BV due to DFNA9 (n=12)	BV not due to DFNA9 (n=26)
FIhigh best ear (dB HL)					
Mean (SD)	40.4 (18.7)	39.4 (13.3)	44.7 (22.4)	63.3 (18.0)	36.1 (18.9)
Median	38.3	43.3	48.3	68.3	32.5
Range	6.7, 76.7	11.7, 61.7	5.0, 78.3	11.7, 78.3	5.0, 70.0
SPIN best aided (SRT)					
Mean (SD)	-0.3 (4.4)	-0.2 (2.1)	0.3 (5.5)	5.1 (6.0)	-2.0 (3.4)
Median	-2	0	-1.7	5.2	-2.7
Range	-6, 12.3	-5.6, 3.0	-6.3, 14.3	-2.3, 14.3	-6.3, 7
Hearing aid use					
Yes/no	13/22	3/14	19/19	11/1	8/18

7.4 Applications in clinical practice

Translating (fundamental) research into clinical practice is an important step in the scientific process. As such, this doctoral thesis provides recommendations for clinical practice based on its results.

When working with MCI and AD patients, the use of the cVEMP and in particular its p13 latency as a measure of saccular function can aid in the early identification of people at risk for MCI and AD as an additional parameter to the current diagnostic process. Furthermore, clinical balance testing should gain awareness. Due to time constraints in clinical practice, the TUG is recommended because of its time-efficiency, simplicity, feasibility to conduct in a small consulting room, and most sensitive balance parameter across the AD continuum, with already a decline in performance happening before a diagnosis of MCI was made. Finally, potential hearing loss has to be taken into account when working with older adults (as is often the case in MCI and AD patients) and the neuropsychological assessment needs to be adapted to ensure adequate evaluation of cognition. As such, the RBANS-H is recommended to use in patients with hearing loss.

When working with BV patients, it is recommended to include a cognitive evaluation as some people may be at higher risk for MCI and may need an extensive neuropsychological evaluation. As such, these patients can be identified early and further steps necessary to preserve cognition can be undertaken. Furthermore, it can be hypothesized that vestibular rehabilitation to improve central compensation may have a positive effect on cognition. Finally, given the broad spectrum of nonmotor symptoms, it can be hypothesized that cognitive rehabilitation may aid in preserving cognition. However, future research is needed to substantiate these hypotheses.

7.5 Future perspectives

When discussing previous results, a few suggestions for future perspectives have already been given and are summarized here.

To further evaluate **vestibular function in AD**, the current study could benefit from adding utricular function measurements to the protocol by means of the oVEMP. As such, functioning of the entire peripheral vestibular end-organ can be mapped in subjects with MCI and AD. In addition, studies evaluating **balance in AD**, for example by using kinematic data to provide an in-depth characterization of mobility patterns, are of added value in providing guidelines regarding (vestibular) physical therapy to reduce falls and to maintain the maximum possible quality of life for as long as possible. It will be interesting to follow updates on the forthcoming (pilot) randomized controlled trial applying vestibular therapy in AD to reduce falls (Yesantharao et al., 2022).

To gain a detailed overview of the **preserved as well as affected cognitive domains and subdomains in BV**, more specified and extensive neuropsychological tasks are recommended. As such, ceiling effects are avoided and a detailed cognitive profile can be obtained. Results from this detailed cognitive evaluation can be used to make treatment recommendations, for example cognitive rehabilitation. A computational perspective of cognitive rehabilitation in BV can be found in Ellis et al. (2018).

To identify **potential brain changes in BV**, multiple suggestions can be made. For example, future studies may want to explore the role of the brainstem and cerebellum in BV, and potential structural or functional alterations in these brain areas. Furthermore, future studies including subjects with BV may want to look at a structure-function dissociation, where functional changes may take place earlier or even in the absence of any structural changes. Finally, future studies may focus on a different population with vestibular pathology. As BV is primarily focused on semicircular canal dysfunction, and areas involved in spatial orientation (such as the hippocampus) may rather be associated with otolith function, it will be interesting to evaluate whole-brain and hippocampal morphology and functional connectivity in patients with otolith dysfunction.

Finally, all future studies evaluating the association between vestibular, balance, and cognition should **include hearing level** as an important covariate.

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Curriculum Vitae

Joyce Bosmans was born on September 20th, 1995, in Diest, Belgium. She graduated cum laude as a Master in Clinical and Health Psychology in 2019 at KU Leuven. Her Master's thesis focused on the role of body partonomics and biological class in the representation of animacy in the ventral visual pathway. Her Master's internship featured primarily neuropsychological diagnostics of psycho-organic disorders in older adults. She chose this thesis and internship because of her fondness for neuroscience. In October of 2019, she started her PhD at the University of Antwerp under the joint supervision of prof. dr. Vincent Van Rompaey, prof. dr. Griet Mertens, and prof. dr. Patrick Cras. The work performed during her PhD is funded by a Fonds voor Wetenschappelijk Onderzoek (FWO) Fundamental Research Project (FWO grant number G042819N). Joyce's PhD research focuses on the association between vestibular function, balance, and cognition in older adults. Her main research interests are dementia, balance, and human brain imaging. She enjoys communicating her research via publications in scientific journals as well as via science popularizing outreach channels to the broader audience.

Publications

Related to this doctoral thesis

Bosmans, J., Jorissen, C., Cras, P., Van Ombergen, A., Engelborghs, S., Gilles, A., Princen, E., Moyaert, J., Mertens, G., & Van Rompaey, V. (2020). Impact of hearing loss and vestibular decline on cognition in Alzheimer's disease: a prospective longitudinal study protocol (Gehoor, Evenwicht en Cognitie, GECkO). *BMJ Open, 10*(9), e039601. https://doi.org/10.1136/bmjopen-2020-039601. Q2 journal.

Bosmans, J., Jorissen, C., Gilles, A., Mertens, G., Engelborghs, S., Cras, P., Van Ombergen, A., & Van Rompaey, V. (2021). Vestibular Function in Older Adults With Cognitive Impairment: A Systematic Review. *Ear And Hearing*, *42*(5), 1119-1126. https://doi.org/10.1097/aud.0000000000001040. Q1 journal.

Bosmans, J., Gommeren, H., Mertens, G., Cras, P., Engelborghs, S., Van Ombergen, A., Vereeck, L., Gilles, A., & Van Rompaey, V. (2022). Associations of Bilateral Vestibulopathy With Cognition in Older Adults Matched With Healthy Controls for Hearing Status. *JAMA Otolaryngology- Head & Neck Surgery, 148*(8), 731. https://doi.org/10.1001/jamaoto.2022.1303. Q1 journal.

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Unrelated to this doctoral thesis

First author

Bosmans, J. & Gommeren, H., Cardon, E., Mertens, G., Cras, P., Engelborghs, S., Van Ombergen, A., Gilles, A., Lammers, M.J.W., & Van Rompaey, V. (2021). Cortical Auditory Evoked Potentials in Cognitive Impairment and Their Relevance to Hearing Loss: A Systematic Review Highlighting the Evidence Gap. *Frontiers in Neuroscience, 15*. https://doi.org/10.3389/fnins.2021.781322. Q2 journal.

Co-author

Ritchie, J. B., **Bosmans, J.**, Sun, S., Verhaegen, K., Zeman, A., & De Beeck, H. O. (2019). The role of body partonomics and biological class in the representation of animacy in the ventral visual pathway. *Journal of Vision*. https://doi.org/10.1167/19.10.114. Q3 journal.

Ritchie, J. B., Zeman, A., **Bosmans, J.**, Sun, S., Verhaegen, K., & op De Beeck, H. (2021). Untangling the Animacy Organization of Occipitotemporal Cortex. *The Journal of Neuroscience, 41*(33), 7103–7119. https://doi.org/10.1523/jneurosci.2628-20.2021. Q1 journal.

Van Rompaey, V., Gommeren, H., **Bosmans, J.**, Verdoodt, D., JanssensdeVarebeke, S. P. F., De Vrieze, E., Pennings, R. J., Van De Berg, R., Lammers, M. O., Vanderveken, O. M., Fransen, E., Van Camp, G., & Van Wijk, E. (2022). Pathogenic Variants in the COCH Gene That Lead to Hearing Loss and Vestibular Deficit: Update on DFNA9 and Introducing DFNB110. *B-ENT, 18*(4), 273–283. https://doi.org/10.5152/b-ent.2022.21791

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Andries, E., **Bosmans, J.**, Engelborghs, S., Cras, P., Vanderveken, O. M., Lammers, M. J. W., Van De Heyning, P. H., Van Rompaey, V., & Mertens, G. (2023). Evaluation of Cognitive Functioning Before and After Cochlear Implantation in Adults Aged 55 Years and Older at Risk for Mild Cognitive Impairment. *JAMA Otolaryngology- Head & Neck Surgery*. https://doi.org/10.1001/jamaoto.2022.5046. Q1 journal.

Gommeren, H., Moyaert, J., **Bosmans, J.**, Mertens, G., Cras, P., Engelborghs, S., Van Ombergen, A., Gilles, A., Van Dam, D., & Van Rompaey, V. (2023). Cognition and Auditory-Evoked Potentials in DFNA9 Patients: From Normal Function to Adults-Onset Otovestibular Decline – A Prospective Longitudinal Study Protocol. *BMJ Open.* Accepted for publication. Q2 journal.

Grants

Doctoral fellowship at the Faculty of Medicine and Health Sciences, University of Antwerp, funding: patrimony; 01/02/2022 – 31/12/2022.

FWO Grant for participation in a conference abroad, XXXV World Congress of Audiology (WCA); 10-13/04/2022, Warschau, Poland. How bilateral vestibulopathy affects cognition in older adults matched for hearing status.

FWO Grant for a long stay abroad, Ludwig-Maximilian-Universität München; 06/03/2023 – 29/04/2023, Munich, Germany. Unraveling the neural correlates of vestibular loss as a risk factor for Alzheimer's disease: an in-depth understanding of state-of-the-art MRI techniques.

FWO Grant for participation in a conference abroad, 16th Congress of European Federation of Audiology Societies (EFAS); 3-6/05/2023, Sibenik, Croatia. Evidence of vestibular and balance dysfunction in patients with Mild Cognitive Impairment and Alzheimer's disease.

FWO Grant for participation in a conference abroad, 8th Scientific Meeting of the Federation of the European Societies of Neuropsychology (FESN); 27-29/09/2023, Thessaloniki, Greece. Associations of Bilateral Vestibulopathy With Cognition in Older Adults Matched With Healthy Controls for Hearing Status.

Presentations

Oral presentations

Congress of the Belgian Society of ORL, Head and Neck Surgery (B-ORL); 07/03/2021, Antwerp, Belgium (online). Vestibular (dys)function in older adults with cognitive impairment.

15th Congress of European Federation of Audiology Societies (EFAS); 20-21/05/2021, Oldenburg, Germany (online). Vestibular (dys)function in older adults with cognitive impairment.

XXXV World Congress of Audiology (WCA); 10-13/04/2022, Warschau, Poland. How bilateral vestibulopathy affects cognition in older adults matched for hearing status.

XXXI Bárány Society Meeting; 9-11/05/2022, Madrid, Spain. How bilateral vestibulopathy affects cognition in older adults corrected for hearing status.

LOK cognitie; 27/06/2022, Antwerp, Belgium. Impact van vestibulaire functie op cognitie.

Researchdag TNW-NKO; 15/10/2022, Antwerp, Belgium. Evenwicht en cognitie.

16th Congress of European Federation of Audiology Societies (EFAS); 3-6/05/2023, Sibenik, Croatia. Evidence of vestibular and balance dysfunction in patients with Mild Cognitive Impairment and Alzheimer's disease.

NEUROday; 12/05/2023, Antwerp, Belgium. The human vestibular network.

8th Scientific Meeting of the Federation of the European Societies of Neuropsychology (FESN); 27-29/09/2023, Thessaloniki, Greece. Associations of Bilateral Vestibulopathy With Cognition in Older Adults Matched With Healthy Controls for Hearing Status.

Poster presentations

Association for Research in Otolaryngology 46th Annual MidWinter Meeting; 11-15/02/2023, Orlando, Florida, USA. Evidence of vestibular and balance dysfunction in Mild Cognitive Impairment and Alzheimer's disease.

Moderator

XXXI Bárány Society Meeting; 9-11/05/2022, Madrid, Spain. Session: Audiovestibular cognition.

8th Scientific Meeting of the Federation of the European Societies of Neuropsychology (FESN); 27-29/09/2023, Thessaloniki, Greece. Session: Cognition across the lifespan.

Scientific outreach

PRESS > SPEAK writing contest for young researchers; 19/03/2021. Wie valt, vergeet meer. *Finalist*.

Luchtige Lezing WINA; 21/04/2021. Heeft mijn oma dementie?

FWO Instagram takeover; 07-11/06/2021. #fwovlaanderen.
QR-code:

PRESS > SPEAK presentation contest for young researchers; 02/03/2023. Brengt Alzheimer je uit balans?
Finalist.

Glashelder, video item in online magazine University of Antwerp “Stroom”; 12/05/2023. Joyce Bosmans traint het brein met evenwichtsoefeningen. Alzheimer en evenwicht: een wankele balans.

Wetenschap Uitgedokterd (Science Figured Out); 22/05/2023. Alzheimer brengt je uit balans.

Courses and training

2019-2020

Practical course methods in human neuroimaging, Ludwig-Maximilian-Universität München, Germany, 20-31/01/2020.

ADS course: Under pressure (3h)

2020-2021

Developing a publication strategy in the physical sciences and life sciences (1h30)

StatUA course: Multivariate data analysis (12h)

StatUA course: Multiple linear regression (10h)

StatUA course: Introduction to JMP Pro 15 software (7h)

StatUA course: Analysis of grouped and longitudinal data using linear mixed models (12h)

ADS course: Mindmapping (3h)

ADS course: Creating a scientific poster (7h)

ADS course: Giving presentations in English (18h)

ADS course: Communication skills basics (7h)

2021-2022

Elective course ICH-GCP: Good Clinical Practice

Good Academic research Practices – mind the GAP

Coaching sessions for the PRESS>SPEAK writing competition (2h30)

C-SSRS (Columbia-Suicide Severity Rating Scale) training

Let's Talk Science Summer School for Science Communication: Wetenschap voor kinderen: een ideale match!; Understanding (social) media

Vlaamse AI Academie: Machine-learning: Bias in, bias out (2h)

StatUA course: R online (18h)

StatUA course: Excel: intermediate tips and tricks (8h)

FLAMES Summer School Methodology & Statistics: Bayesian analysis (18h)

ADS course: Time management (10h)

ADS course: Intro to Data Management Plans (9h)

ADS course: PowerPoint (8h)

ADS course: Leiderschap en teamwerking (24h)

ADS course: Grow your future career (24h)

ADS course: Applying for a job (4h)

ADS course: Personal development plan PhD (8h)

ADS course: authentic networking (1h)

2022-2023

Coaching sessions for the PRESS>SPEAK presentation competition (8h)

Academic experience

Supervision of thesis – Master

Luna Van Hoyweghen. The association between vestibular function and cognitive impairment in older adults. 2020-2021. Master Biomedical Sciences. University of Antwerp.

Jens Claessens. Volumetric MRI changes in people with bilateral vestibulopathy in comparison with healthy older adults. 2021-2022. Master Biomedical Sciences. University of Antwerp.

Guillaume Carp and Kobe Wouters. Cortical Auditory Evoked Potentials in Alzheimer's disease and hearing loss. 2021-2023. Master Medicine. University of Antwerp.

Supervision of thesis – Bachelor

Lana Biot. De rol van het vestibulair systeem in de ziekte van Alzheimer. 2019-2020. Bachelor Biomedical Sciences. University of Antwerp.

Jens Claessens. Invloed van gehoorverlies op de afname van hersenvolume. 2019-2020. Bachelor Biomedical Sciences. University of Antwerp.

Alex Evenblij. Invloed van het evenwichtsorgaan op volumes van verschillende regio's in de hersenen. 2020-2022. Bachelor Biomedical Sciences. University of Antwerp.

Mina Diri. De associatie tussen het evenwichtsorgaan en de ziekte van Alzheimer. 2021-2022. Bachelor Biomedical Sciences. University of Antwerp.

Yasmina Begdouri. Balans en de ziekte van Alzheimer. 2021-2022. Bachelor Biomedical Sciences. University of Antwerp.

Cedric Vandeginste. Impact van Gehoorapparaten op Cognitieve Prestaties bij Oudere Patiënten met Gehoorverlies. 2022-…. Bachelor Audiology. University College Ghent.

Dankwoord

Een doctoraat schrijf je natuurlijk niet alleen. Dit is dan ook het uitgelezen moment om enkele personen verbaal in de bloemetjes te zetten.

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Constructive feedback is the best present your research can get. Therefore, I would like to thank the members of the jury, **professor Monica Dhar, professor David Crosiers, professor Hannah Keppler**, and **professor Doris Bamiou** for reading this doctoral thesis and engaging in an interesting discussion on its findings and implications.

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Dr. Ellen Andries. Kort maar krachtig: jou verhuis ik graag van ICF categorie e325 naar e320.

Dr. Emilie Cardon, ik vond het een voorrecht om jou mijn manager te mogen noemen. Jouw gedrevenheid voor wetenschapscommunicatie werkt aanstekelijk en heeft van mij een betere onderzoeker gemaakt. Ik kijk er al naar uit om jouw date te mogen zijn op de toekomstige edities van Nerdland festival.

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